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REVIEW

Recent Update of Natural Compounds as HIF-1α Inhibitors in Colorectal Carcinoma

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Abstract: Hypoxia-inducible factor (HIF)-1 is a transcription factor that regulates the expression of target genes associated with oxygen homeostasis under hypoxic conditions, thereby contributing to tumor development and progression. Accumulating evidence has demonstrated that HIF-1α mediates different biological processes, including tumor angiogenesis, metastasis, metabolism, and immune evasion. Thus, overexpression of HIF-1α is strongly associated with poor prognosis in cancer patients. Natural compounds are important sources of anticancer drugs and studies have emphasized the decisive role of these mediators in modulating HIF-1α. Therefore, the pharmacological targeting of HIF-1α has emerged as a novel cancer therapeutic approach in recent years. The novelty of this review is that it summarizes natural products targeting HIF-1α in colorectal cancer that have not been presented earlier. We studied research publications related to the HIF-1α domain in cancer from 2010 to 2024. However, our main focus was to identify a better targeted approach for colorectal carcinoma management. Our review described HIF-1α role in tumor progression, summarizes the natural compounds employed as HIF-1α inhibitors, and discusses their potential in the development of natural compounds as HIF-1α inhibitors for colorectal cancer treatment.

Keywords: HIF-1α, colorectal cancer, natural compounds, inhibitors, hypoxia

Introduction

A significant advancement in cancer treatment over the last decade has been the emergence of targeted therapies. Unlike traditional chemotherapy, which indiscriminately kills cells, targeted therapy focuses on blocking specific proteins and genes.[1,2] Targeted therapy is an innovative and elective strategy that effectively extends the overall lifespan of patients with colorectal cancer (CRC). New drugs that target many key pathways and immunological checkpoints have appeared rapidly after the successful use of anti-angiogenesis agents (bevacizumab) and anti-EGFR agents (cetuximab). Targeted medicines can effectively impede the growth, specialization, and movement of cancer cells. Targeted medications can modify the TME, including nearby blood arteries and immune cells, to hinder tumor growth and enhance immune surveillance and attack.[3,4] Tumor hypoxia is a prevalent medical condition that occurs when there is insufficient oxygen to reach tissues.[5] This leads to changes in metabolism and an increased ability of cancer cells to spread to other parts of the body.[6] Cancer cells have the ability to regulate their growth and metabolism in hypoxic environments by altering the tumor microenvironment (TME) in response to hypoxia.[7,8] These hypoxic responses are predominantly affected by Hypoxia-inducible factor (HIFs) and their signaling pathways. Hypoxia, caused by insufficient oxygen delivery to tumor tissues, is a critical clinical state that leads to angiogenesis, cellular proliferation, and

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metastasis.[9] Tumor cells exhibit increased ROS levels in hypoxic environments. ROS production initiates the degradation of cellular macromolecules including RNA, lipids, DNA, and proteins, ultimately resulting in cell death. However, cancer cells employ several strategies to evade apoptosis and ultimately persist in adverse environments.[10] The primary survival characteristics of cancer cells involve an increased focus on metabolic reprogramming, angiogenesis, and metastasis. The regulation of these reactions is controlled by the HIF protein family, whose expression is modified in response to hypoxia.

HIF was initially discovered by Semenza et al, who reported the existence of a hypoxia response element in every HIFs-regulated target gene.[11,12] HIF proteins have different alpha and beta subunits, which form a structure called a heterodimers. This protein has a basic helical loop. In addition to HIF-1, the HIF family encompasses two other members: HIF-2 and HIF-3. HIF-1α is a 120 kDa subunit that is sensitive to oxygen levels and is found in all tissues, whereas HIF-2α and HIF-3α have a more limited presence in certain organs. Both share a common functional domain called the basic helix-loop-helix (bHLH) motif, which is responsible for DNA-binding. Additionally, they possess PAS-A and PAS-B domains that facilitate heterodimerisation.[13] Hypoxia triggers an imbalance in the production of pro- and anti-angiogenic factors, resulting in the accelerated and disordered development of blood vessels. HIF-1α controls a wide array of genes responsible for epithelial-to-mesenchymal transition. This process involves the disruption of the basement membrane in the surrounding tumor tissue, leading to invasion. Hypoxia facilitates the movement of cells from the initial tumor to a distant location where it forms a secondary tumor by controlling the activity of HIF-1α.[14,15] Furthermore, modifications to these novel traits enhance the aggressiveness of cancer cells under hypoxic conditions. Consequently, they may serve as potential targets for cancer therapies. Although numerous reviews have summarized natural compounds as HIF-1α inhibitors in various human carcinomas but to the best part of our knowledge, no review has enlisted natural compounds as HIF-1α inhibitors in colorectal carcinoma. Such review would aid in developing more specific therapeutic approach for colorectal and colon cancer patient with minimal side effects. This review comprises of different sections including: (i) HIF-1α in colorectal cancer (ii) Natural compounds inhibiting HIF-1 α in colorectal cancer and (iii) Overcoming chemoresistance in colorectal carcinoma. Altogether, this review would provide a thorough understanding of the HIF-1α inhibitor in colorectal and colon cancer that has not been explained anywhere.

HIF-1α Expression in Colorectal Cancer

HIF-1α is essential for tumor growth, cellular energy production, and the spread of cancer to other body parts. HIF-1 activation is strongly influenced by the translocation of HIF-1α into the nucleus, a process that can be disrupted by the von Hippel-Lindau (VHL) protein.[16] PHD2 uses O_2 (as a substrate) and introduces hydroxyl functional groups to HIF-1α under normoxic conditions. This results in ubiquitination of HIF-1α after binding to the VHL protein, resulting in the breakdown of HIF-1α via the recruitment of ubiquitin ligases.[17] Under hypoxic conditions, a decrease in hydroxylation results in a reduction in the synthesis of the VHL and HIF-1α complex, which in turn promotes the stable production of HIF-1α.[18] Oxygen levels in animal cells are closely correlated with changes in gene expression, which in turn trigger rapid oxygenation and cellular stress response via activated HIFs. Along with its involvement in maintaining physiological cellular processes in the normal cardiovascular system and embryonic development, HIF-1α also participates in tumor angiogenesis, cancer progression, anti-apoptosis, and metastasis throughout tumor development in numerous carcinomas, including prostate, hepatocellular, lung, cervical, and gastrointestinal carcinomas.[19] Mounting data indicate that the adaptation of cancerous cells to hypoxia is directly associated with poor prognosis and metastasis in numerous malignancies. Hyperoxic breathing can reverse hypoxia-induced carcinogenesis. Furthermore, significant evidence indicates the potential involvement of HIF-1α and HIF-2α in the regulation of HIF-1 transcription in the TME (under low oxygen concentrations).[20] Colorectal cancer (CRC) ranks third in terms of its prevalence as a malignant tumor and second in terms of its contribution to cancer-related deaths worldwide. The prevalence of colorectal cancer has progressively increased owing to lifestyle modifications. Despite advancements in chemotherapy, the overall rate of positive responses to treatment remains unsatisfactory.[21,22] The ineffectiveness of this method is ascribed to chemoresistance of malignant tumors. Similar to other solid tumors, colorectal cancer (CRC) undergoes hypoxia.[23] The consensus is that the existence of hypoxia in the tumor microenvironment might promote tumor proliferation and metastasis, as well as increase their resistance to pharmaceutical interventions.[24]

HIF-1α plays a role in controlling the activity of over 70 specific genes involved in different aspects of tumor growth. Four specific types of genes are strongly associated with tumors. These genes are associated with glucose transport and glycolysis, angiogenesis, tumor growth, cell death, and tumor spread and invasion. They elicit a cascade of reactions in tissues and cells to acclimate to an oxygen-deprived atmosphere, facilitating the growth of blood vessels in tumors and enhancing the ability of the tumor to invade surrounding tissues, along with its resistance to radiation and chemotherapy.[25,26] A significant discovery in understanding how hypoxia contributes to drug resistance is the identification of HIF-1α as a key activator of the multidrug resistance gene 1 (MDR1). This gene encodes for P-glycoprotein (P-gp), which functions as a drug efflux pump and reduces the concentration of drugs in cells.[27–29] Therefore, it is crucial to discover innovative methods to inhibit HIF-1α activation and MDR1 expression in cancer cells exposed to low oxygen levels.

HIF-1α in tumor cells not only stimulates angiogenesis but also facilitates the acquisition of energy through the reconfiguration of cellular metabolic pathways, with glycolysis being a crucial mechanism.[30] Initially, HIF-1α activates lactate dehydrogenase A (LDHA) and glucose transporters to facilitate the transformation of the metabolic pathway from oxidative to non-oxidative carbon metabolism as well as ATP-producing pathways (glycolysis).[31] Furthermore, the PDK protein, which is produced by the pyruvate dehydrogenase kinase-1 (PDK1) gene, acts as a target of HIF-1α. This hinders the synthesis of acetyl-CoA, obstructs the tricarboxylic acid cycle (TCA), and reduces the ingestion of oxygen.[32] Cells deficient in HIF-1α were found to have decreased ATP synthesis in low-oxygen settings, resulting in increased ROS production and the facilitation of programmed cell death. Furthermore, activated HIF-1α affects the pentose phosphate pathway by converting the intermediate products of glycolysis into 5-phosphoribose, which is a crucial substance used in the production of nucleotides.[33,34] These findings indicate that HIF-1α enhances cell survival under low-oxygen conditions by reorganizing the cellular metabolic pathways. This reorganization is necessary to transform glucose metabolism into DNA and RNA, which are crucial for the survival and proliferation of tumor cells in low-oxygen environments.[35]

HIF-1α additionally enhances the growth of cancer cells by controlling associated factors. For instance, HIF-1α stimulates the synthesis of substances, including transforming factor-2 (TGF-2) and insulin-like growth factor-2 (IGF-2), which further stimulate the MAPK/PI3K signaling pathways by binding to specific receptors. This leads to cell hyperplasia, which enhances HIF-1α activation and accelerates the transcriptional activity of HIF-1α-induced genes that are crucial in tumors. HIF-1α stabilizes p53 by preventing p53 from being broken down and preventing p53 from moving out of the nucleus. This leads to the activation of various genes involved in programmed cell death, and promotes apoptosis.[36] Transcriptional initiation is a crucial regulatory process that affects HIF-1α mRNA expression. The activation of the HIF-1α gene locus is triggered by the interaction between transcription factors, such as STAT3 and NF-κB, and their promoter regions [Figure 1]. Owing to the excessive expression of HIF-1α in various types of human malignancies and their metastases, targeting the HIF-1 pathway

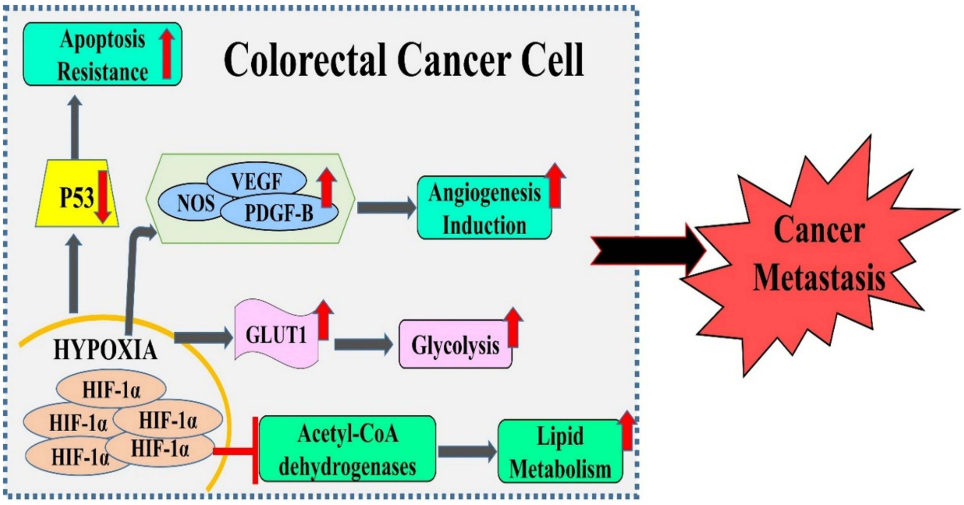

Figure 1 The role of HIF1 alpha in drug resistance mechanisms of colorectal cancer. Under hypoxia, HIF-1α accumulates leading to modulated metabolic pathways and angiogenesis induction which further potentiate cancer initiation and metastasis.

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shows potential as a viable strategy for cancer treatment.[37] Researchers argue that inhibiting the hypoxic response within solid tumors increases their vulnerability to radiotherapy and chemotherapy, leading to better patient outcomes.

Natural Compounds Inhibiting HIF-1 α in Colorectal Cancer

Several natural substances are under consideration for the research and development of novel, secure, and dependable chemicals for cancer prevention of cancer.[38] There is substantial circumstantial evidence suggesting that consuming relatively large amounts of fruits and plant-based foods is associated with a decreased risk of colorectal cancer (CRC). Previous reports have indicated that these natural compounds can affect gene expression and the resulting products via flexible modulatory signaling pathways. This enables them to regulate various cellular processes, including migration, survival, the cell cycle, differentiation, and apoptosis.[39–41] Furthermore, there is a higher occurrence of excessive production of pro-inflammatory transcription factors and cytokines, which are significant contributors to the risk of colitis and development of CRC. This overproduction is particularly observed in the colon due to repeated inflammation.[42] However, the anti-inflammatory properties of various phytochemicals have been shown to inhibit this process, thereby preventing CRC onset. Researchers have discovered several methods to primarily downregulate HIF-1α, including inhibition of HIF-1α/p300 connections, reduction of HIF-1α mRNA production, and decrease in HIF-1α protein stability. Various natural medications and TCM prescriptions effectively reduce HIF-1α levels, leading to a therapeutic impact in modern research.[43,44] Therefore, certain compounds reduced HIF-1 transcription by (i) preventing the phosphorylation of HIF-1α, which affects its movement from the cytoplasm to the nucleus, (ii) inhibiting the interaction between Hsp90 and HIF-1α, (iii) interfering with the mitochondrial ETC, (iv)inhibiting protein synthesis, and (v) destabilizing proteins [Figure 2]. Multiple mechanisms are associated with the downregulation of HIF-1 transcriptional activity by some flavonoids such as apigenin, chrysin, and 4′-O-methylalpinumisoflavone. Consequently, angiogenesis is suppressed, leading to an increased susceptibility of tumor cells to radiation and chemotherapy. The phosphorylation of HIF-1α is regulated by the p42/p44 MAPK and PI3K/Akt signaling pathways. Some flavonoids such as quercetin, luteolin, and kaempferol can interfere with the MAPK pathway. This interference leads to a decrease in the nuclear concentration of HIF-1α, subsequently affecting its transcriptional activity.[45–48] Thus, different classes of natural compounds targeting HIF-1α in colorectal carcinoma are summarized in the subsequent section in more detail [Figure 3].

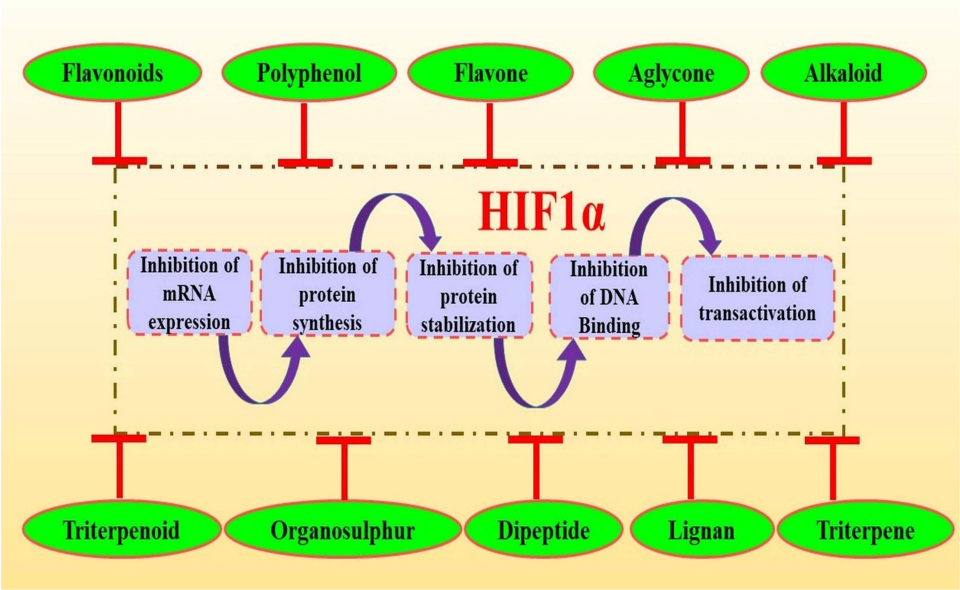

Figure 2 Natural compounds targeting HIF-1α in colorectal cancer via inhibiting the mRNA expression, protein synthesis, protein stabilization, DNA binding and transactivation of HIF-1α in colorectal cancer.

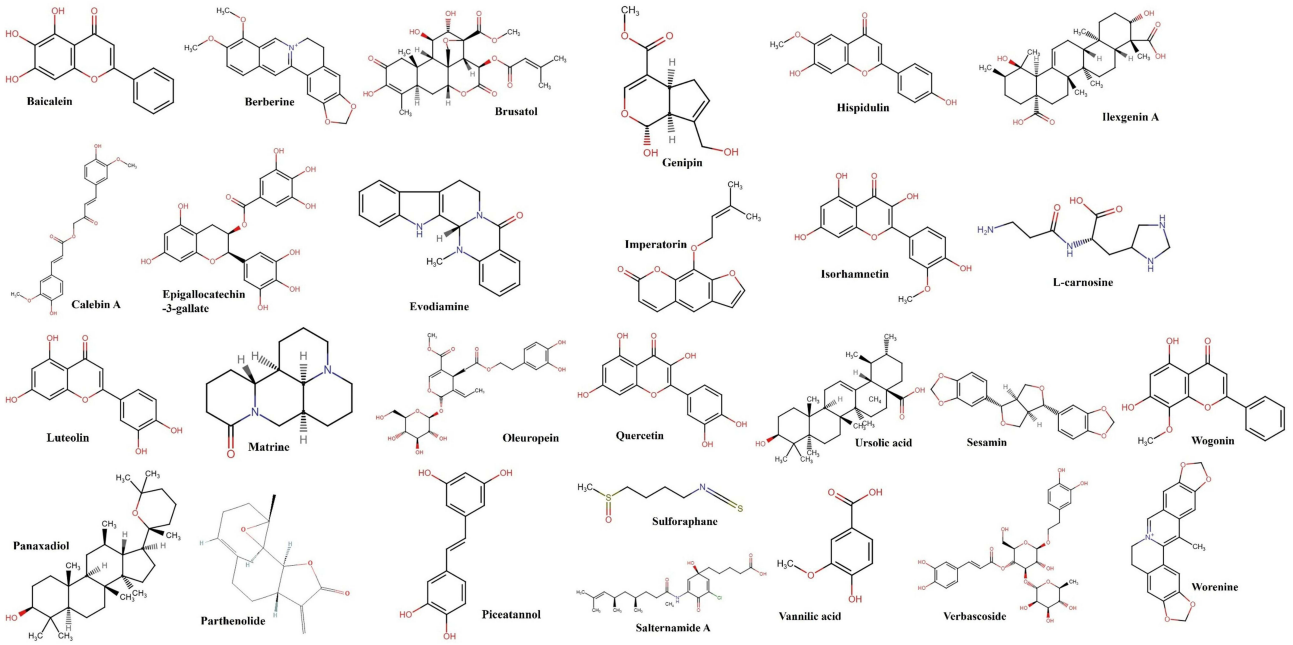

Figure 3 Representation of chemical structure of various natural compounds as HIF-1α modulators.

Polyphenols Targeting HIF-1α

The term polyphenol lacks a precise definition; however, it is generally accepted that polyphenols are naturally occurring compounds with hydroxyl groups (one or more) attached to the aromatic rings. Polyphenols can be classified into four main categories: phenolic acids, flavonoids, stilbenes, and lignans. The effect of flavonoids on HIF-1α activation varies significantly depending on the specific methods through which flavonoids disrupted the HIF-1 pathway.[49] Flavonoids function as iron chelators because of their keto and hydroxyl functional groups. Flavonoids, such as (-)-epicatechin -3-gallate, quercetin, fisetin, baicalein, galangin, and luteolin, bind to iron inside cells, which then affects the function of iron-dependent enzymes such as PHDs. Therefore, PHD activity is hindered, resulting in HIF-1α stabilization under normoxic conditions. Flavonoids imitate hypoxia and trigger adaptive cellular responses. However, flavonoids disrupt the HIF-1 pathway regardless of their ability to chelate iron. Vanillic acid (a dietary phenolic compound) suppresses HIF-1α expression in HCT116 cells via inhibition of the MEK/ERK and mTOR cellular pathways, and has emerged as an efficient HIF-1α inhibitor in colon cancer.[49]

Quercetin

The anticancer potential of quercetin has been exploited to address hypoxia. Pharmacological processes have been explored by focusing on AMP-activated protein kinase (AMPK).[50] Quercetin effectively reduced tumor growth in both vivo and vitro models of HCT116 cancer xenografts by drastically decreasing AMPK activation. Quercetin significantly increased the occurrence of programmed cell death (apoptosis) in HCT116 cancer cells exposed to low-oxygen conditions (hypoxia) compared to those exposed to normal oxygen levels (normoxia). This effect is strongly linked to suppression of hypoxia-induced AMPK activity.[51] Quercetin decreases HIF-1α activation, which is a transcription factor responsible for the adaptive cellular response to low oxygen levels.[52] Quercetin significantly reduced angiogenesis generated by HT-29 cells in Human umbilical vein endothelial cells (HUVECs). Quercetin also suppresses the expression of VEGF-A, NF-κB, and p65. Furthermore, quercetin effectively suppressed the expression and movement of VEGFR-2 in human vein endothelial cells (HUVECs) when they were exposed to high concentrations of quercetin-treated HT-29 cells. Collectively, quercetin inhibited the formation of new blood vessels (angiogenesis) by blocking VEGF-A activity through the NF-κB signaling pathway in HT-29 cells. Additionally, it decreased the expression and movement of VEGFR-2 in HUVECs.[53]

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Luteolin

Luteolin, a flavonoid, exhibited significant cytotoxicity against both HCT116 and MDA-MB231 cell lines. It induces apoptosis (cell death) owing to injury (necrosis), and this outcome is not influenced by the activation of HIF-1α. Luteolin induced autophagy and inhibited HIF-1α transcriptional activity in these cells, which was accompanied by a reduction in the number of protein markers linked to stem cell traits and invasion as well as a decrease in the ability of cells to migrate. Thus, luteolin has emerged as a promising therapeutic agent for hypoxic cancers.[54] Luteolin has a notable ability causes cell death in HCT116 and MDA-MB231 cells. This was achieved by triggering apoptotic and necrotic cell death. Importantly, the activation of HIF-1α does not affect this effect. Luteolin has been utilized as an effective therapeutic drug to target hypoxic malignancies.[55] Compound 7f, a derivative of the 5,6,7-Trimethoxy flavonoid salicylate, efficiently reduced the expression of glycolysis-related proteins (PKM2, HIF-1α, and PFKM) and tumor angiogenesis-related protein (VEGF).[56]

Hispidulin

Hispidulin (a naturally occurring flavonoid) inhibits hypoxia-induced EMT (epithelial-mesenchymal transition) in human colorectal cancer cells, which is necessary for cancer metastasis.[57] Hispidulin administration effectively reversed the EMT-related phenotype, including hypoxia-induced cell migration, morphological alterations, and E-cadherin down-regulation. This impact was partially achieved by the suppression of HIF-1α (at both the mRNA and protein levels) through the regulation of the PTEN/PI3K/Akt pathway. Xie et al (2015) found that hispidulin effectively inhibits hypoxia-induced EMT in human colon cancer cells.[57]

Isorhamnetin

Isorhamnetin is a significant monomethoxyflavonol present in the G. biloba leaf extract. Isorhamnetin strongly inhibited $CoCl_2$- and HIF-1α- induced activity of the hypoxic response element reporter gene, as well as HIF-1α-dependent gene transcription, including carbonic anhydrase-IX, glucose transporter 1, pyruvate dehydrogenase kinase 1, and lactate dehydrogenase A, in HCT116 and HT29 cells. The antioxidant properties of isorhamnetin were verified by measuring the ROS generation using $CoCl_2$ or H_2O_2. In HEK293 cells, the overexpression of HIF-1α was consistently reduced by N-acetyl-l-cysteine and isorhamnetin. Isorhamnetin hinders the buildup of HIF-1α through the inhibition of ROS, thereby enhancing its effectiveness in preventing metastasis.[58]

Piceatannol

Piceatannol is a naturally occurring polyphenol with anticancer and anti-inflammatory activities.[59] PIC–BSA nanoparticles (where PIC was encapsulated within bovine serum albumin) showed greater efficacy in reducing the expression of nuclear HIF-1α and p65 in colon cancer cells than free PIC. A notable decrease in inflammation caused by chemical colitis in mice treated with PIC–BSA NPs. In addition, the mouse model of colorectal cancer (colitis-associated) showed a notable decrease in both the number and size of colon tumors when treated with PIC–BSA NPs compared to free PIC. These findings suggested that the therapeutic potential of PIC is enhanced when they are formed as PIC-BSA NPs. These findings have paved the way for the development of a novel range of secure and efficient treatments for individuals with cancer.[60]

Other Phenolic Compounds

Hypoxia-induced medication resistance poses a significant challenge for the advancement of effective cancer treatments.[61] Wogonin (O-methylated flavone) effectively counteracted the hypoxic resistance of HCT116 cells by reducing glycolysis and HIF-1α activity. This was achieved by suppression of the PI3K/Akt pathway. Thus, wogonin is a potential candidate for the development of new medicines to reverse multidrug resistance (MDR). The mechanism of reversal is likely to be inhibition of HIF-1α production by blocking the PI3K/Akt signaling pathway.[62] Oleuropein (OL) is the predominant phenolic component found in the fruits of olive trees. The growth of HT-29 cells is restricted, and programmed cell death is triggered by OL through the activation of the p53 pathway, which modifies the response of HIF-1α to low oxygen levels.[63]

Calebin A (CA), a natural polyphenol extracted from turmeric, is known for its ability to inhibit cancer growth by regulating the NF-κB pathway. CA partially hindered the migration of HCT-116 cells by suppressing HIF-1α, a crucial factor for the survival of CRC cells. It also suppresses HIF-1α activation and metastatic biomarker expression initiated by the tumor microenvironment while promoting apoptosis through caspase-3 activation.[64] Parthenolide (PT) can be extracted from Mexican Indian medicinal herbs and exhibits anti-inflammatory characteristics. Parthenolide inhibits HIF-1α signalling and hypoxia-induced EMT in colorectal cells PT suppresses growth in colorectal cancer xenograft models and modulates NF-κB, HIF-1α, and EMT-specific markers in tissue samples. The results showed that PT blocked HIF-1α signaling and prevented hypoxia-induced EMT. This suggests a new molecular mechanism by which HIF-1α contributes to cancer metastasis.[65]

Traditional Chinese Medicine Targeting HIF-1α

Several malignant tumors, such as colorectal cancer, develop functioning blood arteries to facilitate tumor growth and spread to other body parts. Vasculogenic mimicry (VM) is the capacity of a vastly invasive tumor to connect with one another and create vasculature and is linked to a negative cancer prognosis.[66] TCM has also been used in cancer treatment.[67] Jianpi Jiedu decoction (JPJD), a long-standing traditional Chinese medicinal formula, has been used for several decades to treat colorectal cancer. JPJD substantially inhibited the viability and proliferation of colorectal cancer cell lines. Flow cytometry analysis revealed that JPJD induced apoptosis in HCT116 cells. Moreover, JPJD efficiently restricted the movement of tumor cells, their invasion, and new blood vessel formation by blocking the mTOR/HIF-1α/VEGF signaling pathway. JPJD significantly inhibited HCT116 tumor growth (in athymic nude mice) when tested in vivo. Additionally, it reduces CD34 and VEGF levels and downregulates the mTOR/HIF-1α/VEGF pathway, as reported by Peng et al in 2018.[68]

Zong et al (2020) found that Astragalus Atractylodes mixture (AAM), a TCM, effectively inhibited the migration and formation of vascular mimicry (VM) in colorectal cancer (HCT-116 and LoVo) cells under hypoxic conditions.[69] This inhibition was achieved by the suppression of the ROS/HIF-1α/MMP2 pathway. These findings suggest the therapeutic potential of AAM in the prevention of VM in human colorectal cancer cells.[69] Imperatorin triggered a significant HIF-1α protein reduction in accumulation produced by hypoxia. Imperatorin inhibited the expression of HIF-1 target genes in response to hypoxia. Flow cytometric analysis revealed that imperatorin causes G1 phase arrest. Imperatorin reduced the production of HIF-1α protein in human colon cancer cells (HCT116) by reducing the activity of the mTOR/p70S6K/4E-BP1 and MAPK pathways. This study suggested that imperatorin is an efficient inhibitor of HIF-1α in colon cancer cells.[70]

Evodiamine (Evo), (quinolone alkaloid) is derived from the traditional herbal remedy, *Evodia rutaecarpa*. Evo caused a noticeable decrease in HIF-1α activity (in vivo and *vitro)*. Introducing HIF-1α from an external source can weaken the inhibitory effect of Evo on LoVo cell proliferation Conversely, reducing the levels of HIF-1α enhances this inhibitory effect to a significant extent. The anticancer effect of Evo in colon cancer is partially achieved by reducing the production of HIF-1α, which is triggered by deactivation of the PI3K/Akt signaling pathway by reducing IGF-1 expression in colon cancer cells.[71]

Ursolic acid (UA) is a pentacyclic triterpenic acid present in various plants, including Chinese medicinal herbs.[72] Cancer cells are expected to exhibit increased levels of HIF-1α when exposed to low oxygen levels (hypoxic stress) or treated with chemotherapy. Normal cells rarely encounter hypoxic stress and, hence, maintain normal HIF-1α levels. UA effectively inhibited MDR1 expression by decreasing hypoxia-induced HIF-1α build-up. This discovery offers limited clarification on how UA may counteract the resistance of colon cancer cells to chemotherapy in low-oxygen environments.[73,74] HIF-1α is a prominent transcription factor that plays a significant role in regulating various tumor characteristics, including the growth, spread, and formation of new blood vessels.

Alkaloid Targeting HIF-1α

Matrine

Matrine (an alkaloid) is derived from the roots of TCM (*Sophora flavescens* Ait. Matrine) has been shown to exhibit specific cytotoxicity towards cancerous cells.[75] Matrine counteracted the Warburg effect by limiting lactate formation and glucose uptake. Matrine effectively reduced HIF-1α mRNA and protein expression Matrine significantly decreased the expression levels of LDHA GLUT1, and HK2 which are downstream targets of HIF-1α and are involved in the regulation

of glucose metabolism. Furthermore, the suppressive effect of matrine was notably diminished when HIF-1α was depleted or artificially elevated in the colon cancer cells. Matrine has the potential to be used as a therapeutic drug for colon cancer by specifically targeting the HIF-1α-mediated Warburg effect, as suggested by Hong et al in 2019.[76]

Berberine

Hyperactivated glucose absorption and glycolytic metabolism are the characteristic features of cancer.[77] Berberine, a naturally occurring alkaloid, exhibits selective anticancer effects in tumors and has been demonstrated to enhances glucose uptake in metabolic organs and cells. Berberine effectively slowed the growth of colon cancer (HCT116 and KM12C) cells. Berberine treatment significantly suppressed the protein production HIF-1α that played a crucial role in the abnormal glucose metabolism in colon cancer cell lines.[77] However, no significant effect on HIF-1α mRNA expression was observed. Regulation occurs through protein synthesis rather than through protein stability. The effect of berberine was not affected by obstructing the degradation of HIF-1α protein using the hypoxia mimic desferrioxamine (DFX) or proteasome inhibitor MG132. Furthermore, berberine suppresses mTOR signaling, which has been previously shown to influence HIF-1α protein synthesis. These findings demonstrated that berberine effectively suppressed excessive glucose metabolism in colon cancer cells by inhibiting HIF-1α protein synthesis, which is dependent on the mTOR pathway. This study provides a theoretical foundation for its potential use in colon cancer treatment.

Other Natural Compounds Targeting HIF-1α (Sulforaphane, Epigallocatechin Gallate, Salternamide A, Verbascoside, Ilexgenin A, Desferrioxamine, Worenine, Sesamin, Genipin, Brusatol, Panaxadiol)

Another study examined the effect of sulforaphane, a naturally occurring substance often present in broccoli,[78] on the expression of HIF-1α in HCT116 (colon cancer) and AGS (gastric cancer) cells. Sulforaphane suppressed HIF-1α protein expression in HCT116 and AGS cells when exposed to low-oxygen conditions. Furthermore, sulforaphane administration suppresses VEGF expression in HCT116 cells under hypoxic conditions.[79] Inhibition of HIF-1α protein expression by sulforaphane has been linked to the instability of the protein itself and avoidance of the activation of genes targeted by HIF-1α. Sulforaphane additionally suppressed the movement of cells generated by hypoxia. These studies indicate that sulforaphane can hinder the growth of blood vessels and movement of human colon cancer cells by suppressing the production of HIF-1α and VEGF under low-oxygen conditions. Sulforaphane inhibits the latent-to-hindered advancement of colon cancer and blood vessel formation in human cancer cells by suppressing the production of HIF-1α and VEGF.[80] Epigallocatechin gallate (green tea) inhibited the growth of colorectal cancer cells by blocking the activation of the VEGF/VEGFR pathway. This effect is achieved by suppressing the expression of HIF-1α and other important growth factors. Therefore, it may have potential applications in the prevention and treatment of colorectal cancer.[81]

Salternamide A (SA) is A newly discovered compound obtained from the halophilic Streptomyces sp. It has been shown to have strong cytotoxic properties in numerous human cancer cells. SA effectively suppressed hypoxia-induced buildup of HIF-1α in various types of human cancer cells, with the inhibition dependent on both time and concentration. Furthermore, SA inhibited the activation of the HIF-1α signaling pathway under hypoxic conditions. Moreover, SA triggers cell death in colorectal cancer cells by promoting G2/M (cell cycle) phase arrest and apoptosis.[82] SA, a small-molecule HIF-1α inhibitor derived from natural marine products, has been recognized as a promising candidate for the development of anticancer medicines.

Colorectal cancer cells (specifically HT29 cells) show an increase in the expression of Rac-1 and HIF-1α, which are crucial for the initiation and advancement of cell movement, new blood vessel formation, and cancer spread to other body parts. A study by Seyfi et al (2018) found that verbascoside demonstrated notable anti-metastatic and anti-invasion effects by inhibiting Zeb-1, Rac-1, and HIF-1α signaling pathways. These findings suggest that verbascoside is a promising candidate to combat the metastatic characteristics of colon cancer.[83] Ilexgenin A (IA), the primary biologically active component of Ilex hainanensis Merr., exhibits hypolipidemic properties. It has the potential to decrease the levels of triglycerides (TG) and expression of ACC, HIF1α, FASN, and SREBP-1 in colon (HT 29 and HCT 116) cancer cells. Desferrioxamine (DFX) was shown to weaken the inhibitory effect of IA on SREBP-1, indicating that HIF1α plays a role in the regulation of SREBP-1 by RA. The study conducted by Zhang et al (2019) found that IA

inhibited the early development of colon cancer in mice treated with AOM/DSS. Additionally, IA partially alters lipid metabolism via the involvement of HIF1α/SREBP-1.[83]

HIF-1α is essential for cancer metastasis. Inhibition of CRC cell migration was observed when baicalein administration decreased HIF-1α expression. However, this effect was reversed by overexpression of TLR4. Baicalein directly interacts with TLR4 and inhibits the TLR4/HIF-1α/VEGF signaling pathway in CRC.[84] In the Warburg effect, cancerous cells preferentially utilize glycolysis over oxidative phosphorylation to metabolize glucose, even when oxygen is available, resulting in the production of lactate as an end-product. The metabolic shift to aerobic glycolysis promotes tumor cell proliferation by allowing cancer cells to survive and redirect metabolic intermediates from energy production to biosynthesis. This phenomenon arises because of the ability of certain transcription factors, such as HIF-1α, to alter the expression of various isoforms of glycolytic enzymes in cancerous cells. Worenine, extracted from Coptis chinensis, was found to possess anticancer properties in SW620 and HCT116 cells. In vitro, worenine effectively suppressed cell proliferation, growth phase (cell cycle) arrest, and the Warburg effect in colorectal cancer cells by specifically targeting HIF-1α. According to Ji et al (2021), Worenine has the ability to reverse the Warburg effect and hinder the proliferation of colon cancer cells by exerting a negative regulatory effect on HIF-1α.[85]

Sesamin (sesame seeds) effectively suppressed the formation of new blood vessels in colorectal cancer under low-oxygen conditions in a dose-dependent manner, as observed in laboratory experiments. Furthermore, ingestion of sesamin in nude mice significantly inhibited the development of new blood vessels in matrigel plugs containing CRC cells. Sesamin decreases VEGFA expression, hindering new blood vessel formation in hypoxia-induced colorectal cancer produced by hypoxia.[86] Furthermore, sesamin prevented the phosphorylation of IκBα, thereby preventing the activation of NF-κB p65 and the transcription of HIF-1α under hypoxic conditions. These findings demonstrated that sesamin effectively suppressed new blood vessel formation in colorectal, driven by low oxygen levels through the NF-κB/HIF-1α/VEGFA signaling pathway. These findings serve as a theoretical and experimental foundation for utilizing sesamin in CRC prevention and treatment, as suggested by Huang et al (2022).[87] Genipin inhibits HIF-1α buildup in different cancer cells, such as HCT116, under low-oxygen conditions by regulating the breakdown of proteins. Genipin inhibits VEGF expression and the invasion of colon cancer cells by obstructing the extracellular signal-regulated kinase signaling pathway.[88] Brusatol (Bru, a quassinoid), derived from Brucea Esters, suppresses the HIF-1 signaling pathway and inhibits HIF-1 transactivation activity and the production of its target genes, including LDHA, VEGF, HK2, and GLUT1, under hypoxic conditions. Furthermore, Bru reduced glucose intake under low-oxygen conditions by inhibiting the HIF-1α signaling pathway. Subsequent research has indicated that the suppressive effect of Bru on the HIF-1 signaling pathway could be ascribed to its ability to enhance the degradation of HIF-1α.[89] Remarkably, ROS levels within the cells and mitochondria were reduced by BRU therapy, suggesting the involvement of mitochondrial ROS regulation in the mechanism of action of Bru. The collective findings present strong evidence supporting the control of HIF-1α by Bru, and indicate its potential as a therapeutic approach for colon cancer.[90]

Another study examined whether l-carnosine targets HIF-1α in HCT-116 cells. HIF-1α is highly expressed in several human cancers and is the primary factor responsible for drug and radiation resistance in solid tumors. l-carnosine was found to lower the protein level of HIF-1α, thereby reducing its stability and inhibiting HIF-1 transcriptional activity. Furthermore, L-carnosine plays a role in the UPS, which aids HIF-1α degradation of.[91] Panaxadiol inhibited hypoxia-induced HIF-1α production by acting on the PI3K and mitogen-activated protein kinase pathways. Panaxadiol hindered the activation of STAT3 via JAK1, JAK2, and Src pathways. Furthermore, prior administration of panaxadiol enhanced the efficacy of cytotoxic T lymphocytes and restored their ability to eliminate tumor cells in a co-culture system including T cells and tumor cells. Immunoprecipitation demonstrated that panaxadiol hindered the production of PD-L1 by obstructing the interaction between HIF-1α and STAT3. This study demonstrates the antitumor properties of panaxadiol and provides valuable information on the potential use of PD-L1 inhibition in cancer treatment.[92] Table 1 summarizes all reported phytocompounds that target HIF-1α in both colorectal and colon cancer cells.

Overcoming Chemoresistance in Colorectal Carcinoma

Hypoxia during carcinogenesis promotes aggressive tumor development and resistance to radiation and chemotherapy and is associated with poor prognosis. The effectiveness of chemotherapy in cancer treatment is limited by drug resistance caused by the hypoxia-induced stabilization of HIF-1α. HIF-1α overexpression has been detected in a wide

Table 1 Phytocompounds Targeting HIF-1α in Both Colorectal and Colon Cancerous Cells

Phytocompound	Class of the Compound	Mode of Action in Colorectal Cancer Cells	Reference
Vanillic acid	Polyphenol	Reduced expression of HIF-1α Inhibition of mTOR and ERK signaling pathway	[49]
Quercetin	Flavonoid	Suppressed hypoxia-induced AMPK activity Increased apoptosis induction Reduced activity of HIF-1α	[52]
	Flavonoid	Decreased angiogenesis Suppressed expression of NF-κB, p65 and VEGF-A proteins Blocked activity of VEGF-A via NF-κB signaling pathway	[53]
Luteolin	Flavonoid	Increased apoptosis and necrosis Autophagy induction Inhibited HIF-1 transcriptional activity	[54]
Compound 7f (derivative of 5,6,7-Trimethoxy flavonoid salicylate)	Flavonoid	Reduced expression of HIF-1α Decrease in PFKM, and PKM2 expression level Decreased VEGF expression	[55]
Hispidulin	Flavonoid	Inhibited hypoxia-induced epithelial-mesenchymal transition Down-regulated E-cadherin levels Downregulated hypoxia-induced cell migration and invasion Suppressed mRNA and protein levels of HIF-1α	[57]
Isorhamnetin	Monomethoxyflavonol	Strong HIF-1α- and CoCl2-induced activity inhibition of the hypoxia response element reporter gene Inhibition of HIF-1α-dependent genes transcription Hindered accumulation of HIF-1α through inhibition of ROS Inhibition of metastasis	[58]
Piceatannol	Polyphenol	Reduced expression of nuclear HIF-1α and p65 Decreased inflammation	[59]
Wogonin	O-methylated flavone	Reduced activation of HIF-1α Reduced glycolysis Reversal of multidrug resistance via inhibition of HIF-1α production Blocking of PI3K/Akt signaling pathway	[62]
Oleuropein	Phenolic component	Reduced growth proliferation Increased apoptosis by activated p53 pathway Altered response of HIF-1α to low oxygen levels	[63]
Calebin A	Polyphenol	Inhibited cancer growth via regulation of NF-κB pathway Suppressed HIF-1α activity Reduced cancer cell survival Apoptosis induction via caspase-3 activation	[64]
Parthenolide	Sesquiterpene lactone	Inhibited signaling of HIF-1α Blocked HIF-1α signaling Inhibition of hypoxia-induced EMT	[65]

(*Continued*)

Table 1 (Continued).

Phytocompound	Class of the Compound	Mode of Action in Colorectal Cancer Cells	Reference
Jianpi Jiedu decoction	Traditional Chinese medicine formula	Substantial inhibition of viability and proliferation Apoptosis induction Restricted invasion of tumor cells Inhibited formation of new blood vessels Blocked mTOR/HIF-1α/VEGF signaling pathway	[68]
Astragalus Atractylodes mixture	Traditional Chinese medicine formula	Inhibited migration and formation of vascular mimicry Suppressed ROS/HIF-1α/MMP2 pathway	[69]
Imperatorin	Furocoumarin	Reduced accumulation of HIF-1α protein produced by hypoxia Growth arrest at G1 phase Reduced activity of mTOR/4E-BP1/p70S6K and MAPK signaling pathways	[70]
Evodiamine	Quinolone alkaloid	Decreased activation of HIF-1α Deactivation of PI3K/Akt signaling pathway Reduced IGF-1 expression	[71]
Ursolic acid	Pentacyclic triterpenic acid	Inhibited expression of MDR1 Decreased accumulation of HIF-1α caused by hypoxia Counteract the resistance of colon cancer cells to chemotherapy in low-oxygen environments	[72]
Matrine	Alkaloid	Counteracted Warburg effect by limiting lactate formation and glucose uptake and Inhibited growth Reduced HIF-1α mRNA and protein expression levels Suppressed production of HIF-1α	[75]
Berberine	Alkaloid	Suppressed protein production of HIF-1α Suppressed mTOR signaling to influence HIF-1α protein synthesis Suppressed excessive glucose metabolism via inhibiting the synthesis of the HIF-1α protein	[77]
Sulforaphane	Organosulfur	Suppressed HIF-1α protein expression Suppressed cellular movement generated by hypoxia Suppressing production of HIF-1α and VEGF under low-oxygen conditions.	[79]
Epigallocatechin gallate	Polyphenol	Inhibited growth Blocked activation of the VEGF/VEGFR pathway Suppressed expression of HIF-1α	[80]
Salternamide A	Chlorinated compound	Apoptosis induction Triggered cell death Increased G2/M cell cycle arrest Inhibited activation of HIF-1α signaling pathways under hypoxic conditions.	[81]
Verbascoside	Phenylethanoid glycoside	Anti-metastatic and anti-invasion effects via inhibiting the Zeb-1 Rac-1, and HIF-1α signaling pathway	[82]
Ilexgenin A	Triterpenoid	Altered lipid metabolism via the involvement of HIF1α/SREBP-1 Inhibition of early development in mice treated with AOM/DSS	[83]

(*Continued*)

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Table 1 (Continued).

Phytocompound	Class of the Compound	Mode of Action in Colorectal Cancer Cells	Reference
Baicalein	trihydroxyflavone	Facilitate interaction with TLR4 Inhibition of TLR4/HIF-1α/VEGF signaling pathway	[84]
Worenine	Alkaloid	Suppressed growth and proliferation Suppressed cell cycle growth progression Suppressed Warburg effect via specific HIF-1α targeting	[85]
Sesamin	Lignan	Suppressed formation of new blood vessels under low oxygen conditions Decreased expression of VEGFA Hindered formation of new blood vessels produced by low oxygen levels through the NF-κB/HIF-1α/VEGFA signaling pathway	[86]
Genipin	Aglycone	Inhibited HIF-1α accumulation Inhibited expression of VEGF and invasion Obstruction of extracellular signal-regulated kinase signaling pathway	[87]
Brusatol	Triterpene lactone	Suppressed HIF-1 signaling pathway Inhibited transactivation activity of HIF-1 Reduced production of VEGF, GLUT1, HK2, and LDHA, in hypoxic conditions Enhanced HIF-1α degradation	[88]
L-carnosine	Dipeptide molecule	Lowered protein level of HIF-1α Reduced stability and inhibition of HIF-1α Degradation of HIF-1α	[89]
Panaxadiol	Triterpenoid	Inhibited production of HIF-1α Hindered STAT3 activation via the JAK1, JAK2, and Src pathways Enhanced the efficacy of cytotoxic T lymphocytes Hindered the production of PD-L1	[90]

range of human carcinomas, including colon and colorectal cancer.[91] Therefore, focusing on HIF-1α is a promising approach for overcoming chemoresistance and improving the efficacy of chemotherapy for CRC. The frequent emergence of resistance to the chemotherapeutic medication 5-fluorouracil (5-FU) poses challenges for the treatment of advanced colorectal cancer. Resveratrol uses β1-integrin receptors to overcome 5-FU chemoresistance in CRC cells. The β1-integrin/HIF-1α signaling pathway plays a crucial role in enhancing the sensitivity of CRC cells to 5-FU and overcoming resistance to chemotherapy. Resveratrol activates this pathway, highlighting its potential as a supportive treatment for CRC. Sanguisorba officinalis DiYu (DY) has traditionally been used in China for cancer therapeutics because it has the potential to enhance the immune system and reduce hematological toxicity. DY hinders the growth and movement of 5-FU-resistant cells and enhances their responsiveness to 5-FU. These results suggest that DY is a promising medication for therapeutic management and a supplementary therapy for drug-resistant CRC.[92]

Dihydromyricetin, a flavonoid compound derived from *Hovenia dulcis* (Japanese raisin tree), suppressed the expression of MRP2 and its promoter activity by inhibiting the NF-κB-Nrf2 signaling pathway in HCT-8/VCR and HCT116/L-OHP cells. This contributes to the reversal of L-OHP/VCR resistance in colorectal cancerous cells.[93] Curcumin, a lipid-soluble polyphenol, effectively inhibits cell proliferation, increases cell apoptosis, blocks G0/G1 (growth phase) arrest, and reduces TET1 (a DNA demethylase) activity and NKD2 (a negative regulator of Wnt signaling). These findings suggest an anti-resistance effect of curcumin on 5-FU-resistant HCT116 cells via modulation of the TET1-NKD2-Wnt signaling pathway, thereby inhibiting the progression of epithelial-mesenchymal transition (EMT).[94] Fan et al discovered that curcumin could prevent the advancement of tumors and reverse multidrug resistance in HCT-8/5-FU cells by inhibiting the heat shock protein-27 and P-gp. Resveratrol, a naturally occurring polyphenol, increased the

sensitivity of HCT116/5-FU and SW480/5-FU cells to 5-FU. This occurs by slowing the process of epithelial-mesenchymal transition (EMT), which involves strengthening the connections between cells and reducing the NF-κB pathway.[95] Resveratrol reversed resistance to L-OHP by enhancing drug accumulation, blocking the NF-κB/MDR1 pathway, and reducing the transcriptional activity of cAMP-responsive regions (in L-OHP-resistant) HCT116 cells.[96] β-Elemene (sesquiterpene molecule), derived from the Chinese plant *Curcumae rhizoma*, effectively suppresses cell growth and overcomes the resistance of HCT116 cells to 5-FU by triggering cell cycle arrest and autophagy in a cyclin D3-dependent manner.[97,98] Atractylenolide II, a single compound derived from the traditional Chinese medicinal plant *Atractylodes macrocephala*, can suppress tumor growth and enhance the sensitivity of Lovo and SW480 cell lines to the chemotherapy drugs 5-FU, mitomycin, and Adriamycin.[98]

Emodin, a naturally occurring compound derived from anthraquinone, counteracts 5-FU resistance in SW480/5-FU cells. It inhibits cell proliferation and migration, promotes cell death, and suppresses the PI3K/Akt pathway.[99] Tanshinones are diterpene quinones extracted from the roots of Salvia miltiorrhiza Bunge. It possesses antioxidation, anticancer, anti-inflammation, and other pharmacological properties. Additionally, they have been shown to reverse chemoresistance. Dihydrotanshinone, Tanshinone IIA, and cryptotanshinone are three constituents of tanshinone that partially counteract chemoresistance in CRC. Tanshinone IIA can overcome L-OHP resistance in the SW480/L-OHP cell line by inhibiting the ERK/Akt signaling pathway. The application of Tanshinone IIA in combination with L-OHP led to a considerable decrease in the levels of Bcl-2, p-ERK, and p-Akt while increasing Bax and active caspase 3 levels.[100] Cryptotanshinone and dihydrotanshinone inhibited the proliferation of MDR-resistant SW620/Ad300 cells by triggering p53-independent cytotoxicity and autophagic cell death and.[101] Hypericin, an organic compound belonging to the anthraquinone class, is extensively studied in photodynamic therapy. Hypericin-based photodynamic therapy has the potential to restore sensitivity to L-OHP in CRC-resistant cells, specifically the HCT-8/L-OHP and HCT116/L-OHP cell lines. This restoration is achieved by reducing drug efflux (downregulating MRP2 levels), inhibiting GSH-related detoxification, and suppressing nucleotide excision repair (NER)-mediated DNA repair.[93]

Evodiamine, an alkaloid, can impede cell proliferation and trigger programmed cell death as well as reduce ABCG2-mediated multidrug resistance in HCT116/L-OHP cells by blocking the p50/p65 NF-κB pathway.[102] Ginsenoside Rh2 prevents the growth and movement of cells, triggers cell death, and reduces the expression of genes associated with drug resistance, including glutathione S-transferase (GST), MRP1, lung resistance-related protein (LRP), and MDR1. This reversal of chemoresistance has been observed in HCT-8/5-FU and LoVo/5-FU cell lines.120 β-Sitosterol, a phytosterol, can counteract L-OHP multidrug resistance in HCT116/L-OHP cells by suppressing breast cancer resistance protein (BCRP/ABCG2). This is achieved by disrupting the interaction between murine double minute 2 (MDM2), an enzyme that attaches ubiquitin molecules to proteins, and p53.[103] Thus, ubiquitination and degradation of p53 are inhibited, leading to p53 activation and increased apoptosis. Salvianolic acid B (phenolic acid) was obtained from the dried roots and rhizomes of *Salvia miltiorrhiza* Bge. (Labiatae) counteracted multidrug resistance (MDR) in HCT-8/VCR cells by increasing reactive oxygen species levels. Elevated ROS levels lead to apoptosis and reduced P-gp expression, thereby enhancing the sensitivity of drug-resistant cancer cells to chemotherapy.[104]

Photodynamic therapy (PDT) causes death of tumor cells via ROS generation. However, its effectiveness is hindered by hypoxia, one of the primary factors restricting its efficiency. Bufalin (BU) improves the effectiveness of mTHPC-mediated PDT for CRC. This was achieved through controlled release of BU, which suppressed HIF-1α and decreased VEGF-induced angiogenesis by targeting the SRC-3/HIF-1α pathway. As a result, a powerful PDT effect was observed against CRC. Bufalin enhances the effectiveness of photodynamic therapy in treating colorectal cancer by specifically targeting the SRC-3/HIF-1α pathway. The co-delivery of mTHPC and BU using nanoparticles effectively increased the therapeutic efficacy of PDT by suppressing the SRC-3/HIF-1α pathway in CRC. This study presents a successful approach to address the problem of tumor resistance caused by hypoxia and to overcome the obstacles associated with PDT treatment.[104–106] Solid tumors are responsible for high morbidity globally. Tumors of solid origin often have hypoxic microenvironments that can be treated with immunotherapy, chemotherapy, and radiation. However, the effectiveness of molecular-targeted therapies in cancer treatment is low. HIF-1α inhibitors have been used in various clinical trials to treat solid tumors. Regrettably, there are currently no licensed medications available for the treatment of cancer patients that directly inhibit HIFs, either because of safety concerns or inadequate therapeutic efficacy. Thus, to pursue a specific approach for targeting HIF-1α, it would be

worthwhile to investigate other natural chemicals to increase the likelihood of successful clinical trials for improved anticancer treatments. Additional research involving the use of both natural and synthetic substances in combination could offer a different approach for studying therapies that target HIF-1α.

Conclusion and Future Perspective

HIF-1α is upregulated in different tumor types in the absence of oxygen, leading to activation of gene transcription associated with tumor advancement. These genes are associated with the formation of new blood vessels, metabolic changes, cancer cell spread, and immune evasion. Various HIF-1α inhibitors have been developed to effectively treat cancer by targeting their fundamental role in promoting carcinogenesis under hypoxic conditions. The investigation of HIF-1α targeting in cancer therapy is a crucial and evolving area of study with the capacity to profoundly change current therapeutic approaches. Continued research and intervention in HIF-1 cancer-causing pathways are crucial for advancing colorectal cancer treatment and enhancing patient outcomes; thus, directing efforts towards HIF-1α in colorectal cancer treatment shows great potential as a therapeutic approach. This study discusses the discovery of several HIF-1α inhibitors derived from natural products that have shown promising antitumor properties in colorectal cancer. In general, natural products offer new molecules that can be used to develop HIF-1α inhibitors. However, additional structural modifications are necessary to generate medications with a greater potential. In summary, natural compounds show significant promise for further development as innovative and effective HIF-1α inhibitors and anticancer medicines by boosting their feasibility and minimizing their toxicity. Synergistic association between phytochemicals and synthetic HIF-1α inhibitors could prove to be effective in managing colorectal carcinoma. Thus, studies on the synergistic mechanism of action of both synthetic and natural drugs may create a unique avenue for HIF-1α targeting anti-colorectal cancer therapeutics. Further research is required to investigate the pharmacological and pharmacokinetic properties of natural compounds targeting HIF-1α and their associated mechanisms, along with modification of these molecules.

Data Sharing Statement

Not applicable as this is a review article.

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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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Disclosure

The authors declare no conflicts of interest in this work.

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