Asian Journal of Biology

Volume 16, Issue 3, Page 29-42, 2022; Article no.AJOB.84327
ISSN: 2456-7124

Hepatocellular Carcinoma & Hypoxia: A Review

Mohamed Elborei [a*]

[a] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, October 6th University, Egypt.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/AJOB/2022/v16i3304

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/84327

Review Article

Received: 02/02/2022
Accepted: 05/04/2022
Published: 27/12/2022

ABSTRACT

Liver is the largest gland inside our body, and it is accounted for many functions in the body but like any other organ in the body it is prone to different disease but the most dangerous one of them is hepatocellular carcinoma. Hepatocellular carcinoma is fetal, and it is having low survival rate and it is resistant to the most of the know therapy that's why there is always a need for new treatment modalities. It has different causative agents, different staging methods, different mechanism for hepatocarcinogenesis and different treatment modalities like liver resection, liver transplantation and sorafenib. Tumor hypoxia is a common feature of hepatocellular carcinoma and other solid tumours, and it results from a lack of blood supply to the rapidly expanding cancer cells. Tumor hypoxia is an unfavourable prognosis factor since it enhances the tumor's aggressiveness and resistance to treatment, which is why reducing tumour hypoxia has a lot of therapeutic benefits for cancer patients. Drug resistance, metastasis, angiogenesis, metabolic shifting, radiotherapy resistance, and overall tumour aggressiveness and poor prognosis are all caused by hypoxia inducible factor 1, which causes drug resistance, metastasis, angiogenesis, metabolic shifting, radiotherapy resistance, and overall tumour aggressiveness and poor prognosis. There is keen research working on the tumor hypoxia and trying to discover new drugs and approaches to correct the tumor hypoxia like prodrugs activated by hypoxia, hyperbaric oxygen, nanoparticles, oral oxygen therapy and finally hypoxia inducible factors inhibitors like for example benzopyranyl 1,2,3-triazole, glyceollins and vorinostat.

**Corresponding author: E-mail: Pharmacist900@gmail.com;*

Keywords: Liver; hepatocellular carcinoma; tumor hypoxia.

1. INTRODUCTION

1.1 Liver

1.1.1 Anatomy

1.1.1.1 Hepatic macrostructure

The liver is a large gland, and it is weight in the adult measures roughly 1851 g in males and 1591 g in females [1,2]. "It is surrounded by a fibrous membrane known as Glisson's capsule and occupies the area inferior to the right and a portion of the left diaphragm" [2]. "Liver is very vascular more than any other organ as it takes up to 25% of total cardiac output through dual blood supply which divided between the hepatic artery, that accounts for 25% to 30% of the blood supply, and the portal vein, which is accounts for the remaining 70% to 75% and it ultimately mixes within the hepatic sinusoids before draining into the systemic circulation via the hepatic venous system" [3].

1.1.1.2 Hepatic microstructure

"Liver consists of hepatocytes which comprise of approximately 60% of the liver, Kupffer cells which are phagocytic cells found on the walls of sinusoids, endothelial cells that line the walls of sinusoids and pit cells which are a type of natural killer cell found in the liver" [4].

1.1.2 Physiology and functions

1.1.2.1 Fat metabolism

"Liver is responsible for the digestion of dietary fats trough producing bile salts that are essential for the emulsification of the digested fats" [4].

1.1.2.2 Ammonia detoxification

"Liver is responsible for ammonia (NH3) detoxification which is produced by the degradation of plasma amino acids and plasma proteins within the reticuloendothelial system by converting it to urea through a biochemical process called the urea cycle" [4].

1.1.2.3 Protein synthesis

Liver can make around 48 g of protein per day and the major protein synthesized is albumin, which is the predominant cause of the oncotic pressure of blood and a major part of the blood [4].

1.1.2.4 Clotting factor synthesis

Liver is responsible for the synthesis of the clotting factors and their inhibitors and that's why liver damage will cause prolongation of the prothrombin time, which is used as a marker of the hepatic synthetic ability [4].

1.1.2.5 Carbohydrate metabolism

Liver plays a role in the regulation of blood glucose levels by the conversion of glucose to glycogen and vice versa by two essential pathways which involves glucose uptake and release through liver [5].

1.1.2.6 Processing xenobiotics

Xenobiotic compounds like drugs for example enter the liver through either the hepatic artery or the portal vein and they are metabolized in the liver either by detoxification or activation through two phase's process; in phase one, enzymes detoxify drugs by generating reactive chemical groups through oxidation, reduction, or hydroxylation and in phase two, other molecules are conjugated with these reactive chemical groups to facilitate their ultimate elimination outside the body [5]. The conjugation pathway includes glucuronidation, sulfation, and glutathione and amino acid conjugation [6].

1.2 Hepatocellular Carcinoma

1.2.1 Epidemology

Hepatocellular carcinoma is considered the second common reason of death from cancer worldwide and the fifth most common cancer in men and the ninth in women and it is the estimated to be responsible for around 745,000 deaths in 2012 due it is association with bad prognosis [7].

1.2.2 Risk factors

1.2.2.1 HBV

HBV can cause carcinogenesis by three different mechanisms either by a mutagenesis insertion with the integration of the viral DNA into the host cancer genes or by causing promotion of genomic instability through the activity of viral proteins and the integration of viral DNA into the host DNA or through affecting the cell

functions by the wild type and mutated viral proteins [8].

1.2.2.2 HCV

It induces carcinogenesis by oxidative damages, chronic liver inflammation, cirrhosis, DNA damage and induction of cell proliferation through interaction of HCV proteins with host cell proteins [9].

1.2.2.3 Aflatoxin B1 (AFB1)

AFB1 is metabolized by the liver cytochrome P450 enzymes into the highly reactive AFB1-8, 9-epoxide, which may either bind to the DNA to initiate mutations especially in the tumor suppressor gene p53 or binds to proteins and cause acute toxicity (aflatoxicosis) [10].

1.2.2.4 Alcohol

Aldehydes generated from ethanol oxidation causes HCC formation through formation of DNA-adducts, cirrhosis and activation of pathways that promote tumor cell proliferation, survival, loss of cell cycle checkpoints, activation of oncogenes and immunosuppression [11].

1.2.2.5 Non-alcoholic steatohepatitis (NASH)

It resembles the alcoholic hepatitis in it is histological features but with a prominent fat deposition and storage in the parenchymal cells of the liver which will promote inflammation, necrosis and increase the susceptibility of the liver to the changes in adipokines, inflammatory cytokines, mitochondrial damage and elevated oxidative stress that together will promote fatty liver, fibrosis and HCC [12].

1.2.2.6 Obesity

Obesity causes insulin resistance which is a predisposing factor for the development and progression of fatty liver diseases like steatohepatitis [13,14] and at the end liver fibrosis [15]. Increased body mass index (BMI) above the normal ratio has been linked with HCC development. It was reported that there is a significant relationship between BMI and HCC when the BMI is more than 30 [16].

1.2.2.7 Diabetes

A reported study in the United States explained the role of diabetes as a possible risk factor for HCC development [17]. In another reported case control study, it was explained that the possibility of HCC development in non-diabetic patients is half the possibility in the diabetic ones [18]. Diabetes is responsible for more advanced liver tumors and responsible for the increase in the death rate at one year when compared to non-diabetic HCC patients [19]. “Data reported from geographical studies on the causes of HCC in the south of Europe, demonstrated the role of diabetes and obesity as single causing agents for HCC or preferably as co-factors” [20].

1.2.3 Hepatocellular carcinoma diagnosis

The HCC diagnosis is depending on many factors like for example if the patient is presented with liver cirrhosis and a liver mass more than 2 cm in diameter on the ultrasound there is a greater than 95% chance to develop HCC [21].

Also, when the AFP level is more than 200ng/ml, in addition to the presence of radiology signs consistent with HCC like for example hypervascularity which obtained on two different imaging methods such as Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT)), prove the diagnosis of HCC and with no need for hepatic biopsy [22]. On the other hand, if the AFP level is less than 200ng/mL and there is not a vascular characteristic profile seen during imaging then hepatic biopsy is needed to confirm the diagnosis.

Mass with a diameter range from 1-2cm needs liver biopsy to be done, regardless of the vascular profile [22]. However, Bruix et al highlighted that there is a technical difficulty of performing biopsy on small lesions and this leads to different opinion on the biopsy results by clinical pathologists in differentiation between dysplasia or pre-cancer and well-differentiated HCC. So, they recommended that these lesions should first be imaged with two different imaging techniques before doing biopsy and only if the results are not characteristic for HCC [23].

Lesions which are smaller than 1cm in diameter and fail to be displayed on dynamic imaging are less likely to be malignant, especially if there is no cirrhosis [24]. However, even tiny nodules can be transformed into malignant ones over time [25,26] so patients must follow-up with ultrasound every 3 to 6 months in order to check for HCC development [23]. At the end when

there is no increasing in the size over a period greater than one to two years patients can return to the routine surveillance program [23].

1.2.4 Hepatocellular carcinoma molecular mechanisms

There has been a great interest in understanding the molecular mechanisms of HCC in order to develop newer targeted therapies. It was reported that the Wnt β-catenin pathway activation is responsible for the one third of HCC cases studied [27]. Also, it was found that up to thirty percent of the HCC known cases show an over-expression of IGF2 (insulin-like growth factor 2) [28]. In addition to the previously mentioned over expression of the IGF2, there are reported genetic mutations in the IGF2 receptor appeared in over sixty percent of dysplastic nodules found in the liver [29]. “Fifty percent of the HCC patients experience activation of the P13/Akt pathway and dysfunction of the Akt regulator, phosphatase and tensin homolog (PTEN)” [30] which is associated with worsened prognostic outcome [31]. Furthermore, the apoptotic pathways derangement has been reported to be responsible for up to forty percent of HCC [32].

1.2.5 Surveillance

The main purpose of HCC screening is the early discovering of the HCC in order to provide the patients with a better survival rate. The worldwide recommended guidelines for the surveillance of HCC depends on using the ultrasound every 6 months with or without serum AFP levels [22,23]. Patients at great risk for developing HCC like for example patients with cirrhosis due to HBV, HCV, alcohol and primary biliary cirrhosis (PBC) must be included in the HCC surveillance program along with chronic hepatitis B carriers depending on viral DNA load, race and age [23].

1.2.6 Staging methods for hepatocellular carcinoma

Depending on the analysis of various previous HCC studies, the Barcelona-Clinic Liver Cancer (BCLC) staging system was made and incorporated in patients with early, intermediate, and advanced terminal disease [33]. The BCLC system explains the variables related to the prognosis in every group [33] and it is the widely most accepted staging system for HCC currently [34,35,36,37].

In contrast to other staging systems, the previously mentioned staging system recommends both treatment modalities and gives the physician clear view about the prognostic outcomes. Patients are classified into different four groups: early, intermediate, advanced, and end-stage depending on Child-Pugh (CP) scores. Patients with class A and B or those with only one lesion or up to 3 lesions with a size equal to 3 cm are considered as having early-stage disease. In these cases, the recommended therapy includes either liver section (LR), liver transplantation (LT) or radiofrequency ablation (RFA) which gives the patient a five-year survival rate. Intermediate stage disease contains those with CP score A, B and those with large and /or multifocal HCC without the presences of cancer symptoms, macrovascular invasion or extra-hepatic spread. The survival time without treatment at 3 years will not exceeds fifty percent and therefore the best treatment for these patients is transarterial chemoembolisation (TACE). While advanced stage disease in which there are cancer symptoms, vascular invasion and/or extrahepatic spread, the predicted survival at 1 year is 50%, and thus these patients are considered as candidates for new therapeutic clinical trials. Furthermore, Patients with a CP score of C where extensive tumors are present are thought to have an end-stage disease [36] and the symptoms relive mediated treatment is the best option for those patients because the median survival time for them is less than 3 months.

1.2.7 Treatment modalities

1.2.7.1 Liver resection

“Hepatic resection is the only curative treatment for HCC and back in the 1980s the mortality rate of liver resection was 10% but due to the early diagnosis, better patient selection, good preoperative and postoperative management, advanced surgical technique and development of new technologies has allowed us to obtain a lower mortality and morbidity rate” [38].

1.2.7.2 Transcatheter arterial chemoembolization (TACE)

It benefits from the liver cancer preferential blood supply to deliver standard chemotherapy and embolic material selectively to the tumor vascular bed while saving the near hepatic parenchyma and it has been shown to have a good survival benefit for patients with intermediate and advanced HCC [39].

1.2.7.3 Portal vein embolization (PVE)

Patients with liver fibrosis or cirrhosis who undergo major liver resection can experience a sudden increase in the venous portal pressure and insufficient functional remnant of liver both of which will increase postoperative morbidity and mortality, so PVE has been massively used to increase the volume of the future liver reserve and cause liver atrophy to be easily resected [40].

1.2.7.4 Local ablative therapy

Local ablation is used for patients with small HCC node limited to the liver and can't undergo liver resection due to compromised hepatic function and it can be chemically done using ethanol and acetic acid or thermally by radiofrequency, microwaves, cryoablation, lasers and ultrasound [41].

1.2.7.5 Radiotherapy

It is use has been limited as a therapeutic choice and it does not play a major role in the context of liver cancer treatment due to the limited ability of the surrounding healthy cells of the liver parenchyma to survive the high doses of radiation required for controlling the tumor locally beside the therapeutic window of radiation therapy [42].

1.2.7.6 Sorafenib

Sorafenib is a small molecule which work as a multityrosine kinase inhibitor which inhibits both the tumor-cell proliferation and the tumor angiogenesis, and it is the only drug that have showed survival benefits in patients with advanced liver carcinoma [43]. Sorafenib has increased the survival rate to 10.7 months compared to the placebo group which showed only a survival rate near 7.9 months, and it is only prescribed for patients with adequate liver function and advanced disease [43].

1.2.7.7 Liver transplantation

Liver transplantation (LT) is considered as an effective therapy for liver cancer especially in patients with decompensated liver function and advanced disease however, there is an aroused attention about the high risk of the tumor recurrence and the poor survival rate after the surgery [44] moreover, a few number of the patients can have liver transplantation surgery even when they need it because there is a shortage of the donors which does not cope with the worldwide needs and that makes the waiting lists very long worldwide [45].

1.3 Hypoxia

1.3.1 Brief background

Oxygen consumption is required for energy production in the form of adenosine triphosphate (ATP) in an efficient way for each individual cell. Therefore, and in order to maintain the metabolic homeostasis in case of oxygen deficiency the eukaryotic organisms have developed different mechanisms to adapt to the changes in O_2 levels in their environment. Activation of the hypoxia inducible factor (HIF) is considered the major pathway in regulating the response of the cell to the low O_2 tensions and it was early characterized and identified by the Semenza and Wang in 1992 [46]. "Under normal oxygen levels the HIF-α is hydroxylated by oxygen-dependent prolyl hydroxylases (PHD) and causing ubiquitination by the von Hippel-Lindau protein (pVHL) E3 ligase complex which will finally result in HIF-α proteasomal degradation" [47]. Under hypoxic and low oxygen tension conditions the pVHL binding is terminated and the oxygen-dependant α-subunit (HIF-1α or HIF-2α) is stabilized and heterodimerizes with the normally expressed HIF-1β [48,49,47]. "The HIF-1α/β heterodimer is then recruited to the hypoxia response element and activates the target genes expression involved in vascularization, energy metabolism, cell migration and glucose transport, to adapt to low oxygen tension conditions" [50].

1.3.2 Physioolgical hypoxia

The oxygen tension in the normal tissues is usually kept at 3–7% oxygen while the oxygen tension level in the physiological hypoxia will be normally around the range of 2–6% oxygen and at this oxygen level the tissues will respond in order to maintain their preferred oxygen level by many physiological means like for example vasodilation, increasing blood flow and upregulation of hypoxia response genes [51].

1.3.3 Tumor hypoxia

"Hypoxia is very common in many of the solid tumors, including hepatocellular carcinoma. Hypoxic HCC microenvironment is characterized by high level of HIF-1 which will cause tumor progression, induce radiation and chemotherapy

resistance, enhanced proliferation and survival of HCC cells" [52]. "The uncontrolled oncogene mediated cancer cell proliferation leads to the exhaustion of the nutrients and oxygen from the normal vasculature and will finally cause the cells to be hypoxic. Finally, this hypoxic condition will cause the overproduction of the angiogenesis mediated factors from the hypoxic tumor sites, which will eventually cause the vascularization of the tumor mass" [53]. "Tumor hypoxia will increase the genetic instability, disease progression, cancer metastasis and inhibit the tumor response to cytotoxic and targeted therapies" [54].

1.3.3.1 Tumor hypoxia and angiogenesis

"Angiogenesis is a growth factor dependent process which is stimulated by hypoxia where new blood vessels are formed from the preexisting ones also angiogenesis is critical for tissue repair" [55]. "HIF-1 is one of the well-studied stimuli for inducing angiogenesis and the expression of a number of genes, including vascular endothelial growth factor (VEGF), in a variety of tissues" [56]. "VEGF is mostly associated with angiogenesis and vascular permeability" [57]. "HIF-1 stimulates VEGF and its receptor VEGF-R2 expression in the endothelium, regulating an autocrine VEGF signaling loop that is critical for endothelial cell survival, proliferation, migration, and tube formation" [58].

1.3.3.2 Tumor hypoxia and metabolism

"Under hypoxic settings, HIF-1 has been found to directly regulate the genes of numerous enzymes involved in the cellular import and conversion of glucose, resulting in an increase in the cell's glycolytic activity (anaerobic glycolysis)" [59]. "This distinct metabolic profile confers numerous selective advantages to cancer cells, including adaptation to hypoxia, resistance to mitochondria-mediated apoptosis, and acidification of the tumour microenvironment, which leads to increased tumour invasion and metastasis" [60]. "HIF-1 stabilization has long been known to induce transcription of the pyruvate dehydrogenase kinase genes 1 and 3 and these kinases phosphorylate and inactivate the E1 subunit of pyruvate dehydrogenase, preventing pyruvate from entering the tricarboxylic acid (TCA) cycle and reducing mitochondrial oxygen consumption while increasing cellular pyruvate levels" [61]. "The stabilisation of HIF-1 has been shown to cause a generic increase in transcript and protein levels for glycolytic enzymes to ensure adequate flux through the pathway, and it has been demonstrated that most glycolytic enzymes are inherently over-expressed in 70% of human cancers, with the most prevalent glucose transporter isoforms GLUT1 and GLUT 3 expressed under hypoxic conditions" [62].

1.3.3.3 Tumor hypoxia and acidosis

"The glycolytic pathway implies excessive proton production, which, if retained within the cells, would result in fatal intracellular acidosis; however, malignant cells solve this problem by increasing proton transport mechanisms, which expel the excess acidity and this mechanism allows cancer cells to maintain a normal intracellular pH or even overshoot this mechanism, allowing for a slightly alkaline intracellular tensile strength." [63]. "Clinical studies have revealed that tumors in an acidic environment have a worse prognosis and a higher metastatic incidence, as well as increased mutation rates and resistance to chemotherapy and radiotherapy" [64].

1.3.3.4 Tumor hypoxia and cell proliferation

"HIF-1 has been shown to stimulate the production of growth factors such as TGF-, insulin-like growth factor 2, interleukin-6 (IL-6), interleukin-8, macrophage migration inhibitory factor (MIF), and growth factor receptors such as the epidermal growth factor receptor (EGFR), resulting in continuous proliferative signaling" [65]. "C-Myc is a cell cycle regulator and oncogene, and HIF-2 can increase c-Myc activity and promote cell cycle progression" [66].

1.3.3.5 Tumor hypoxia and metastasis

"It has previously been demonstrated that hypoxic cells are more aggressive and invasive, with a greater ability to metastasize" [67]. "Hypoxia facilitated HCC cell migration, invasion, and distant pulmonary metastasis" [68]."Hypoxia/HIF-1 has previously been shown to regulate the expression of metalloproteases such as matrix metalloprotease-1 (MMP1) and MMP3 in order to promote metastasis" [69]. "Cancer cells could continue to redesign the vessels to gain access by secreting the HIF-1-regulated metalloproteinases MMP1 and MMP2" [70].

1.3.3.6 Tumor hypoxia and radioresistance

"Cancerous cells can stay alive in hypoxic environments and play an essential part in cancer cell radioresistance" [71]. "Radioresistance manifests in oxygen <10 mmHg and becomes maximal around 0.5 mmHg" [72]. "The o2 impact is frequently measured using the oxygen enhancement ratio (OER), which is the ratio of dosage necessary to attain the very same biological effect under hypoxic and oxic circumstances" [73]. "Ionizing radiation (IR) causes DNA double-strand breaks (DSBs), DNA single-strand breaks (SSBs), DNA base damage, and DNA–DNA and DNA–protein crosslinks under normoxic conditions (DPCs)" [74] "while inadequate amount of O_2 in the tumor cells environment may result in ionizing radiation–induced harm that can be fixed and normal cellular function regained" [75].

1.3.3.7 Tumor hypoxia and chemotherapy resistance

Multidrug resistance (MDR) is a primary cause of chemotherapy-based therapeutic failure [76]. In response to hypoxia, HIF-1 can trigger the multidrug resistance 1 (MDR1) gene, which encodes for the membrane-resident P-glycoprotein (P-gp), which belongs to a group of ATP-binding cassette (ABC) transporters that can reduce the intracellular levels of a variety of chemotherapeutic agents [77]. Hypoxia can also produce chemoresistance by regulating the ATP-binding cassette subfamily G member 2 (ABCG2), which is one of the key multidrug-resistance transporters [78].

1.4 Hypoxia as a Therapy Target

1.4.1 Prodrugs activated by hypoxia

Cancer cell hypoxia is a primary cause of therapy failure in a wide range of cancers. Hypoxia, on the other hand, provides therapy prospects, as evidenced by the development of new drugs that address hypoxic areas within tumors [79]. The production of hypoxia activated prodrugs (HAPs), which include chemical constituents that are metabolized by enzymatic reduction, is a potential technique for targeting hypoxic malignancies [80]. Hypoxia-activated prodrugs are deactivated or disguised cytotoxins that undergo biotransformation after reductive metabolism by intrinsic human cellular oxidoreductases, a mechanism that is normally blocked by o2, hence conferring selectivity for the hypoxic tumor environment [81].

1.4.2 Hyperbaric oxygen

The use of oxygen under increased atmospheric pressure, that is, at a pressure greater than the pressure found on the earth's surface at sea level, which is defined as 1 atm, is known as hyperbaric oxygen treatment (HBO) [82]. HBO therapy has been used for millennia to treat or alleviate illnesses involving hypoxia and ischemia by increasing the quantity of dissolved oxygen in the plasma and hence improving O2 delivery to the cells [83]. HBO can raise the concentrations and pressure of oxygen in the blood, as well as the pace and distance of oxygen diffusion in tissues, reducing hypoxia and boosting oxygen levels in the cancer cells, resulting in improved susceptibility to chemo- and radiotherapy [84]. HBO coupled with sorafenib causes synergistic inhibitory effect on cell growth and death in hepatoma cells, indicating that HBO coupled with sorafenib might be used to treat HCC patients [84].

1.4.3 Manganese dioxide nanoparticles

Hypoxia and high cancer cell proliferation generate an excess of reactive oxygen species (ROS), such as hydrogen peroxide (H2O2), which increases mutagenesis, spread of cancer cells, angiogenesis, and resistance to treatments, all of which contribute to therapeutic failure [85]. The high reactivity of manganese dioxide nanoparticles (MnO2 NPs) toward H2O2 allows for constant synthesis of O2, pH modulation, and efficient cancer hypoxia reduction by targeted administration of MnO2NPs to hypoxia [86]. MnO2 nanoparticles are used for continuous and localized synthesis of molecular O2 in cancers to alter the tumor microenvironment (TME) and improve radiation effectiveness, since the efficacy of radiation is significantly dependent on the relative level of oxygen in the cancer at the moment of irradiation [87].

1.4.4 Sliver Nanoparticles

"Sliver nanoparticles (AgNPs) which has been used before as broad-spectrum antimicrobial agent and was found to act as anticancer agent as AgNPs act by inhibiting the function of HIF-1α in cells under hypoxic conditions, leading to the downregulation of VEGF-A and GLUT1 and inhibition of angiogenesis impaired glucose metabolism and thus cannot meet the energy

demand of the tumor cells and eventually cause tumor cell death" [88].

1.4.5 Oral oxygen therapy

Eble M et al outlined "the idea of oral oxygen treatment, indicating that oral administration of oxygen-enriched water enhanced the dissolved quantity of oxygen in blood in patients with head and neck carcinomas" [89]. It was also reported by El-Boreay M that "administration of oxygenated water which is freshly prepared water rich with oxygen increased the efficacy of the anticancer drug doxorubicin against hepatocellular carcinoma compared to the efficacy of doxorubicin alone" [90].

1.4.6 HIF-1α/HIF-2α inhibitors

It is now widely recognised that most solid tumours contain a significant portion of hypoxic area, and it is also well known that hypoxia causes the tumour to become more aggressive, metastatic, and resistant to both chemotherapy and radiotherapy, but it also exploits the hypoxic tumour microenvironment to develop targeted therapy for cancers such as HIF-1/HIF-2 inhibitors [91], of which we will list a few in the following lines.

1.4.6.1 Benzopyranyl 1,2,3-triazole

"It is a brand-new chemotherapeutic agent which is reported to cause HIF-1 inhibition through increasing it is hydroxylation and proteasomal degradation and it is also decrease the expression of the VEGF and angiogenesis in a dose dependent way" [92].

1.4.6.2 BIX-01294 (diazepin-quinazolin-amine derivative)

"BiIX-01294 has been shown to reduce HIF-1 expression in HepG2 hepatocellular carcinoma cells by boosting PHD2 and pVHL expression, hence decreasing HIF-1 stability" [93].

1.4.6.3 Glyceollins

"They are members of the phytoalexins group which are de novo synthesized in the soybean in response to microbial invasion and chemical stressing" [91]. Glyceollins reported to "cause inhibition of the VEGF expression through regulating the HIF-1α and this is done through two pathways either through blocking HIF-1α translation via blocking the PI3K/AKT/mTOR pathway under hypoxic conditions or through decreasing the Hsp90 binding activity and therefore decreasing the HIF-1α stability" [94,95].

1.4.6.4 IDF-11774

"Is an aryloxyacetylaminobenzoic acid analogue it exhibits it is anticancer activity through increasing the expression of VHL which will result in the inhibition of the HIF-1α accumulation and through inhibiting the expression of the mRNA of the hypoxia targeted genes like VEFGF and EOP" [96,97].

1.4.6.5 Vorinostat

"It is known as suberoylanilide hydroxamic acid and it is having dual action as anti HIF-1/HIF-2 activity and it is shown anti-tumor action against HCC in both in vivo and in vitro" [98]. "It is exhibits it is action through inhibiting the HIF-1/2 stabilization by direct acetylation of heat shock protein 90 and by increasing the HIF-1/2 degradation through a ubiquitin-based mechanism" [99].

1.4.6.6 PT2385 and PT2399

"They are selectively HIF-2α inhibitors through inhibiting it is dimerization with HIF-1β and it showed to be effective in renal cell carcinoma with good safety profile" [100].

2. CONCLUSION

Liver is the largest gland, and it is consisted mainly of hepatocytes which are the liver parenchymal cells and account for around 60% of the liver. Liver is responsible for many functions like protein synthesis and drug detoxification and carbohydrate metabolism. Hepatocellular carcinoma is a major liver disease, and it causes around 745,000 in 2012 due it is association with poor prognosis. It can be induced by HBV, HCV, aflatoxin B1, diabetes, obesity and alcohol. Hepatocellular carcinoma is diagnosed by measuring the serum alpha fetoprotein with radiological features like hypervascularity. Hepatocarcinogenesis happen due to the promotion of the Wnt β-catenin pathway, mutations in the IGF2 receptor, activation of the P13/Akt pathway, impairment of the Akt regulator and the derangement of apoptotic pathways. It can be staged using the CP score into class A, B and C which is the end stage disease, and it is characterized by extensive tumor invasion and only symptomatic treatment is provided for them. The treatment

modalities for HCC vary from liver resection which is useful only in the early stage, TACE which is useful for the intermediate and advanced cases, PVE, local ablative therapy, radiotherapy, Sorafenib which work by inhibiting the cell proliferation and angiogenesis and the last one is the liver transplantation which is the best choice for the decompensated liver cirrhosis patient. Most solid tumors like HCC contain substantial area of hypoxia due to the rapid proliferation rate of the cancer cells and the inadequate blood supply which don't match this proliferation rate that led to the deficiency of oxygen and nutrition and finally hypoxia and it is considered as a poor prognostic factor of cancer which means that the severe the hypoxia the more aggressive the cancer and finally the low survival rate. Hypoxia mediate it is effect through the HIF-1α, HIF-2α and HIF-3α but the most prominent one is the HIF-1α as it is the responsible one for the deleterious effect of the hypoxia as it causes the stimulation of the angiogenesis by increasing the expression of the VEGF. It also causes the over expression of the dehydrogenase kinase genes 1 and 3 and the glycolytic enzymes like GLUT1 and GLUT3 which lead to the shifting from the aerobic respiration to the anaerobic glycolysis that will lead in the end to the resistance of the mitochondria-mediated apoptosis and acidification of the tumor microenvironment leading to increased tumor invasion and metastasis. It was also reported that HIF-1α stimulates the cell proliferation of the cancer cells through increasing the production of the TGF-β, IGF-2, IL-6, IL-8 and EGFR while HIF-2α c-Myc activity and promote cell cycle progression. On the other hand, HIF-1α enhance metastasis through the over expression of the MMP-1 and MMP-3. Hypoxia enhance the chemotherapy and radiotherapy resistance through the over expression of the MDR1 and gene which encodes for the membrane-resident P-glycoprotein that accountable for the drug efflux outside the cancer cell which result in chemotherapy resistance and the lack of oxygen decreases the efficacy of the radiotherapy which lead to radiotherapy resistance. As being explained earlier hypoxia causes the cancer to be more aggressive and more resistance to therapy but it on the other hand offers a great opportunity as a therapy target with great specificity to the cancer cell only without harming the normal one and this is a great advantage as many anticancer drugs has low safety profile and the patient may suffer more from the side effects of the drug than the disease itself. One of the methods to target cancer hypoxia is developing a prodrug which only will be activated under hypoxic conditions by cellular oxidoreductases, another method is the hyperbaric oxygen which depend on the usage of oxygen under high pressure mainly higher than the atmospheric pressure which is defined to be 1 atm and it was found that using the HBO along with the sorafenib resulted in synergistic growth inhibition and apoptosis in hepatoma cells. Manganese dioxide nanoparticles is another method for targeting cancer hypoxia originated from the principle that tumor microenvironment has high levels of H_2O_2 and the high reactivity of the MnO_2 NPs towards it which will results in release of pure oxygen inside the hypoxic area of the tumor which will enhance the radiotherapy efficacy while on the other hand sliver nanoparticles (AgNPs) act by inhibiting the function of HIF-1α in cells under hypoxic conditions, leading to the downregulation of VEGF-A and GLUT1 and finally the tumor cell death. Oral oxygen therapy is another attempt for the correction of the tumor hypoxia, and it depend on administration of drinking water highly saturated with oxygen and it can be used either alone or along with other anti-cancer drugs to increase their efficacy as correction of the hypoxia increase the activity of the chemotherapeutic agents. Finally, HIF-1α/HIF-2α inhibitors are small molecules designed to block the effect of the HIF-1α/HIF-2α and as a result will block the deleterious effect of the cancer hypoxia and enhancing both the chemotherapy and radiotherapy activity. Those inhibitors can work by increasing the degradation of the HIF-1, decrease the expression of HIF-1, interfering with the Hsp90 binding activity, the expression of the mRNA of the hypoxia targeted genes like VEFGF and EOP and by inhibiting it is dimerization with HIF-1β which in the end will lead to better prognosis and better treatment outcome.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Garby L, Lammert O, Kock K, Thobo-Carlsen B. Weights of brain, heart, liver, kidneys, and spleen in healthy and apparently healthy adult Danish subjects. American Journal of Human Biology. 1993;5(3):291-296.

2. Juza R, Pauli E. Clinical and surgical anatomy of the liver: A review for clinicians: Clinical and Surgical Anatomy of the Liver. Clinical Anatomy. 2014;27(5): 764 769.
3. Abdel-Misih S, Bloomston M. Liver anatomy. Surgical Clinical North America. 2010;90(4):643- 653.
4. Sargent S. Liver diseases: An essential guide for nurses and health care professionals. Chichester, U.K.; Ames, Iowa: Wiley-Blackwell; 2009. Available:http://public.eblib.com/choice/publicfullrecord.aspx?p=470721.
5. Diehl-Jones W, Fraser Askin D. The neonatal liver, Part 1: embryology, anatomy, and physiology. Neonatal Network. 2002;21(2):5 12.
6. Liska D. The detoxification enzyme systems. Altern Med Rev.1998;3(3):187 198.
7. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015; 136(5):E359- E386.
8. Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. Journal of Hepatology. 2016;64(1):S84 - S101.
9. Poortahmasebi V, Poorebrahim M, Najafi S, Jazayeri S, Alavian S, Arab S, et al. How Hepatitis C Virus Leads to Hepatocellular Carcinoma: A Network-Based Study. Hepatitis Monthly. 2016;16 (2):e36005.
10. Rieswijk L, Claessen S, Bekers O, van Herwijnen M, Theunissen D, Jennen D, et al. Aflatoxin B1 induces persistent epigenomic effects in primary human hepatocytes associated with hepatocellular carcinoma. Toxicology.2016;350-352:31-39.
11. Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. World Journal of Gastroenterology. 2014;20(47):17756-17772.
12. Charrez B. Hepatocellular carcinoma and non-alcoholic steatohepatitis: The state of play. World Journal of Gastroenterology. 2016;22(8):2494-2502.
13. Ratziu V, Giral P, Charlotte F, Bruckert E, Thibault V, Theodorou I, et al. Liver fibrosis in overweight patients. Gastroenterology. 2000;118(6):1117-1123.
14. Adinolfi L, Gambardella M, Andreana A, Tripodi M, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Journal of Hepatology. 2001;33(6):1358-1364.
15. Ohata K, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, et al. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. Cancer. 2003;97(12):3036-3043.
16. Polesel J, Zucchetto A, Montella M, Dal Maso L, Crispo A, La Vecchia C, et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. Annals of Oncology . 2009;20(2):353 357.
17. Davila J, Morgan R, Shaib Y, McGlynn K, El-Serag H. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut. 2005;54(4):533-539.
18. El-Serag H, Tran T, Everhart J. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004;126(2):460-468.
19. Amarapurkar D, Patel N, Kamani P. Impact of diabetes mellitus on outcome of HCC. Annals of Hepatology. 2008;7(2):148-151.
20. Donato F, Gelatti U, Limina R, Fattovich G. Southern Europe as an example of interaction between various environmental factors: A systematic review of the epidemiologic evidence. Oncogene. 2006;25(27):3756-3770.
21. Frazer C. Imaging of hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 1999;14(8):750-756.
22. Bruix J, Sherman M, Llovet J, Beaugrand M, Lencioni R, Burroughs A, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. Journal of Hepatology. 2001;35(3):421-430.
23. Bruix J, Sherman M. Management of hepatocellular carcinoma. Journal of Hepatology. 2005;42(5):1208-1236.
24. Iwasaki M, Furuse J, Yoshino M, Ryu M, Moriyama N, Mukai K. Sonographic appearances of small hepatic nodules without tumor stain on contrast-enhanced computed tomography and angiography.

Journal of Clinical Ultrasound. 1998; 26(6):303-307.
25. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Okazaki N, Takayasu K, et al. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. The Lancet. 1990; 336(8724):1150-1153.
26. Fracanzani A, Burdick L, Borzio M, Roncalli M, Bonelli N, Borzio F, et al. Contrast-enhanced Doppler ultrasonography in the diagnosis of hepatocellular carcinoma and premalignant lesions in patients with cirrhosis. Journal of Hepatology. 2001;34(6):1109-1112.
27. Llovet J, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J, et al. Sorafenib in advanced hepatocellular carcinoma. The New England Journal of Medicine. 2008;359:378 -390.
28. Breuhahn K, Longerich T, Schirmacher P. Dysregulation of growth factor signaling in human hepatocellular carcinoma. Oncogene. 2006;25(27):3787-3800.
29. Yamada T, De Souza A, Finkelstein S, Jirtle R. Loss of the gene encoding mannose 6-phosphate/insulin-like growth factor II receptor is an early event in liver carcinogenesis. Proceedings of the National Academy of Sciences of the United States of America. 1997;94(19): 10351-10355.
30. Hu T, Huang C, Lin P, Chang H, Ger L, Lin Y, et al. Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma. Cancer. 2003;97(8):1929-1940.
31. Schmitz K, Wohlschlaeger J, Lang H, Sotiropoulos G, Malago M, Steveling K, et al. Activation of the ERK and AKT signalling pathway predicts poor prognosis in hepatocellular carcinoma and ERK activation in cancer tissue is associated with hepatitis C virus infection. Journal of Hepatology. 2008;48(1):83-90.
32. Bressac B, Kew M, Wands J, Ozturk M. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. Nature. 1991;350(6317):429-431.
33. Llovet J, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Seminars in Liver Disease. 1999;19(3):329-338.
34. Conill C, Verger E, Salamero M. Performance status assessment in cancer patients. Cancer. 1990;65(8):1864-1866.
35. Verger E, Salamero M, Conill C. Can arnofsky performance status be transformed to the Eastern cooperative oncology group scoring scale and vice versa? European Journal of Cancer. 1992;28A(8-9):1328- 1330.
36. Sorensen J, Klee M, Palshof T, Hansen H. Performance status assessment in cancer patients. An inter-observer variability study. British Journal of Cancer. 1993;67(4):773-775.
37. Bruix J, Boix L, Sala M, Llovet J. Focus on hepatocellular carcinoma. Cancer Cell. 2004;5(3):215-219.
38. Memeo R, de Angelis N, de Blasi V, Cherkaoui Z, Brunetti O, Longo V, et al. Innovative surgical approaches for hepatocellular carcinoma. World Journal of Hepatology. 2016;8(13):591-596.
39. Liapi E, Geschwind J. Combination of Local Transcatheter Arterial Chemoembolization and Systemic Anti-angiogenic Therapy for Unresectable Hepatocellular Carcinoma. Liver Cancer. 2012;1(34):201 -215.
40. Shindoh J, Tzeng C, Vauthey J. Portal Vein Embolization for Hepatocellular Carcinoma. Liver Cancer. 2012;1(3 4):159-167.
41. Lin S, Hoffmann K, Schemmer P. Treatment of Hepatocellular Carcinoma: A Systematic Review. Liver Cancer. 2012;1(3 4):144-158.
42. Dionisi F, Guarneri A, Dell Acqua V, Leonardi M, Niespolo R, Macchia G, et al. Radiotherapy in the multidisciplinary treatment of liver cancer: A survey on behalf of the Italian Association of Radiation Oncology. La radiologia medica. 2016;121(9):735 -743.
43. Pascual S, Herrera I, Irurzun J. New advances in hepatocellular carcinoma. World Journal of Hepatology. 2016;8(9): 421-438.
44. Xu D, Wan P, Xia Q. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria: a review. World Journal of Gastroenterology. 2016; 22(12): 3325-3334.
45. Mazzanti R, Arena U, Tassi R. Hepatocellular carcinoma: Where are we? World Journal of Experimental Medicine. 2016;6(1):21-36.
46. Wielockx B, Meneses A. PHD2: from hypoxia regulation to disease progression. Hypoxia. 2016;4:53-67.

47. Koh M, Gagea M, Sargis T, Lemos R, Grandjean G, Charbono A, et al. A new HIF-α/RANTES-driven pathway to hepatocellular carcinoma mediated by germline haploinsufficiency of SART1/HAF in mice. Journal of Hepatology. 2016;63(5): 1576-1591.
48. Wang G, Zhang J, Liu L, Sharma S, Dong Q. Quercetin potentiates doxorubicin mediated antitumor effects against liver cancer through p53/Bcl-xl. PLoS One. 2012;7(12):e51764.
49. Keith B, Adelman D, Simon M. Targeted mutation of the murine arylhydrocarbon receptor nuclear translocator 2 (Arnt2) gene reveals partial redundancy with Arnt. Proceedings of the National Academy of Sciences of the United States of America. 2001;98:6692 -6697.
50. Kim Y, Nam H, Lee J, Park D, Kim C, Yu Y, et al. Methylation-dependent regulation of HIF-1α stability restricts retinal and tumor angiogenesis. Nature Communications. 2016;7:10347.
51. McKeown S. Defining normoxia, physoxia and hypoxia in tumors implications for treatment response. The British Journal of Radiology. 2014;87(1035):20130676.
52. Luo D, Wang Z, Wu J, Jiang C, Wu J. The role of hypoxia inducible factor-1 in hepatocellular carcinoma. BioMed Research International. 2014;2014: ID 409272.
53. Eales K, Hollinshead K, Tennant D. Hypoxia and metabolic adaptation of cancer cells. Oncogenesis. 2016;5(1): e190.
54. LaGory E, Giaccia A. The ever expanding role of HIF in tumor and stromal biology. Nature Cell Biology. 2016;18(4):356-365.
55. Rosmorduc O, Housset C. Hypoxia: A link between fibrogenesis, angiogenesis, and carcinogenesis in liver disease. Seminars in Liver Disease. 2010;30(3):258- 270.
56. Ahluwalia A, Tarnawski A. Critical role of hypoxia sensor-HIF in VEGF gene activation. Implications for angiogenesis and tissue injury healing. Current medicinal chemistry. 2012;19(1):90 -97.
57. Losso J, Bawadi H. Hypoxia inducible factor pathways as targets for functional foods. Journal Agricultural and Food Chemistry. 2005;53(10):3751 3768.
58. Krock B, Skuli N, Simon M. Hypoxia-induced angiogenesis: Good and evil. Genes & Cancer. 2011;2(12):1117-1133.
59. Zimmer A, Walbrecq G, Kozar I, Behrmann I, Haan C. Phosphorylation of the PDH complex precedes HIF-1-mediated effects and PDK1 upregulation during the first hours of hypoxic treatment in HCC cells. Hypoxia. 2016;4:135-145.
60. Ho N, Coomber B. Pyruvate dehydrogenase kinase expression and metabolic changes following dichloroacetate exposure in anoxic human colorectal cancer cells. Experimental Cell Research. 2015;331(1):73-81.
61. Denko N. Hypoxic regulation of metabolism offers new opportunities for anticancer therapy. Expert Review of Anticancer Therapy. 2014;14(9):979-981.
62. Smith H, Board M, Pellagatti A, Turley H, Boultwood J, Callaghan R. The effects of severe hypoxia on glycolytic flux and enzyme activity in a model of solid tumors. Journal of Cellular Biochemistry. 2016; 117(8):1890 -1901.
63. Koltai T. Cancer: fundamentals behind pH targeting and the double-edged approach. OncoTargets and Therapy. 2016;9:6343-6360.
64. Peppicelli S, Bianchini F, Calorini L. Extracellular acidity, a 'reappreciated trait of tumor environment driving malignancy: perspectives in diagnosis and therapy. Cancer and Metastasis Reviews. 2014; 33(2 3):823- 832.
65. Feitelson M, Arzumanyan A, Kulathinal R, Blain S, Holcombe R, Mahajna J, et al. Sustained proliferation in cancer: mechanisms and novel therapeutic targets. Seminars in Cancer Biology. 2015;35:S25 -S54.
66. Wigerup C, Påhlman S, Bexell D. Therapeutic targeting of hypoxia and hypoxia-inducible factors in cancer. Pharmacology & Therapeutics. 2016;164: 152 -169.
67. Muz B, de la Puente P, Azab F, Azab A. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia. 2015;3:83-92.
68. Mao X, Wong S, Tse E, Ko F, Tey S, Yeung Y, et al. Mechanisms through which hypoxiainduced caveolin-1 drives tumorigenesis and metastasis in hepatocellular carcinoma. Cancer Research. 2016;76(24):7242 -7253.
69. Tsai Y, Wu K. Hypoxia-regulated target genes implicated in tumor metastasis. Journal of Biomedical Science. 2012;19(1): 102.

70. Chang J, Erler J. Hypoxia-Mediated Metastasis. Advances in Experimental Medicine and Biology. 2014;772:55-81.
71. Horsman M, Overgaard J. The impact of hypoxia and its modification of the outcome of radiotherapy. Journal of Radiation Research. 2016;57(S1):i90- i98.
72. Barker H, Paget J, Khan A, Harrington K. The tumor microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nature Reviews Cancer. 2015;15(7):409 -425.
73. Antonovic L, Lindblom E, Dasu A, Bassler N, Furusawa Y, Toma-Dasu I. Clinical oxygen enhancement ratio of tumors in carbon ion radiotherapy: the influence of local oxygenation changes. Journal of Radiation Research. 2014 ;55(5):902- 911.
74. Bristow R, Hill R. Hypoxia and metabolism: hypoxia, DNA repair and genetic instability. Nature Reviews Cancer. 2008;8(3):180 192.
75. Arvold N, Guha N, Wang D, Matli M, Deen D, Warren R, et al. Hypoxia-induced radioresistance is independent of hypoxia-inducible factor-1A in vitro. International Journal of Radiation Oncology Biology Physics. 2005;62(1):207- 212.
76. Chen J, Ding Z, Peng Y, Pan F, Li J, Zou L, et al. HIF inhibition reverses multidrug resistance in colon cancer cells via downregulation of MDR1/P-glycoprotein. PLoS ONE. 2014;9(6):e98882.
77. Rohwer N, Cramer T. Hypoxia-mediated drug resistance: novel insights on the functional interaction of HIFs and cell death pathways. Drug Resistance Updates. 2011;14(3):191-201.
78. He X, Wang J, Wei W, Shi M, Xin B, Zhang T, et al. Hypoxia regulates ABCG 2 activity through the activation of ERK1/2/HIF and contributes to chemoresistance in pancreatic cancer cells. Cancer Biology & Therapy. 2016;17(2):188-198.
79. Liapis V, Zinonos I, Labrinidis A, Hay S, Ponomarev V, Panagopoulos V, et al. Anticancer efficacy of the hypoxia activated prodrug evofosfamide (TH-302) in osteolytic breast cancer murine models. Cancer Medicine. 2016;5(3):534 -545.
80. Rey S, Schito L, Koritzinsky M, Wouters B. Molecular targeting of hypoxia in radiotherapy. Advanced Drug Delivery Reviews. 2017;109:45- 62.
81. Guise C, Mowday A, Ashoorzadeh A, Yuan R, Lin W, Wu D, et al. Bioreductive prodrugs as cancer therapeutics: targeting tumor hypoxia. Chinese Journal of Cancer. 2014;33(2):80- 86.
82. Stepien K, Ostrowski R, Matyja E. Hyperbaric oxygen as an adjunctive therapy in treatment of malignancies, including brain tumors. Medical Oncology. 2016;33(9):101.
83. Moen I, Stuhr L. Hyperbaric oxygen therapy and cancer-a review. Targeted Oncology. 2012;7(4):233 -242.
84. Peng H, Liao M, Zhang M, Xie Y, Xu L, Zhang Y, et al. Synergistic Inhibitory Effect of Hyperbaric Oxygen Combined with Sorafenib on Hepatoma Cells. PLoS ONE. 2014;9(6):e100814.
85. Prasad P, Gordijo C, Abbasi A, Maeda A, Ip A, Rauth A, et al. Multifunctional albumin MnO2 nanoparticles modulate solid tumor microenvironment by attenuating hypoxia, acidosis, vascular endothelial growth factor and enhance radiation response. ACS Nano. 2014;8(4):3202-3212.
86. Song M, Liu T, Shi C, Zhang X, Chen X. Bioconjugated manganese dioxide nanoparticles enhance chemotherapy response by priming tumor-associated macrophages toward M1-like phenotype and attenuating tumor hypoxia. ACS Nano. 2016;10(1):633 -647.
87. Abbasi A, Gordijo C, Amini M, Maeda A, Rauth A, DaCosta R, et al. Hybrid manganese dioxide nanoparticles potentiate radiation therapy by modulating tumor hypoxia. Cancer Research. 2016; 76(22):6643-6656.
88. Yang T, Yao Q, Cao F, Liu Q, Liu B, Wang X. Silver nanoparticles inhibit the function of hypoxia-inducible factor and target genes: Insight into the cytotoxicity and antiangiogenesis. International journal of Nanomedicine. 2016;11:6679–92.
89. Eble M, Lohr E, Wannenmacher M. Oxygen tension distribution in head and neck carcinomas after peroral oxygen therapy. Oncology Research and Treatment. 1995;18(2):136- 140.
90. El- Boreay M, Mansour A, ELShafie M, Helal G. Oxygenated Water could augment Doxorubicin to act against Diethylnitrosamine induced Hepatocellular Carcinoma in Rats. International Journal of Pharma Sciences. 2017;7(4):1817-1825.
91. Albadari N, Deng S, Li W. The transcriptional factors HIF-1 and HIF-2 and their novel inhibitors in cancer therapy. Expert Opinion on Drug Discovery. 2019;14(7):667–682.

92. Park K, Lee H, Lee S, Lee D, Lee T, Lee Y. Molecular and functional evaluation of a novel HIF inhibitor, benzopyranyl 1,2,3-triazole compound. Oncotarget. 2017;8(5): 7801–7813.
93. Oh S, Seok J, Choi Y, Lee S, Bae J, Lee Y. The Histone Methyltransferase Inhibitor BIX01294 Inhibits HIF-1alpha Stability and Angiogenesis. Molecules and Cells. 2015;38(6):528–534.
94. Lee S, Lee J, Jung M, Lee Y. Glyceollins, a novel class of soy phytoalexins, inhibit angiogenesis by blocking the VEGF and bFGF signaling pathways. Molecular Nutrition & Food Research. 2013;57(2): 225–234.
95. Lee S, Jee J, Bae J, Liu K, Lee Y. A group of novel HIF-1alpha inhibitors, glyceollins, blocks HIF-1alpha synthesis and decreases its stability via inhibition of the PI3K/AKT/mTOR pathway and Hsp90 binding. Journal of Cellular Physiology. 2015;230(4):853–862.
96. Lee K, Kang J, Park S, Jin Y, Chung K, Kim H, et al. LW6, a novel HIF-1 inhibitor, promotes proteasomal degradation of HIF-1alpha via upregulation of VHL in a colon cancer cell line. Biochemical Pharmacology. 2010;80(7):982–989.
97. Naik R, Won M, Kim B, Xia Y, Choi H, Jin G, et al. Synthesis and structure-activity relationship of (E)-phenoxyacrylic amide derivatives as hypoxia-inducible factor (HIF) 1alpha inhibitors. Journal of Medicinal Chemistry. 2012;55(23):10564–10571.
98. Zhang C, Yang C, Feldman M, Wang H, Pang Y, Maggio D, et al. Vorinostat suppresses hypoxia signaling by modulating nuclear translocation of hypoxia inducible factor 1 alpha. Oncotarget. 2017;8(34):56110–56125.
99. Kong X, Lin Z, Liang D, Fath D, Sang N, Caro J. Histone deacetylase inhibitors induce VHL and ubiquitin-independent proteasomal degradation of hypoxia-inducible factor 1alpha. Molecular and Cellular Biology. 2006;26(6):2019–2028.
100. Wallace E, Rizzi J, Han G, Wehn P, Cao Z, Du X, et al. A Small-Molecule Antagonist of HIF2alpha Is Efficacious in Preclinical Models of Renal Cell Carcinoma. Cancer research. 2016;76(18):5491–5500.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/84327