



## **A Review on Medicinal Plants with Antiangiogenic Activity Available in Iraq**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author AHK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EJK and HBS managed the analyses of the study. Author OHA managed the literature searches. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Aims:** To correlate the antiangiogenic effect of medicinal plants available in Iraq.

**Study Design:** Study design by correlate different study and article about the antiangiogenic activity of different plant available in Iraq and make collection of different information of medicinal plant grow in Iraq.

**Methodology:** We included the irregular growth of blood vessels contributes to the pathogenesis of many diseases, which has a major impact on human health. Indeed, a long list of disorders is characterized and caused by excessive angiogenesis. Historically, the best known disorders stemming from angiogenesis are cancer, psoriasis, arthritis and blindness, but many additional common disorders such as obesity, asthma, atherosclerosis and infectious disease and correlate different plant by activity with antiangiogenic properties.

**Results:** The plant sources of Iraq are likely to provide effective antiangiogenic substances. All

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examples that are provided in this review of promising bioactive materials obtained from different plants with other therapeutic uses.

**Conclusion:** Aerial part of different plant in Iraq possess antiangiogenic activity has crucial activity to treat disease relate angiogenesis.

*Keywords: Medicinal plants; phytochemicals; bioactive materials; antiangiogenic activity; Iraq.*

## 1. INTRODUCTION

Angiogenesis is a process that involves the growth of new blood vessels from pre-existing vessels [1]. Physiological angiogenesis takes place mainly during wound healing and during the menstrual [2], whereas, pathological angiogenesis occurs in diseases such as cancer, rheumatoid arthritis, endometriosis and diabetic retinopathy. An abnormal or high level of angiogenesis also contributes to vascular malformation, obesity, chronic inflammation, while on the other hand insufficient angiogenesis is related to Alzheimer's disease, coronary artery disease, stroke, myocardial infarction and ulcer formation [3]. Various challenges in treating cancers are linked to tumour progression and metastasis [4]. The growth of solid malignancies and their metastasis in addition to many other disorders depends on adequate oxygen and nutrient supply, which ensures the formation of new blood vessels (angiogenesis) within the tissue that are vital for disease development [5]. Therefore, anti-angiogenic agents may contribute in suppressing cancer growth by preventing nutrient and oxygen supply to the tumour tissue.

With growing interest the anti-angiogenic therapy has received considerable attention and is widely administered in several types of human cancers.

Nonetheless, this type of therapy may induce multiple signaling pathways compared with cytotoxics and lead to worse outcomes in terms of resistance, invasion, metastasis [6].

Plants have long been used as an important source of therapeutic agents against several diseases including cancer [7]. The detection of plant extracts with anti-angiogenic activity and limited toxicity can increase the use of natural products that exhibit limited side effects. The aim on to Iraqi medicinal plants having antiangiogenic properties. The information presented could be of value in the development of new drugs formulated for the treatment of angiogenesis related diseases.

### 1.1 Angiogenesis Related Disorders

The irregular growth of blood vessels contributes to the pathogenesis of many diseases, which has a major impact on human health. Indeed, a long list of disorders is characterized and caused by excessive angiogenesis. Historically, the best known disorders stemming from angiogenesis are cancer, psoriasis, arthritis and blindness, but many additional common disorders such as obesity, asthma, atherosclerosis and infectious disease are included, and the list is still growing (Table 1).

**Table 1. Diseases characterized or caused by abnormal or excessive angiogenesis [3]**

Organ	Diseases in mice or humans
Numerous organs	Cancer, infectious diseases, autoimmune disorders
Blood vessels	Vascular malformations , DiGeorge syndrome; HHT (mutations of endoglin or ALK-1; cavernous hemangioma; atherosclerosis; transplant arteriopathy
Adipose tissue	Obesity , weight loss by angiogenesis inhibitors
Skin	Psoriasis, warts, allergic dermatitis, scar keloids, pyogenic granulomas, blistering disease, Kaposi sarcoma in AIDS patients
Eye	Persistent hyperplastic vitreous syndrome , diabetic retinopathy, retinopathy of prematurity, choroidal neovascularization
Lung	Primary pulmonary hypertension, asthma, nasal polyps
Intestines	Inflammatory bowel and periodontal disease, ascites, peritoneal adhesions
Reproductive system	Endometriosis, uterine bleeding, ovarian cysts, ovarian hyperstimulation
Bone, joints	Arthritis, synovitis, osteomyelitis, osteophyte formation

**Cancer:** Several studies have shown that angiogenic activators play a crucial part in the development and spread of tumours. For example, on immunohistochemical examination, the Vascular endothelial growth factors (VEGF) family and their receptors were found to be expressed in about 50% of human malignant tumours that have been investigated [9]. The VEGF family is known to significantly highly affect the prognosis of adeno-carcinomas that have developed in the uterine cervix, [10], endometrium, [11], ovary [12], and stomach [13]. In addition, a significant relation between the expression of VEGF and prognosis has been described in colorectal cancer [14], breast cancer [15], lung cancer [16], head and neck squamous cell carcinoma [17]. These studies also indicated that the levels of angiogenic factors in tissue reflect the aggressive spread of tumour cells, and thus have indicative value in the detection of the high-risk patients with poor prognosis.

**Inflammation:** Inflammatory proteins are highly linked to angiogenesis [18]. Pro-inflammatory cytokines such as Tumour Necrosis Factor-Alpha (TNF- $\alpha$ ), Interleukin-1 Beta (IL-1 $\beta$ ), IL-6, IL-8 and Monocyte Chemoattractant Protein (MCP)-1 potentially promote inflammation cascades of rheumatoid arthritis (RA) and inflammation coupled angiogenesis [19]. Rheumatoid arthritis is characterized by the proliferation of endothelial cell, angiogenesis, leukocyte activation and pannus formation [20]. Therefore, angiogenesis inhibitors could be used to treat arthritis [21].

**Diabetic retinopathy:** Proliferative diabetic retinopathy is one complication of diabetes mellitus caused by excessive angiogenesis [22]. Reactive oxygen species (ROS) play a crucial role in encouragement of VEGF expression, proliferation, migration and tube formation of retinal endothelial cells [23].

**Endometriosis:** Outgrowth of endometrium-like tissue into the uterine cavity, is a common disease among females of reproductive age. It has become apparent that angiogenesis plays an important role in its pathophysiology [24]. It is further known that epigallocatechin gallate (EGCG) inhibited the estrogen-induced activation of endothelial cells [25]. It also elevated apoptosis in an endometriosis mouse model by decreasing the mRNA levels of VEGF and enhancing the mRNA levels of Nuclear factor (NF- $\kappa$ B) and Mitogen-activated protein kinase 1 (MAPK1) [25].

**Obesity:** Evidence suggests that obesity is linked to the substantial modulation of adipose tissue structure, the process that involves angiogenesis and extracellular matrix remodelling. In the early steps of adipose tissue outgrowth, blood vessel formation and pre-adipocyte differentiation are stimulated by adipose tissue explants and endothelial cells respectively. Therefore, modulation of angiogenesis and of proteolysis may impair adipose tissue development [26].

## 2. METHODOLOGY

Conventional textbooks and databases such as Web of Science, Scopus, PubMed were searched for scientific articles published until August, 2019, using the following descriptors: "Angiogenesis", "herbal medicine" or "Iraqi plants", "medicinal plants Iraq" or "traditional medicine in Iraq" without limiting the search items. According to citation from different research and articles with different years.

### 2.1 Data Collection

A literature search was performed regarding the use of aerial medicinal plants to treat angiogenesis diseases. This included all possible sources of information regarding in vivo and in vitro studies regardless of language or publication status (published, unpublished, in press and in progress). Computerized literature searches were performed on MEDLINE, SCOPUS, GOOGLE SCHOLAR, MEDLINE EBSCOHOST AND SCIENCE DIRECT databases. In addition, the Global Electronic Thesis and Dissertations (ETD) and Iraqi ETD were searched for Grey literature. For the retrieval of publications in the databases, the researchers conducted a specific search to define the maximum Medical Subject Headings (MeSH) terms that were related to the research goal. The key terms were "Plant (MeSH)" And "angiogenesis", In addition to these key words all plants from the Iraqi Pharmacopoeia Monograph project were included in the searches [26] Each plant was searched individually and in conjunction with the aforementioned (MeSH) terms. Further papers were retrieved from reference lists of review articles. Due to the limited number and diversity of studies, including the difficulty to prove comparisons between studies, a meta-analysis was not conducted.

### 2.2 Study Selection

**Inclusion criteria:** Publications that described the use of medicinal plant species (alone or with

any combination of Iraqi herbs) indigenous to treat angiogenesis were included in the review. This included in vivo and in vitro studies with no language restrictions and date limitation.

**Exclusion criteria:** Non-Iraqi plants (not endemic to Iraqi, and imported plants) were excluded. Lastly, viral and bacterial studies were excluded.

### 2.3 Selection of Data/ Reports

The inclusion of data was assessed by all authors. Discrepancies and disagreements were resolved by consensus among the researchers in several meetings. The first phase of this study was the retrieval of articles based on titles and abstracts of potentially relevant studies in each database. In the second phase the full PDF articles were downloaded and assessed for eligibility. The reference list of review articles was also evaluated in search of other publications of interest not retrieved in the database search in phases.

### 2.4 Data Analysis

An investigative reading of the bibliographic materials was conducted, assessing the title and abstract of the research. Then, the articles that appeared in the results of all were verified. After completing the analysis, a selective reading of the articles that included plants and materials with botanical name were done and checked in as information contained in the consulted periodicals were done, thus allowing the summation of the data from the review. Information on antiangiogenic action was identified directly in the selected article. More than one articles and criteria according to documented article.

## 3. RESULTS

In the present study, a total of 69 abstracts were identified from electronic searches. The search identified 65 articles, with 0 from PUBMED, 6 from MEDLINE, 7 from SCOPUS, 32 from GOOGLE SCHOLAR, 7 from SCIENCE DIRECT and 8 from the GLOBAL and SOUTH AFRICAN ETD. An additional 5 articles were retrieved from reference lists of review articles. After the removal of duplicates, as well as screening from relevant titles and abstracts, a total of 49 articles underwent a full text review and 10 articles met the inclusion and exclusion criteria. Table 1 below illustrates the 10 studies selected.

### 3.1 Diversity and Distribution of Medicinal Plants

***Vitex agnus-castus:*** *Vitex agnus castus* also known as chaste berry herb. *Vitex agnus castus* extracts may hold promising activity against tumour treatment as adjuvant with chemotherapy or in targeting angiogenesis attributed diseases. Methanol extract showed dose -dependent inhibitory activity on rat aorta assay and the IC<sub>50</sub> was (21.73 µg/ml). Methanol extract of *Vitex agnus castus* leaves showed the significant free radical scavenging activity IC<sub>50</sub>—was (126.79 µg/ml), compared to other extracts [27].

***Zizyphus spina-christi:*** *Zizyphus spina-christi* (L.) Wild. Commonly known as Christ's thorn. Usually in Arabic the fruits take the name of the tree, but in the case of *Zizyphus spina-christi*, the tree is called siddir and the fruit nabag [28]. The methanol leaves extract of *Zizyphus spinachristi* has potential anti-angiogenic activity and this activity may be attributed to the high free radical scavenging ability. Methanol leaves extract was the most biologically active extract in terms of blood vessels growth inhibition compared to petroleum ether, chloroform and water extracts (P< 0.05). Methanol extract serial concentrations showed significant dose-dependent inhibition activity (P<0.05) on rat aorta assay with an IC<sub>50</sub> of (29.08 µg/ml) [28].

***Matricaria Chamomilla:*** *Matricaria chamomilla* is mainly used as a sedative, anxiolytic and anti-inflammatory. The major biochemical content of *Matricaria chamomilla* flowers are chamazulene, apigenin, and bisabolol [29]. Results showed that methanol extracts of *Matricaria chamomilla* flowers have the most significant anti-angiogenesis effect and this activity may be attributed to the high free radical scavenging capacity. Methanol extract of *Matricaria chamomilla* flowers exhibited a significant dose-dependent anti-angiogenesis effect with an IC<sub>50</sub> value of (29.85 µg/ml) [29].

***Anabasis articulate:*** *Anabasis articulata*, also called Eshnan, Ajremor Berry bearing glasswort, is distributed in Syria, Algeria, Egypt and Iraq countries. *Anabasis articulata* is widely used in traditional medicine to manage diabetes, fever, eczema and kidney infections. Their stems have many active molecules that may have more than one pharmacological effect [30]. Phytochemical screening on *Anabasis articulata* show the presence of saponin, coumarins, flavonoids,

**Table 2. Demographic information about the available plants with antiangiogenic properties**

<b>Scientific name</b>	<b>Family</b>	<b>Arabic name</b>	<b>Province</b>	<b>Part used</b>	<b>IC<sub>50</sub></b>	<b>Reference</b>
<i>Vitex agnuscastus</i>	Lamiaceae	Kaf Mariam	Karbala	Leaves	21.73 µg/ml	27
<i>Zizyphus spina-christi</i>	Rhamnaceae	Zizyphon	Nasiriyah	Leaves	29.08 µg/ml	28
<i>Matricaria Chamomilla</i>	Asteraceae	Babunag	Baghdad	Flowers	29.85 µg/ml	29
<i>Anabasis articulata</i>	Amaranthaceae	Sidir	Baghdad	Stem	18.27 µg/ml	30
<i>Trigonella foenum-graecum</i>	Fabaceae	Helba	Baghdad	Seeds	3.15 µg/ml	31
<i>Phoenix dactylifera</i>	Arecaceae	Nakhil	Baghdad	Seeds	28.4 µg/ml	32
<i>Olea europaea</i>	Oleaceae	Zaitoon	Baghdad	Seeds	24.85 µg/ml	33
<i>Mentha piperita</i>	Lamiaceae	Neana'a	Baghdad	Leaves	3.7 µg/ml	34
<i>Cuminum cyminum</i>	Apiaceae	Kammon	Baghdad	Seeds	-----	35
<i>Cyperus rotundus</i>	Cyperaceae	Si'ed	Babil	Whole plant	15.39 µg/ml	8

*IC<sub>50</sub>: The half maximal inhibitory concentration of methanol extract on rat aorta assay*

phenolics, alkaloids, anthraquinones, irodoids, Cyanogenic glycosides, Cardiac glycosides, Carbohydrates or Gglycosides, Unsaturated sterols or triterpenoids, and Tannins [36]. Literature surveys showed high concentrations of many chemical groups which may have a potent activity in angiogenesis process such as flavonoids, coumarins, saponin, glycine, alkaloids and others that exist in the stems of *Anabasis articulata* [37].

***Trigonella foenum-graecum*:** This annual herb have been used in various countries to treat of diabetes, hyperlipidemia, cancer, infection, gastrointestinal ulcer, and obesity, etc The biological and pharmacological effect of fenugreek herb are thought to be due to the diversity of its constituents: steroids, N-compounds, poly phenolic substances, volatile substances, amino acids. The seeds are rich in vitamins, flavonoids, terpenoids, carotenoids, cumarins, curcumins, lignin, saponin, phenol [38] and it is exhibited significant anti – angiogenesis activity, however methanol extract shows the highest anti – angiogenesis activity as well as significant dose – dependent anti – angiogenic effect. In addition, methanol extract exhibited a significant free radical scavenging activity by DPPH assay and in concentration dependent manner [39].

***Phoenix dactylifera*:** Also known as Date palm seeds represent a good source of fatty acids, phenolic acids, and flavonoids, sterols, dietary fibers, proteins, minerals, vitamins and antioxidants [40]. The seeds extract exhibited significant anti–angiogenesis activity. However, chloroform and methanol extracts demonstrated the best anti–angiogenesis activity as well as significant dose–dependent anti–angiogenic effect [41].

***Olea europaea*:** Also known as the olive tree. Olive oil is well known for its flavour and medicinal benefits, the leaves has been used medicinally in a variety of regions. Olive leaf and olive leaf extracts have anti-aging, antioxidant, immunostimulator, cardio protective, blood sugar regulating, anti-inflammatory and antibiotic materials [42]. Phenolic acids were the first group of phenolic compounds identified in virgin olive oil. Tyrosol, vanillic acid, luteolin, and apigenin, tocopherols and tocotrienols, were identified and quantified by LC-MS [43]. Each of chloroform and methanol extracts of *Olea europaea* seeds shows a significant dose-dependent antiangiogenic effect with IC<sub>50</sub> (22.379 µg/ml and

24.85 µg/ml) respectively. Furthermore, chloroform and methanol extracts exhibited a significant free radical scavenging activity with IC<sub>50</sub> (37.61 µg/ml and 52.69 µg/ml) respectively [44].

***Mentha piperita*:** *Mentha piperita* is also peppermint. is the known as a flavour that is often used in many applications. In addition, peppermint is found in soaps, topical care products as well as shampoos. Peppermint oil is generally used to relieve or treat symptoms such as nausea, vomiting, morning sickness, anorexia, abdominal pain, indigestion, and flatulence. Skin preparations having peppermint oil are utilized for treating of headache, muscle pain, joint conditions, allergic rash and pruritus [45]. Peppermint leaves as well as oil usually used internally (upper-gastrointestinal tract and bile ducts) for management of diarrhea, irritable bowel syndrome, Crohns disease, and ulcerative colitis, catarrh of the respiratory tract, and inflammation of the oral mucosa [46]. Leaves were found to be a good source of volatile oils (menthol, menthone, menthofuran, menthyl acetate, cineol, and limonene), phenolic acids (caffeic, chlorogenic and rosmarinic acid), flavonoids (menthoside, isorhoifolin, flavonones and luteolin), and tannins. Other constituents include azulene [47], A phenolic compound in peppermint leaves possess numerous health benefits and anti–angiogenesis characteristics [48,49].

***Cuminum cyminum*:** This plant cultivated extensively in Iraq, Turkey, India, China, Libya, and Palestine [50]. In traditional medicine, cumin was used to treat hoarseness, jaundice, dyspepsia and diarrhoea. The plant seeds were used for stomachic, diuretic, carminative, stimulant, astringent and abortifacient effect [51]. The pharmacological activity of *Cuminum cyminum* herb thought to be due to the variety of its chemical constituents like alkaloid, anthraquinone, coumarin, flavonoid, glycoside, protein, resin, saponin, tannin and steroid [52]. Methanolic extract of *Cuminum cyminum* seeds inhibit new blood vessels creation and structure of existing vasculature was disrupted, the blood vessels count significantly decreased and This data may be due to the existence of many chemicals having anti-angiogenesis effect. The data showed that monoterpenes (cuminol), Propanal, 2-methyl-3-phenyl and Cumin aldehyde are highly existed. Blood vessels growth inhibition may be correlated with these constituents, past study showed that *Cuminum*

*cyminum* seeds contain terpenes [53]. Terpen has known of its activity as antioxidant, anticancer, tumor inhibitors through anti angiogenic effect [54].

**Cyperus rotundus:** *Cyperus rotundus*, the Arabic common name is Saed, Sajal, Seil and in English it is called nut grass, purple nutsedge, Nagarmotha and in China known as Xiang Fu. *Cyperus rotundus* is distributed in many countries such as in Iraq, Egypt, Tunisia, China and India [55]. Fruits were used as carminative, diuretic, tonic, stomachic, anti-bilious and refrigerant [56]. Whereas, the tubular part used for the treatment of dysmenorrhoea and irregular menstrual cycle. Different pharmacological and biological activities including anti-Candida Albicans [57], anti-inflammatory [58], antidiabetic [59], anti-diarrhoeal, antioxidant [60], cytoprotective [61], antimutagenic [62], antimicrobial, antibacterial [63], cytotoxic and apoptotic, anti-pyretic and analgesic activities have been reported for *Cyperus rotundus* [64]. *Cyperus rotundus* ethanol extract showed significant dose-dependent blood vessels inhibition compared to the negative control ( $p < 0.05$ ). Phytochemical investigation of alcoholic extract indicated the presence of different chemical constituents like alkaloids, glycosides, steroids, tannins, carbohydrates and flavonoids [9].

#### 4. CONCLUSION

Medicinal plants play a significant role in the management of angiogenesis coupled disorders gradually in near future. Available Iraqi medicinal plants with ability to decrease the expansion of angiogenesis or be utilized as adjuvant with other drugs for patients were described through this comprehensive review. Data that is provided will basically help to design new molecule not only in Ayurvedic but also modern drugs. In addition, further research should be conducted on these plants.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

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#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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