

A Review on Medicinal Plants with Antiangiogenic Activity Available in Iraq

ABSTRACT

Angiogenesis plays a critical role in diseases progression and exacerbations. This article has been prepared to review some medicinal plants that have been analysed for their antiangiogenic activity. The plant sources of Iraq are likely to provide effective antiangiogenic substances. All examples that are provided in this review of promising bioactive materials obtained from different plants with other therapeutic uses. The phytochemical exploration of these plants has contributed for the discovery of new treatments for many disorders. Last years owing to the fear of adverse effects people favour the use of natural plant products for disease treatment. This review also helps to summarize the diverse methodologies and various ways to evaluate the potential natural compounds having antiangiogenic activity. The information collected here will take part in an essential role to develop new drug formulation for treatment of angiogenesis related diseases and further research should be done on above mentioned plants.

Keywords

Medicinal plants, phytochemicals, bioactive compounds, Antiangiogenic activity.

INTRODUCTION

Natural products have been used for the treatment of different diseases from thousands of years. Diverse plants have been used as medicaments in many civilizations in Mesopotamia, Egypt, China, India, and Greece from ancient times and a large number of modern drugs have been developed from them. Records on the medicinal uses of plants appeared in about 2600 BC from the Sumerians and Acadians⁽¹⁾. Angiogenesis is the process involving the growth of new blood vessels from pre-existing vessels⁽²⁾. Physiological angiogenesis takes place mainly during wound healing and menstrual cycle of the female⁽³⁾, 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, on the other hand insufficient angiogenesis is related to Alzheimer’s disease, coronary artery disease, stroke, myocardial infarction and ulcer formation ⁽⁴⁾. Various challenges in treating cancers are linked to tumour progression and metastasis ⁽⁵⁾. The growth of solid malignancies and their metastasis in addition to many other disorders depends closely on adequate oxygen and nutrient supply, which ensures the formation of new blood vessels (angiogenesis) within the tissue that are vital for disease development ⁽⁶⁾. Therefore, anti-angiogenic agents may contribute in suppressing cancer growth by preventing nutrient and oxygen supply to the tumour tissue. Plants have long been used as an important source of therapeutic agents against several diseases including cancer ⁽⁷⁾. While several natural products are widely used in cancer treatment, the use of other plant products is limited to the support of the immune system and/or the increase in the anticancer effects of other anticancer drugs ⁽⁸⁾. The detection of plant extracts with anti-angiogenic activity and limited toxicity can increase the effects of presently used anticancer drugs without increasing their side effects. Like other countries in Iraq, there are lot of research has been done and some of them are still going on as it is to be mentioned that **till now the best source of antiangiogenic agents is medicinal plant(This statement is not very strong??)** ⁽⁹⁾. The major target of this review article was to give some information to Iraqi researchers about some medicinal plants having antiangiogenic properties available in Iraq.

Angiogenesis related disorders

The irregular growth of blood vessels has a major impact on our health and contributes to the pathogenesis of many diseases, some quite unexpected. Indeed, a long list of disorders is characterized or caused by excessive angiogenesis. Historically, the best known 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 ⁽⁴⁾

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. On immunohistochemical examination, the vascular endothelial growth factors (VEGF) family and their receptors were found to be expressed in about 50% of the human malignant tumours that have been investigated ⁽¹⁰⁾. These factors are known to be highly affect the prognosis of adeno-carcinomas that have developed in the uterine cervix, ⁽¹¹⁾, endometrium, ⁽¹²⁾, ovary ⁽¹³⁾, and stomach ⁽¹⁴⁾. In addition, a significant relation between the expression of VEGF and prognosis has been described in colorectal cancer ⁽¹⁵⁾, breast cancer ⁽¹⁶⁾, lung cancer ⁽¹⁷⁾, head and neck squamous cell carcinoma ⁽¹⁸⁾. 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 ⁽¹⁹⁾. Pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), IL-6, IL-8 and monocyte chemoattractant protein (MCP)-1 potentially promote inflammation cascades of rheumatoid arthritis (RA) and inflammation coupled angiogenesis ⁽²⁰⁾. Rheumatoid arthritis is characterized by proliferation of endothelial cell, angiogenesis, leukocyte activation and pannus formation ⁽²¹⁾. Therefore, angiogenesis inhibitors could be indicated to treat arthritis ⁽²²⁾.

Diabetic retinopathy

Proliferative diabetic retinopathy is one complications of diabetes mellitus caused by excessive angiogenesis ⁽²³⁾. Reactive oxygen species (ROS) play a crucial role in encouragement of VEGF

expression, proliferation, migration and tube formation of retinal endothelial cells⁽²⁴⁾. - out of alignment

Endometriosis

Outgrowth of endometrium-like tissue into the uterine cavity, is a common disease among females of reproductive age. It has currently become apparent that angiogenesis plays an important role in its pathophysiology⁽²⁵⁾. EGCG inhibited the estrogen-induced activation of endothelial cells⁽²⁶⁾. It also elevated apoptosis in an endometriosis mouse model by decreasing the mRNA levels of VEGF and enhancing the mRNA levels of NF- κ B and MAPK1⁽²⁷⁾.

Obesity

Evidences suggests that obesity is linked to the substantial modulation of adipose tissue structure, the process which 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⁽²⁸⁾.

Methodology

Conventional text books and databases such as Web of Science, Scopus, PubMed were searched for scientific articles published till 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. Since when have the bibliographic research been conducted?

Data analysis

An investigative reading of the bibliographic materials were 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. How many articles were found? What is the criterion of the selected articles?

Outcomes

There are a lot of work has been carried out on the antiangiogenic effect of plants. A demographic description of available plants having antiangiogenic properties in Iraq is provided in Table 2.

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

Scientific Name	Family	Arabic Name	Province	Part used	IC ₅₀	Reference
<i>Vitex agnus-castus</i>	Lamiaceae	Kaf Mariam	Karbala	Leaves	21.73 µg/ml	29
<i>Zizyphus spina-christi</i>	Rhamnaceae	zizyphon	Nasiriyah	Leaves	29.08µg/ml	30
<i>Matricaria Chamomilla</i>	Asteraceae	Babunag	Baghdad	Flowers	29.85µg/ml	31
<i>Anabasis articulata</i>	Amaranthaceae	Sidir	Baghdad	Stem	18.27µg/ml	32
<i>Trigonella foenum-graecum</i>	Fabaceae	Helba	Baghdad	Seeds	3.15 µg/ml	33
<i>Phoenix dactylifera</i>	Arecaceae	Nakhil	Baghdad	Seeds	28.4 µg/ml	34
<i>Olea europaea</i>	Oleaceae	Zaitoon	Baghdad	Seeds	24.85 µg/ml	35
<i>Mentha piperita</i>	Lamiaceae	Neana'a	Baghdad	Leaves	3.7µg/ml	36
<i>Cuminum cyminum</i>	Apiaceae	Kammon	Baghdad	Seeds	-----	37
<i>Cyperus rotundus</i>	Cyperaceae	Si'ed	Babil	Whole plant	15.39 µg/ml	9

IC₅₀: The half maximal inhibitory concentration of methanol extract on rat aorta assay

The scientific names of plants should be corrected to italic (Ex: *Cyperus rotundus* ; *Vitex agnus castus*)

Vitex agnus-castus

Vitex agnus castus F. is a Lamiaceae also known as chaste berry herb. It is widely used medicinally in homeopathic regulation of amenorrhea, infertility, menopause due to estrogenic activity of phytoestrogens present in *Vitex agnus castus* ⁽³⁸⁾. ~~Vitex agnus-castus~~ These extracts have high inhibition activity against this process, this herbs may has promising activity against tumour as adjuvant with chemotherapy or in targeting angiogenesis attributed diseases. Methanol extract showed dose-dependant inhibitory activity on rat aorta assay and the IC₅₀ was (21.73 µg/ml).

Methanol extract of *Vitex agnus castus* leaves showed the significant free radical scavenging activity IC_{50} was (126.79 μ g/ml), compared to other extracts. IC_{50} was (126.79 μ g/ml)⁽²⁹⁾.

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⁽³⁹⁾. 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 IC_{50} was (29.08 μ g/ml)⁽³⁰⁾.

Matricaria Chamomilla

Matricaria chamomilla is widely used in many countries as the traditional treatment for various diseases. The use of *Matricaria chamomilla* uses return to ancient Greece and Rome⁽⁴⁰⁾. Its mainly uses are as a sedative, anxiolytic and anti-inflammatory. The major content of *Matricaria chamomilla* flowers are chamazulene, apigenin, and bisabolol⁽⁴¹⁾. The 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 IC_{50} (29.85 μ g/ml)⁽³¹⁾.

Anabasis articulata

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. *Anabasis articulata* Their stems have many active molecules that may have more than one pharmacological effect⁽⁴²⁾. Phytochemical screening on *Anabasis articulata* show the presence of saponin, coumarins, flavonoids, phenolics, alkaloids, anthraquinones, irodoids, Cyanogenic glycosides, Cardiac glycosides, Carbohydrates or Glycosides, Unsaturated sterols or Triterpenoids, and Tannins⁽⁴³⁾. 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*.⁽⁴⁴⁾

Trigonella foenum-graecum

An annual herb belongs to the family Leguminosae, the species name is *Trigonella foenum-graecum*; its English name comes from the Latin words meaning Greek hay indicating its use as a forage crop in the past. It is an old plant that has been documented in ancient herbal medicine. Fenugreek leaves and seeds are used in various countries worldwide for different purposes like medicinal uses for treatment of diabetes, hyperlipidemia, cancer, infection, gastrointestinal ulcer, and obesity, etc. **And** **it** is mainly used in cooking food due to its strong flavour and aroma in addition to that it is a rich source of calcium, iron, β -carotene and other vitamins B6 (ref??). 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, coumarins, curcumins, lignin, saponin, phenol⁽⁴⁵⁾ 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⁽³³⁾.

Phoenix dactylifera

It is also known as date palm F. Palmaceae. From the viewpoint of botany, *Phoenix dactylifera* is derived from a Phoenician "Phoenix," which means date palm, and "dactylifera" from a Greek word "daktulos" meaning a finger. The date palm is considered the most important nutritional source for human in arid and semi-arid areas and an integral part of Arabian diet⁽⁴⁶⁾. The plant fruit used for treatment of sore throat, cold, relief of fever, abdominal problems in addition the pollens were used by the Egyptians to ameliorate fertility in women⁽⁴⁷⁾. The seeds of date palm are widely used in animal feed to improve growth; the oil of the seeds is used in cosmetics, and the quality of these products is found to be promising⁽⁴⁸⁾. Date palm seeds represent a good source of fatty acids, phenolic acids, and flavonoids, sterols, dietary fibers, proteins, minerals, vitamins and antioxidants⁽⁴⁹⁾. 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 ⁽³⁴⁾.

Olea europaea

Also known as the olive tree, belongs to the family Oleaceae. 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 ⁽⁵⁰⁾. 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 ⁽⁵¹⁾. Each of chloroform and methanol extracts of **Olea europaea** seeds shows a significant **dose**-dependent antiangiogenic effect with **IC₅₀50** (22.379µg/ml and 24.85 µg/ml) respectively. Furthermore, chloroform and methanol extracts exhibited a significant free radical scavenging activity with **IC₅₀50** (37.61µg/ml and 52.69µg/ml) respectively ⁽³⁵⁾.

Mentha piperita

Mentha piperita is also peppermint. Mentha (mint) is a genus of the plants in the family Lamiaceae. The plant distributed in Europe and the Middle East, but now widespread by cultivation in many lands of the world. It is regarded as the earliest and most popular herb which can be used in many shapes (leaf, leaf water, leaf extract and oil). 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 ⁽⁵²⁾. 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 ⁽⁵³⁾. **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 ⁽⁵⁴⁾, A phenolic compound in peppermint leaves possess numerous health benefits and anti-angiogenesis characteristics ^(55,56).

Cuminum cyminum

This plant is cultivated extensively in Iraq, Turkey, India, China, Libya, and Palestine⁽⁵⁷⁾. 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⁽⁵⁸⁾. 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⁽⁵⁹⁾. 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 Cuminaldehyde are highly existed. Blood vessels growth inhibition may be correlated with these constituents, past study showed that **Cuminum cyminum** seeds contain terpenes⁽⁶⁰⁾. Terpenes has known of its activity as antioxidant, anticancer, tumor inhibitors through anti angiogenic effect⁽⁶¹⁾.

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⁽⁶²⁾. Fruits were used as carminative, diuretic, tonic, stomachic, anti-bilious and refrigerant⁽⁶³⁾. Whereas, the tubular part used for the treatment of dysmenorrhoea and irregular menstrual cycle. Different pharmacological and biological activities including anti-Candida **albicans**⁽⁶⁴⁾, anti-inflammatory⁽⁶⁵⁾, antidiabetic⁽⁶⁶⁾, antidiarrhoeal, antioxidant⁽⁶⁷⁾, cytoprotective⁽⁶⁸⁾, antimutagenic⁽⁶⁹⁾, antimicrobial, antibacterial⁽⁷⁰⁾, cytotoxic and apoptotic, anti-pyretic and analgesic activities have been reported for **Cyperus rotundus**⁽⁷¹⁾. **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⁾.

The scientific names of plants should be corrected to italic (Ex: *Cyperus rotundus* ; *Vitex agnus castus*), the name of plants are repeated unnecessarily throughout paragraph and it is necessary to standardize the information by writing more details about IC50 in the text.

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.

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