

## PROBABLE NATURAL SOURCES OF ANTIANGIOGENIC AGENTS

Ankur Datta<sup>1</sup> Shankhajit De<sup>2</sup> and Ajoy Kumar Ghosh<sup>2\*</sup>

<sup>1</sup>Department of Pharmacology, Gupta College of Technological Sciences, Asansol, Burdwan, West Bengal, Pin - 713301, India.

<sup>2</sup>Vinayaka Missons Sikkim College of Pharmaceutical Sciences, Vinayaka Missons Sikkim University, NH 31-A, Tadong-737102, East Sikkim, India.

Mobile No.: 09732146097 E. Mail- [akg\\_mail@yahoo.com](mailto:akg_mail@yahoo.com).

**ABSTRACT:** Angiogenesis is the formation of new blood vessels which is a key part of tumor growth and spread. New blood vessels convey nutrients to the cancer, fueling their abnormal growth and metastasis. The first successful antiangiogenic inhibitor interferon alfa2a has been used for the treatment of pulmonary hemangiomatosis in 1989. Tumors cannot grow or spread without the formation of new blood vessels, so researchers have begun studying 'antiangiogenic agents' by counting severe side-effects for radiation, chemotherapy as well as other ways of management of cancer. Advantages of antiangiogenic therapy are that this class of drugs show only mild side effects, non toxic to most healthy cells and not develop any resistance over a long period of therapy. Unfortunately no suitable natural or synthetic antiangiogenic agent has been developed still now. Therefore this review gives an insight that the natural sources might be the key target for the development of more potent, less toxic and cheapest antiangiogenic agents.

**Key words:** Angiogenesis, cancer, tumor, antiangiogenic agents,

### INTRODUCTION

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels and plays a vital role in growth and development, as well as in wound healing. However, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. The identification of angiogenic diffusible factors derived from tumors was identified long days before by Greenblatt and Shubik in 1968 (Greenblatt M et al., 1968). The process of angiogenesis is very much important in the procession of the tumor growth.

Herbalism is a traditional medicinal or folk medicine practice based on the use of plants and plant extracts but some time it include fungal and bee products, as well as minerals, shells and certain animal parts, that is why it is also known as botanical medicine, medical herbalism, herbal medicine, herbology, and phytotherapy (Acharya D et al., 2008). Many plants synthesize different substances that are useful for the maintenance of health of humans and other animals. These include aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins.

Many are secondary metabolites, of which at least around 12,000 have been isolated are also beneficial for us. In many cases, substances such as alkaloids, glycosides, tannins, essential oils etc are very important for human use. Many of the herbs and spices used by humans to season food yield useful medicinal compounds (Lai PK, 2004; Tapsell LC, 2006). According to the source about 40% of the marketed drugs come from the herbal source (Bruneton J, 1995). But unfortunately still by the date there is no suitable antiangiogenic drug for herbal source for the better treatment of angiogenesis-dependent diseases. So, in this review we tried to summarize the all probable herbal sources of more potent, less toxic antiangiogenic drugs for some deadly diseases including cancer. Side by side it will give the up to date information about the expecting natural source of anti-angiogenic agents at a glance to the scientist who would like to engage his research on this important topic.

## PROBABLE NATURAL SOURCES OF ANTI ANGIOGENIC DRUGS:

### 1. *Curcuma longa*

It consists of the dried rhizome of *Curcuma longa* Linn; Family: Zingiberaceae.

#### Chemical Constituents

Major: Curcuminoids (6%), the yellow coloring principles, of which curcumin constitutes 50-60%; Essential oil (2-7%) with high content of bisabolane derivatives (Ohshiro M, 1990).

Minor: Desmethoxycurcumin, bisdesmethoxycurcumin, dihydrocurcumin (Ravindranath V, et al., 1980); common phytosterols, fatty acids (Moon CK, et al., 1977) and polysaccharides (Tomoda M, et al., 1990) etc.

#### Pharmacology

Cytotoxic effects of curcuminoids could play an important role in the external treatment of certain cancerous conditions (Bissett NG, 1994). Also has antitumor (Chen XG, et al., 1998; Udupa N, 1997; Limtrakul Pn, 2001; Singhal SS, et al., 1999; Navis I, et al., 1999; Ushida J, et al. 2000) activity.

### 2. *Emblica officinalis*

Drug consists of fresh and dried fruits of *Emblica officinalis* Gaertn; Family: Euphorbiaceae

#### Chemical Constituents

Major: Vitamin C (= L-(+)-threo-ascorbic acid, 2%) (Shishoo CJ, et al., 1997)<sup>20</sup>; tannins (5%) (Handa SS, et al., 1989; Pillay PP, et al., 1958)<sup>21, 22</sup> viz., gallic acid, ellagic acid, phyllemblic acid and emblicol.

Minor: Alkaloids (Khanna P, et al., 1975) viz., phyllantidine and phyllantine; pectin and minerals.

#### Pharmacology

The drug has cytoprotective (Biswas S, et al., 1999) and antitumor (Jose JK, et al., 2001) activity.

### 3. *Glycyrrhiza glabra*

Drug consists of the dried, peeled or unpeeled roots of *Glycyrrhiza glabra* Linn; Family: Fabaceae

#### Chemical Constituents

Major: Triterpenoid saponin-glycyrrhizin (2-20%) (Takino Y, et al., 1979; Okada K, et al., 1981), a mixture of potassium and calcium salts of glycyrrhizic (glycyrrhetic) acid (Bradley PR, et al., 1992).

Minor: Includes other triterpenoid saponins viz., glabranin A&B, glycyrrhetol, glabrolide, isoglabrolide (Hikino H, 1985); isoflavones viz., glabrone, neoliquiritin, hispaglabridin A&B; coumarins viz., herniarin, umbelliferone; triterpene sterols viz., onocerin,  $\beta$ -amyrin, stigma sterol (Bissett NG, 1994).

#### Pharmacology

The drug is used in Oncology adjuvant therapy (Razina TG, et al., 2000).

#### 4. *Ocimum tenuiflorum*

Drug consists of leaves of *Ocimum tenuiflorum*; Family: Lamiaceae

##### Chemical Constituents

Major: Volatile oil (0.4 – 0.8%) (Handa SS, et al., 1998) containing chiefly eugenol (21%) and  $\beta$ -caryophyllene (37%).

Others: A number of sesquiterpenes and monoterpenes viz., bornyl acetate (Skaltsa H, et al., 1988),  $\beta$ -elemene (Skaltsa H, et al., 1990), methyleugenol, neral,  $\beta$ -pinene, camphene,  $\alpha$ -pinene, etc (Lal RN, et al., 1978); ursolic acid, campesterol, cholesterol,  $\beta$ -sitosterol and methyl esters of common fatty acids (Skaltsa H, et al., 1987).

##### Pharmacology

Radioprotective (Uma DP, et al., 1995) and antitumor (Prashar R, et al., 1995) activity.

#### 5. *Phyllanthus amarus*

Drug consists of aerial tender branches of *Phyllanthus amarus* Schum and Thonn; Family: Euphorbiaceae.

##### Chemical Constituents

Major: Lignans – a diarylbutane, phyllanthin (0.5%) and an aryltetrahydronaphthalene, hypophyllanthin (0.2%) (Sharma A, et al., 1993).

Minor: Hydrolysable tannins viz., Phyllanthusiin D (Foo L.Y, et al., 1992), amariin (Foo LY, 1993), amarulone (Foo LY, 1993) and amarinic acid, nyryphyllin (Foo L.Y, 1995); alkaloids viz., ent-norsecurinine, a diarylbutane, and a neolignan, phyllnirurin (Bruneton J, 1993), sobubbialine, epibubbialine (Houghton PJ, et al., 1996);

##### Pharmacology

Antimutagenic and anticarcinogenic activity (Sripandikulchai B, et al., 2002).

#### 6. *Podophyllum hexandrum*

Drug consists of the dried rhizome and roots of *Podophyllum hexandrum* Royle. Family: Berberidaceae

##### Chemical Constituents

The medicinally important and major portion of the drug is constituted by a resinous mixture-podophyllin a resinous lignin.

Major: Podophyllotoxin, an aryltetralin lignin (4%).

Others: 4'-demethylpodophyllotoxin,  $\alpha$ -peltatin,  $\beta$ -peltatin, desoxypodophyllotoxin, podophyllotoxone, isopicro-podophyllone, 4'-demethyl-desoxypodophyllotoxin, 4'-demethyl-podophyllotoxone (Jackson DE, et al., 1984; Yim M. et al., 1988).

##### Pharmacology

The importance of podophyllotoxin as a potent antitumor agent when affixed to a glucopyranose moiety (e.g. etoposide, teniposide) is well known (Yalowich JD, et al., 1982). Besides, many derivatives of podophyllotoxin have been investigated for antitumor properties (Tian X, et al., 1997; Terada T, et al., 1992).

#### 7. *Ricinus Communis*

The leaves, root and seed oil of *Ricinus Communis* linn; Family: Euphorbiaceae are used as drugs.

##### Chemical Constituents

Major: Lipids- fixed oil (45 to 55%) a mixture of triglycerides, triricinolein (75%) which on hydrolysis yields ricinoleic acid responsible for the cathartic effect.

Minor: Common fatty acids with carbon numbers from C<sub>14</sub> to C<sub>20</sub> (Acharya KT, et al., 1964). An alkaloid ricinine about 1%. Leaves contain besides ricinine, N-demethylricinine, 3-O- $\beta$ -D-glucopyranosides and 3-O- $\beta$ -D-rutinosides of kaempferol and quercetin (Kang SS, et al. 1985).

##### Pharmacology

The drug poses antitumour activity (Queshi SA, et al., 1997; Oda T, et al., 1997).

### 8. *Sida cordifolia*

Drug consists of root of *Sida cordifolia* linn; Family: Malvaceae.

#### Chemical Constituents

Major: A phytosterol, ecdysterone (0.06%) .

Others: Alkaloids (Ghosal S, et al., 1975; Ghosal S, et al., 1930; Begerhotta A et al., 1985; Leslie Gunatilaka A.A, et al., 1980), carboxylated tryptamines, quinazolines viz. vasicinone, vaccine and vasicinol; an acylsterylglycoside – sitoindoside X.

#### Pharmacology

*Sida cordifolia* reduces cotton pellet granuloma formation in albino rats (Ghosal S, et al., 1988; Alam M, et al. 1991).

### 9. *Solanum xanthocarpum*

Drug consists of mature, dried whole plant of *Solanum xanthocarpum*; Family: Solanaceae

#### Chemical Constituents

Major: Steroidal alkaloid solasodine (Verbist J.F, et al., 1975; Siddiqi S., et al., 1983), about 0.2%.

Minor: Include steroidal alkaloids (Kusano G, et al., 1973) viz. solamargine,  $\beta$ -solamargine, solasonine; sterols viz. cycloartenol, norcarpesterol, cholesterol and their derivatives (Kusano G, et al. 1975; Kasano G, et al. 1975).

#### Pharmacology

The drug has cytoprotective (Prashanta KV, et al., 2001) and anticancer (De LMS et al., 2001) activity.

### 10. *Syzygium aromaticum*

Drug consists of flower buds of *Syzygium aromaticum* linn; Family: Myrtaceae

#### Chemical Constituents

Major: Volatile oil (15-20%) (Bisset NG, 1994) containing chiefly a phenol eugenol (55-85%) and  $\beta$ -caryophyllene (10-20%).

Minor: Eugenol acetate and derivatives of  $\beta$ -caryophyllene,  $\alpha$ -humulene and its epoxide (Zheng GQ, et al., 1992; Iwamuro H, et al., 1983; Uchida T, et al., 1986), acetophenone, benzyl salicylate,  $\alpha$ -cardinol,  $\gamma$ -decalactone, fenchone, hexanal, 2-hexanone, methyl palmitate,  $\gamma$ -muurolene, palustrol, propylbenzoate and  $\alpha$ -thujene (Muchalal M, et al., 1985).

#### Pharmacology

The sesquiterpenes of the drug are known to possess activity in inducing the detoxifying enzyme glutathione S-transferase in mouse liver and small intestine and the ability of natural anticarcinogenes to induce such detoxifying enzymes correlates well with their ability to inhibit chemical carcinogenesis (Zheng GQ, et al., 1992).

### 11. *Tinospora glabra*

Drug consists of dried, matured pieces of stem of *Tinospora glabra*; Family: Menispermaceae.

#### Chemical Constituents

It contains clerodane furano diterpenes (Bhatt RK, et al., 1990; Wazir V, et al., 1995), viz., columbin, tinosporaside; a lignin (Hanuman J.B, et al., 1986), 3,4-bis-(4-hydroxy-3-methoxy benzyl) tetrahydrofuran; alkaloids (Bisset NG, et al., 1983; Pachey P, et al., 1981) viz., jactrorhizine, palmatine, berberine, tembeterine; a sesquiterpene glucoside, tinocordifolisoide (Maurya R, et al., 1997); phenylpropene disaccharides viz., cordifolioside A & B (Maurya R, et al., 1996); Others include choline, tinosporic acid, tinosporal, tinosporon (Quadrat M, et al., 1996).

#### Pharmacology

The drug has anticancer activity (Thatte U, et al. 1997; Mathew S, et al., 1999).

## 12. *Withania somnifera*

Drug consists of dried roots of *Withania somnifera*; Family: Solanaceae.

### Chemical Constituents

Majority of the constituents are withanolides (steroidal lactones with ergostane skeleton) and alkaloids. These include Withanone (Dhalla NS, et al., 1961), Withaferin A (Mc Phail AT, et al., 1968)<sup>88</sup>, Withanolides (Bhakuni DS, et al., 1995) I, II, III, A, D, E, F, G, H, I, J, K, L, M, WS-I, P and S, withasomidienone (Attaur R, et al., 1993), withanolide C (Bessale R, et al., 1992) and alkaloids viz., cuscohygrine, anahygrine, tropine, pseudotropine, anaferine, isopellatierine, 3-tropylogloate, Total alkaloids about 0.2%.

### Pharmacology

Roots of the plant show antitumour and radiosensitizing effects in animal model (Devi PU, et al., 1993).

## CONCLUSION

The progression of chronic and proliferative inflammation depends on angiogenesis (Jackson JR, et al., 1997). It is required not only for the maintenance of tissue perfusion, but also to allow an increase in the cellular traffic required for chronicity (Colville N, et al., 1995). Therefore, the inhibition of angiogenesis would be a valid target for drug development in chronic inflammatory diseases such as rheumatoid arthritis (Colville N, et al., 1992), atherosclerosis (Sueishi K, et al., 1997), diabetic retinopathy (Ishibashi T, et al., 1999), psoriasis (Li VW, et al., 1996), wound healing (Suzuki N, et al., 1998), and chronic airway inflammation (Thurston G, et al., 1998), as well as for antineoplastic therapy and Kaposi's sarcoma (Folkman J, et al., 1995). Vascular endothelial growth factor (VEGF) is a potent inducer of angiogenesis (Breier G, et al., 1992). Hypoxia conditions induce VEGF production, in which the transcription factor hypoxia-inducible factor-1 is activated (Forsythe JA, et al., 1996). In addition, PGE2 induces VEGF production via the cAMP-protein kinase pathway (Hoper MM, et al., 1997) and enhances angiogenesis in carrageenin-induced proliferative granulation tissue (Ghosh AK, et al. 2000) and in cultures of human umbilical vein endothelial cells treated with the conditioned medium of colon cancer cells (Tsuji M, et al., 1998). However, it has been suggested that mediators other than PGE participate in VEGF production by the inflammatory granulation tissue, because the cyclooxygenase inhibitors indomethacin and NS-398 only partially suppressed the VEGF production. It is arguably true to say that few researchers in the field of angiogenesis expected the growth of new blood vessels to be a simple event, nevertheless the molecular complexity of the process and the number of pathways involved has been a surprise. A significant outcome of this complexity has been the pleasing number of potential new targets available for therapeutic intervention. Studies of antiangiogenesis and vascular targeting are clearly at an exciting stage.

While over 300 angiogenesis inhibitors have been discovered, only handfuls have been formally studied. But with more than \$4 billion invested in the research and development of antiangiogenic medicines, something has to come of this massively-financed area of research. Over 10,000 cancer patients have already received some form of experimental antiangiogenic treatment.

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