HYPOXIA INDUCIBLE FACTOR (HIF): A POTENTIAL MOLECULAR TARGET FOR HERBAL MEDICINE TO TREAT CANCER

A Project Report Submitted

In Partial Fulfillment of the Requirements

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BACHELOR OF PHARMACY

by

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List of abbreviations

HIF: Hypoxia Inducible Factor

ROS: Reactive Oxygen Species

MAPK: Mitogen-Activated Protein Kinase

ETC: Electron Transport Chain

VEGF: Vascular Endothelial Growth Factor

PDGF: Platelet-Driven Growth Factor

PDK 1: Pyruvate Dehydrogenase Kinase 1

TCA: Tricarboxylic Acid Cycle

VHL: Von Hippel-Lindau

DMOG: Dimethyloxalylglycine

LDH-A: Lactate Dehydrogenase A

ccRCC: Clear Cell Renal Cell Carcinoma

DHT: Dihydrotestosterone

PTX: Paclitaxel

CERTIFICATE

This is to certify that project work entitled **"Hypoxia Inducible Factor (HIF): A Potential Molecular Target for Herbal Medicine to Treat Cancer"** done by **Ms. Samiksha Dewangan** submitted to Department of Pharmacy, is a bonafide research work done by **Ms. Samiksha Dewangan** under the supervision and guidance of **Dr. Prem Shankar Mishra**, Associate Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy during the academic year 2021-2022. The project report has not formed the basis for the award of any Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Date:

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
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BONAFIDE CERTIFICATE

This to certify that the project work entitled **"Hypoxia Inducible Factor (HIF): A Potential Molecular Target for Herbal Medicine to Treat Cancer"** is the bonafide research work done by **Ms. Samiksha Dewangan**, who carried out the research work under my supervision and guidance for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2021-2022. To the best of my knowledge the work reported herein is not submitted for award of any other degree or diploma of any other Institute or University.

Dr. Prem Shankar Mishra

Guide

Associate Professor

School of Medical and Allied Sciences

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DECLARATION

I hereby declare that the work embodied in this project report entitled **"Hypoxia Inducible Factor (HIF): A Potential Molecular Target for Herbal Medicine to Treat Cancer"** in Partial fulfillment of the requirements for the award of Bachelor of Pharmacy, is a record of original and independent research work done by me during the academic year 2021-22 under the supervision and guidance of **Dr. Prem Shankar Mishra**, Associate Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted this project for award of any other degree or diploma of any other Institute or University.

Date: Ms. Samiksha Dewangan

Place: Greater Noida (U.P.) **Name and Signature of candidate**

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Ms. Samiksha Dewangan

Abstract

Research in a developing field of medicine known as Integrative oncology research is seeking to determine whether complementary therapies, including herbal medications, are safe and beneficial when used in conjunction with traditional cancer treatments. HIF-1 (Hypoxia-Inducible Factor 1) acts as transcriptional activator which intervenes versatile reactions to hypoxic condition. HIF-1 movement has been expanded to most malignant growths in humans because of intratumoral hypoxia and hereditary adjustments. Variation in low oxygen pressure (hypoxia) in tissues and cells prompts transcriptional acceptance of progression of qualities which take an interest in iron digestion, angiogenesis, glucose digestion, & cell multiplication/endurance. Essential component intervening the reaction is HIF-1 (hypoxia-inducible element 1), an Oxygen-touchy transcriptional activator. HIF-1 is made up of two subunits: one that is constitutively transmitted and one that is oxygen-controlled. Hypoxia has a better and strong impact by means of quality articulation, on mammalian physiology and cell science. The research of the HIF-1 pathway is attracting a lot of attention. Also acts on human infections like malignant growth. Hypoxia consequently addresses and oddity for those concentrating on cancer development all the oxygen deficiency could have adverse effect in the cells development hypoxia reaction may moderate such impacts and can even trigger basic carcinogenic transformations. Hypoxia goes about the physiological used to induce articulation of genes the result of which advance attack. At the attacking growing edge of human colon and brain malignant growth biopsies, HIF-1 upregulation was observed.

In this article various aspects of herbal medicines have been discussed which play a significant role in prophylaxis of cancer. Many studies have been done to determine the impact of herbal drugs in cancer treatment. Herbal components suppress tumour growth, inhibit proliferation and cause apoptosis of tumour cells.

Keywords: Hypoxia, Hypoxia inducible factor, malignant growth, Gene articulation, Reactive oxygen species (ROS), Mitogen-activated protein kinase (MAPK), Angiotensin.

1. INTRODUCTION

Hypoxia-inducible factor is the responsible factor that reacts to diminish in accessible oxygen in the environment of cell. Hypoxia has a better and strong impact, by means of gene articulation on mammalian physiology and cell science. There is enormous developing interest in HIF-1 pathway science. Also has a function in human illnesses such as cancer and malignant development [1]. HIF-1α mRNA was discovered to be expressed in PCA cell lines of 6 rats that were matched to typical prostate and potential of metastasis was linked to mRNA levels of HIF-1α in those lines of cells [2]. Under non hypoxic culture conditions, a PCA cell line of humans obtained as a result of bone metastasis was discovered to be overexpressed HIF-I α protein [2,3]. Since HIF-1α articulation in PCA cell lines was dysregulated, speculation has been tried, HIF-1α for the most part is overexpressed in strong tumors [3]. Hypoxia consequently addresses and oddity for those concentrating on cancer development: although oxygen shortage might have a detrimental impact on cell growth, hypoxic reaction may moderate those impacts and can even trigger basic carcinogenic transformations [4].

In the existence of O_2, cells make ATP by full glucose oxidation to CO_2 and water by action of the tricarboxylic acid enzymes, glycolytic enzymes, pyruvate dehydrogenase and ETC (Electron transport chain). According to ongoing research, the switch to glycolytic metabolism from oxidative metabolism is a functional reaction to hypoxia, which is intervened by hypoxia inducible factor-I [5]. A result of expanded cell number inside a cancer is a comparing expansion in O_2 utilization. Cancer movement and patient mortality are related with both microvascular thickness also intratumoral hypoxia [6,7]. The reason for the evident paradox is that in spite of the fact that angiogenesis is invigorated inside tumor, the subsequent vessels are functionally and structurally unusual, coming about in an inability to covey sufficient O_2. Cancer cell endurance is accordingly reliant on angiogenesis stimulation and cancer cell metabolic diversity in response to hypoxia [7].

Hypoxia, according to theory, is a physiological boost that causes gene articulation, which leads to an increase in attack. Ex vivo studies show that cancer cells which are briefly exposed to hypoxia have increased attack rates through the cellular film, supporting this paradigm [8]. At the attacking growing edge of colon malignant growth and human brain biopsies, HIF-I upregulation was observed.

Blend of numerical and test examination to comprehend the HIF-1α flagging network. This is accomplished by developing an iterative dynamic model which is approved by in-house test information and which has adequate prescient ability to precisely display the HIF transcriptional reaction to hypoxia both spatially and transiently. This model consolidates both PHD and FIH as significant controllers of HIF-1α movement. It likewise thinks about cell compartmentalisation and criticism guideline which were deficient in past models. In expansion to controlling the oxygen pressure [9,10]. Through sensitivity analysis of the model and subjective examination of the centre module, we recommend that asparaginyl hydroxylation gives upon HIF-1α protection from proteosomal corruption. Utilizing a blend of in-Vitro trial and error and in silico expectations, we affirm the network geography of the hypoxia reaction, build up the wirings controlling the powerful guideline of HIF-1a transcriptional movement [11] by hydroxylases and utilize the model to offer naturally conceivable clarifications to irrational exploratory perceptions [12].

1.1. Origin and Discovery of HIF 1: HIF 1 discovery by identifying element which is response element of hypoxia in the gene (HRE; 5' - RCGTG-3'). The protein binding to HRE in hypoxia circumstances was discovered by virtue of the research. HIF-1, a hypoxically inducible component, is a part of heterodimeric complex. HIF-1 is otherwise called as aryl hydrocarbon atomic translocator that was at first distinguished like limited aryl hydrocarbon receptor accomplice. These proteins have a place with the fundamental helix-loop protein family [1].

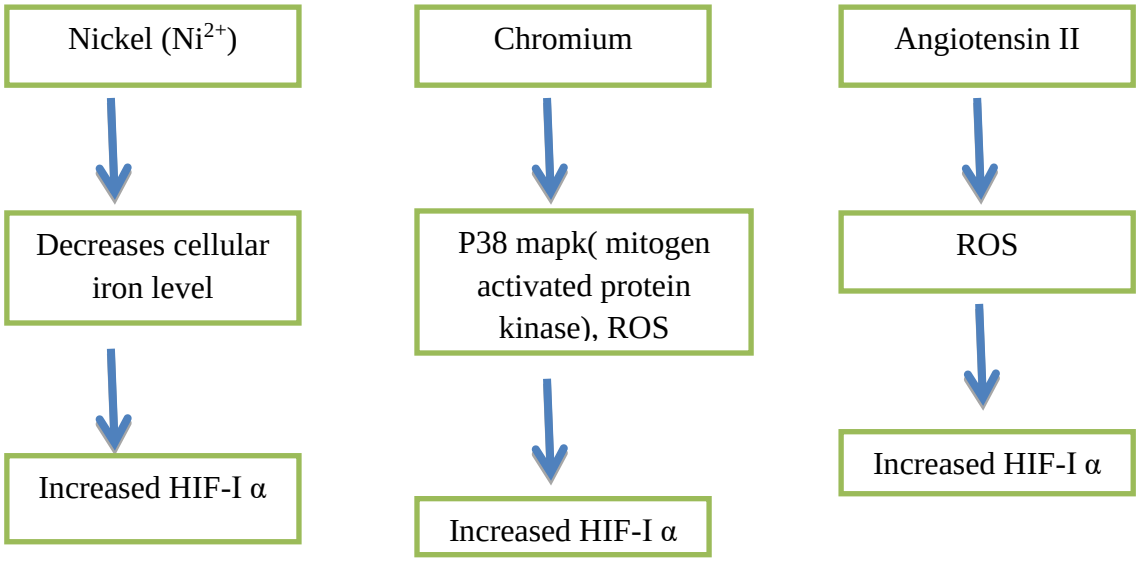


Fig. 1: Regulator's function and pathways within the consequences

2. HIF-1 ROLE IN DISEASES AND DEVELOPMENT

HIF pathway and hypoxia has attached to the pathophysiology and embryonic developement of most diseases in humans. The Warburg effects have been identified as necessary for powerful cancer to develop and enhance delivery of oxygen to cells through angiogenesis and glycolysis commencement. HIF-1 importance is given with enacting traits necessary for these cycles, it's no surprise that HIF-1 and HIF-2 both are implicated into tumour growth and grading, providing a distinct benefit to tumour cells [1].

In addition, progressing endeavors in focusing on HIF-α dimerization with HIF-1β may prompt unforeseen outcomes [12,13], given the new obvious accomplishment in identifying the inhibitors of small molecules of protein-protein interactions. No one of these specialists has been up to this point proposed for clinical improvement. Interestingly, in the last several years, a non selective HIF-1 inhibitor has been developed [14,15]. Two factors should be considered in HIF inhibitors advancement. Firstly, HIF-I α articulation identified often times among incendiary penetrate on strong growths, an element ineffectively addressed in creature models [16]. Over expression of HIF was found in different human malignant growths, possibly due to intratumoral hypoxia or hereditary adjustment. Inside cancerous mass turns out to be dynamically hypoxic because its size increases until tumours obtain enough veins or blood arteries.

Hypoxia conditions inside growths can lead to expanded HIF-I activity and stability. Studies of Immunohistochemical exposed about HIF-I protein levels that they are perceivable in benign tumours, elevated levels in critical harmful malignancies, and a controlled quantity in cancer growth metastasis. Articulation of HIF target genes is for the most part predictable with the degrees of HIF-I. Furthermore, infusion of HIF-I is positive element to tumorigenesis [1]. Enormous progress occurred to understand hypoxic transformation on subatomic grade during the last decade. Reducing intracellular oxygen strain up-regulates an increasing amount of relevant genes physiologically by means of novel system for detection of oxygen and flagging that stimulates the actuation of the HIF-I hypoxia-inducible record factor [17].

Although the guidance of HIF-1 in estromal invading cells in still ineffectively perceived, evidence or proof has revealed that HIF-1α has a basic part in myeloid cells [18] just like endothelial cell [19,20] capacities. In preclinical models, the influence of inhibitors of smaller molecules of HIF-1 on cell sections of the cancer atmosphere is not addressed properly, and HIF modification function in such cells might get crucial to treatment accomplishment. Secondly, HIF-1 suppression may not be enough to prevent cancer growth and angiogenesis, since HIF-independent mechanisms might escape or conquer inhibition of HIF [21]. The significance of this pathway is proposed by its quality in for all intents and purposes all cells inside basically entire higher eukaryotes, reaching to man from worms & flies. It is also examined that couple of biological views of HIF-depending expression of genes, specifically those related to angiogenesis & tumour research [17,22].

There is developing assemblage of proof for debilitated HIF-1 actuation in diabetes, however some discussion is still left. Examples of heart tissue of human in angina and coronary biopsies detour a medical procedure showed diminished VEGF levels and HIF-1α in patients of type 2 diabetes contrasted with non-diabetics [23]. Work on diabetic rodents induced by streptozotocin revealed that hyperglycaemic rodents had larger infarcts, which were related with lower levels of HIF-1α [24,25]. In individuals having diabetes type 2 & diabetic rats treated with STZ, a negative link among cardiac HIF-1α grades and glycemic regulation has been identified [25,26]. We recently shown that in diabetes the mechanism of HIF-1α obstruction has origin of biotransformation, accelerated by higher unsaturated fats. It raised reliance on unsaturated fat digestion smothers glycolysis, which brings about myocardial succinate downregulation during hypoxic condition, causing decrease in HIF-1α adjustment [27]. It is recommended that HIF-1β weakness could go before type 2 diabetes advancement [28]. Tumor pathogenesis and Biomedical relevance – Furthermore, cancer causing mutations regularly upgrade HIF expression or articulation. In a variety of human malignancies, the inactivation of p53 tumour silencer gene occurs. Loss in wild kind of p53 in the tumor upgrades levels of HIF-I and HIF-dependent transcription increases. Brain hypoxia and respiratory depression is produced by opioid drugs: Morphine, heroin, oxycodoneand fentanyl in Table 1.

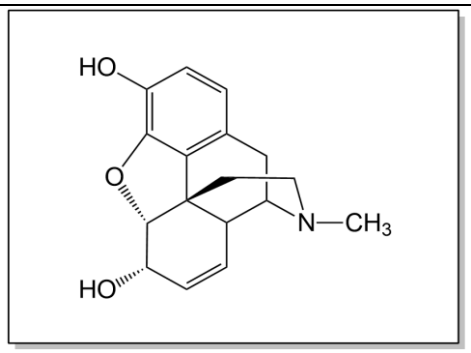
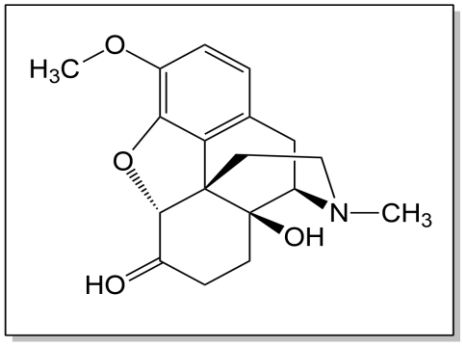
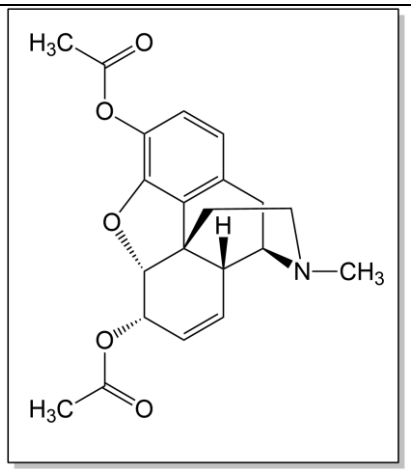
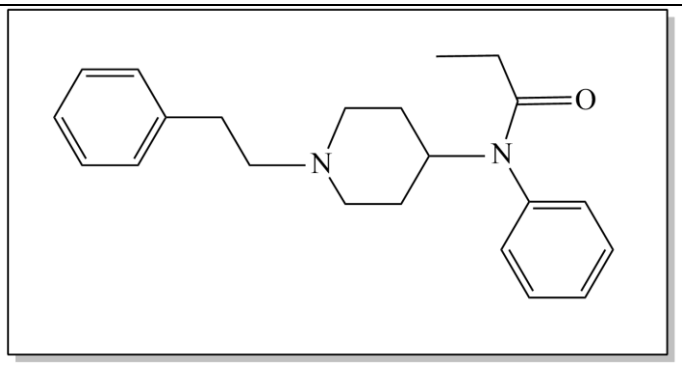
Drugs Name	Structure
Morphine($C_{17}H_{19}NO_3$)	
Oxycodone($C_{18}H_{21}NO_4$)	
Heroin ($C_{21}H_{23}NO_5$)	
Fentanyl($C_{22}H_{28}N_2O$)	

Table 1: Opioid drugs

Cancer cells found near a vein are presented to moderately high oxygen fixations; the oxygen focus then, at that point, decreases as distance increases from the vein (although this angle may be seen in all tissues, it is substantially more articulated in malignancies). In putrefaction zones, concentration of oxygen is reported up to plummet into near nil (malignant growth cell bite the dust because of deficient oxygenation). Thus hypoxia inhibits cancer enhancement, demonstration revealed growth is unsuited to proliferate beyond 2 mm3 unless it is supported by neovascularisation [29]. Overexpressing HIF-1 and HIF-2 is discovered in most people malignancies, as well as their metastasis, since HIF is crucial element in the onset of diverse action to decreased oxygen supply [30]. Hypoxia in intertumor may be an important factor, it is found that there is increase in the level of HIF-α in tumors, HIF-α is thought to be balanced out in certain tumors at oxygen levels much above those deemed hypoxic and in this way free of hypoxic PHD inactivation [31].

Expanded movement of tyrosine kinase the HER2 receptor in carcinoma of breasts is closely related to aggressiveness of cancer and reduced patient endurance [32]. Upgraded signalling of HER2 expands the synthesis rate of HIF-I [17,32].

3. HIF-1 A PROTEIN EXPRESSION SCREENING

Expression of HIF-1α examined in wide spectrum of tissues and malignant tumours in humans are removed using standard oncology procedures. 21 typical tissues of humans (174 specimens), primary cancer 19 (131 specimen) and metastases 36 from 6 cancer type were cross examined [3]. Therefore astounded to learn that HIF-1 A deficiency didn't adjust vascularisation of tumour in H-ras-change fibrosarcomas. Rather, tests when VEGF is not present in growth or malignant cell environment, a significant drop across vascular thickness is seen [33], furthermore rather than the test proof from ES cell- derived cancer where huge, though unpretentious contrasts in vascular thickness are seen [4,34,35].

HIF actuation brings about the development of a few development variables and receptors engaged with neovascularisation, inclusive of VEGF (Vascular Endothelial Growth Factor), Vascular Endothelial Development Factor receptor 1 (Flt1), Ang2 (angiopoietin) & PDGF (Platelet-Driven Growth Factor). HIF also causes chemical erythropoietin to be produced (in hypoxic conditions), causing augmentation of red platelet making and improving the endurance through protection against apoptosis. Enactment of HIF-1

additionally controls cell oxygen use, advancing the preservation of oxygen by changing from high-impact to breath in anaerobic way. This metabolic shift is made possible by increasing the production of glycolytic catalysts, for example, lactate Dehydrogenase A and hexokinase 1 and hexokinase 2, and hindering section in the carboxyl Corrosive (Tricarboxylic Acid Cycle) cycle by inciting PDK1 (Pyruvate Dehydrogenase Kinase 1). Pyruvate dehydrogenase phosphorylation by PDK1 restrains pyruvate change into acetyl-CoA, this is needed to enter the TCA cycle [36].

4. OXYGEN HOMEOSTASIS REGULATION BY HIF-I AND ROS COMPLEXITY

HIF-1 is a heterodimeric record or transcription element [37,38]. Although HIF-1β subunit is essentially transmitted, cellular oxygen fixation regulates its articulation and function [37,39,40]. Aspargine hydroxylation buildup across transactivation area blocks the limiting of the coactivators p300. Though the investigations portrayed above show that HIF-I directs ROS creation, several investigations have found that under hypoxic settings, the production of ROS by electron transport complex-III of mitochondria increases dramatically, which is required for HIF-I α expression acceptance [37,41]. Hypoxia Inducible Factor-1 additionally might manage anaerobic digestion. In presence of oxygen, majority of cells make ATP by oxidative phosphorylation. For cases, involving hypoxia conditions, anaerobic digestion is used to generate cell energy. HIF-1 is one of the most important factors in coordinating the shift [42], since it activates a variety of glucose carriers and glycolytic enzymes, for example, pyruvate kinase M and aldolase An, which helps cells create efficient energy during hypoxia circumstances [43]. By activating Pyruvate Dehydrogenase Kinase I and halting the citric acid cycle, mitochondrial oxygen usage is lowered by HIF-1 [40,44].

The Von-Hippel Lindau (pVHL) Protein interacts with HIF-an, also causes the 26S proteasome multiprotease compond to degrade and ubiquitinate, is responsible for the rapid corruption of HIF-2α and HIF-1α (in Normoxia). PHD (Propyl hydroxylase Area) proteins, otherwise called HPH (HIF-propyl hydroxylase), initiate this cycle by hydroxylating two proline deposits inside the ODDD. These proteins have a place with 2-oxoglutarate (2-OG)- subordinate dioxygenases group and there is requirement of oxygen, 2-oxoglutarate,

ascorbate and iron to work. The hydroxylation of deposits of 2 proline (P564 & P402 in HIF-1a, or P531& P405 in HIF-2α) causes pVHL to be limited to HIF-an. PHD1, PHD2, and PHD3 are three developmentally monitored PHD isoforms that have been identified. Despite this, siRNA disassemble of PHD2 is adequate in balancing HIF-1α levels in normoxia, to indicate PHD2 is critical variable controlling anoxic levels of HIF-1α [45]. PHD research is associated with subatomic 02 levels due to using oxygen by way of substrate. O2 particle's single iota is transported to a buildup of proline of HIF-α, while other one is reacted with 2-OG so that to produce carbon dioxide and succinate [46].

5. RENAL CELL CANCER AND VHL TUMOR SUPPRESSOR

People are heterozygous with disorder Von Hippel-Lindau forgemline declining work change across gene VHL and are prone to develop renal cell (bilateral) and multifocal carcinomas causing substantial inactivation of staying wild-type VHL allele [37,47]. VHL movement loss brings about deficiency O_2 subordinate ubiquitination along with HIF-I α and HIF-II α degradation [37,48].

Xenograft of tumor development by renal carcinoma cells which are VHL deficient is reliant on dysregulated articulation of HIF-2 α, that isn't dependent upon O_2 - subordinate ubiquitination and degradation without VHL [37,49]. The systems of HIF-1 mediated cancer persistence is uncovered by crafted to some extent by Semenza et al. on carcinoma renal cells that lacks VHL [50,51]. HIF-1 was discovered to diminish O_2 utilization by repressing C-MYC in these cells, a record factor which directs oxygen utilization and mitochondrial mass and it is familiar to be down-controlled in an assortment of tumors in humans. According to Semenza et al., HIF-1 lowers C-MYC levels by growing expression of MXI1, a C-MYC inhibitor, enhancing C-MYC protein proteasomal debasement rate [42]. C-MYC reduction in cancer developing cells was discovered eventually resulting in expanded glycolysis along with mitochondrial reduced respiration, pivotal diseased cells characteristic which proliferate in hypoxia condition of miniature climate of cancer [18].

HIF-1a is broadly communicated in tissues, though HIF-2α expression is confined to specific types of cell in a few organs [52]. HIF-1α articulation can be seen predominantly in cylindrical cells of the kidney. Interestingly, kidney interstitial fibroblasts, few glomerular cells and endothelial cells show HIF-2αinspiration [53,54]. Other than the

guideline of EPO, examinations of different cis-acting administrative groupings has uncovered that hypoxic quality guideline by HIF is a typical and far reaching instrument that incorporates the guideline of significant qualities for keeping up with oxygen and biotransformation homeostasis. The collection of HIF-subordinate transcriptional targets incorporates qualities managing angiogenesis, chromatin renovating, glycolysis, cell cycles & surprisingly itself oxygen-detecting mechanism. For sure, Genome wide examination of transcriptomic reaction to Hypoxia combined with HIF restricting uncovered that in any event 500-1000 qualities are heavily influenced by HIF [55,56-60] in a specific cell type. In particular, HIF is an activator of quality record, and its chromatin restriction can transactivate quality articulation by collaborating with advertisers over vast genomic distances [55-57]. Besides, the collection of HIF targets is profoundly cell-type subordinate, with just few HIF-controlled qualities preserved across all cell types [61].

6. REGULATION OF GENE EXPRESSION BY HIF-I

HIF-I target genes around 40 have been investigated and from these majorty are known to show important roles in cancer progression like angiogenesis, glucose metabolism, proliferation of cell and homeostasis (iron) [62].

Tumor type	Affiliation	Reference
Breast	-Vascular endothelial growth factor -Estrogen receptor -Microvascular density	66
Ovarian	-Mortality -Microvascular density	67
Cervix	-Mortality	68
Brain	-Grade, Microvascular density	69
Oesophagus	-Response to photodynamic therapy	70

Table 2: Human cancer and HIF-Iα Immunohistochemistry

HIF-I is exposed to protease degradation and ubiquitination in normoxic condition [63-65] because of von Hippel-Lindau cancer suppressor protein binding [42], which is substrate acknowledgement subunit of an E3 ubiquitin-protein ligase. HIF-I may play role in Cancer science, it's double job in advancing cell endurance and apoptosis induction, and the availability of double HIFα sub groups i.e. HIF-Iα & HIF-IIα, each of them may consist distinct and explicit jobs for various types of cancer, have all contributed to some early debate over HIF-1's role as a beneficial goal. Whether or if HIF-I is a good target for improving malignant growth therapies is investigated in a variety of test models, that have led to some questionable results. To be sure, various outcomes have been accounted for relying upon the cell type utilised [71-73], the HIF-α subunit designated [9,44,74], 10 site of growth infusion and the circumstance of HIF-1α restraint, more dynamic in early rather than late cancer development [75]. Since HIF-1 has not been straight forwardly embroiled in oncogenic change, despite the fact that proof has furnished that it could help out AKT in melanomagenesis [76], it's proven hard to decipher results to creature models from in vitro investigations [77].

The reaction to hypoxia incorporates a progression of variation components that advance cell endurance. At its most basic level present, the carotid body inside the carotid supply route faculties diminished O2 levels and invigorates cardiovascular and breathing result [15]. These reactions include voltage and calcium actuated K directs communicated inside the carotid body, furthermore by neuroepithelia, α sub groups of them are touchy in elective grafting, with hypoxia instigating consideration of pressure managed exon STREX that give aversion to tissue hypoxia explicit example, giving a tissue-explicit system to control cell reactions to hypoxia. Cell atomic oxygenation detecting relies likewise on oxygen-subordinate oxygenases, contained a group of 2-oxoglutarate-subordinate oxygenase, that includes hypoxia-inducible variable (HIF) oxygen-subordinate prolyl-hydroxylase PHD [72,78]. Hypoxic condition represses PHD movement bringing about aggregation, adjustment and actuation of HIF record factors, advancing HIF-target gene articulation, elective joining to non-HIF target & HIF target qualities, furthermore instigate 4E-BP1 phosphorylation-subordinate hindrance to covered non-HIF target genes mRNA interpretation [5,76].

Hypoxia-initiated elective grafting is basic for variation of both typical and cancer cell atmosphere and it is integral across one main elements of ordinary & growth hypoxia

reactions, angiogenesis, answerable to hypoxic tissues that are vascularizing [79]. Hypoxia tissues angiogenesis has been accomplished through bringing down proportion of angiogenesis blockers into angiogenesis advertisers in addition relies on hypoxia-incited, HIF-reliant, elective grafting which advances supportive of angiogenic VEGFA, alternative join balance, to the detriment of the counter angiogenic VEGFA, isoform [22,80]. Hypoxia likewise controls HIF-1α joining at the time of angiogenesis and advances articulation of the angiogenesis interdictory then again grafted HIF-3α IPAS isoform, which ties HIF1α yet not HIF-β to restrain HIF-1-intervened record, up-manages elective HIF-3α 4 joining to stifles HIF-subordinate record [18,42].

7. HIF-I A DEFICIENCY EFFECT ON CELL METABOLISM AND THERAPEUTIC IMPLICATIONS

Few studies exhibited that intense hypoxic condition leads to expanded ROS grades, needed for restraint of PHD movement & HIF-1 adjustment in hypoxia cells [81]. Consequently, hypoxia promotes expanded mitochondrial ROS, that instigate HIF-I, which subsequently intervenes in a variety of events to reduce ROS levels by adjusting mitochondrial oxidative biotransformation [5,82]. Few studies have featured the hypoxia-inducible element as an expected restorative objective for frailty. Inside the previous year, clinical preliminaries have exhibited the viability of HIF stabilizers in expanding haemoglobin levels of both non-dialysis and dialysis CKD patients. The outcomes are promising as up until this point, treatment has not been connected with genuine unfavorable impacts. HIF-I intercedes versatile angiogenic reactions that serve to increment O2 accessibility [43, 83], like those metabolic transformations that function to control O2 usage, impeding HIF-I movements have significant impacts on cancer development and progression [84].

Various investigations have clarified the job of HIF-1α in different tumors, making it an appealing possible objective for new treatments. Research has shown that there is a connection between expanded degrees of HIF-1α and factors like growth metastasis, angiogenesis, and helpless patient forecast. The HIF-1α pathway has been distinguished as an essential endurance pathway, and new investigations are investigating novel treatments

that could take advantage of this pathway. Restraint of HIF-I activity might add to the viability of an enormous amount of novel and accepted standard anti-cancer drugs [85,86].

HIF-1α – enacting pharmacological mixtures can be categorized as one of a few kind, all of them have an impact via forestalling HIF-1α debasement. 2-OG mimetics are functioned as apparatus chemicals in pre-clinical trial studies in a number of instances. In a hare model of myocardial ischaemia-reperfusion, pre-treatment with dimethyloxalylglycine (DMOG) caused significant size reduction of subsequent blockade after reperfusion [87]. Likewise, into ex vivo perfused heart arrangement, hearts of rodents pretreated with DMOG exhibited further developed practical recuperation followed by ischaemia-reperfusion [88]. The majority of the concentrations on these mixes were directed prior to the onset of damage or on the other hand ischaemia, which could place being referred to their value in a clinical surrounding. They are scrutinized for their helpless selectiveness and hazard of mistaken impacts because of their hindrance of different 2-OG subordinate catalysts [89,90]. Iron chelators, for example, hydralazine and desferrioxamine, have displayed having HIF-1α balancing out capabilities via PHD hindrance. In a rodent aneurysmal subarachnoid drain model, Desferrioxamine therapy was displayed to further develop blood stream of brainstem and decrease vasospasm [91].

8. ACIDOSIS BY TUMOUR METABOLISM AND CELL SURVIVAL/DEATH

The result of a high pace of glucose take-up joined by raised glucose utilization for example glycolysis (survey [42]). Otto Warburg found during the 1920s that cancers, dissimilar to ordinary cells, changed glucose over to pyruvate and afterward to lactate, even within the sight of plentiful measures of oxygen.

HIF-target quality lactate dehydrogenase A (LDH-A) that is up-controlled in changed cells. In this manner profoundly multiplying cells with a high-energy request quickly discard a supply of ATP. In any case, the outcome is an over-burden in lactate and CO_2 that adds to the abatement in the extracellular pH [81].

HIF-1α and HIF-2α have been found having contrary roles in carcinogenesis in specific tumours. Contrary to previous results, HIF-1α expressions were observed to correspond to reduced disease phase like case having neuroblastoma, clear cell renal cell carcinoma

(ccRCC), neck and head squamous cell carcinoma and non-small-cell lung cancer; HIF-2α expression, otherwise, was shown being associated with superior phases and it was constantly evaluated like negative prognostic indicator [92]. The VHL-deficient ccRCC has amassed the most persuasive information concerning the various actions of HIF-1α and HIF-2α: on the other hand, ccRCC occasionally overexpress HIF-1α& consistently overexpress HIF-2α, only HIF-2α is essential to develop them [93]. Furthermore, both HIF-1α and HIF-2αmay transcriptionally down-regulate HIF-1α transcription in ccRCC after VHL inactivation by a process that requires binding of any component to a reverse HRE in the HIF-1α proximal promoter succeeded through sequence containing restrictive modifications of histone [94].

9. HIF IN METASTASIS AND TUMORIGENESIS

As an outcome HIF1α is steady and dynamic in RCC cells and growths are exceptionally vascularized. VHL sickness is described by the presence of vein growths (haemangioblastomas) of the focal sensory system or CNS and retina that are regularly connected with tumours like RCC. These qualities give a solid interface between HIF, angiogenesis and tumourigenesis, which is further built up by perceptions of expanded articulation of HIF 1α in various essential and metastatic growth types [95].

According to research, HIF-1 target genes expression is expanded into triple-negative breast malignant growth subclass. HIF-1 assumes key parts in numerous pivotal parts of breast malignant growth science, including angiogenesis, undifferentiated organism support, metabolic reconstructing, EMT, metastasis, attack, and opposition to chemotherapy and radiation treatment. HIF-1restraint movement into mice following orthotopic transplantation of triple-negative breast malignant growth cell dramatically affects essential cancer development just as metastasis to lungs and lymph nodes [96].

ccRCC mouse models have likewise revealed that renal epithelium-explicit inactivation of HIF1α or HIF2α gene impedes ccRCC development [97-99], demonstrating that both HIF1α and HIF2α are associated with ccRCC inception. Notwithstanding, in 30-40% of plain ccRCCs, HIF1α articulation is gone, since HIF1α goes about like a cancer silencer during additional movement of ccRCC via lessening independent VHL-lacking growth cell multiplication. Alternately, HIF2α goes about as an oncoprotein in ccRCC [100-102].

Subsequently, plain ccRCC might be partitioned in such situations in which HIF1α and HIF2α both are expressed, and those who main reveal HIF2α articulation illustrated by improved ccRCC cell expansion & adverse forecast [100,103-105]. Accordingly, oncoprotein capacity of HIF2α in ccRCC induced the advancement of HIF2α PT2385 and PT2399 to fight the activity of such growths [106, 107].

10. HIF IN BREAST AND PROSTATE CANCER

HIF-1a articulation grades might fill in as an unique indicator to helpless result for positive & no denegative both breast cancer. Be that as it may, these significant degrees of gene articulation are not really coming about because of gene enhancement or changes in the oxygen-subordinate debasement spaces of HIF-1α. These rising HIF-1α probably creates whether expansion toHIF-1α gene transcription or on the other hand some change in the debasement pathway. Most tumor over articulating HIF-1 exhaustion seriously blocks growth development and angiogenesis [108].

Hypoxic areas persist in human prostate cancer, and higher clinical stages are associated with increasing grade of hypoxia. Among clinical perception of high-grade prostate intraepithelial neoplasia injuries, examined forerunner to larger part in obtrusive prostate adenocarcinoma, revealed enhancing HIF-1α comparative with the individual typical epithelium, benign prostatic hyperplasia & stromal cells. Adverse impacts on patient endurance are found in cervical [109], ovarian [110], Breast [111], stomach cancers [78] and endometrial [112]. HIF-1α level of protein in human prostate malignant development have been reported to be adjusted by androgens. Theory demonstrated overexpression of HIF-1α could not simply be antigenic from intratumoral hypoxia, however is impacted by androgens and androgen receptor. In any case, clashing outcomes connecting with the HIF-1α overexpression in neck and head diseases and non small cell cellular breakdowns in the lungs saw as either expended mortality [50,113], or diminished mortality [80,114].

These contrasting outcomes may be clarified by the association of HIF-1α with genes engaged with apoptosis as Bcl-2 family and p53 [79,115,116]. The impact of HIF-1α articulation in individual diseases is by all accounts reliant upon the particular disease type just like the absence or presence of hereditary modification which influence the harmony either between antiapoptotic effect or Pro effect. Despite the fact that HIF-1 articulation is

associated with the hypoxia level, hypoxia-free mechanisms, such as oncogene activation and glucose restriction, increase its expression even more [117]. We further tested the hypothesis that enemies of androgens inhibit the HIF-1α transcriptional pathway in androgen-responsive PCA cells, resulting in anti-angiogenic effects. We discovered in vitro DHT (dihydrotestosterone) animates HIF-1α protein articulation, HIF-1α transcriptional movement, and VEGF creation in androgen receptor positive LNCaP cells; on the other hand, the counter androgen flutamide diminished such impacts. The acceptance of androgens in HIF-1α protein articulation is also controlled to some extent by an autocrine circular system [118]. Prior studies have shown that HIF-1α invalid transformations seriously obstruct cancer development by lessening articulation of glycolytic catalysts, with growths incapable to develop past 2 mm3 except if upheld by neovascularization interceded through hypoxia enlistment of HIF-1 [119,120]. Interestingly, HIF-1 inhibitors, with VEGF inhibitors, have displayed diminish breast malignant growth cell metastasis among mouse orthotopic transplantation models [22] and sharpen growths to radiation therapy [121]. As HIF-1 intercedes various cancer endurance instruments and its overexpression emerges not just due to the activities of biologically active lipid arbiters, contaminations by virus, & intratumoral hypoxia yet additionally via oncogene gain-of-function [10] and cancer silencer gene [122] deprivation-of-work changes, HIF-1 might address last normal mechanism in malignant growth pathogenesis. Subsequently, HIF-1 is an alluring objective in case of disease treatment.

Cancers cure these by creating angiogenic factors that resulted in development of cancer vasculature, despite the fact that, with primary and practical inconsistencies. These incorporate arteriovenous shunts, blind Closes, impediments, high point stretching designs, what's more broken, flawed vessels [123]. Irregularities in the cancer vasculature limit oxygen conveyance, prompting intense hypoxia [124]. Hypoxic growths are further impervious to chemotherapy and radiation, are more intrusive, are hereditarily temperamental, oppose apoptosis and contain prominent metastatic potential, which all results in less fortunate forecast generally for patients [125, 126]. It is exhibited that cancer light is 3 multiplications more powerful while conveyed under anoxic vs oxygen-higher circumstances. As HIF-2α or HIF-1α gather, they tie to HIF1β and structure the HIF heterodimers, that move to core furthermore, alongside co-activators (CBP &p300),

structure the transcriptional edifices that tight spot to hypoxic reaction components (HREs) in the administrative locales of numerous qualities [127].

11. PLANT DERIVED DRUGS IN CLINICAL TRIALS AND RESEARCH

11.1. Taxol (Paclitaxel): Paclitaxel (PTX) is considered as a natural chemical discovered in 1967 by Wall and Wani of the Research Triangle Institute [128]. It was isolated originally from the Pacific Yew tree. It was used as first taxane in case of cancer treatment [129].

According to a crystallographic analysis, when PTX interacts with its target β-tubulin, it acquires a T-shaped structure, that is similar to α-tubulin extended loop in α,β-tubulin dimer [130]. PTX binding to the β-tubulin found inside microtubules stabilises and accelerates microtubule polymerization [129], microtubule dynamics are disrupted, that arrests cells at G2/M phase [131,132] and cause death in growing cancer cells [133]. Since cells are most vulnerable to radiation at G2/m phase, PTX is also utilised as radio sensitizer [131]. Because of this unique PTX method of action, PTX has shown tremendous promise in suppressing a large variety of carcinoma cells from many origins, including ovarian cancer, brain cancer, pancreatic cancer, breast cancer, non-small-cell lung cancer and Kaposi's sarcoma [134].

11.2. Sulphoraphane: Sulphonaphane is a naturally occurring isothiocyanate compound in vegetable Brassicaceae [135]. Sulphoraphane targets multiple pathways inside the cell to reduce, reverse, or stop the carcinogen effect. It provides primary chemical prevention by blocking phase 1 biotransformation enzymes and cytochrome P450 mostly [136], promoting detoxification phase 2 enzyme activity and decreasing pro-inflammatory reactions in the cell.

Sulphoraphane enhances secondary chemoprevention by influencing epigenetic modifications in the cell which stimulates the transcription of cell cycle arrest and apoptotic genes like p21 and cyclin D1. Finally, it provides tertiary chemoprevention by preventing oncogenesis and metastatic development via targeting stem cancer cells in prostate & pancreatic tumor [137].

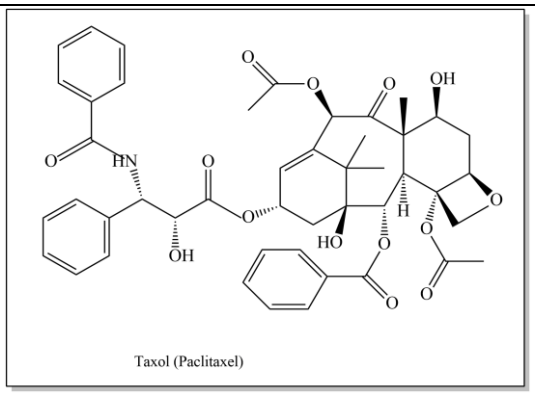
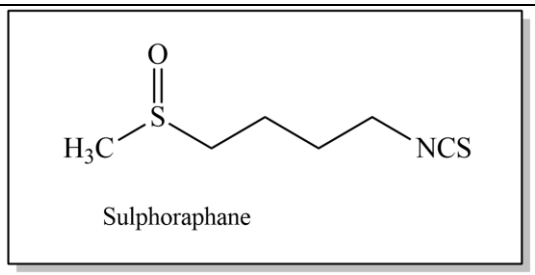
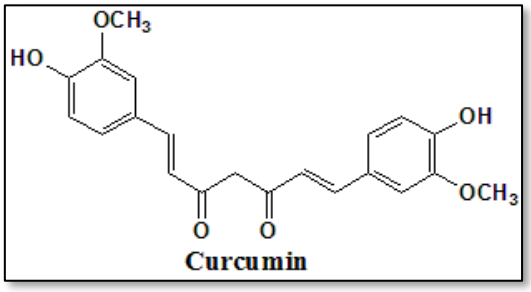
Anticancer agent (Drug Name)	Structure	Derived or Isolated from:	Activity
Taxol (Paclitaxel)		Taxus brevifoliaL. ,Taxane	Induce apoptosis, blocks mitosis, disruption of formation of spindle, Microtubule disruptor [130-133]
Sulpho-raphane		Isothio-cynanate in cruciferous vegetable Brassica	Inhibits the tumor growth in breast cancer, Induces phase 2 detoxification enzymes, antiproliferative effects [136,137]
Curcumin		Rhizomes of Curcuma longa, family Zingiberaceae	Chemo preventive, antiproloferative capacity, immunomodulatory ability, anticancer property, anti-inflammatory effect

Table 3: Plant derived drugs in clinical trials and research

11.3. Curcumin: Curcumin commonly known as turmeric, is isolated from rhizomes of Curcuma longa, family Zingiberaceae. It has various properties beneficial to humans that can enhance the human health like anti-cancer, anti- inflammatory, anti-proliferative, immunomodulatory, etc.

Curcumin's anticarcinogenic efficiency is primarily mediated through apoptosis, inhibiting proliferation and reducing tumour growth and invades through suppression of varieties of cellular signalling mechanisms [138].

Curcumin has been shown to have antitumor action against lung cancer, breast cancer, neck and head squamous cell cancer, brain tumours, & prostate cancer, demonstrating its potential to target varieties of cancer cell lines [139].

12. DISCUSSION

Hypoxia-inducible factor is the responsible to diminish in accessible oxygen in the environment of cell. HIF-1 acts as drug target of cancer. There is correlation between HIF-1 and metastasis of cancer, angiogenesis, tumor resistance therapy, etc. It has activity in diseases of humans like cancer and malignant development. HIF-1 movement has been expanded to most malignant growths in humans because of intratumoral hypoxia and hereditary adjustments. Hypoxia condition or variation in oxygen level does not allow cells to grow properly and cause hindrance in normal functioning of cells along with multiplication of cells. Hypoxia has a better and strong impact by means of quality articulation, on mammalian physiology and cell science. Many studies have been conducted to correlate the role of HIF in cancer proliferation and tumorigenesis. It has significant impact on tumor malignancy.

There are various approaches identified to reduce of the effect of HIF as well as for prophylaxis of cancer and malignancies. Using of herbal medicines is one of them. Herbal medicines have shown prominent effect in treating cancer. They have multiple other benefits as well. There are multiple mechanisms through which herbal medicines act, such as preventing cell multiplication, restricting cell division at a particular stage, suppress proliferation, and so on. These suppress various kind of carcinoma cells, such as ovarian cancer, pancreatic cancer, breast cancer and many other type of cancers. Some herbal drugs stop carcinogen effect by reducing inflammation of cells. They cause cell cycle arrest. Prevention of oncogenesis and metastasis development is one of the major function of herbal drugs. They tend to enhance human health by various properties like anti-cancer, anti-inflammatory, anti-proliferative, immunomudulatory, etc. They lead to inhibit proliferation and reduce tumor growth. Some of them suppress varieties of cellular signalling mechanisms and finally cause apoptosis of cancer cells.

Further studies are still going on to enhance the effect of herbal drugs and to determine various other carcinogenic properties of them. In future various new aspects might be developed to reduce the effect of HIF on causing cancer.

13. CONCLUSION

All consequences of current examination may be useful for fostering a novel and powerful enemy of growth. Furthermore, cell reinforcement specialists from flavonoids. Also, the Isoflavone genistein, kaempferol, and quercetin can be considered as lead particles for planning novel antitumor/cell reinforcement specialists focusing on angiogenesis. HIF-1 is broadly perceived like focal arbiter into cell hypoxic condition, instigating key qualities in dedifferentiation, angiogenesis, glycolysis, intrusion, & metastasis to advance oncogenesis.HIF-1 overexpression, which might emerge due to activities of Bioactive lipid arbiters, just as virus diseases, hypoxia, & then again transformations to oncogenes and growth silencer qualities, is in this manner related with helpless anticipation in numerous malignant growth types. Henceforth, we guess that the recognizable proof of novel particular HIF-1 inhibitors will end up being of critical helpful worth.

HIF-1α has arisen as a significant record factor in bosom malignant growth and prostate disease cancer science. Transgenic models of mouse have approved translational examination in individual growth data that HIF-1α is related to angiogenic switch in ahead of schedule oncogenesis. In both bosom malignant growth and prostate with tumors, there is early upregulation, that makes HIF-1α a consistent focus for chemical prevention methodologies in patients at greater hereditary danger of bosom & prostate malignant growth withCOX-2 inhibitors or 2ME 2 just like focusing new ways for dealing with restraining angiogenesis. HIF-1α and HIF-2 up-regulation gets affected through different elements who are antigenic & hereditary escalated unthinking examinations are in process, focusing on HIF-1 emerged to be novel treatment strategy for individuals with bosom disease. In combination with established restorative regimens, novel approaches concentrating on HIF-1 are likely to be beneficial. Future research should focus on identifying more selective HIF-1 inhibitors, focusing on component of activity of them, and combining these in clinical trials.

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