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Prospective Role of Indian Medicinal Plants in Inhibiting Vascular Endothelial Growth Factor (VEGF) mediated Pathological Angiogenesis

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Abstract

Vascular Endothelial Growth Factor (VEGF) plays an important role in physiological as well as pathological angiogenesis. Physiologically, VEGF is essential for embryonic vasculogenesis, endochondral ossification, neovascularisation following injury and collateral circulation to bypass blocked vessels. Solid neoplasms need adequate blood supply to grow in size. Thus, Neoplasm cells over-express VEGF and promote pathological angiogenesis. By virtue of various mechanisms including release of VEGF, the cancer cells grow and metastasize. VEGF also acts as survival factor for endothelial cells and tumor cells and protect them from apoptosis. Drugs which inhibit VEGF can control or slow down the disease process associated with VEGF mediated pathological angiogenesis. VEGF inhibitors from plant sources are matter of great interest in recent times. It was evident from the present study, that Indian medicinal plant like, *Tinosporacordifolia, Ocimum sanctum, Azadirachtaindica, Calotropisprocera, Withaniasomnifera, Curcuma longa, Commiphoramukul, Piper longum, Andrographispaniculata, Peganumharmala, Vernoniacinerea, Boswelliaserrata* described in ancient texts of Ayurvedainhibits VEGF mediated pathological angiogenesis. Anti-VEGF agent from natural sources may complement the efficacy of chemotherapy and radiotherapy without much toxicity.

Keywords: Vascular endothelial growth factor; Pathological angiogenesis; Ayurveda; Indian medicinal plants

Introduction

In recent years the role of Vascular Endothelial Growth Factor (VEGF) in angiogenesis has been studied extensively. VEGF plays an important part in regulation of physiological as well as pathological angiogenesis [1]. Physiologically, VEGF plays an essential role in embroyonic vasculogenesis and angiogenesis. Any derangement in its function is detrimental for the proper development of the embryo [2]. The activities of vascular endothelial growth factor are mediated by two tyrosine kinase receptors Flt-1 (VEGFR-1) and KDR (VEGFR-2). Studies show that VEGF also plays a pivotal role in post natal life. It was observed that in vivo administration of VEGF causes marked increase in circulating endothelial progenitor cells kinetics due to mobilization of bone marrow derived endothelial progenitor cells which ultimately results in increased differentiation of endothelial progenitor cells *in vitro*. Apart from this, *in vivo,* VEGF augments corneal neoangiogenesis which implies the importance of VEGF in post neovascularization [3]. Vascular Endothelial Growth Factor (VEGF) also plays a critical role in Glomerular development and function and is highly expressed within the glomerulus. Abnormalities in form of deletion in VEGF related genes leads to congenital nephropathy and perinatal lethality [4]. VEGF also acts as essential mediator in the process of endochondral ossification [5]. A dose dependent chemoattractive effect of VEGF-A has been demonstrated on Human mesenchymal progenitor cells and this activity is found to be mediated via VEGFR-1 [6].

Role of VEGF in the onset and development of the carcinogenic process

The role of VEGF in pathological angiogenesis associated with solid tumors and hematological malignancies has drawn the attention of researchers. VEGF physiologically is highly specific mitogen for endothelial cells [7] and induces angiogenesis and lymphogenesis [8]. Pathologically, VEGF can lead to increased survival and growth of solid tumors. Angiogenesis is an important pathological event associated with tumor growth and metastasis and VEGF plays an important role in this event [9]. Studies show that VEGF promotes growth of vascular endothelial cells of arteries, veins and lymphatics [10]. Apart from this VEGF modulates apoptotic signal transduction pathways and thus prevents Apoptosis of Human Microvascular Endothelial Cells. This anti-apoptotic effect is thought to be via Opposing Effects on MAPK/ERK and SAPK/JNK Signaling [11].

VEGF also acts as survival factor for endothelial cells and tumor cells and protect them from apoptosis [12]. It has been found to be upregulating Bcl-2 expression in endothelial cells [13]. Bcl-2 gene is the founding member of the Bcl-2 family of regulator proteins that regulate apoptosis. Stressed cells survival or death is largely determined by interplay between opposing members of the Bcl-2 protein family. Bcl-2 and its closest homologs promote cell survival, but two other factions promote cellular apoptosis [14]. VEGF mediated abnormal upregulation causes increased survival of endothelial cells as well as tumor cells.

Investigations report that VEGF also induces plasminogen activators and plasminogen activator inhibitor-1 in microvascular endothelial cells. This leads to extracellular proteolysis which is an essential step in angiogenesis process [15]. This process in pathological condition helps the tumor cell for increased survival and vascular supply. VEGF was initially known as Vascular Permeability Factor (VPF) and it is considered as one of the important regulators of vascular permeability. This activity is thought to be activation of PKB/akt, endothelial nitric-oxide synthase, and MAP kinase pathways [16]. All these factors help the neoplasm to survive and grow effectively.

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In many human neoplasms, the levels of circulating VEGF are found to be very high. This high level of VEGF has a prognostic role in overall survival of various cancers including lung cancer [17], and gastric cancers [18]. In this context, it is reported that, Anti VEGF treatment with chemotherapy is found to more effective than either treatment alone [19,20]. Studies show that, VEGF enhances radioresistance of neoplasm cells and in this perspective, it is important to mention that Tumor cell radiosensitivity is an important determinant of radiocurability. Thus, anti-VEGF treatment enhances the radiosensitivity of the tumor cells and ultimately increased effectiveness of radiotherapy [21].

Molecular triggering factors VEGF up regulation

There are various environmental and cellular factors which triggers the release of VEGF. These factors are mainly hypoxia, Oncogenes, Tumor suppressor genes. In absence of independent blood supply, tumors survive by virtue of diffusion process and obtain oxygen and other nutrients from blood. But, through this process, tumor cannot grow beyond 2 mm^3 in size. Gradually, in absence of adequate vasculature, tumor becomes hypoxic and starts secreting Vascular Endothelial Growth Factor (VEGF) in order to promote neo angiogenesis towards the tumor and ultimately getting adequate blood supply to the cancer cells.In response to VEGF, blood vasculature starts growing towards tumor and provides nutrients to tumor. As the tumor grows in size, there is upregulation of VEGF gene expression, primarily through the activity of hypoxia inducible factor-1 (HIF-1), a protein consisting of 2 subunits (HIF-1α and HIF-1β) [22].

VEGF inhibitors from plant sources are matter of great interest in recent times.In a recent investigation, Mangoni et al. reported unexpected side effects with combination of bevacizumab (anti-VEGF agent) and radiotherapy. Normal tissues toxicity was found to be triggered by the combined anti-angiogenic and radiation therapy [23]. Thus, combination of targeted drugs like VEGF inhibitors with radiotherapy or chemotherapy should be dealt with utmost caution. In this context, Advantage of Anti-VEGF compounds derived from natural sources is that they are safer and their action may be mediated through multiple cell-signaling pathways and thus, reduces the chances of developing resistance by cancer cells. They can be used as complementary therapy to increase the effectiveness of conventional chemotherapy and radiotherapy. The aim of the present review is to screen important Indian medicinal plant with anti-VEGF activity.

Materials and methods

PUBMED, MEDLINE databases and Google Scholar were searched for screening Indian medicinal plants with VEGF inhibitory activity. The key words used for the search was 'Indian Medicinal plants, 'Vascular Endothelial Growth Factor' etc. *In-vitro* as well *in-vivo* analysis was included in the review. Only research articles in English language were considered. Other languages were approved when there was an English abstract containing data essential for extraction.

Indian Medicinal Plants with anti-VEGF Activity

Systematic review shows that, many Indian Medicinal plants possess anti –VEGF activity (Table 1). Some of the research studies are summarized as follows:

Tinosporacordifolia

In vivo angiogenesis assay has shown that octacosanol (long-chain aliphatic alcohol) isolated from the plant *Tinosporacordifolia* down regulates VEGF gene expression. This activity was found due to the inhibition of matrix metalloproteinases activity and translocation of transcription factor nuclear factor kappa B to nucleus [24]. In another study, antiangiogenic potential of *Tinosporacordifolia* was investigated in *in vivo* as well as *in vitro* models. B16F10 melanoma cell-induced capillary formation was used to assess *in vivo* antiangiogenic activity. Inhibition of tumor directed capillary formation induced by melanoma cells was evident by intraperitoneal administration of the extract (20 mg/kg). It was observed that, the antiangiogenic potential of this plant is partly due regulation of the levels of cytokines (IL-1β, IL-6, TNF-α) and growth factors (vascular endothelial cell growth factor) in the blood of the angiogenesis-induced animal [25].

Ocimum sanctum

Administration of ethanolic *Ocimum sanctum* leaf extract in a dose of 300 mg/kg body weight three times per week resulted in decreased expression of Proliferating cell nuclear antigen, glutathione S-transferase-pi, Bcl-2, cytokeratin and vascular endothelial growth factor, and overexpression of Bax, cytochrome C, and caspase 3 in N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis experimental model [26].

In another experimental study involving male wistar rats,

Latin name	Family	Sanskrit Name	Author	Year
Tinospora cordifolia	Menispermaceae	Guduchi	Thippeswamy et al. [24]	2008
Tinospora cordifolia	Menispermaceae	Guduchi	Leyon and Kuttan [25]	2004
Ocimum sanctum	Lamiacea	Tulsi	Manikandan et al. [26]	2007
Azadirachta indica	Meliaceae	Nimba	Mahapatra et al. [28]	2012
Azadirachta indica	Meliaceae	Nimba	Babykutty et al. [29]	2012
Calotropis procera	Apocynaceae	Arka	Mathur et al. [30]	2011
Withania somnifera	Solanaceae	Aswagandha	Mathur et al. [32]	2006
Withania somnifera	Solanaceae	Aswagandha	Christina et al. [33]	2004
Curcuma longa	Zingiberaceae	Haridra	Gururaj et al. [34]	2002
Curcuma longa	Zingiberaceae	Haridra	El-Azab et al. [35],	2011
Commiphora mukul	Burseraceae	Guggul	Xiao and Singh [36]	2008
Piper longum	Piperaceae	Pippli	Sunila and Kuttan [37],	2006
Andrographis paniculata	Acanthaceae	Kalmegh	Sheeja et al. [38]	2007
Peganum harmala	Nitrariaceae	Harmal	Hamsa and Kuttan [39]	2010
Vernonia cinerea	Asteraceae	Sahadevi	Pratheeshkumar and Kuttan [40]	2011
Vernonia cinerea	Asteraceae	Sahadevi	Pratheeshkumar and Kuttan [41]	2011
Boswellia serrata	Burseraceae	Shallaki	Pang et al. [42]	2009

Table 1: The list of Indian medicinal plants with anti-VEGF activity.

combined chemopreventive efficacy of *Azadirachtaindica* (100 mg/kg body weight i.g) and Ocimum sanctum (150 mg/kg body weight i.g.) against N-methyl-N'-nitro-N-nitrosoguanidine induced gastric carcinogenesis was evaluated. It was observed that Co-administration of extracts resulted in inhibition of angiogenesis as evident by down regulation of vascular endothelial growth factor [27]. Thus, *Ocimum sanctum* possess anti-angiogenic activity as well it inhibits tumor proliferation, invasion and promotes apoptosis as evident by various experimental studies.

Azadirachtaindica

Neem (*Azadirachtaindica*) is widely acclaimed in Ayurveda for its therapeutic potential. In a recent investigation anti-angiogenic potential of ethanol extract of Neemleaves in human umbilical vein endothelial cells was evaluated. It was found that ethanol extract of neem leaves inhibited VEGF induced angiogenic response *in vitro* and *in vivo* [28]. In another in vitro study, Nimbolide, a plant-derived limonoid of *Azadirachtaindica* was found to suppress the nuclear translocation of p65/p50 and DNA binding of NF-κB, which is an important transcription factor for controlling MMP-2/9 and VEGF gene expression. Thus, *Azadirachtaindica* possess strong inhibitory response for VEGF expression and thus acts as antiangiogenic agent [29].

Calotropisprocera

In a recent investigation, roots of *Calotropisprocera* were found to possess anti-angiogenic activity mediated via VEGF pathway. Chicken egg chorioallantoic membrane assay and sponge implantation assay in mice was used for the investigation. Methanolic extract at the dose of 10ng most effectively inhibited neovascularization induced by 10ng of VEGF in Chicken egg chorioallantoic membrane assay. Neovascularization induced by 100 ng VEGF was inhibited effectively by 100 ng of methanolic, n-hexane, ethylacetate extracts of roots of *Calotropisprocera* in sponge implantation assay. However, Water extract did not showed anti-antiangiogenic activity in both types of assays [30]. Apart from antiangiogenic activity, *Calotropisprocera* also demonstrates antiproliferative activity in *in vitro* and *in vivo* models [31].

Withaniasomnifera

The roots of *Withaniasomnifera* possess anti-angiogenic activity as evident by *in vitro* and *in vivo* assays. VEGF mediated neovascularization was significantly inhibited in chickchorio-allantoic membrane assay as well as in mouse sponge implantation method [32]. Various studies have reported the anticancer property of this plant. In an experimental study involving swiss albino mice model ethanolic extract of the root of *Withaniasomnifera Dunal* was found to effective against Dalton's Ascitic Lymphoma [33]. Thus, the anticancer property of *Withaniasomnifera* is partly mediated by its VEGF inhibitory activity as evident by studies.

Curcuma longa

Curcumin is a carotenoid pigment found in the rhizome of *Curcuma longa*. The role of curcumin in modulating angiogenic ligands and their receptor gene expression in tumor and endothelial cells was evaluated using two *in vivo* angiogenesis assay systems, viz. peritoneal angiogenesis and chorioallantoic membrane assay. Curcumin was found to be a potent angioinhibitory compound as evident by down-regulation of the expression of proangiogenic genes, in Ehrlich ascites tumor cells, NIH3T3, and endothelial cells. Apart from this, Northern blot analysis also demonstrated a time-dependent (0-24 h) inhibition of VEGF, angiopoietin 1 and 2 gene expression in Ehrlich ascites tumor cells, as well as VEGF and angiopoietin 1 gene expression in NIH3T3 cells, and KDR gene expression in human umbilical vein endothelial cells [34].

Similar investigation also reported the anti-angiogenic effect of resveratrol or curcumin when used alone or in combination with carboplatin in Ehrlich Ascites Carcinoma (EAC)-bearing mice. It was found that in Plasma levels of VEGF were significantly reduced in groups on day 7 post-inoculation. Resveratrol or curcumin also demonstrated reduction of microvessel density in experimental model. It can be derived that, curcuminposses anti-angiogenic effect which is caused by inhibition of VEGF and its receptor type-2 [35].

Commiphoramukul

In a recent investigation, z-guggulsterone, a constituent of Indian Ayurvedic medicinal plant *Commiphoramukul*, was found to be inhibiting *in vitro* angiogenesis by suppressing the secretion of proangiogenic growth factors like vascular endothelial growth factor and granulocyte colony-stimulating factor. It was also found to be responsible for down-regulation of VEGF receptor 2 (VEGF-R2) protein levels, and inactivation of Akt. Apart from this, z-guggulsterone inhibited in vitro neovascularization by human umbilical vein endothelial cells in a concentration- and time-dependent manner [36].

Piper longum

Intraperitoneal administration of the methanolic extract of *P. longum* in a dose of 10 mg/dose/animal was able to regulate the increased level of proinflammatory cytokines such as IL-1 β, IL-6, TNF-α, GM-CSF and the direct endothelial cell proliferating agent, VEGF induced by injecting B16F-10 melanoma cells on the ventral side of C57BL/6 mice. Apart from this, extract at non-toxic concentrations (10 microg/ml, 5 microg/ml, 1 microg/ml) inhibited the VEGF-induced vessel sprouting in rat aortic ring assay. Moreover, it also inhibited the VEGF-induced proliferation, cell migration and capillary-like tube formation of primary cultured human endothelial cells [37]. This indicate that *Piperlongum* possess anti-angiogenic property as evident by *in vivo* and *in vitro* assays. Its anti-angiogenic property is partly due to inhibition of vascular endothelial growth factor.

Andrographispaniculata

Sheeja et al. [38] evaluated the antiangiogenic activity of *Andrographispanniculata* extract and its major component andrographolide using both *in vitro* and *in vivo* models. It was observed that administration of these agents lead to reduction in the elevated levels of proinflammatory cytokines such as IL-1β, IL-6, TNF- αand GM-CSF and the most potent angiogenic factor VEGF in angiogenesis induced animals. Most importantly, it was found to reduce the level of expression of VEGF mRNA in B16F-10 line [38].

Peganumharmala

Intraperitoneal administration of Harmine (a beta-carboline alkaloid present in *Peganumharmala*) at dose of 10 mg/kg body weight significantly decreased tumour directed capillary formation as evident in an *in-vivo* assay. Treatment with Harmine also significantly reduced the elevated levels of pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF), Nitric Oxide (NO) and pro-inflammatory cytokines in angiogenesis induced animals [39].

Vernoniacinerea

Vernolide-A, a sesquiterpene lactone from *Vernoniacinerea*,

was found to inhibits the tumour specific angiogenesis by regulating proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and GM-CSF, VEGF, MMPs and TIMP in angiogenesis induced C57BL/6 mice [40]. In another study, the effect of vernolide-A on the inhibition of radiation-induced tumor angiogenesis in C57BL/6 mice was studied. It was observed that administration of Vernolide-A significantly reduced the tumor volume of radiation-exposed mice. Moreover, Serum vascular endothelial growth factor levels were significantly reduced after Vernolide-A administration. It also found to inhibit the radiation-induced gene expression of hypoxia-inducible transcription factor-1α (HIF-1α) and VEGF in B16F-10 cells and VEGF receptor (Flk-1) expression in human umbilical vein endothelial cells [41]. This indicates that *Vernoniacinerea* possess anti-VEGF activity.

Boswelliaserrata

Acetyl-11-keto-beta-boswellic acid (an active component of *Boswelliaserrata*) was found to suppress human prostate tumor growth through inhibition of angiogenesis induced by VEGFR2 signaling pathways. Moreover, it was found to suppress VEGF-induced phosphorylation of VEGF receptor 2 (VEGFR2) kinase (KDR/Flk-1) as evidenced by Western blot analysis and *in-vitro* kinase assay [42].

Conclusion

Research studies demonstrate the presence of anti VEGF agents from various medicinal plants. These agents may enhance the efficacy of treatment of conditions associated with VEGF mediated pathological angiogenesis. VEGF mRNA over expression and high level of circulating VEGF is associated with many human solid tumors and VEGF is found to be responsible for increased survival and rapid growth of many human tumors. Thus, in this context anti-VEGF agent from natural sources may complement the efficacy of chemotherapy and radiotherapy without much toxicity. Further preclinical studies are required to decide the use of single compound or complex formulation for therapeutic trials.

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