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**Innovation development and standardization of Novel Herbal Formulation**
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# Herbal biomarkers in angiogenesis

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**Abstract**
Angiogenesis is physiological process through which new blood vessels are form from pre-existing blood vessels. It is a normal and vital process in growth and development as well as wound healing and in formation of granulation tissue. It is also a fundamental step in transition of tumors from benign state to Malignant. Solid cancers cannot grow beyond a limited size without an adequate blood supply. There are many factors cause angiogenesis such as VEGF-A (Vascular endothelial growth factor), FGF-2 (Fibroblast growth factor), Angiopoietin 1 & 2, PDGF (platelet derived growth factor). It cannot grow beyond a certain size or spread without a blood supply. Hence, there are many drugs developed called Angiogenesis Inhibitors such as Bevacizumab, cetuximab etc. The plant sources are matter of great interest in recent times. Under this, extraction of plants such as *Curcuma longa*, *Tinospora cordifolia*, *Azadirachta indica*, etc.

**Keywords:** curcumin, angiogenesis, vascular endothelial growth factor, angiogenesis inhibitors

## Introduction

### Angiogenesis

Angiogenesis is the physiological process through which new blood vessels form from pre-existing blood vessels. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, it is also an important step in the transition of tumors from a benign state to a malignant state, leading to the use of angiogenesis inhibitors in the treatment of cancer [1]. A tumour needs nutrients and oxygen to grow and spread which are available in the blood. The tumour sends chemical signals that stimulate blood vessel growth; these vessels carry blood to tumour

Tumour grew beyond 2 mm [3] when placed in an area where angiogenesis is possible, but the cancer cells growth is stopped to 1-2 mm [3] with adequate blood supply. In the absence of vascular support, tumors may become necrotic or even apoptotic (Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression [10].

### Factors cause Angiogenesis

1) VEGF-A (VASCULAR endothelial growth factor – A
2) FGF-2 (fibroblast growth factor)
3) angiopoietin 1&2
4) PDGF (platelet derived growth factor)
5) MMP (matrix metalloproteinase)

### Turmeric (curcuma longa)

Turmeric is a flowering plant of the ginger family, Zingiberaceae, the roots of which are used in cooking. The plant is rhizomatous and is native to the Indian subcontinent and Southeast Asia. It requires temperatures between 20 and 30 °C (68 and 86 °F) and a considerable amount of annual rainfall to thrive [1]. Turmeric is a perennial herbaceous plant that reaches up to 1 m (3 ft. 3 in) tall [2]. Turmeric has been used in Asia for thousands of years and is a major part of Ayurveda, Siddha medicine, traditional Chinese medicine and Unani [3]. The origin of the

*name is uncertain. Turmeric word derives from Middle English or Early Modern English as turmeryte or tarmaret [4]. The name of the genus, Curcuma, is derived from the Sanskrit kuṅkuma*, referring to both turmeric and saffron, used in India since ancient times [5].

**Phytochemical components**

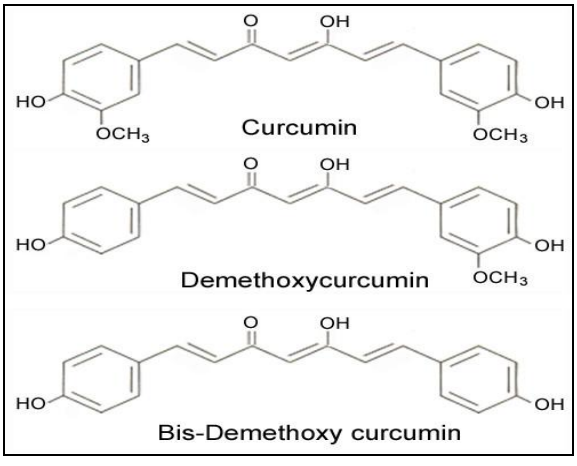
Turmeric powder is approximately 60-70% carbohydrates, 6-13% water, 6-8% protein, 5-10% fat, 3-7% dietary minerals, 3-7% essential oils, 2-7% dietary fiber, and 1-6% curcuminoids. Phytochemical components of turmeric include diarylheptanoids, a class including numerous curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin [1].

**Curcumin**

Curcumin is a component of the spice turmeric (Curcumin longa) in India, a type of ginger. Curcumin is curcuminoids present in turmeric, there are also other two curcuminoids being desmethoxycurcumin and bis-desmethoxycurcumin. These curcuminoids give turmeric its yellow colour and curcumin is used as a yellow food colorant and food additive [1]. Curcumin is obtained from the dried rhizome, which is a perennial herb. The rhizome is processed to form turmeric which contains 2% to 5% curcumin. Curcumin is present in two tautomeric forms known as keto and enol and the enol form is the more stable in both solid and solution phases. Curcumin can also be used for the quantification of boron since it reacts with boric acid to form a red colored compound called rosocyanine [6].

**Chemical formula:** $C_{21}H_{20}O_{8.}$
**Molar mass:** 368.39 g·mol$^{-1}$
**Melting point:** 183 °C (361 °F; 456 K)

Aside from being employed as a flavoring and colouring agent in food, turmeric has also been widely used in Ayurvedic medicine for its anti-oxidant, antiseptic, analgesic, antimalarial and anti-inflammatory properties [7]. Curcumin has been consumed as a dietary supplement for centuries and is considered pharmacologically safe [8]. Curcumin is a lipophilic polyphenol and thus is insoluble in water, but is readily soluble in organic solvents such as dimethylsulfoxide, acetone and ethanol [7]. The curcuminoids consist of two methoxylated phenols connected by two α, B unsaturated carbonyl groups that exist in a stable enol form [9]. Curcumin has shown to suppress the activation of NF-κB. Curcumin has been studied in multiple human carcinomas.




**Effect of curcumin on angiogenesis**

**1) Effect on VEGF**

Vascular endothelial growth factor (VEGF) plays an essential role in angiogenesis during embryonic development as well as periods of increased physiological, demand including the menstrual cycle, pregnancy and wound healing [12].Enhanced expression of VEGF also occurs in disease conditions leading to pathological angiogenesis including chronic inflammation (i.e. rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD), diabetic retinopathy and adenocarcinoma [11]. VEGF plays a key role in cancer biology and contributes to tumour neovascularisation in response to the increased demand for delivery of nutrients and oxygen.

Angiogenesis involves many events such as endothelial cells, including cell migration, proliferation and tube formation. VEGF activation of HIMECs resulted in cell migration, proliferation, tube and stress fibre formation. It can be also determined as the anti-angiogenic potential of curcumin and its potential mechanism of action through inhibition of COX-2 expression, in vitro angiogenesis assays following VEGF stimulation measuring growth, proliferation, transmigration and tube formation were performed in HIMECs, using NS398 as a specific COX-2 inhibitor [13].

**2) Effect on FGF-2**

Curcumin has also been shown to inhibit the angiogenic response to FGF-2 stimulation in mouse endothelial, enzyme involved in tissue remodeling that is important fosr the growth of new blood vessels.. Using cultured corneal cells, FGF-2 stimulates DNA binding activity of transcription factor AP-1 but not NF-kappaB and that AP-1 stimulation is inhibited by curcuminoids [14].

**3) Effect on MMP**

Matrix metalloproteinases (MMPs) is an important role in the invasion, metastasis and angiogenesis of cells of cancer. Curcumin has potential for the therapy and prevention of cancer. Curcumin can inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development. There is no available information on the effects of curcumin on migration and invasion of human lung cancer cells. The anti-tumor invasion and migration effects of lung cancer cells induced by curcumin were also examined. Hence, the result is curcumin suppresses the migration and invasion of human non-small cell lung cancer cells (A549) *in vitro*. Therfore, findings suggest that curcumin has anti-metastatic potential by decreasing invasiveness of cancer cells. This action was involved in the MEKK3, p-ERK signaling pathways resulting in inhibition of MMP-2 and -9 in human lung cancer A549 cells. Overall, the above data shows that the anticancer effect of curcumin is also exist for the inhibition of migration and invasion in lung cancer cells [15]

**Extraction process of curcumin**

**1) Soxhlet Extraction**

A soxhlet Extractor has three main sections: A percolator (boiler and reflux) which circulates the solvent, a thhimble (usually made of thick filter paper) which

retains the solid to be extracted, a siphon mechanism, which empties the thimble periodically. The process is followed as the solvent is heated to reflux. For extraction of Curcumin ethanol is use as solvent. The solvent vapour travels up a distillation arm and floods into the chamber housing the thimble of turmeric. The condenser ensures that any solvent vapours cools, and drips back down into the chamber housing the solid material. The chamber containing the turmeric powder slowly fills with warm ethanol. Some of the desired compound dissolves in the warm solvent. When the Soxhlet chamber is almost full, the chamber is emptied by the siphon. The solvent is returned to the distillation flask. The thimble ensures that the rapid motion of the solvent does not transport any solid material to the still pot. This cycle may be allowed to repeat many times, over hours or days. During each cycle, a portion of the non-volatility compound dissolves in the solvent. After many cycles the desired Curcumin is concentrated in the distillation flask.

**Discussion**

Although, Curcumin show good antiangiogenic activity, it also have instability & low bioavailability. As per article of author Zhongping Fu, Xiao Chen, [...], and Zi-Chun Hua shows Curcumin inhibits angiogenesis and improves defective hematopoiesis induced by tumor-derived VEGF in tumor model through modulating VEGF-VEGFR2 signaling pathway and the above review article show its effect on VEGF, FGF-2, MMP, Still**,** multiple studies over the past decade have indicated the safety and efficacy of this polyphenol and have provided a solid basis for evaluating its efficacy in human clinical trials. As to improve the efficacy of curcumin various strategies are performed such as modulation of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, and conjugation and structural modifications of curcumin. In spite of these, improvements in curcumin bioavailability enhancement and efficacy have not gained significant attention in human.

**Conclusion**

Active constituent of Turmeric i.e. Curcumin show anti-angiogenic activity. This agent may enhance the efficacy of treatment in conditions of cancer. Curcumin show anti-angiogenic effect and also not showing any toxicity. Thus, anti angiogenic agent from natural sources may complement the efficacy of chemotherapy and radiotherapy without much toxicity.

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