REVIEW ARTICLE

Potential Ability of Phytochemical in Inhibition of Invadopodia Formation and HIF-1α in Cancer Metastasis

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ABSTRACT

Cancer metastasis is a multistep process, which results in cancer cells disseminating to other organs. The crucial metastasis step involves cancer invasion which occurs via actin-protrusion by invasive malignant cells, termed as invadopodia. In solid tumours, invadopodia formation increases as a result of hypoxia which is found to be resistant against chemotherapy and radiotherapy. Phytochemicals have been potentially identified as a prime source of effective conventional drugs for metastasis treatments, which target cancer cell invasion, particularly molecular components of the invadopodia formation. The Hypoxia-Inducible Factor-1α (HIF-1α) is an essential target in terms of treatment for hypoxic tumour, as well as helping to identify the mode of action for the drugs, particularly phytochemical compounds. The aim of this review is to highlight the current development with regards to the ability of phytochemicals in targeting cancer metastasis, as well as phytochemical compounds which are able to inhibit HIF-1α and invadopodia formation. The use of phytochemicals for targeting hypoxic cancer cells may open new prospects for reducing cancer metastasis.

Keywords: Invadopodia, Hypoxia, Metastasis, Phytochemicals, HIF-1α

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INTRODUCTION

Cancer is one of the leading causes of death globally. In 2018, about 18.1 million patients were estimated to have been diagnosed with cancer across 185 countries (1). The majority of cancer mortality incidents were not caused by the primary tumour itself, but due to effects of cancer metastasis. Metastasis was revealed to account for 90% of mortalities (1,2). Metastasis is defined as a systemic disease, in which cancer cells have the ability to invade and migrate across other organs (3). Metastasis undergoes several stages, including invasion, angiogenesis, as well as migration. The most critical step in metastasis is cancer cell invasion through specific protrusion structures, these protrusions are termed as invadopodia (4). Invadopodia has been proven to play a fundamental function in the degradation of the extracellular matrix (ECM) (5). Invadopodia consists of a rich actin core which is surrounded by important recruit components which are essential for the invasion. The components include adhesion proteins, invasion proteins, cytoskeletal modulators, and signaling molecules (6).

Subsequently, invadopodia formation, ECM degradation, and invasiveness of the cancer cells gradually increase due to a series of events which occur in the solid tumor itself, which is termed as hypoxia (7). Hypoxia is a common tumour microenvironment phenomenon which exists across 90% of patients diagnosed with solid tumors (7). HIF-1α is a transcriptional factor which expresses in hypoxia. Interestingly, hypoxia enhances the ability of the solid tumour to become resistant toward chemotherapy and radiotherapy therapies. Because chemotherapeutic agents require cell activity in order to carry out its action. Radiotherapy on the other hand, needs oxygen as well to allow the radiation to effectively make small breaks in the DNA within the cells (8,9). Thus, any therapy which seeks to decrease the HIF-1α expression may be represented as a very useful complementary treatment for tumor hypoxia, as well as for invadopodia formation. Based on literature works, phytochemicals have been widely recognized as being able to target multiple signaling pathways across cancer cells, both directly and indirectly (10). Over than 5000 specific phytochemical compounds have been known to decrease the threat of developing chronic diseases, such as diabetes, cancers and cardiovascular diseases (11). The number of the phytochemical compounds have increased tremendously over the last couple years due to numerous identification, isolation and characterization techniques (12,13). Therefore, the aim of this review

is to highlight the phytochemical compounds, which are able to target hypoxia, and invadopodia formation which lead to decrease metastasis.

ROLE OF INVADOPODIA FORMATION AND ITS MECHANISM OF ACTION IN METASTASIS

Cancer cell invasion is the primary step of metastasis (14). The invasion pervades via actin-foot protrusions, termed as invadopodia. Typically, it is formed in the ventral of the invasive cancer cells. Invadopodia is typically assayed by an ECM degradation assay which is composed of a gelatin coated coverslip in-vitro. Invadopodia can be formed in several cancer cell lines, such as MDA-MB-231 breast cancer cells, A375 melanoma cells, RT25 bladder cancer cells, and HCT116 colon cancer cells which enable them to be widely used in invadopodia studies (15,16,17).

In order for cancer cells to metastasis successfully, cancer cells are required to move across ECM barriers into the blood flow stream. ECM has been identified as a barrier which enables cell movement. Thus, invadopodia is required for penetration of these barriers (18,19). Studies have shown that invadopodia recruits various components and signalling to drive the degradation of ECM, for example actin filaments, integrins and metalloproteinases (MMPs), and signaling proteins, which regulate the actin cytoskeleton (20). Most importantly, invadopodia is only present in highly invasive carcinoma cells, and not all types of cancer cells are able to form invadopodia. However, many of these cell types can form protrusions, for example, endothelial cells, immune cells, dendritic cells and macrophages. These cells use protrusions for migration and/or phagocytosis, not for ECM degradation. This characteristic makes the carcinoma cells different from normal cells (21,22).

The main function of invadopodia is to degrade the ECM in order to facilitate migration. ECM is defined as a collection of materials such as periostin, hyaluronan, proteoglycans, minerals and fibrous proteins collections which fill the spaces between cells and surrounding tissues (4). Moreover, to complete the invadopodia function, it has to go through several initiation stages, including adhesion of cancer cells to ECM, degradation of ECM molecules, expansion, and footing of invasive cell into ECM. Finally, the cell body moves through the consequential space within the ECM, and migrates into the blood flow (23,24).

The mechanical initiation of invadopodia could be divided into four steps. First, during the early initiation phase, the invadopodia precursors are non-degradable (75). During the second phase, these precursors are motile, and move around the ventral membrane. The third and fourth steps involve the maturation of the invadopodia. In the third step, the activation of the actin polymerization, stimulation by the NHE-1 cofilin pathway, and the actin polymerization, continues to drive the invadopodia elongation. In the fourth step, microtubules and intermediate filaments are recruited to degrade the ECM using metalloproteinase proteins (25). Thus, targeting invadopodia helps reduce cancer metastasis (26).

INVADOPODIA FORMATION AS A POTENTIAL PROGNOSTIC MARKER FOR METASTASIS

Highly invasive tumour cells have the ability to invade the surrounding tissues through invadopodia via intravasation and extravasation. Intravasation and extravasation are one of several metastasis events which initiate the release of cancer cells through ECM, into and out of lymphatic and blood vessels. Therefore, metastatic cascade is highly associated with invadopodia formation (4,101). Primary tumour cells obtained from cases which displayed malignant tumours have been shown the ability to form invadopodia (27). Invadopodia markers such as actin, cortactin and MMPs proteins were present in the primary cancer cells when they were cultured via in-vitro on the gelatine coated coverslip by determining the gelatine degradation (27). Thus, in-vitro invadopodia formation and ECM degradation assays can be used together as a prognostic indicator for invasive tumours in patient's biopsies (28). In this literature work, we propose the use of invadopodia formation as a tool for predicting the response of cancer cell lines for phytotherapy or chemotherapy, as well as to investigate of the cancer invasiveness in malignant cancer patients via in-vitro.

MECHANISMS OF HYPOXIA AND ITS ROLE IN METASTASIS

Hypoxia occurs during the early phase of cancer metastasis. It promotes invasion and angiogenesis (29). The level of oxygen in the tumour tissue should be less than 5 - 10 mmHg for it to be considered as hypoxia in human tissues. However, the level of oxygen is typically low due to the exponential cellular growth and inadequate vascular supply (30). Thus, the metabolic activity of cancer cells in hypoxia rely on glycolysis to generate energy (31). This helps hypoxic cancer cells to increase their invasiveness. Studies have found that hypoxia exist in several cancer types, including breast, brain and cervical cancers (32). Previous studies have supported the fact that the molecular key in hypoxia is HIF-1α, which plays a fundamental role in interceding the survival of cancer cells (33). On the other hand, in normoxia, HIF-1α is typically hydroxylated by prolyl hydroxylases (PHDs) that demand O2 molecules to function as a substrate. The Von Hippel-Lindau (VHL) is part of the E3 ubiquitin ligase complex which helps to regulate the proteasome pathway to degrade HIF-1α (34). Therefore, HIF-1α is highly expressive under hypoxic conditions since PHDs and VHLs are

inhibited (Figure 1). Thereafter, HIF-1α translocate to a nucleus to alter major genes which regulate survival, metastasis, angiogenesis and invasion (35,36). Data from various studies have shown that hypoxia is resistant to radiotherapy and chemotherapy. Some of the chemotherapy drugs known to be resistant to hypoxia include sorafenib, adriamycin, gemcitabine, 5-fluorouracil, cisplatin, and 6-thioguanine (37). These drugs were tested in cell lines, which included HepG2, BEL-7402, and SMMC-7721 (37). At present, hypoxia is recognized as a highly influential factor in terms of solid tumor treatment (38). Moreover, hypoxia increases the aggressiveness of cancer cells due to the instability of genes which regulate HIF-1α and increase the glycolysis pathways, such as GLUT1 and GLUT3 (39). Thus, the synthesis of drugs which is non-resistant under hypoxic conditions may give an opportunity for the treatment of hypoxic tumors (40,41).

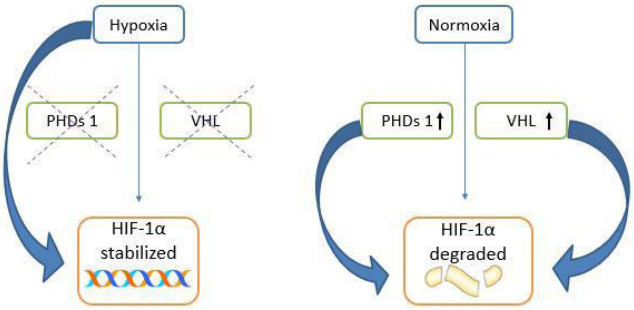

Figure 1: Mechanism of HIF-1α in the hypoxic tumor cells. HIF-1α enables tumor progression after translocation into the nucleus in hypoxic condition by inducing alternative metabolic pathways within cancer cells. The possible therapeutic intervention goal is hydroxylation that leads to HIF-1α degradation binding.

Possibility of phytochemical use for cancer prevention

Recently, Phytochemicals have been used to prevent cancer formation or development. Previous reports have exhibited that phytochemicals containing phenolic compounds, such as phenolic acids, flavonoids, tannins, curcuminoids, coumarins and quinones have the capability to prevent cancer progression. This can be achieved through inhibition of metastasis processes, such as the proliferation of cell regulators, including Erk1/2 and angiogenic factors, including VEGF, FGFR1 and MIC-1. Invasion and migration regulators include MMPs, β-PIX, F-actin, Cortactin, Arp2/3, and N-WASP (70,71). The antioxidant potential of the phytochemical compound is well-thought-out in the treatment and prevention of cancer (72). Previous reports have suggested that phenolic compounds directly affect the cell regulation cycle. The studies also concluded that regular utilization of natural foods which have suitable phenolics, may be useful for cancer prevention (73,74).

The potential role of phytochemicals in cancer therapy

Phytochemicals are a group of bioactive compounds that are metabolically formed and synthesized in plants. Recently, considerable attention has been drawn toward the roles of phytochemicals against hallmark diseases such as bacterial infections and inflammation (42). Numerous studies have proposed the use of phytochemicals as complementary drugs to treat several types of cancer (43). In addition, chemoprevention through the use of phytochemicals is much more cost efficient, safer and non-toxic when compared to chemotherapy (43). Furthermore, pharmacological mechanism studies on natural products have shown that phytochemicals do not only show beneficial bioactivities for treatment of inflammation and antioxidation, but also target multiple cancer-related processes (44). For example, cancer cell invasion and proliferation in MDA-MB231, MCF-7 and BT-483 breast cancer cells can be suppressed using curcumin, a phytochemical compound which is extracted from turmeric. It targets NF-kB and MMP-1 (45). In addition, when H460 and A549 lung cancer cells were treated using the same compound, apoptosis was increased, and metastasis progression which targeted ROS, MMP9, Nox2 and ATF2 was decreased (46,47). On the other hand, resveratrol which is a part of the polyphenol compound group, successfully suppressed ROS-induced migration and proliferation via inhibition of NFkB, ERK and E-cadherin in PANC1 and BxPC3 pancreatic cancer cells (48). In addition, resveratrol inhibited the survival of cancer cells by targeting angiogenesis in breast cancer cells (49). Several examples of phytochemicals which have displayed a molecular effect against a variety of cancer types are shown in Table I. Thus, phytochemicals are a promising alternative in cancer therapy measures. Several phytochemicals have low solubility and stability, which limit their application for such treatment. Therefore, recent studies have sought the use of nanoparticles from phytochemicals in order to increase the solubility and stability of the compounds, besides enhancing their cellular uptake in in-vitro and in-vivo modules (43,49,50).

THE PROSPECTIVE APPROACH TO TARGET INVADOPODIA IN HYPOXIC CELLS VIA PHYTOTHERAPY

During cancer invasion, invadopodia formation increased with HIF-1α expression in hypoxia. Several reports have indicated that HIF-1α expressions increased the number of cells formed with invadopodia, which was treated with dimethyl-oxaloylglycine (DMOG) (7). DMOG is a chemical inducer which is widely used to mimic hypoxia. In addition, DMOG helped to quickly stabilize HIF-1α levels. It not only exhibited invadopodia-forming activities, but also increased the gelatine degradation in MDA-MB-231 cells by increasing the protrusion numbers in each cell (Figure 2) (7,51). Many studies have demonstrated that the molecular components of invadopodia, such as metalloproteinases (MMPs) in membrane type 1 matrix metalloproteinase (MT1-MMP), and matrix metalloproteinase-2 (MMP2) will increase upon exposure to hypoxia in MDA-MB231 breast cancer cells (52,53). Recent studies have shown that

Table I: Potential phytochemicals obtained from medicinal plants against various types of cancer

Name of the plant	Compound name	Study type	Molecular target	Reference
Chrysanthemum morifolium	Luteolin	*In-vitro*	Inhibited VEGF production and it's receptor's activity.	(102)
Rabdosia rubescens	Oridonin	*In-vitro*	Induced apoptosis, displayed anti-proliferation and anti-angiogenesis properties across various cancer types.	(103)
Ligustrum lucidum, Sambucus chinensis	Ursolic acid	*In-vitro*	Activated the apoptosis via ROCK/PTEN in the LNCaP human prostate cancer cells.	(104)
Panax Ginseng	Ginsenoside Rh2	*In-vitro & in-vivo*	Inhibited cancer cell growth and survival.	(105)
Sinomenium acutum	Sinomenin	*In-vitro*	Suppressed cell proliferation and migration in breast cancer cells.	(106)
Coptidis Rhizoma, Coptis japonica	Berberine	*In-vitro & in-vivo*	Induced apoptosis via the AMPK-p53 pathway in breast cancer cells.	(107)
Epimedium brrvicornum	Icariin	*In-vitro*	Decreased migration and viability of HCT116 colon cancer cells.	(108)
Allium sativum	Allicin	*In-vitro*	Reduced cell viability and proliferation across various cancer cells.	(109)
Tripterygium wilfodii	Celastrol	*In-vitro*	Displayed anti-angiogenic, anti-metastatic and inti-inflammatory characteristics across different cancer cells.	(110)
Trichosanthes kirilowii	Cucurbitacin D	*In-vitro & in-vivo*	Showed anti-cancer activities via inhibition of the expression of E6, Cycline D1, and CDk4. Also helped induce the protein levels of P21 and P27 in cervical cancer cells.	(111)

invadopodia formation is affected by the high passage number, suggesting that only low passage numbers should be used in order to get accurate results (54). Recent studies have shown that a compound known as 2,6-bis-(4-hydroxy-3-methoxybenzylidine) cyclohexanone, a phytochemical derived from turmeric, helps to reduce invadopodia formation, and significantly lowers the molecular components of invadopodia, such as MT1-MMP, the Rho guanine nucleotide exchange factor 7 known as β-PIX, and MMP-9 in MDA-MB231 cells under normoxic conditions (55). Further phytochemical compounds studied the molecular components of invadopodia, suggested that phytochemicals have the ability to decrease cancer progression (76). Therefore, based on the presented information, by targeting invadopodia formation, this has helped to open an interesting area of research in hypoxic solid tumors using phytochemicals as a synergistic treatment.

INFLUENCE OF PHYTOCHEMICALS ON HIF-1α AND RELATED INVASION SIGNALING PATHWAYS

HIF-1α is a major molecular factor in hypoxia, which regulates the expression of genes involved in many cancer biology properties, including angiogenesis, proliferation, invasion and metabolism (41,56, 57,58). Literally, little information was found, which involves studying the effects of natural compounds on invadopodia formation under hypoxia. Some of studies have shown that neolamellarins extracted from marine sponge Dendrilla Nigra inhibit HIF-1α in T47D human breast cancer cells (59,60). Another study showed that apigenin, a phytochemical compound, belongs to the flavonoids group, which successfully inhibited HIF-1α and vascular endothelial growth factors (VEGF) in PC3-M prostate carcinoma cells (61). VEGF regulated by HIF-1α in hypoxic condition, it induces angiogenesis in tumour hypoxia (61). Furthermore, an active compound used in traditional Chinese medicine called vitexin, was also found to have anti-cancer properties. Vitexin is an apigenin flavone glucoside, found in various medicinal plants and used as an antioxidant, anticancer and anti-inflammatory agent (62). It has been shown to inhibit

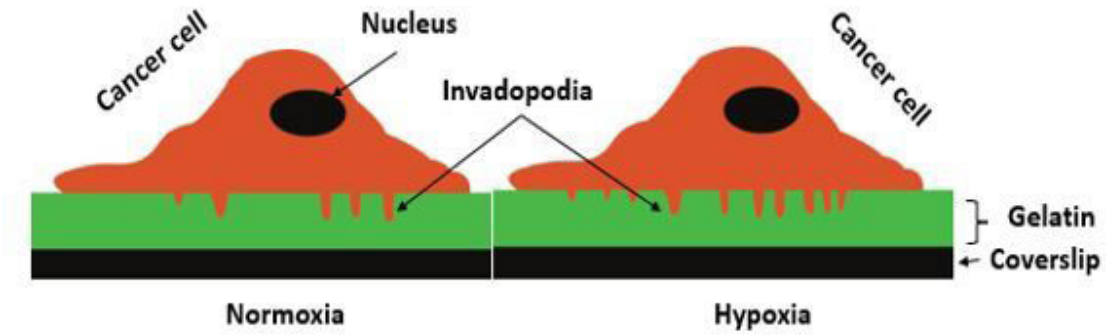

Figure 2: Illustrate cancer cells forming invadopodia in normoxia and hypoxia. The figure shows the number of invadopodia formation in hypoxia is higher than normoxia. This is largely due to the high expression of HIF- 1α in hypoxia that induces many signaling pathways involved in invadopodia.

HIF-1α expressions in PC12 aderenal medulla cells, a tumor adrenal gland of a rat (63). To date, curcumin is one of the most widely studied phytochemicals for treating hypoxic cells. Curcumin is a bright yellow pigment produced from the rhizome of the plant Curcuma longa L., which is widely employed in Asian traditional medicine for treating numerous illnesses such as diabetes, cough, inflammation and tumours (64,65,65). Previous studies have reported the use of curcumin in various kinds of cancer treatments, including colon, pancreatic, breast, and brain, by inhibition of cell invasion, migration and angiogenesis. The effects of curcumin on hypoxic tumour cells have been widely discussed. Curcumin significantly inhibits HIF-1α protein levels by inducing HepG2 hepatocellular carcinoma cells (66,67). Curcumin plays a vital function in suppressing hypoxia-induced invasion, migration and in-vitro proliferation by reducing Hedgehog signalling pathway in pancreatic cancer cells (68). Moreover, curcumin helped prevent hypoxia-stimulated angiogenesis in vascular epithelial cells by reducing HIF-1α and VEGF expressions (69). These studies have suggested that curcumin could be a possible candidate to target hypoxic tumour via inhibition of HIF-1α. We have organized several phytochemical compounds according to their effects on HIF-1α and invasion (invadopodia) related signaling pathways in Table II. Based on the information presented, further investigations are needed on new phytochemical compounds which are able to inhibit HIF-1α at the molecular level, in order to decrease the metastasis.

Table II: Phytochemical compounds inhibit HIF-1α and related signaling pathways of invadopodia formation.

Phytochemical compound	Effects on HIF-1α and cell invsion related signaling pathways	References
Luteolin	Caused inhibition of invadopodia formation and reduced the phosphorylation of cortactin and Src in A431-III cells.	(76)
	Inhibited hypoxia-induced VEGF and HIF-1α expressions in the low micromolar range within NCI-H157 cells.	(77)
Apigenin	Inhibited motility and invasion of PC3-M prostate carcinoma cells by focal adhesion of kinase/Src via signalling mechanisms.	(78)
	Inhibited HIF-1α, GLUT-1 and VEGF mRNA protein expressions in pancreatic cancer cells under hypoxic and normoxic conditions.	(79)
Vitexin	Inhibited HIF-1α, collagen type III and VEGF in PC12 cells.	(63)
Deguelin	Blocked HIF-1α and angiogenesis in lung cancer cells.	(80)
	Inhibited the essential invasion signals, including CD44, MMP2, MMP-9, Rac1 and Rock1 in the mRNA, as well as protein levels in A549 and H460 human lung cancer cell lines.	(81)
Quercetin	Inhibited invadopodia formation and decrement in ECM A431-III cells. May potentially inhibit cancer metastasis via Akt/mTOR/c-Myc signalling pathways in A431-III cells.	(76, 82)
	Induced HIF-1α expressions in hypoxic and normoxic conditions in the human HepG2 hepatoma cells and activated the HIF-1α signalling pathways in human lens epithelial cells.	(83, 84)
Curcumin	Suppressed lung cancer cell line growth via *in-vitro* and *in-vivo* invasiveness through MMP2 and MMP-9.	(85)
	Inhibited HIF-1α in many cell lines including Hep3B hepatoma cells, MCF-7 breast cancer cells, HT29 colon carcinoma, PC3 prostate carcinoma cells, Caki-$_1$ renal carcinoma, H596 lung carcinoma, MDA-MB-231 breast cancer, 1A9 human ovarian cells and xeno-grafted tumours.	(86, 87, 88)
Sodwanones	Inhibited hypoxia-induced HIF-1 activation in T47D breast tumour cells.	(89)
	Effects of Sodwanones on cancer invasiveness was not elucidated.	(90)
Baicalein	Inhibited HIF-1α stability.	(90)
	Suppressed adhesion, migration and invasion of MDA-MB-231 breast cancer cells through down-regulated expressions of MMP-2 and MMP-9.	(91)
Zerumbone	Inhibited CXL12-induced invasion of breast cancer and pancreatic tumour cells.	(92)
	Effects of Zerumbone on HIF-1α is not elucidated.	
Silibinin	Reduced HIF-1α expressions in PCa prostate cancer cells.	(93)
	Inhibited the invasiveness of PC3 prostate cancer cells via integrin signalling.	(94)
Resveratrol	Inhibited breast cancer cells invasion through inactivated Rho/YAP signalling axis and decreased the levels of MMP-2 and MMP-9 in human hepatocarcinoma cells.	(95, 96)
	Reduced HIF-1α and VEGF expressions in human tongue squamous carcinoma cells.	(97)
Anthocyanins	Inhibited cancer invasion through inhibition of MMP-2 expressions in a dose-dependent manner in Hela cervical cancer cells as well as A549 lung carcinoma cells.	(98,99)
	Effects of Anthocyanins on HIF-1α is not elucidated in cancer related research works.	

CONCLUSION

Hypoxic cancer cells pose a unique problem. It brings about an opportunity for the design of therapeutic approaches based on the biological and physiological treatment activities. By targeting HIF-1α, invadopodia and angiogenesis under hypoxic conditions could be an alternative for the treatment of solid tumour using phytochemical compounds. The molecular targets of hypoxia and invadopodia are mostly understood, but the specific treatment that inhibits these targets without harming the healthy cells still needs more investigation. Therefore, studies on the biological activities of phytochemicals which target hypoxia tumours, invadopodia and angiogenesis, may be added to the growing understanding of treatment with regards to phytochemicals in hypoxic tumour cells. In the future, the potential effects of phytochemicals on hypoxia tumours and invadopodia formation, as well as angiogenesis should be considered.

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