



Mini Review

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# Iranian Herbal Medicines: Possible Potent Therapeutic Agents for Angiogenesis



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## Abstract

Angiogenesis is a major pathological component of diseases like a coronary heart disease and cancer. While major advances have been made and encouraging clinical results obtained, safer and more effective approaches are required. The identification of new drugs from medical plants has a long and successful history, and certain pro-angiogenic and anti-angiogenic plant components have been used in Iranian herbal medicine for thousands of years. More evidence based research and chemical optimization of these compounds could further enhance the effectiveness of these plant-based medicines in angiogenesis therapy. This review aims to assess the current status of research on medical herbs for the development of anti-angiogenic agents for cancer and other angiogenesis related diseases including inflammation, diabetic retinopathy and obesity.

**Keywords:** Angiogenesis; Alternative medicine; Iran; Herb

## Introduction

### What is angiogenesis?

The word angiogenesis is first named by Hertig in 1935 and the mechanism was revealed by Folkman

[1] in studying tumor angiogenesis [1,2]. Angiogenesis is defined as the formation of new blood vessels from pre-existing capillary vessels, including a series of coordinated events: proliferation of endothelial cells, movement of cells to distal points, vessel formation, and making of a new basement membrane [3,4]. It occurs in physiologic processes (for example: menstruation, ovulation, and wound healing). In the heart, in particular, angiogenesis promotes vascular ramification of coronary vessels, increase blood flow, and cardiac contractility. Angiogenesis also happens in pathological processes such as chronic arthropathy, diabetic retinopathy, psoriasis, tumoral growth, and metastasis dissemination [4].

Up to now, different studies have been conducted with the aim of finding substances that can induce or inhibitor angiogenesis, since the possibilities of clinical application of these substances in myocardial vascularity, and the central nervous system (CNS) are extensive, after injury or ischemia, partial replacement of large arteries, and even in wound healing.

However, it is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the

use of angiogenesis inhibitors in the treatment of cancer [5,6]. The chick embryo Chorioallantoic membrane (CAM) model is an extra-embryonic membrane that is commonly used *in vivo* to study both angiogenesis and anti-angiogenesis [7]. An angiogenic response happens 72–96hr after stimulation in the form of improved vessel density around the implant, with the vessels, radically converging toward the center like spokes in a wheel [7].

In opposition, when an angiogenesis complex is tested, the vessels become less dense around the

implant and even disappear [8]. Quantization of vessels in large amount of CAM models can be used to screen drugs from samples of herbal medicine extracts. The food sources listed for anti-angiogenesis must be without any herbicides, Insecticide, acaricide and etc. used in its growing proceeding as to get the most from the seed and produce. Medicinal plants and substances extracted from them have been used for thousands of years, fostering the prevention and treatment of dysfunctions and disorders in humans [3]. Several plant species have shown biological activity that induces angiogenesis *in vivo*, namely Ginkgo biloba, Aloe vera, Angelica sinensis, Dalbergiaodorifera, Trichosantheskirilowii, Patriniavillosa, Heveabrasiliensis, and Synadeniumumbellatum [9].

Since the popular use of medicinal plants provides evidence of biological activity, proper scientific research using adequate experimental models is necessary to validate the therapeutic use of these plants, or even to contribute to the formulation of a new drug [10]. In the present study, we aimed to an assay to measure the angiogenic activity of flaxseed (*Linum usitatissimum*) by using the chicken embryo Chorioallantoic membrane assay.

### Screening herbs for anti-angiogenic activity

**Silybum marianum (Milk thistle):** *Silybum marianum* has other common names include (Persian) Marythiqal and Kharmariam, (Arabic) Akub and Hharshafbarri, (Germany) Mariendistel and (Chinese) ShuiFeiji. This species is biennial or an annual plant of the Asteraceae family. This fairly typical thistle has purple to red flowers and shiny pale green leaves with white veins [11].

Milk thistle is commonly found in the provinces of Mazandaran, Gilan, West and East Azerbaijan, Kermanshah, Khuzestan, Fars and Bushehr [11]. In one of the experiments, Shokrpour et al. [12] compared milk thistle accessions coming from some provinces of Iran for quantitative and qualitative features. Silibinin and silymarin are polyphenolic flavonoids isolated from the fruits or seeds of *Silybum marianum*. In the laboratory, silymarin demonstrates strong activity against a variety of tumours by down regulation of VEGF and EGFR [13,14]. Silymarin suppresses VEGF when used as a single agent against human ovarian cancer [15].

**Teucrium polium:** *Teucrium polium* is a medicinal plant. It has several species of which have been used over 2000 years in traditional medicine. Its white or pale cream-colored flowers appear in April until August. The plant is usually found in most parts of Mediterranean and Irano-Turaian regions [16]. *Teucrium polium* is widely used in inflammatory conditions, rheumatism and ulcers [17,18]. Its flowers and its leaves are used both in cooking and for therapeutic purposes, particularly for the treatment of stomach ailments. *Teucrium polium* has been long used in Iran commonly as decoctions or infusions for its diuretic, antipyretic, antispasmodic, diaphoretic, tonic, anti-inflammatory, anti-hypertensive analgesic, antibacterial, and antidiabetic effects [19-22].

An infusion of the leaves and flowers of the plant is also consumed as a refreshing beverage [23]. Recent studies showed that, *Teucrium polium* has beneficial effects on nonalcoholic steatohepatitis [24] and it has been shown to be considered as an effective and safe chemo sensitizer agent for cancer therapy [25]. *In vitro* study on its aqueous extract of *Teucrium polium* has shown that it can effectively prevent oxidative processes and has substantial antioxidant activity [26].

Based on some isolated compounds from this plant such as diterpenoids, flavonoids, iridoids, sterols, and terpenoids [27], it might have cytotoxic activity and antitumor properties. Rajabalin et al. [12], evaluate the chemo sensitizer effect of the metabolic extract of *Teucrium polium* on cytotoxic and apoptotic activity of

four conventional chemotherapeutic drugs (include vincristine, vinblastine, doxorubicin, and cisplatin), this research showed that *Teucrium polium* potentiates the cytotoxic and apoptotic effects of drug (vincristine, vinblastine, and doxorubicin) against a panel of cancerous cell lines. Their suggested that this plant has the potential to be an effective and safe chemo sensitizer agent for cancer therapy [25]. Also, Eskandary et al. showed a cytotoxic activity of *Teucrium polium* methanolic extract on glioblastoma multi-forme, which is one of the most aggressive primary brain tumors with a grim prognosis [28]. Besides, the few adverse effects of *Teucrium polium* have been reported, which indicate the relatively safe nature of this medicinal herb [28].

**Prosopis farcta:** *Prosopis farcta*, the Syrian mesquite, is a species of the genus *Prosopis*, is native to Asia distributed from India to Iran [29]. *Prosopis farcta* exhibit a high degree tolerance to salt and plays an essential ecological role in the protection and improvement of soils since its root systems grows vertically as well as laterally. Plants have acceptable nutritional characteristics and capacity to grow under scarce water conditions [30]. *Prosopis farcta* is well adapted to drought [31]. *Prosopis farcta* is an invasive weed that is very hard to control [29]. Species belonging to this genus are multipurpose. Some of the compounds existing in *Prosopis* plant are: Quercetin (flavonoids), tryptamine, apigenin 5-hydroxytryptamine (alkaloids), L-arabinose, and Lectin [31,32]. Moreover, a number of phenolic compounds with strong antioxidant activity has been identified in extracts of this plant such as vicenin-2, apigenin C-glycoside, iso-orientin, vitexin, luteolin 7-O-glucoside, isovitexin, quercetin 3-O-glucoside, rutin, kaempferol 3-O-rutinoside, caffeic acid derivative, and luteolin [31].

Antioxidants play an important role in inhibiting and scavenging free radicals and thus, providing protection against infections and degenerative diseases [33]. Plants have been used for paint, cordage, gum [34,35], as supplements for feeding ruminants [30], and as medications. *Prosopis farcta*, commonly known as mesquite, is distributed throughout Iran. It has leaves, spines, beans (pod), and peas (seed).

Leaves and beans of *Prosopis farcta* have been used as a traditional medicine for treatment of some diseases and disorders. Some of this effect have been proven by researchers. In other cases, the plant is used as a folk remedy without academic confirmation of its effects. For example, *Prosopis farcta* may be used in the treatment of colds, diarrhea, measles, inflammation, diabetes [36,37], skin diseases, and prostate disorders. The plant also may be used in the healing of wounds [38], to reduce cardiac or chest pain [39], and to interrupt urine [40]. Antitumor activity [41], antioxidant capacity [42,43] antiparasitic and antimicrobial activity [44], and the ability to kill the *Leishmania* major parasites [32] have been noted recently.

**Lotus corniculatus:** *Lotus corniculatus* is a common flowering plant in the pea family Fabaceae. *Lotus corniculatus* can fix nitrogen through the root nodules making it useful as a cover crop. It has been studied for its falconoid content [45-47].

*Lotus corniculatus* is known for its medicinal values. The flowers are antispasmodic and sedative [48]. The root is carminative and febrifuge [49]. While *Lotus corniculatus* belongs to the legume family, none of the *Lotus* species have been investigated for the lectins.

Photochemical studies of *Lotus corniculatus* showed that the plant contains substances well known to have important anti-inflammatory properties, such as flavonoids (quercetin and kaempferol) [50], triterpene (oleanolic acid), and saponins [51]. The anti-inflammatory properties of these isolated compounds have been demonstrated in several *In vivo* and/or *in vitro* studies. Quercetin acts as an antioxidant [52] and an anti-inflammatory agent [53]. Kaempferol seems to exert its anti-nociceptive and anti-inflammatory actions by inhibiting pro-inflammatory mediators and transcription factors such as nuclear factor- $\kappa$ B (NF $\kappa$ B) [53-55]. Also, oleanolic acid and saponins exhibit anti-inflammatory properties via the inhibition of leukotriene synthesis [56], nitric oxide release [57], and levels of tumor necrosis factor- $\alpha$  (TNF-R), prostaglandin E2 (PGE2), and cyclooxygenase-2 (COX-2) [58].

***Verbascum thapsus*:** *Verbascum thapsus* L. (Khardhag or Common mullein), a member of the family Scrophulariaceae, is a well-known herb that is found all over Europe, in temperate Asia, widely in north of Iran and North America and is well-reputed due to its medicinal properties [59]. The flowers and leaves are analgesic, anti-inflammatory, spasmolytic, antiseptic, astringent, emollient, diuretic, expectorant and vulnerary [60-62]. Homeopathic formulations containing fresh leaves are used in the treatment of longstanding headaches accompanied with the oppression of the ear [63].

Ointments prepared from leaves are used for burns and earache [64]. Topically, the poultice of the leaves is a good healer of wounds and is also applied to ulcers, tumors, and piles. A poultice made from the seeds and leaves is used to draw out splinters [63]. Infusion of the flowers in olive oil is used as earache drops having strong bactericidal properties [65,66]. An infusion or tea of the plant is taken internally in the treatment of a wide range of chest and abdominal complaints including a productive cough and diarrhea [65-67]. It is used as a tobacco substitute [68] and rheumatic problems [69].

A decoction of the seeds is used to soothe chilblains and chapped skin [62]. The juice of the plant and powder made from the dried roots is said to quickly remove rough warts when rubbed on them. A decoction of the roots is said to too thache and relieve also cramps and convulsions alleviate [63]. A number of pharmacological activities such as anti-inflammatory, anti-cancer, anti-oxidant, anti-microbial, anti-hepatotoxic, anti-viral and anti-hyperlipidemic activity have been ascribed to this plant. *Verbascum thapsus* was evaluated for its anti-hepatoma activity on five human liver cancer cell lines, i.e. HepG2/C3A, SK-HEP-1, HA22T/VGH, Hep3B and PLC/PRF/5.

The hot water extract of crude drug was examined by *in vitro* evaluation for its cytotoxicity. The results of them showed that the effect of the crude drug on hepatitis B virus genome-containing cell lines was different from non those against hepatitis B virus genome-containing cell lines. The inhibitions at 2000  $\mu$ g/ml dose were 31% (HepG2/C3A), 69.9% (HA22T/VGH) and 11.6% (PLC/PRF/5) on HBV (-) and HBV (+) cell lines. V. Thapsus was observed to be potent effective against the growth of three cell lines [70]. Aqueous extract and alcoholic extract of *V. thapsus* anti-cancer resulted *in vitro* enzyme MMP-9 and Cathepsin B inhibition assay [71]. Turker and Camper studied Biological activity of common mullein extracts (water; methanol, ethanol) and commercial Mullein products using selected bioassays, antitumor and two toxicity assays (brine shrimp and radish seed). The compound 3,5-dihydroxy-6,7-dimethoxy flavones, beneficial as an anti-asthmatic and anti-allergic was isolated from *Verbascum thapsus*, showed 24.8% inhibition of leukotriene biosynthesis in guinea pig ileum at  $1.6 \times 10^{-5}$  M [72]. Follow-up studies should be performed to identify the responsible bioactive principle and to determine the anticancer mechanism of action.

### Conclusion

Angiogenesis is the formation of new blood vessels. It involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. There is approved drugs that have anti angiogenic activity, including sorafenib (Nexavar), pazopanib (Votrient), and everolimus (Afinitor) [73]. However, the biologic response modifiers are available in the market but still under critical examination for their effects in angiogenesis patients. With increasing awareness, a large section of angiogenesis patients has started adopting the alternate therapeutic measures. There is a need for screening and scientifically evaluating a number of known ancient Iranian medicinal plants for providing newer and safer treatment options with minimum side effects.

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