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Reassessing vascular endothelial growth factor (VEGF) in anti-angiogenic cancer therapy

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ABSTRACT

Vascularization is fundamental to the growth and spread of tumor cells to distant sites. As a consequence, angiogenesis, the sprouting of new blood vessels from existing ones, is a characteristic trait of cancer. In 1971, Judah Folkman postulated that tumour growth is angiogenesis dependent and that by cutting off blood supply, a neoplastic lesion could be potentially starved into remission. Decades of research have been devoted to understanding the role that vascular endothelial growth factor (VEGF) plays in tumor angiogenesis, and it has been identified as a significant pro-angiogenic factor that is frequently overexpressed within a tumor mass. Today, anti-VEGF drugs such as Sunitinib, Sorafenib, Axitinib, Tanibirumab, and Ramucirumab have been approved for the treatment of advanced and metastatic cancers. However, anti-angiogenic therapy has turned out to be more complex than originally thought. The failure of this therapeutic option calls for a reevaluation of VEGF as the major target in anti-angiogenic cancer therapy. The call for reassessment is based on two rationales: first, tumour blood vessels are abnormal, disorganized, and leaky; this not only prevents optimal drug delivery but it also promotes hypoxia and metastasis; secondly, tumour growth or regrowth might be blood vessel dependent and not angiogenesis dependent as tumour cells can acquire blood vessels via non-angiogenic mechanisms. Therefore, a critical assessment of VEGF, VEGFRs, and their inhibitors could glean newer options such as repurposing anti-VEGF drugs as vascular normalizing agents to enhance drug delivery of immune checkpoint inhibitors.

Introduction

Cancer is a general term used to describe a group of at least a hundred diseases that occur when a series of genetic mutations remove the normal checks on cell cycle stability [1]. Cancer is an important cause of morbidity and mortality worldwide; it is the single most important barrier to increasing life expectancy globally [2]. The global cancer statistics from 191 countries in 2018 showed that cancer is the first or second leading cause of death in 91 countries and the third and fourth leading cause of death in the remaining countries [3]. In 2018, the global cancer burden was estimated to have increased to 18.1 million new cases and 9.6 million deaths. Based on the 2020 GLOBACAN estimates, almost 10 million cancer deaths occurred in 2020, with 19.3 new cancer cases recorded [4]. Female breast cancer has become the most commonly diagnosed cancer globally, surpassing lung cancer [4].

The migration of tumor cells from a clonal origin to distant sites is a major contributor to cancer-associated deaths. It occurs via a series of steps involving: alterations in cell-cell and cell-matrix adhesion; departure from the clonal sites; entry into circulation; and eventually colonization of distant sites [5,6]. The route of transport of tumor cells to distant sites is often via blood vessels [6]. Blood vessels are essential in tumor growth and metastasis; in fact, tumors cannot grow beyond 2-3mm or metastasize unless new blood vessels form [7–9].

The formation of new blood vessels around tumor cells is largely through angiogenesis, the sprouting of new blood vessels from existing ones. Angiogenesis is a tightly regulated process usually initiated during mensural cycles, embryogenesis, tissue growth, and wound healing [10]. However, cancer cells have devised a means of tweaking the

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angiogenic switch to favor the overexpression of pro-angiogenic factors. By initiating the formation of new blood vessels, tumors can access nutrients, oxygen, metabolic wastes and even metastasize to distant sites [7].

Vascular endothelial growth factor (VEGF) is a renowned pro-angiogenic factor upregulated in most cancer cells and has become a major target in most anti-angiogenic cancer therapies. Thus, this review is aimed at assessing anti-VEGF therapies and suggesting future outlooks toward improving the efficacy of anti-angiogenesis cancer therapies.

Tumor angiogenesis

The word 'angiogenesis' is coined from two Greek words, "angêion" (vessel) and "genesis" (birth or emergence). Technically, angiogenesis refers to the branching and extension of existing capillaries. In simple terms, angiogenesis is the sprouting of new blood vessels from existing ones. Although angiogenesis is a normal biological process initiated during embryogenesis, mensural cycles, tissue growth, and wound healing, it is also a hallmark of cancer, ischemia, atherosclerosis, and various inflammatory diseases [10–13].

The relationship between tumor growth and angiogenesis was first described by Judah Folkman in 1971. By definition, tumor angiogenesis refers to the growth of new blood vessels that infiltrate cancerous tumors, supplying the tumor with nutrients and oxygen. According to Folkman, to grow over a few millimeters in size, tumors must initiate the formation of new blood vessels [11]. A substantial body of research over the years has firmly established that solid tumors are "angiogenesis-dependent" [8,11,14].

Angiogenesis is controlled by an equilibrium of naturally occurring proangiogenic and antiangiogenic regulators. In diseased states such as cancer, pro-angiogenic factors often outweigh anti-angiogenic factors, leading to aberrant blood vessel formation. Some of the angiogenic stimulating factors include hypoxia inducing factors (HIFs), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), integrins, and angiopoietin-1, while angiogenic inhibiting factors include transforming growth factor β (TGF-β), angiogenin, angiostatin, thrombospondin, and endostatin [15–20]. Depending on the specific conditions of the tumor microenvironment, TGF-β could act as an anti-angiogenic or pro-angiogenic factor [21–24]. TGF-β stimulates a complex signaling pathway involving both inhibitory and activating Smads; thus, the nature of angiogenic molecules expressed in response to TGF-β [24] is determined by the specific Smad activated.

As tumor size increases, intra-tumoral O_2 levels fall and the center of the mass becomes hypoxic, leading to an up-regulation of the hypoxia-inducible factor (HIF1), which stimulates the expression of pro-angiogenic genes such as VEGF, FGF, IGF, integrins, and extracellular matrix proteins (see Fig. 1) [25,26]. The overexpression of angiogenic stimulating factors and a significant reduction in angiogenic inhibiting factors tilts the angiogenic switch towards a pro-angiogenic state, thus sustaining aberrant tube formation [27].

Vascular endothelium growth factors (VEGF) in the tumor angiogenesis

The vascular endothelial growth factor (VEGF) is the most potent inducer of neovasculature, and its increased expression is associated with worse clinical outcomes in many diseases [28,29]. VEGFs and their receptors (VEGFRs) are involved in the regulation of both vasculogenesis (embryonic blood vessel formation) and angiogenesis [30]. The increased expression of VEGF mRNA has been detected in a variety of tumors; this often serves as an important prognostic marker in cancer patients [29].

VEGF is a signal protein known as a diffusible endothelial cell-specific mitogen. It is a member of the VEGF/PDGF superfamily of hormones and signaling molecules, which includes VEGFs, PDGFs, and TGF [31]. Amino acid analysis of the VEGFs shows that they all share the highly conserved VEGF homology domain (VHD), which contains: binding sites for their receptors (VEGFR); the cysteine knot motif composed of eight characteristically spaced cysteine residues; as well as heparin and neuropilin (NP) binding sites [32]. VEGF proteins are the products of a gene whose promoter contains a hypoxic-response element (HRE); this HRE binds to the hypoxia-inducible factor-1α (HIF-1α), transcription factor when conditions are hypoxic [32,33]. Alternative splicing of the VEGF gene produces four different human isoforms: VEGF121, VEGF165, VEGF189, and VEGF206- containing varying lengths of amino acids [34]. To date, five VEGF members have been identified in mammals, namely, VEGF-A, -B, -C, -D, and Placenta growth factor (PIGF) [34].

The expression of VEGFs genes and their associated receptors is dramatically upregulated in a hypoxic microenvironment. Hypoxia allows the stabilization of HIF-1α which binds to the hypoxia response element, present in the promoter region of the VEGF gene [35].

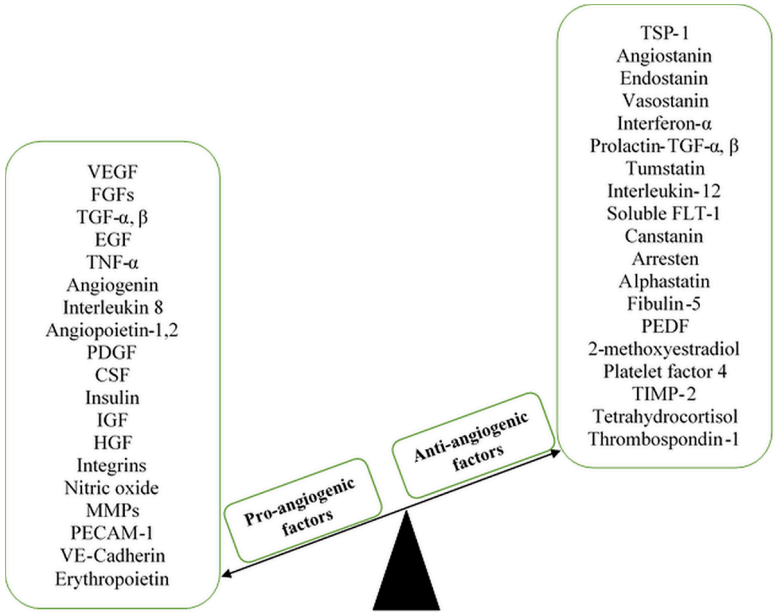

Fig. 1. Pro- and anti-angiogenic factors.

Interestingly, in response to a lack of nutrients, VEGF can be induced independently of HIFs via the induction of peroxisome proliferator-activated receptor gamma coactivator-1a (PGC-1a), a potent metabolic sensor and regulator. Aside from oxygen tension and lack of nutrients, several growth factors, including EGF, TGF-α, TGF-β, keratinocytes growth factor, IGF-1, FGF, and PDGF, upregulate VEGF mRNA expression [36]. Furthermore, cytokines, oncogenes, and hormones have also been reported to induce VEGF expression [37].

VEGF receptors

The VEGF receptors (VEGFRs) are members of the type III transmembrane tyrosine kinases (TKs) superfamily of receptors; they are in the same subclass as PDGFR and FGFR receptors. They consist of an extracellular domain, a transmembrane domain, and a cytoplasmic domain [38]. There are three VEGF receptors, VEGFR-1, 2, and 3. VEGFR-1 and VEGFR-2 are primarily found on vascular endothelial cells, whereas VEGFR-3 is mostly found on lymphatic endothelial cells. VEGF-A binds to both VEGFR-1 and VEGFR-2, whereas VEGF-B and PIGF are selective ligands for VEGFR-1. VEGF-C and VEGF-D are the only known ligands for VEGFR-3 but can also bind VEGFR-2 [39]. In other words, VEGF-A, -B, and PIGF exert angiogenic activities, while VEGF-C and -D are mainly involved in the formation of lymphatic vessels by activating VEGFR-3 [40].

VEGF signaling and regulation

VEGF-A expression is up-regulated during embryogenesis and becomes down-regulated afterwards, but both VEGF-A and VEGFR-2 become upregulated again in settings of physiological and pathological angiogenesis [41]. VEGF-A signaling through VEGFR-2 is the major pathway that activates angiogenesis via the induction of endothelial cell proliferation, survival, sprouting and migration; it also increases endothelial permeability [30,42].

As shown in Fig. 2, when VEGF-A binds to the VEGFR-2 receptor, dimerization of the receptors occurs, resulting in kinase activation and auto-phosphorylation of tyrosine residues [43]. Phosphorylation of these residues leads to the activation of phospholipase C (PLC), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), Ras, Src, and mitogen-activated protein kinases (MAPK). This cascade of events subsequently stimulates the release of Ca^{2+} from internal stores, thus leading to the activation of protein kinase C (PKC). Activation of PKC stimulates the Raf/MEK/ERK pathway, which promotes cell proliferation and vascular permeability via activation of endothelial nitric oxide synthase activity [43].

Ligand binding to VEGFR-2 also triggers the activation of the Ras pathway, via the activity of Grb2, an adaptor protein which binds pTyr1214 on VEGFR-2; RAS activation intensifies vascular tube formation via VEGF biological responses such as cell proliferation, survival, migration, and endothelial cell arrangement [44].

VEGF as a target in anti-angiogenic therapy

Folkman proposed in 1971 that tumor growth and metastasis are angiogenesis-dependent, and he later proposed that inhibiting angiogenesis could stop cancer progression. According to him, targeting the tumor vasculature may be a more effective strategy than targeting the tumor itself for several reasons. Firstly, cancer is a relatively large collection of heterogeneous diseases. As such, a single chemotherapeutic agent cannot effectively treat cancer, but a therapeutic agent that can effectively inhibit angiogenesis is likely to be effective against a larger subset of the disease. Secondly, cancer cells continually accumulate genomic aberrations. Therefore, chemotherapeutics might not be able to effectively inhibit the gene products aberrantly expressed at a particular stage of cancer. Thirdly, anti-angiogenic drugs will be less likely to have adverse side effects such as bone marrow suppression, gastrointestinal symptoms, or hair loss since angiogenic endothelial cells express specific cell-surface proteins that are absent in endothelial or other cells.

Biochemical targeting of tumor vasculature involves the biochemical targeting of VEGF, which has been a major target in this therapy owing to its unique potency and selectivity for vascular endothelium [11,45]. VEGF is also the only recognized angiogenic factor that renders micro-vessels hyper-permeable to circulating macromolecules. VEGF is the central positive regulator of vasculogenesis, angiogenesis and lymphangiogenesis, and it is expressed in almost every type of human tumor, especially in hypoxic regions of tumors and in blood vessels

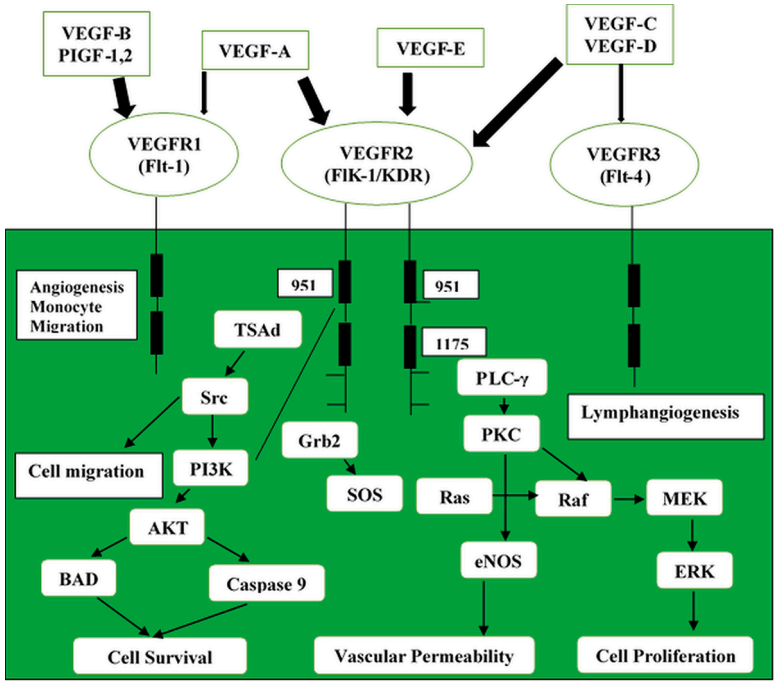

Fig. 2. VEGF signaling pathway.

within or near tumors [46]. The list of some approved and investigational anti-VEGF agents and their mechanisms of action are shown in Table 1 and Fig. 3.

VEGF/VEGFR inhibitors

Small molecule VEGFRs inhibitors

Over time, small molecule inhibitors that limit the intrinsic tyrosine kinase activity of VEGFRs have been discovered. These small molecules, some of which include: 3-substituted indolinone compound (SU5416), sorafenib, sunitinib, pazopanib, tivozanib, axitinib, and cediranib, have been used to treat lung, breast, gastric, liver, and renal cancers [47–54]. Extensive experimental studies on VEGFR inhibitors have shown that small molecules are capable of slowing the growth of primary tumors [53]. However, these small molecule inhibitors may not be selective as a wide range of kinases that are not VEGFRs could be inhibited, resulting in adverse effects such as hypertension, hepatotoxicity, hyperglycemia, thrombocytopenia, proteinuria, and diarrhea [52,47].

Oligonucleotides

Antisense oligonucleotides are therapeutic agents that specifically bind to target RNA to influence the expression of the VEGF genes and have also been employed in the angiogenic targeting of tumors. These synthetic nucleic acid sequences are short and single-stranded; they elicit their therapeutic effect by annealing to DNA or RNA targets while obeying the rules of the Watson and Crick model. Although the use of antisense oligonucleotides in cancer treatment seems like a promising strategy, to date, no antisense nucleotide has been clinically approved for cancer treatment. Most of the antisense nucleotides that have gone into clinical trials for cancer treatments have been terminated for numerous reasons, some of which include poor cellular uptake, rapid renal clearance, nephrotoxicity, thrombocytopenia, and liver damage [65].

Monoclonal antibodies

The therapeutic targeting of VEGF within the tumor microenvironment was initially demonstrated by using bevacizumab, a VEGF-A specific monoclonal antibody, which helped regress tumor growth by reducing the density of tumor blood vessels [68]. Ramucirumab is another potent humanized monoclonal antibody used in the treatment of gastric, breast, and advanced non-small-cell lung cancer; it works against VEGFR2 by normalizing tumor blood vessels [59]. Anti-VEGF antibodies like Bevacizumab and Aflibercept elicit their anti-angiogenic functions by blocking or reducing the amount of available extracellular VEGF that may activate the VEGF-receptor (VEGFR) system [61,63].

Experimental screening of anti-VEGF agents for anti-cancer properties

Vascular endothelial growth factors and their receptors are overexpressed in most solid tumors, inducing endothelial cell proliferation and migration, leading to the formation of new blood vessels from preexisting ones [69]. Consequently, VEGF and its receptor represent suitable predominant targets for anti-angiogenic drugs. Anti-VEGF therapies are considered alternatives or adjuncts to conventional chemo or radiation therapy. VEGF inhibitors are employed in various cancer therapies, including non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), breast cancer, cervical cancer, esophageal cancer, colorectal cancer, esophageal cancer, and glioblastoma multiforme.

In a report by Yang et al. [70], thymosin alpha-1 was shown to possess an anti-tumor effect in the treatment of NSCLC. The peptide (thymosin alpha-1), usually isolated from the thymus, suppressed the production of VEGF through the downregulation of hypoxia-inducible factor (HIF)-1α in tumor cells. As a result, it enhanced the apoptosis of monocytic myeloid-derived suppressor cells (M-MDSCs), which promote tumor growth and treatment resistance, by reducing the B-cell lymphoma 2/Bcl-2-associated X protein (Bcl-2/BAX) ratio and more significantly blocked the migration of MDSCs to the tumor microenvironment. Several therapeutic measures targeting the VEGF/VEGF

Table 1
Approved and investigational VEGF/VEGFRs inhibitors.

VEGF/VEGFRs inhibitors	Drugs	Targets	Therapeutic use	Status in drug development	Ref
Small molecule VEGFR inhibitors	Sunitinib	VEGFR-1,2,3, PGDFR-α and β	Advanced Renal carcinoma, Meninginoma, Pancreatic cancer	Approved	[47, 48]
	Pazopanib	VEGFR-1,2,3, PGDFR-α	Soft tissue sarcoma, Advanced Renal carcinoma	Approved	[47, 49]
	Foretinib	VEGFR-2, and 3, Tie-2	Head/Neck Cancers, Gastric Cancers	Clinical trials	[50]
	Sorafenib	VEGFR-1,2,3, PGDFR-β	Solid tumours	Approved	[51, 47]
	Tivozanib	VEGFR-1,2,3	Advanced Renal carcinoma	Clinical trials	[52]
	Anlotinib	VEGFR-2,3, EGFR, PDGFR-α	Advanced Renal carcinoma	Clinical trials	[53]
	Axitinib	VEGFR-1,2,3	Advanced Renal carcinoma, colorectal cancer, stroma cancer, breast cancer	Approved	[47, 54]
	Golvatinib	VEGFR-2	Head/Neck cancer, Liver cancer, Hepatocellular carcinoma	Clinical trials	[55, 56]
Monoclonal Antibodies	Fresolimumab	TGF-β-1,2,3	Malignant melanoma, Renal cancer	Approved	[57]
	Trastuzumab	HER-2	Breast cancer	Approved	[58]
	Ramucirumab	VEGFR-2	Advanced renal carcinoma, liver cancer, thyroid carcinoma, advanced gastric cancer	Approved	[59, 60]
	Tanibirumab	EGFR	Recurrent glioblastoma	Approved	[61]
	Sym004	VEGF-A	Metastatic colorectal cancer	Clinical trials	[62]
	Bevacizumab	VEGF-A	Metastatic colorectal cancer	Approved	[63]
	Aflibercept	VEGF-A, B	Colorectal cancer	Approved	[61]
	Sevacizumab	VEGFA	Colorectal cancer	Clinical trials	[64]
Anti-sense oligonucleotide	BB-401	EGFR	Recurrent/metastatic head/neck cancer	Clinical trials	[65]
	Veglin	VEFGR, PDGFR	Kaposi sarcoma, renal cancer	Terminated at clinical trials	[66]
	AP-12009	TGF-β2	Recurrent glioma, advanced pancreatic carcinoma, metastatic melanoma	Terminated at clinical trials	[66, 67]

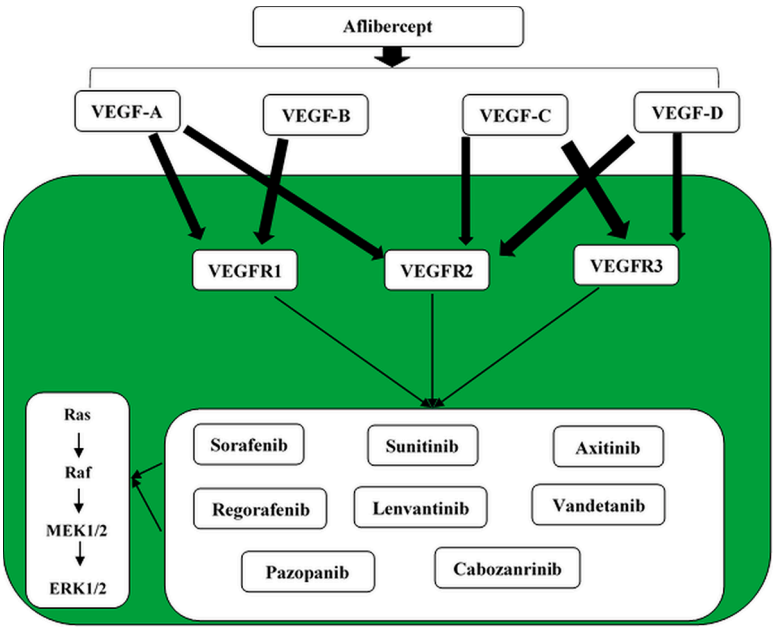

Fig. 3. Anti-VEGF drugs and their protein targets.

receptor pathway, including tyrosine kinase inhibitors (TKIs) sunitinib, tivozanib, cabozantinib, pazopanib, and axitinib, have been approved for use in RCC therapy, but bevacizumab is the most extensively used and characterized anti-angiogenesis drug [69,71]. These anti-VEGF drugs can either be used alone or in combination with chemotherapy and other targeted therapies.

Tocilizumab, an interleukin-6 (IL-6) blocker, has also been demonstrated in vitro to decrease the growth of RCC by repressing the expression of VEGF [72]. Administration of nanoparticulated bevacizumab in glioblastoma multiforme treatment has been shown to obstruct neo-vascularization in glioblastoma carcinogenesis by suppressing intratumoral VEGF secretion [73]. Another instance where VEGF was targeted in oncotherapy is the use of MicroRNA-628-5p (MiR–628–5p), a non-coding ssRNA that is encoded by an endogenous gene and is primarily connected with the post-transcriptional regulation of gene expression, in cervical cancer treatment. MicroRNA-628-5p was reported to inhibit the proliferation of cervical cancer cells and promote apoptosis by targeting and regulating VEGF [74].

In another report, pretreatment with baicalin, an anti-VEGF flavone glycoside, alone and in combined treatment with the anti-metabolite fluorouracil (5-FU), was demonstrated to significantly reduce inflammation and angiogenesis by suppressing NF-kB/IL-1β and VEGF amplification loop with a substantial increase in apoptosis; this was shown by overexpression of BAX, apoptotic caspase-3, pro-apoptotic p53 and downregulation of anti-apoptotic Bcl-2 [75]. Fluorouracil has also been shown to inhibit angiogenesis by suppressing VEGF mRNA expression and protein in MDA-MB-231 cells as well as VEGF mRNA levels in MDA-MB-468 cells [76,77]. Additionally, ethanolic extract of Amomum tsaoko fruit has been shown to inhibit ovarian cancer and repress angiogenesis by inhibiting the cascade amplification loop of p-STAT3/NF-kB/IL-6 and VEGF in vivo [78]. Furthermore, apigenin has also been used to modulate several carcinogenesis pathways in esophageal cancer cells. The findings of Qiu et al. [79] showed that the flavone, apigenin, inhibited esophageal carcinogenesis by suppressing tumor angiogenesis through regulation of the HIF-1/VEGF signaling pathway.

Anti-VEGF agents in medical oncology

Bevacizumab was clinically approved for the treatment of metastatic colorectal cancer in the United States and the United Kingdom in 2004 and 2005, respectively. Today, bevacizumab is a frontline drug in the treatment of a broad range of cancers, including: CRC, breast cancer (BC), NSCLC, renal cell carcinoma (RCC), anaplastic lymphoma (AL), non-squamous NSCLC, glioblastoma (GBM), cervical cancer (CC), and fallopian tube cancer (FTC) [80]. Unfortunately, bevacizumab has not been successfully used in monotherapy as most of the patients treated with this anti-VEGF drug eventually re-establish angiogenesis regardless of VEGF-A blockade [81]. For better efficacy, bevacizumab is combined with standard chemotherapeutic drugs like carboplatin and paclitaxel for the treatment of advanced ovarian cancer [82,83]. A clinical trial conducted by Daniele et al. [84] on ovarian cancer patients showed that the combination of bevacizumab with carboplatin and paclitaxel gave a median PFS and OS of 20.8 and 41.1 months, respectively.

Ramucirumab is an FDA-approved anti-VEGF agent used in the treatment of gastric cancer. Because it inhibits all forms of VEGFs, it has shown better clinical outcomes than bevacizumab in the treatment of gastric cancer [85]. In the RAINBOW and REGARD clinical trials conducted by Wilke et al. [86] and Fuchs et al. [87] respectively, ramucirumab as a monotherapy or combined therapy significantly reduced disease progression and death in gastric cancer patients. The RAINBOW-Asia and RAINFALL clinical trials conducted by Xu et al. [88] and Fuchs et al. [89] also revealed that combining ramucirumab and chemotherapeutic regimens such as paclitaxel and fluoropyrimidine and cisplatin, increases the PFS and OS of gastric cancer patients. However, the addition of ramucirumab to the patients' treatment plan also manifested adverse reactions such as hypertension, neutropenia, gastric hemorrhage, acute kidney damage, septic shock, sudden death, and pneumothorax [89].

Shortcomings of anti-VEGF therapies

Although tumor growth inhibition has been demonstrated in animal studies using small molecule inhibitors, humanized antibodies, and other anti-angiogenic agents; clinical trials have been faced with cases of relapse and drug resistance [90]. This anti-VEGF agent often works best when in combination with other anti-cancer agents. For instance, bevacizumab and other anti-VEGF-A/VEGFR drugs prolong the lives of patients with advanced colon cancer by only 4–5 months, but only when accompanied by chemotherapy [91]. Patients on anti-VEGF therapies

are often frail and sick due to the toxicities associated with high doses of VEGF inhibitors. Anti-VEGF drugs such as Vatalanib, Cediranib, and sunitinib have been shown to increase tumor size, stimulate over-expression of VEGF and its receptors, HIF-, angiopoietin-1, EGFR, and PDGFR, and stimulate migration of CD64+, myeloid cells, and CD133+ cells into the tumor microenvironment [92,93].

One of the possible reasons for the limited effectiveness of anti-VEGF/VEGR therapy could be that anti-VEGF agents do not kill all tumor cells at once; as such, residual tumor cells are rendered hypoxic by a compromised blood supply, which may stimulate increased expression of VEGF and thus overwhelm the anti-VEGF/VEGFR agents used in cancer therapy [94]. Hypoxia plays an important role in tumor resistance to chemotherapeutic agents, favoring more aggressive metastatic disease and hence worse prognosis. HIF-1 plays a critical role in resistance to anti-angiogenic therapy and is the main survival factor used by cancer cells to adapt to oxygen deprivation. Hypoxic tumor cells could facilitate the overexpression of other growth factors, which can substitute VEGF and stimulate the formation of new blood vessels [95,96]. Some of these mechanisms that are likely to be influenced by hypoxia include the production of alternative pro-angiogenic factors, the recruitment of BM-derived cells, vasculogenic mimicry, as well as the increased tumor cell invasiveness and metastatic behavior [97,98].

According to Hanahan and Weinberg [99], in response to mechanism-based targeted therapy, cancer cells may reduce their dependence on a particular capability and become more dependent on another capability, which often results in poor treatment outcomes. A tumor could outwit the effect of VEGF-A inhibitors by stimulating the hyper-production of VEGFs or by switching to an alternative ligand or receptor. For instance, tumors can upregulate VEGF-C or D rather than VEGF-A, which could activate VEGFR-2 [100]. This implies that cancer cells could reduce their dependence on a particular isoform of VEGF after exposure to certain VEGF inhibitors.

Preclinical studies targeting angiogenesis in cancer cells have also revealed that; although potent anti-angiogenic agents could suppress the neovascularization-inducing potential of tumor cells, these transformed cells often adapt and shift from dependence on new blood vessel formation to heightened invasiveness and metastasis [95,101,102]. Also, as tumors grow, they produce a wider variety of angiogenic activators. Therefore, if only one activator, in this instance, VEGF, is blocked, tumors may utilize or up-regulate another activator such as FGF, TGF, or IGF. Also, there is micro-vascular heterogeneity in tumors, which implies that different pro-angiogenic factors could stimulate blood vessel formation within the same subpopulation of tumor cells. As such, a pharmaceutical agent targeting a particular pro-angiogenic factor may not effectively inhibit or regress blood vessel vascularization.

Since VEGF is involved in the normal functioning of several organs, including the liver and kidney, there is a possibility that the administration of anti-VEGF agents can subsequently lead to some clinical complications in patients receiving these medications. Some of these complications include proteinuria, complications in wound healing, cardiac complications, renal dysfunction, gastrointestinal perforations and foot syndrome, clots in arteries, fatigue and hypertension [103–105]. For instance, bevacizumab causes a dose-dependent increase in the blood pressure of cancer patients, furthermore, it is associated with abdominal pain, fatigue, diarrhea, gastrointestinal perforations, hemorrhage, and arterial thromboembolism [80,106].

Cabozantinib, an oral tyrosine kinase inhibitor approved for the treatment of RCC, works by inhibiting the VEGFR, the mesenchymal-epithelial transition receptor (MET), and the anexelekto receptor kinase receptor (AXL), all of which have been linked to RCC metastasis and drug resistance [107,108]. Cabozanitinib also targets other angiogenesis-associated tyrosine kinases, including FMS-related tyrosine kinase 3 (FLT3) and stem cell growth factor receptor (KIT) [109,110]. The ability of cabozantinib to target multiple pathways helps to halt proliferation and metastatic escape and overcome therapeutic resistance associated with treatment using drugs like sunitinib [109,111]. A long-term clinical trial conducted by Motzer et al [108] revealed that RCC patients orally administered 60 mg/kg of cabozantinib had significantly higher survival rates than patients administered 10 mg/kg of everolimus, an mTOR kinase inhibitor. Cabozanitinib also outperformed suntinib in terms of progression-free survival in patients with metastatic RCC [107]. Cabozanitinib has also been effectively treated in patients with advanced non-clear renal cell carcinoma [112], non-small lung cancer [110], advanced medullary thyroid cancer with bone metastasis [113] and advanced hepatocellular carcinoma [114,115].

Vandetanib is a clinically active anti-VEGF oral drug that also targets other tyrosine kinases like RET and EGFR. Vandetanib has effectively increased progressive-free survival time (29.4 months) and a high objective response rate in patients with advanced, symptomatic or metastatic medullary thyroid cancer [116,117]. Vandetsnib has also been clinically explored in the treatment of non-small cell lung cancer and was reported to have a PFS of 6.5 months as determined by an independent radiology review committee [118,119].

Ponatinib is another clinically active multiple kinase inhibitor that targets a variety of tyrosine kinases such as VEGFR, EGFR, FGFR, PDGFR, SRC, RET, KIT, and FLT1 [120,121]. It is efficacious in treating resistant forms of leukemia and also has a high tolerability in patients [120,121]. A five-year follow-up of the PACE trial conducted by, indicates that ponatinib was able to achieve a major cytogenetic response (MCyR) in 56% of the patients with Philadelphia chromosome-positive leukemia within 12 months. The study also revealed that the patients have an 82% chance of maintaining MCyR for 5 years [121].

However, cabozanitib and vandetanib elicit adverse effects such as diarrhea, tiredness, stomatitis, hypertension, nausea, rashes, loss of appetite, weight loss, and palmar-plantar [107,109,122]. A clinical trial on advanced MTC patients also reported incidences of renal failure, health failure, cholecystitis, acute pancreatitis, posterior encephalopathy, and skin cancer following prolonged (48-month) treatment with vandetanib [123]. Some CP-CML patients treated with ponatinib also showed symptoms such as: dry skin, thrombocytopenia, constipation, abdominal pain, headache, chest pain, anemia, pneumonia, pancreatitis, and atrial fibrillation [120].

Reassessing anti-VEGF therapies is cancer treatment

The fact that anti-VEGF/VEGF therapies often work better in animal models than in cancer patients, calls for a reevaluation of VEGF as the primary target in anti-angiogenic cancer therapies. According to Sitohy et al. [124], to optimize antiangiogenic therapies, we must be able to fully elucidate: if tumor growth is angiogenesis-dependent or blood vessel-dependent; the nature of tumor blood vessels and the mechanism through which they are formed; the effect of anti-VEGF/VEGFR agents on tumor and normal blood vessels; and the reasons why anti-VEGF/VEGFR therapies work better in experimental mouse models than in cancer patients.

Understanding tumor blood vessels formation

Unlike normal vessels, tumor blood vessels are abnormal, disorganized, and leaky [125]. The nature of tumor blood vessels could be a contributory factor to the failure of anti-VEGF agents in cancer patients as opposed to the findings recorded in experimental animals. The aberrant nature of tumor blood results in slow blood flow and high interstitial pressure, which makes it difficult for cytostatic drugs to reach the target microenvironment [126]. The high permeability of tumor blood vessels alters blood flow and promotes tumor diffusion into the interstitial space, thus increasing hypoxia and inducing metastasis [14].

Initially, tumor blood vessels were regarded as a "single entity." However, it is now well established that tumor blood vessels are heterogeneous with regards to organization, function, and structure [127]. Other than angiogenesis, tumor cells can acquire blood vessels through mechanisms such as co-opting of existing vessels, vascular mimicry, and postnatal vasculogenesis (see Fig. 4) [125,128,129]. These different mechanisms of tumor vascularization are often present within a tumor

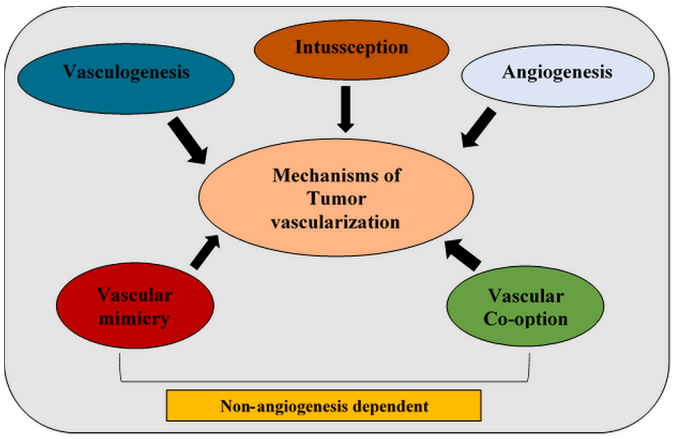

Fig. 4. Mechanisms of tumor blood vessel formation.

mass and can provide an alternative route of vascularization [130].

Vessel co-option is a non-angiogenic process whereby tumor cells directly utilize the pre-existing vasculature of the non-malignant tissue that they colonize. This strategy provides oxygen and nutrients for efficient tumor outgrowth. It was first described in brain tumors arising from the well-vascularized brain parenchyma. During vessel co-option, cancer cells migrate along the abluminal surface of pre-existing vessels and/or the cancer cells infiltrate the tissue space between pre-existing vessels, ultimately leading to the incorporation of pre-existing vessels into the tumor [97]. For instance, vessel co-option was also observed in gliomas and other cancer types, including lung cancers. It was shown to sustain the growth of cerebral metastases from melanomas, liver metastases from breast cancers, as well as lung metastases from different primaries. Interestingly, vessel co-option is independent of the classic angiogenic switch and doesn't require any angiogenic growth factors. As such, vessel co-opting tumors are usually not sensitive to anti-angiogenic agents [131]. For example, patients with CRC and liver metastases demonstrated a poor response to BVZ therapy due to vessel co-option [97]. In this way, tumors co-opt pre-existing vessels to meet their metabolic demands without needing to stimulate angiogenesis (new vessel growth).

Tumor cells also gain access to blood supplies and nutrients by creating canal-like structures without the involvement of endothelial cells; this is known as vascular mimicry [132]. Vascular mimicry is a major cause of tumor resistance to anti-angiogenesis therapies and has been identified in highly aggressive forms of ovarian, breast, lung, and prostate cancers as well as glioblastomas, soft tissue sarcomas, and melanomas [132–134]. Short-term treatment with the anti-angiogenesis drug bevacizumab reduced tumor growth in ovarian cancer xenografts; however, the treatment increased intratumoral hypoxia, promoting distant tumor metastasis and other adaptive responses such as vascular mimicry formation [135]. Bevacizumab treatment also stimulated the formation of vascular mimicry channels [135]. Another study also reported that the anti-VEGF drugs, atalanib and avastin, conferred anti-angiogenic resistance and vascular mimicry formation by upregulating the expression of interleukin-8 and chemokine receptor 2 in glioblastoma tissues [134].

Re-purposing of anti-VEGF agents in anti-angiogenic therapies

Targeted cancer treatments are designed to inhibit important molecules that drive tumor growth and progression through intrinsic and/or extrinsic biologic mechanisms. The presence of numerous alternative pathways in the in vivo pro-angiogenic signaling network has been attributed to the shortcomings of anti-VEGF therapies [136]. Considering VEGF is a primary promoter of tumor angiogenesis, many anti-angiogenic treatments already in use in the treatment of human cancer are focused on disrupting the VEGF signaling axis [137]. However, the advancement of anti-angiogenic regimens may offer greater effectiveness by combining drugs with diverse mechanisms to produce synergy or by repurposing existing drugs to target alternate mechanisms. Anti-VEGF treatment in murine melanoma synergizes with adoptive T cell transfer by increasing leukocyte access into tumors; low-dose VEGFR2 blockade increases the efficacy of anti-tumor vaccination in breast cancer models by generating M1 macrophages, ameliorating tumor perfusion, and facilitating effector T cell infiltration [138]. Furthermore, in mouse models, Apatinib, an anti-VEGF, also elicits anti-PD-1 functions, thus boosting anti-tumor immunity [139].

Drug repurposing has gained significant popularity as it's cost-effective and enables clinicians to quickly expand the treatment options available to them to treat cancer patients by reducing the time needed for pre-clinical testing. It has been postulated that VEGF should serve as a vascular normalizing or promoting agent and can be used alongside other anti-cancer agents rather than as a standalone therapy [27,126,140-142]. Activation and normalization of tumor vasculature, for example, are not mutually exclusive. Rather, tumor vasculature modification is a dynamic system that can result in many phenotypes concurrently or sequentially. Combining vascular modulation with anti-tumor immune therapies is a reliable approach as long as tumor perfusion is not disrupted.

Vascular normalization or promotion, using antiangiogenic agents, is the process by which partial loss of blood vessel density is associated with a temporary increase in blood flow, which can be exploited for drug delivery of other anti-cancer agents [27]. Aside from tube formation, VEGF is also involved in vascular permeability. Therefore, low doses of anti-VEGF agents can help balance the angiogenic switch, leading to decreased vessel permeability by tightening cell-cell junction [143]. Anti-VEGF agents also improve tumor perfusion by promoting pericyte recruitment to blood vessels via activation of Ang-1/Tie-2 signaling and PDGFR- signaling [144,145].

The leakiness of tumor blood vessels can be reduced using low doses of anti-VEGF agents, which could stimulate tumor perfusion leading to increased oxygen and drug delivery to the tumor mass (see Fig. 5) [146]. Wong and his colleagues demonstrated that low doses of the anti-angiogenic drug cilengitide and verapamil, a Ca^{2+} channel blocker, could help enhance tumor angiogenesis and blood flow, which may help improve the delivery of gemcitabine, a chemotherapeutic agent when

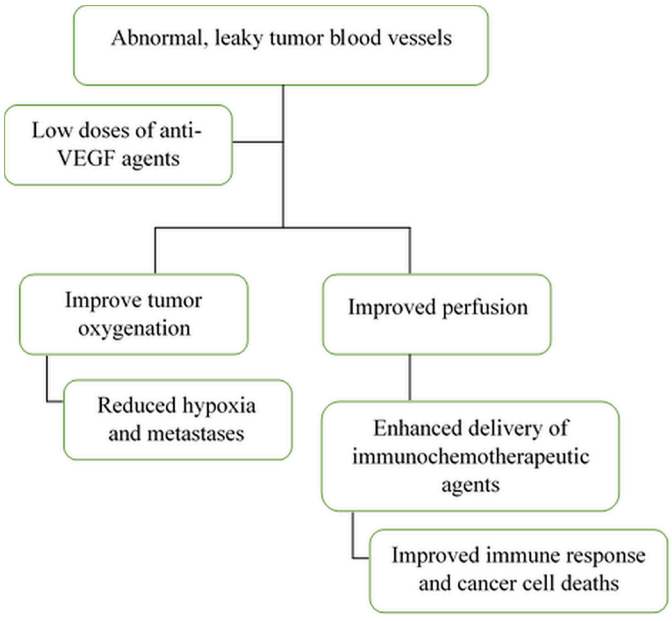

Fig. 5. Schematic representation of the mechanism of vascular normalization cancer therapy.

administered in combination. The triple combination of cilengitide-verpamil-gemcitabine reduced tumor burden and metastases in lung cancer xenograft mouse models [140]. Clinical trials involving the triple combination of immunotherapeutic drug atezolizumab, humanized monoclonal antibody bevacizumab, and chemotherapeutic agents in the treatment of hepatocellular carcinoma and metastatic non-small-cell lung cancer [146,147] support these findings.

A repurposed anti-angiogenic drug was selected and put through clinical testing in non-small cell lung cancer cell lines (NCI-H358, NCI-H1838, NCI-H596, and NCI-H1975). Itraconazole, an antifungal drug, has been found to reduce endothelial cell proliferation and migration, as well as suppress activation of VEGFR2 and FGFR3 *in vitro* and *in vivo*. In a phase II clinical study, itraconazole was used with pemetrexed, a chemotherapeutic medicine, for the management of non-squamous non-small cell lung cancer. Significant differences in overall survival media of 8 months and 32 months were found between the control, pemetrexed monotherapy, and the experimental, pemetrexed and itraconazole combination treatment [148,149]. Furthermore, the two therapies did not differ significantly in terms of toxicity. Furthermore, in metastatic pancreatic cancer, a combination of itraconazole and chemotherapy agents (irinotecan-based) showed promising results (8 percent complete response, 39 percent partial response, 32 percent stable disease, 13 percent progressive disease, and a 47 percent response rate) with minimal side effects [148].

Bevacizumab, an antibody that inhibits VEGF through antibody administration, is one of the most commonly used anti-angiogenic drugs. Yue et al. found that bevacizumab in combination with turmeric ethanolic extract (with absorbable curcumin) had better anticancer effects in HT29 colonic cancer cells than monotherapy. This was due to tumor growth suppression, pro-apoptotic effects, and blood vessel growth inhibition [150]. In a phase 2 open-label randomized study, erlotinib with bevacizumab was utilized as a first-line treatment for patients with advanced non-squamous non-small-cell lung cancer with EGFR mutations. This combination showed promising anticancer efficacy, with all patients' tumors reduced while progression-free survival was maintained and 69 percent of patients showed an objective response, compared to 64 percent of patients in the erlotinib alone group [151]. Efficacy and safety profiles are still being elucidated through the BELIEF (NCT01562028) and ACCRU RC1126 trials, although this combination showed some toxic effects [152].

In a preclinical investigation, researchers found that combining the anti-angiogenic drug pazopanib with the topoisomerase inhibitor oral metronomic topotecan suppressed tumor growth and lower microvessel development in neuroblastoma xenografts, despite partial resistance [153]. Avastin, an anti-angiogenic agent, may also enhance therapeutic regimens by making cancer cells more susceptible to chemotherapy's cytotoxic effects. First, metronomic treatment operates as an anti-angiogenic therapy, promoting hypoxia due to a lack of blood flow to the tumor. Hypoxia stabilizes HIF-1α, which trans activates genes like VEGF. However, because Avastin inhibits VEGF specifically, this combination shows that Avastin makes cancer cells more susceptible to the cytotoxic effects of metronomic treatment [154]. Although this strategy could be a promising mechanism for combating cancer, it is a challenging approach because the efficacy of this therapy relies on a temporal 'window of opportunity' that is both time and dose dependent [155].

Clinical application of the vascular normalization theory

The vascular normalization theory brings a different perspective on the synergistic interactions between anti-VEGF therapies and other therapies such as immune checkpoint inhibition therapy. It has been observed in preclinical and clinical trials that abnormal vessels impede the infiltration of immune cells into the tumor microenvironment via different mechanisms. To begin with, tumor blood vessels lack adhesion molecules such as vasculature cell adhesion molecule-1 (VCAM-1), which impairs T cell extraversion because T cells are unable to adhere to tumor cell endothelium [156,157]. T cells are also unable to effectively overcome the high interstitial fluid pressure required to infiltrate the tumor microenvironment. VEGF overexpression in the tumor environment also impairs dendritic cell function, which is required for tumor cell identification by T cells, allowing tumor cells to evade immune surveillance [157,158]. Lastly, the hypoxic nature of the tumor bed upregulates some inhibitory signals for anti-tumor response proteins such as programmed cell death-ligand 1, indoleamine 2,3-dioxyegenase (IDO), and interleukins-6 and-10 [159,160]. Based on the mathematical model developed by, immune checkpoint inhibition therapy and anti-VEGF therapy possess the strongest synergistic effects against cancer cells [161].

Combination therapy using atezolizumab (PD-Ll inhibitor) and bevacizumab in the treatment of unresectable hepatocellular carcinoma improved PFS in patients (5.6 months) compared to treatment with atezolizumab alone (3.4 months) [162]. Similar findings were also observed in a trial involving the treatment of metastatic RCC with atezolizumab and bevacizumab. Powles et al. [163] reported that the tumor shrank in more than one-quarter of patients treated with atezolizumab and bevacizumab compared with monotherapy with atezolizumab or sunitinib; the side effects were also reported to be manageable. A phase III JAVELIN trial conducted by Choueiri, et al. [164] revealed that combining the PD-L1 inhibitor avelumab with the VEGF inhibitor axitinib in the treatment of sarcomatoid RCC patients significantly improved the PFS and objective response rate of the patients when compared with treatment with sunitinib. The GLIAVAX trial involved the treatment of recurrent glioblastoma using avelumab and axitinib also reported high tolerability compared to treatment with avelumab alone [165,166].

Conclusion

This review highlighted the importance of tumor angiogenesis in tumor growth, metastasis, and drug resistance. Although animal studies have shown that anti-VEGF therapies can reduce tumor blood vessels and shrink tumor size, clinical trial results have been mixed. A critical assessment of tumor vascularization, VEGF and anti-VEGF therapies revealed that the vascular network of tumor cells is heterogeneous, disorganized and hyper permeable. This fact implies that more than one pro-angiogenic factor is involved in tumor angiogenesis. Also, tumor cells can acquire vascular networks via a non-angiogenic mechanism. These challenges and the realization that low doses of anti-angiogenic agents, via the normalization of blood vessels, can help enhance the delivery of chemotherapeutic agents to the tumor, have led to the concept of repurposing anti-VEGF drugs as vascular normalizing agents. Vascular normalization therapy is all about stabilizing tumor blood vessels to improve tumor oxygenation and drug delivery, thus killing tumor cells. The concept of normalization may be a promising strategy in the fight against cancer; however, the 'window of opportunity' during which blood vessels remain normalized is highly time- and dose-dependent. The vascular normalization theory is currently being explored in combination with immune checkpoint inhibitors, and ongoing trials indicate a strong synergy between anti-angiogenesis and immune therapy. Considered together, close collaboration between researchers and physicians across multiple disciplines is key to exploring and optimizing this strategic therapy.

Conflict of interest

The author reports no conflicts of interest in this work.

CRediT authorship contribution statement

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Resources, Investigation, Writing – original draft. **Ikponmwosa O. Evbuomwan:** Writing – review & editing, Conceptualization, Resources, Investigation. **Rotdelmwa Filibus Maimako:** Writing – original draft, Writing – review & editing. **Matthew Iyobhebhe:** Data curation, Methodology, Writing – original draft. **Oluwafemi Adeleke Ojo:** Conceptualization, Writing – review & editing, Data curation, Writing – original draft. **Olarewaju M. Oluba:** Writing – original draft, Project administration, Supervision. **Oluyomi S. Adeyemi:** Writing – original draft, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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