

The Role of Natural Extracts in the Management of Infantile Hemangiomas and Vascular Tumors

Iulia Cristina Roca^{1,*}, Elena Cojocaru², Carmen Daniela Rusu¹, Laura Mihaela Trandafir³, Cătălina Iulia Săveanu⁴, Vasile Valeriu Lupu^{3,*}, Lăcrămioara Ionela Butnariu⁵, Viorel Țarcă^{6,*}, Mihaela Moscalu⁶, Jana Bernic⁷, Ancuța Lupu^{3,*}, Elena Țarcă¹

¹Department of Surgery II, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ²Department of Morphofunctional Sciences I – Pathology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ³Department of Mother and Child Medicine–Pediatrics, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ⁴Surgical Department, Discipline of Preventive Dentistry, Faculty of Dental Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ⁵Department of Medical Genetics, Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ⁶Department of Preventive Medicine and Interdisciplinarity, "Grigore T. Popa" University of Medicine and Pharmacy, Iași, 700115, Romania; ⁷Discipline of Pediatric Surgery, "Nicolae Testemițanu" State University of Medicine and Pharmacy, Chisinau, Moldova

*These authors contributed equally to this work

Correspondence: Carmen Daniela Rusu; Cătălina Iulia Săveanu, Tel +40765485446, Email carmen-daniela.rusu@umfiasi.ro; catalina.saveanu@umfiasi.ro

Abstract: Hemangiomas are vascular tumors resulting from the proliferation of endothelial-like cells; they are the most common childhood tumors, affecting approximately 5–10% of newborns and infants. Besides hemangiomas, which are definitely benign tumors despite their overgrowth potential, there are other vascular tumors like hemangioendotheliomas, which may display intermediate characteristics between benign hemangiomas and highly malignant angiosarcomas. Standard therapy may be constricted by serious adverse effects, high cost, or traumatic influence. Diet is a major resource for health preservation, disease prevention, and treatment. The therapeutic property of edible berries, marine products, or medicinal plants have long been known and used in traditional medicine; a plant-based nutrition can prevent the development and progression of diseases associated with extensive neo-vascularization. The purpose of our review is to highlight those natural treatments that hemangioma and vascular tumor patients can receive in the future, both for their benefit and that of their families. We performed the review according to the Preferred Reporting Items for Systematic Reviews and Metanalysis Statement. We used the Web of Science, PubMed, and EMBASE engines for the study, and searched for the association of hemangioma with naturopathic treatment/plant extract/plants in published articles. We found that natural extracts from plants and fruits are cost-effective and safe treatments for hemangiomas and vascular tumors, as well as for other forms of cancer. In any case, more in vitro and in vivo studies are needed to confirm the proposed signaling pathways in tumors and validate the improvement parameters after natural products administration. The era of molecularly targeted therapy and personalized medicine is approaching and naturally occurring substances are very useful tools for tumor treatment and prevention. Plant extract substances have strong specificity and pertinence, are non-toxic and have few side effects, and may become an emerging cancer treatment.

Keywords: vascular abnormalities, plants, plant extract, naturopathic treatment

Introduction

Hemangiomas are benign vascular tumors resulting from the proliferation of endothelial-like cells, hypoxia playing a crucial role. Infantile hemangiomas are the most common childhood tumors, affecting approximately 5–10% of newborns and infants.¹ Rarely, hemangiomas are present from birth, they usually appear in the first postnatal weeks as a small red spot, and grow rapidly in size in the first months of life, up to the age of one year. After the age of one year, the natural evolution is towards stagnation and spontaneous regression, so that after the age of 5 or 6 years they can slowly and completely involute.² The bad news is that, when they are located on the face, genitals, hand or flexion regions, the increase in size of the hemangioma can affect the functionality of the nearby organ, with the appearance of

Graphical Abstract



serious complications; approximately 1–2% of all hemangiomas are life threatening.³ Also, the rapid increase in size can be complicated by ulceration, infection, repetitive bleeding, pain, functional impairment or permanent disfigurement, and if the localization is multiple (more than five) or affects the internal organs (liver or gastrointestinal tract), complications such as heart failure or intravascular coagulation can occur.^{2–5} If visceral hemangiomas are suspected, evaluation utilizing ultrasound, magnetic resonance imaging, angiography or computed tomographic imaging will differentiate a benign lesion from a malignant process.⁶ In such cases, the standard medical or surgical treatment, according to the protocols of the respective hospital, must be applied, while the remainders of the affected children live with their ugly lesion for 5–9 years until the tumor involutes. The standard therapy may be constricted by serious adverse effects, high cost, or traumatic influence, being difficult to administer by parents and difficult to tolerate by children. Besides, there are some cases in which the hemangioma, although it is located in a non-dangerous area (on the back of the thorax or on the thigh for example), creates anxiety and discomfort for the parents due to the increase in size and color. These unsightly infantile hemangiomas (IH) create anxiety for parents, who insist on applying a form of treatment. The early treatment and results are requested by the families for whom visible IHs may cause social stigma. Both for the parents' peace of mind, and to save the patient from an unnecessary medical or surgical treatment, alternative medicine and naturopathic treatment could be a solution. There are recent studies providing information and better understanding of the pathogenesis and biological features of these vascular tumors, leading to new therapeutic approaches. Angiogenesis, vasculogenesis and tumorigenesis are the main pathogenic mechanisms of hemangioma neovascularization, linked to alterations in cellular signaling pathways. These pathways have to be targeted from a therapeutic perspective, to reverse, delay or prevent infantile hemangioma growth. The major pathways implicated in IH are the VEGF/VEGFR, Notch, β -adrenergic, Tie2/angiopoietins, PI3K/AKT/mTOR, HIF- α -mediated and PDGF/PDGF-R- β pathways.^{7,8} Both in vitro and in vivo studies evaluated anti-proliferation and anti-angiogenesis effects on hemangiomas cells by natural plants extracts.⁹ For example, 15.16-Dihydrotanshinone I (DHTS), an extracted Tanshen compound, was compared with propranolol, the first-line treatment for IH currently. Cai et al demonstrated that DHTS was much more effective than propranolol in inhibiting

hemangioma cells proliferation and angiogenesis, both in vitro and in vivo.¹⁰ DHTS also downregulated HIF-1 α expression by interfering in its posttranscriptional processing, and the RNA-binding protein HuR participated in this mechanism [Duan]. Tanshen is the rhizome of *Salvia miltiorrhiza* and is used in traditional Chinese medicine for multiple therapeutic remedies, as an antioxidant and anticoagulant agent, as well as for its antibacterial and antineoplastic activities.¹¹ Besides hemangiomas, which are definitely benign tumors despite their overgrowth potential, there are other vascular tumors like hemangioendotheliomas (HE), which may display intermediate characteristics between benign hemangiomas and highly malignant angiosarcomas.¹² Some malignant tumors, including vascular ones, have benefited over time from radiotherapy, but when it comes to children, the therapeutic doses must be drastically reduced in order not to cause more harm than good. Lower doses of radiation combined with conventional chemotherapy may be used, but chemotherapeutic drugs are also highly cytotoxic both for tumor cells but also for healthy cells in the child. Therefore, chemosensitizers, radiosensitizers, and enhancers are of great interest. In this context, the association of chemotherapy or ionizing radiation therapy with the administration of dietary active substances from natural sources can be of real benefit in the treatment of vascular cancers in children.^{12,13}

Diet is a major tool in health preservation, disease prevention, and treatment. The therapeutic property of edible berries, marine products, or medicinal plants have long been known and used in traditional medicine;^{14,15} a plant-based nutrition can prevent the development and progression of disorders associated with extensive neovascularization.^{15,16} Regarding vascular tumors with a risk of malignancy, huge efforts are being made by numerous teams of researchers to find those natural extracts with anti-angiogenic and anti-cancer effects, and with as few adverse effects as possible.

The purpose of our review is to highlight those natural treatments that hemangioma and other vascular tumor patients can receive in the future, both for their benefit and that of their families.

Materials and Methods

Search Strategy of Electronic Databases

The main outcome of our study is the systematization of current data from evidence-based medicine regarding the positive effect of natural extracts or specific nutrients in the treatment of vascular tumors. We performed this review according to the Preferred Reporting Items for Systematic Reviews and Metanalysis Statement (<http://www.prisma-statement.org/> (accessed on 25 May 2023)). Five researchers independently performed data search and extraction, as well as quality assessment of the articles. We used the Web of Science, PubMed, and EMBASE engines for the study, and searched for the association of hemangioma with naturopathic treatment/plant extract/plants in published articles. The inclusion criteria were original studies written in English, literature or systematic reviews, randomized controlled trials, observational studies, series of cases, and case report studies, from the earliest time possible until May 2023. We excluded works that were not written in English, those that did not refer to the treatment of vascular tumors or that did not contain a reference to the treatment with substances derived from plants.

Results

From Web of Science, 16338 articles were found discussing about the hemangioma; anyway, only 8 results were obtained after searching for “hemangioma” AND “plant extract”/“plants” OR “hemangioma” AND “naturopathic treatment”.

A total of 27,734 results were obtained from PubMed when searched for hemangiomas, and only 262 when we added the Medical Subject Headings (MeSH) terms “plant extract”/“plants” AND “naturopathic treatment”, to select the appropriate articles for our review. From these, only 82 articles were found to be eligible for our review, based on title and abstract assessment.

A total of 72,057 articles were obtained from EMBASE for the hemangioma search; after using the association “plant extract” OR “plants” OR “naturopathic treatment”, 36, 6, and 1 articles were identified. Of these, only 30 were articles and reviews suited for our review (Publication type – filters applied).

During the second step, we reviewed the titles, abstracts, and the full texts of 243 papers from the last 30 years to extract pertinent data for our review (Figure 1). The bibliography was searched for additional studies to be reviewed. Seventy-five relevant studies with their citations were included in our reference list.

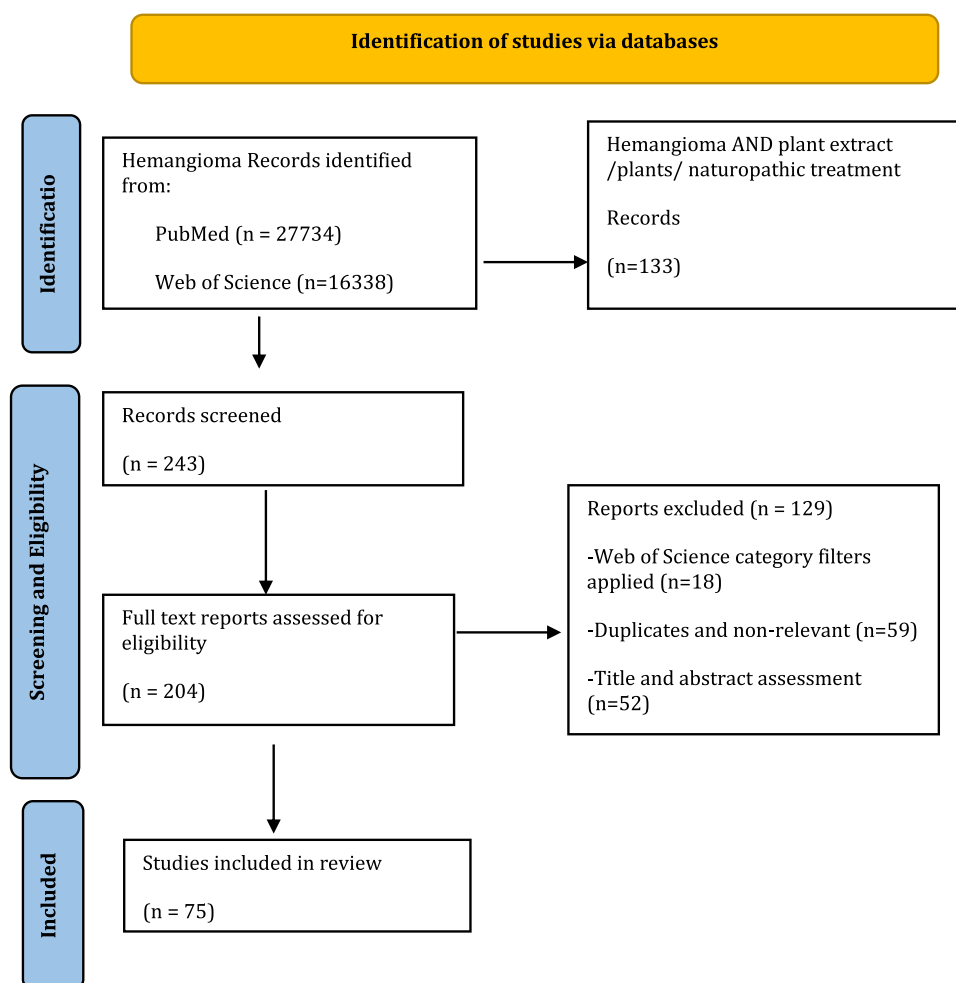


Figure 1 PRISMA flowchart.

Notes: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1–e34.¹⁷ Creative Commons.

Pathogenesis

The origin and pathogenesis of infantile hemangiomas and vascular tumors is still unclear, being the result of multiple factors, such as inactivation of tumor suppressor genes and the activation of proto-oncogenes.^{18,19} Compared with other vascular malformations, glucose transporter-1 (GLUT-1), an erythrocyte-type glucose transporter protein, has been identified as a highly selective marker of IH at all stages, from development to involution.²⁰ GLUT-1 is a downstream target of hypoxia-inducible factor-1-alpha (HIF-1 α), together with vascular endothelial growth factor A (VEGF-A) and insulin-like growth factor 2 (IGF-2), thus sustaining the hypothesis that hypoxia may trigger the appearance of IH.²¹

GLUT1 serves as a marker for distinguishing between vascular tumors and vascular malformations but also as a primary key molecule in endothelial cell glycolysis, facilitating glucose transport into the cell for energy supply. Inhibition of the glycolytic activator phosphofructokinase-1 (PFK-1) suppresses hemangioma-derived endothelial cell (HemEC) proliferation and migration, induces cell arrest, and reduces glucose uptake and lactate and ATP production.^{22,23} Glucose metabolism in HemECs is different from normal endothelial cells, and altering the expression of glycolysis-associated molecules will influence the phenotype of HemECs, providing new therapeutic approaches for IH treatment.²² Endothelial cell glycolysis was confirmed to be closely associated with the pathogenesis of infantile hemangioma, and influencing the expression of glycolytic key enzymes such as PFKFB3 (6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3) may inhibit the occurrence and development of vascular tumors through IH angiogenesis suppression and apoptosis induction.²³

The VEGF – HIF-1 α Pathway in the Appearance of Hemangiomas

Infantile hemangioma appears from excessive angiogenesis/vasculogenesis or hypoxia-induced vascular endothelial cell proliferation, via HIF-1 α and vascular endothelial growth factor (VEGF).²⁴ It is demonstrated that in hemangioma tissue there is a significant increase in the protein and mRNA expression of HIF-1 compared with normal vascular tissue.²⁵ HIF-1 α stimulates the angiogenesis and proliferation of endothelial cells, especially in hypoxia conditions. Furthermore, HIF-1 α induces the expression of VEGF gene (downstream of HIF-1 α), which stimulates the proliferation and migration of vascular endothelial cells, leading to the formation of new vessels.²⁶ VEGF binds to tyrosine kinase receptors (RTKs) and promotes the activity of vascular endothelial growth factor receptors (VEGFRs), mediating mitogenic signals via VEGFR1 and VEGFR2.² The decreased level of VEGFR1 in endothelial cells facilitates VEGFR2 persistent activation in IH. The combination of VEGFR2 and VEGF triggers specific signals and stimulates endothelial cell proliferation and induces more angiogenesis. VEGFR2 signal further activates PI3K/Akt (serine/threonine protein kinase B) pathway and formation of new vessels (Figure 2). Under hypoxia conditions, the spontaneous apoptosis of hemangioma endothelial cells is inhibited via the regulation of mTOR and p70S6K.² This whole mechanism is like an autocrine cycle that promotes the proliferation of endothelial cells and the formation of new blood vessels, leading to the rapid increase in the size of hemangiomas.²

New theories on the pathogenesis of infantile hemangioma include placental origin, somatic endothelial mutation, or other intrinsic defect, and external factors that create an environment conducive to growth.¹⁸

The Role of Transcription Factor Fli-1 in the Appearance of Vascular Tumors

The occurrences of malignant and potentially malignant sarcomas originating from blood vessels are rarely seen and include hemangiosarcomas, Kaposi's sarcomas, and hemangioendothelimas, usually with no known cause. The transcription factor Friend leukemia virus integration 1 (Fli-1) belongs to the E26 Transformation-Specific (ETS) transcription factor family and is expressed in normal hematopoietic stem cells and vascular endothelial cells. But Fli-1 is also abnormally expressed in numerous malignant tumors (Ewing sarcoma, erythroleukemia, lymphoma, breast cancer, etc.) and benign or malignant hemangioma.¹⁹ Fli-1 promotes p110 and GATA-1 expression in leukemia cells and inhibits the transcriptional activity of Rb and SHIP-1 by regulating the PI3K/Akt signaling pathway (also implicated in the

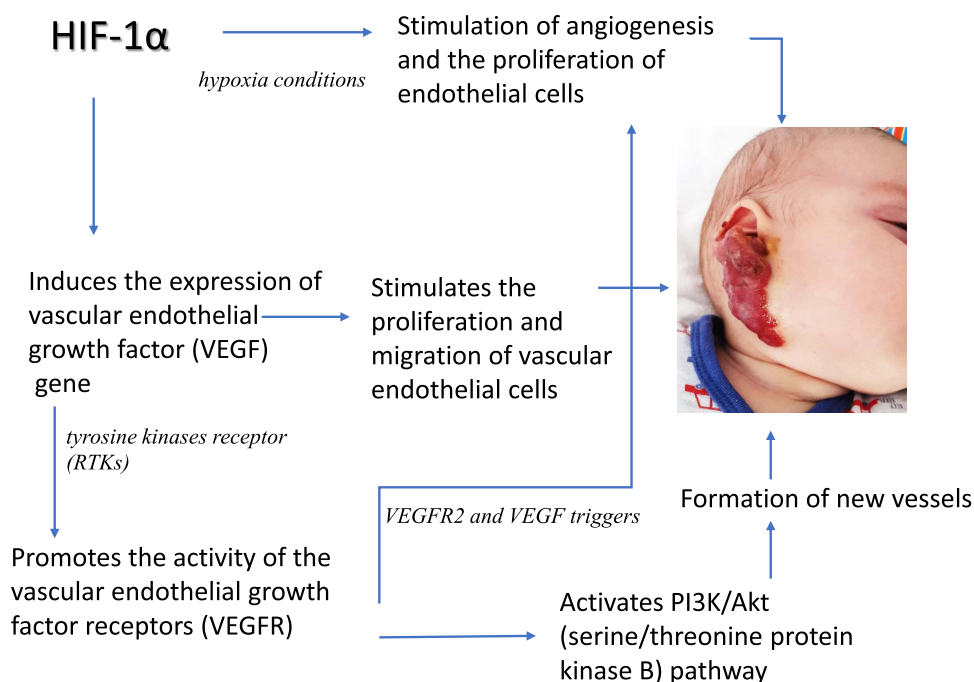


Figure 2 The VEGF – HIF-1 α pathway in the appearance of hemangiomas.

appearance of vascular tumors), thus inducing cell proliferation. Fli-1 favors the transcriptional activity of MDM2 and Bcl-2 and inhibits the activity of phosphorylated Bax and Bad, thus inhibiting cell apoptosis; Fli-1 also interacts with the TGF- β /Smad pathway and inhibits the activity of DAPK, TIMP-1, and Beclin1, promoting the occurrence and development of tumors.¹⁹ In some studies, the knockout of Fli-1 gene was conducted to decrease growth and death of mouse erythroid leukemia cells; therefore, maybe Fli-1 could be used as a target for specific tumor therapy.^{27,28}

Treatment

Standard Therapy

There are very few countries where a standardized approach is applied to hemangiomas; usually, the management is “wait and see” for the IH not implying the face, genitals, or hand. For these special localizations, a variety of therapies may be applied: systemic or topical drugs (propranolol, timolol, corticosteroids, Vincristine, immunosuppressant, and itraconazole), pulsed dye laser treatment, or surgical excision.^{2,3,29} In the last decade, propranolol became the first-line treatment for IH, at a dose between 2 and 3 mg/kg/day, with a positive response of 80–100%.²⁹ Because of the rare, but cited side effects of systemic drugs like neurocognitive impairment, bronchospasm, hypotension, bradycardia, hyperkalemia, or hypoglycemia, some physicians and parents do not agree with this treatment.³⁰ Corticosteroids, at a dose of 2–3 mg/kg/day of prednisone, may be effective in more than 80% of cases, but the adverse reactions are numerous: mood disorders, gastric irritation, Cushing’s phase, weight gain, immunosuppression, spastic diplegia, developmental delays, or adrenal suppression.^{31,32} Topical timolol may have reduced efficiency if utilized early in the development of the IH, or on small thin lesions, but adverse side effects such as local xerosis from medication, ulceration, and infection of the IH were reported.³³

Regarding laser therapy, also effective, traumatic impairments and high cost are major disadvantages. Sclerotherapy and surgical excision of IH in children are associated with the adverse effects of general anesthesia, bleeding, wound infection, or unsightly scars.

Visceral hemangiomas that create shunts and have the potential to cause congestive heart failure are managed with systemic treatments (propranolol, interferon-alpha, prednisone, or sirolimus), but refractory cases may need percutaneous embolization or surgery, depending on the size; as for adults, surgical approaches range from embolization, radio-frequency ablation, radiotherapy to hepatic resection or liver transplantation.³⁴ Zhang et al reported a successfully treated case of hepatic hemangioma with azithromycin, a widely used macrolide antibiotic which, in addition to its antimicrobial activity, exerts anti-inflammatory and antiproliferative effects through inhibition of VEGFR2-mediated downstream signaling pathways.^{4,35}

Ionizing radiation therapy targets rapidly proliferating tumor cells and may be very effective for the treatment of vascular tumors, but depending on its dosage, adverse side effects are of serious concern in children.³⁶ To achieve maximum health benefits, lower doses of radiation may be used in combination with conventional chemotherapy. In any case, the cumulated adverse side effects of radiation and chemotherapy raise serious concerns for the quality of life of the surviving patient.¹²

Role of Proanthocyanidins in Treating Hemangiomas and Vascular Tumor

Proanthocyanidins are natural extracts from grape seeds and red wine, black currant (*Ribes nigrum*, family Grossulariaceae), dawn redwood (*Metasequoia glyptostroboides*, subfamily *Sequoioideae* of the family Cupressaceae), blueberry (*Vaccinium* sect. *Cyanococcus*, family Ericaceae), cranberries (*Vaccinium* subg. *Oxycoccus*, family Ericaceae), and other fruits. Proanthocyanidins are condensed tannins from a group of biologically active polyphenolic bioflavonoids synthesized by many plants; they have demonstrated human health benefits. These phytochemicals are oligo- or polymers of monomeric flavan-3-ols, and they result as an end product of flavonoid biosynthetic pathway, in ingredients containing catechin, epicatechin, gallic acid, or epigallocatechin subunit chains doubly linked by C4-C6 and C4-C8 ether bonds.^{37,38} Proanthocyanidins have natural effects on antiangiogenesis, antiproliferation, immuno-suppressive, anti-inflammatory, and antineoplastic activities, as well as antidiabetic, lipid lowering, anti-obesity, and cardio and

neuroprotective effects.^{37,39} And because there are very few side effects, they can be administered even in infants and pregnant women.^{40,41}

Due to their powerful effects on antiproliferation and antiangiogenesis through suppressing VEGF signaling pathway, proanthocyanidins may have applications in those angiogenesis-related diseases, such as vascular tumors, hemangiomas, and inflammatory diseases. It was already demonstrated that their beneficial effect on osteoarthritis, urinary tract infections in children, and due to their antiangiogenic and anticancer activities, proanthocyanidins could be used as an antitumor agent under various signaling pathways, participating in cell survival, apoptosis, migration, and invasion.^{41–43}

There are studies in the literature that demonstrate the favorable effect of proanthocyanidins in the treatment of hemangiomas, although the beneficial role of these substances in conditions involving the proliferation of vascular endothelial cells and uncontrolled angiogenesis has already been demonstrated.^{37,38,42} Proanthocyanidins bind to VEGF and inhibit HIF-1 α translation; the decrease of VEGF expression through mediating the PI3K/Akt and mTOR/p70S6K signaling pathways arrests the proliferation, invasion, and metastasis of tumor cell. This may be the process of proanthocyanidin controlling hemangioma growth.²

Evidence for Anti-Angiogenic and Anticancer Properties of Berries

Berry fruits, especially lingonberries (*Vaccinium vitis-idaea*, family Ericaceae), blueberries (*Vaccinium angustifolium*), or black currants (*Ribes lacustre*) are very rich in phenolic compounds with high antioxidant, anti-inflammatory, antiseptic, anti-tumoral, and anti-angiogenic capacity. Lingonberries are called “superfruits”, as they are very rich in antioxidants (vitamins C, A, and E), polyphenols, and functional compounds like fibers and minerals.⁴⁴ Anthocyanin glycosides are the responsible pigments for the blue or red colors in berries and are the most frequent phenolic compounds in lingonberries. Lingonberries are hard to find in the marketplace compared to cranberries, strawberries, or other red fruits, but blueberries for example are consumed frequently in Europe, Asia, and also in the United States. There are several in vitro, in vivo and also clinical studies demonstrating the beneficial effect of these aliments as raw fruits or as nutritional supplements on treatment or prevention of carcinogenesis.⁴⁵

Lingonberry extracts inhibit cancer cell multiplication and tumor progression in mice model systems; the anti-proliferative effect is due to the tannin-rich extract, composed of proanthocyanidins.⁴⁶ The inhibition is also correlated with vitamin C and the synergistic effect of vitamin C and other substances contained in the fruits.⁴⁷ In mice, supplementation of food with 10% of freeze-dried lingonberries substantially inhibited adenoma growth by reducing tumor size by over 60% in the distal part of the small intestine. The expression of adenosine deaminase (ADA) and 5'ecto-nucleotidase (5-NT) genes was inhibited, and Prostaglandin E2 (PGE2) receptor subtype EP4 expression was significantly decreased; in this way, the number and size of colonic adenomas were notably reduced in animal models.⁴⁸

Natural berry extract (NBE) was awarded Food and Drug Administration—Investigational New Drug (FDA–IND; 140318) for human testing against infantile hemangioma.¹² It was also demonstrated that a standardized anthocyanin-rich NBE was effective in prolonging survival of hemangioendothelioma bearing mice.¹³

The mouse hemangioendothelioma endothelial (EOMA) cells treated with a blend of powdered NBE highly decreased the activity of multidrug resistance protein-1 (MRP-1) compared to vehicle controls. This was conducted for nuclear accumulation of oxidized glutathione (GSSG) and apoptotic EOMA cell death, as demonstrated by immunocytochemistry. NBE-treated EOMA cells were injected into mice and led to the emergence of smaller tumors compared to vehicle-treated EOMA cells. NBE treatment significantly prolonged survival compared to vehicle-treated controls for tumor-bearing mice, as demonstrated by Kaplan–Meier survival curves.¹³

Recently, the same scientific team also showed that only the mitochondrial dynamics of tumor cells and not of non-tumor cells can be specifically targeted by the standardized natural product NBE and a combination therapy, including weak X-ray therapy (XRT, 0.5 Gy) and NBE significantly (threefold) extended survival of HE-affected mice.¹² Gordillo et al demonstrated that NBE inhibits basal and nonmitochondrial respiration of EOMA cells and does not affect murine aortic endothelial (MAE) cells used as controls. Weak XRT had no effect on basal respiration but inhibited nonmitochondrial respiration in EOMA. The combination of NBE and weak XRT had no effect on healthy MAE cells but inhibited basal and nonmitochondrial respiration in EOMA cells. The mechanism was as follows: NBE decreased the rate of adenosine triphosphate (ATP) production and depleted ATP amount, elevated ADP, and decreased ATP/ADP ratio in

EOMA cells but not in MAE cells. The synergistic effect explains the potentiation of EOMA cell death as a response to the combination of NBE treatment followed by weak XRT [12]. It was again demonstrated that anthocyanins, rich in berries, are able to influence mitochondrial dynamics.

Besides fruits, the leaves of some berries have a much higher antioxidant capacity than the fruits.⁴⁹ Molecular mechanisms include inhibition of pro-inflammatory molecule production, inhibition of oxidative stress and products of this process such as DNA damage, inhibition of cancer cell proliferation, and increased apoptosis.^{50,51} The ingestion of fruits and plant extracts rich in polyphenolic compounds has neuroprotective effects and other positive effects on urinary, gastrointestinal tract, and cardiovascular system.^{49,52,53} The types of berries, active substances, properties, and food methods are summarized in Table 1.

Methods of consumption/administration of active substances from fruits or plants foods with healing properties can be consumed in various forms. Red fruits will usually be eaten raw, but when they are astringent and difficult for children to tolerate, they can be turned into jams, compotes, jellies, and juices. Fermented berry juice is preferred by adults and shows an anti-proliferative and anti-invasive effect on highly proliferative and invasive oral tongue squamous carcinoma cells such as HSC-3 and SCC-25.⁵⁴

In in vivo conditions, raw food goes through gastrointestinal digestion, suffering changes and reduction in the bioactive compound content, but despite these changes, digested berry extracts still showed bioactivity.⁵⁵ Therefore, polyphenols from a diet rich in cultivated or wild berries are bioavailable, but significant inter-individual variation in all compounds' plasma concentrations is found, depending on the differences in the intestinal microflora of each individual.⁵⁶

It has been shown that wild fruits contain higher concentrations of polyphenols compared to the same cultivated variety, but the wild fruits are difficult to procure, instead their leaves are equally valuable. Wild berries are exposed to

Table 1 Types of Berries, Active Substances, Properties, and Food Methods

Types of Berries	Active substances	Properties	Food Methods	Studies
Lingonberries <i>Vaccinium vitis-idaea</i> , family Ericaceae	- polyphenols - Anthocyanin glycosides - functional compounds like fibers and minerals -antioxidants (vitamins C, A, and E) - tannin-rich extract, composed of proanthocyanidins	- high antioxidant, anti-inflammatory, antiseptic, anti-tumoral and anti-angiogenic capacity	- raw fruits - nutritional supplements - supplementation of food with 10% of freeze-dried lingonberries;	Mane C et al, 2011 ⁴⁴ McDougall G.J. et al, 2008 ⁴⁶ Gordillo GM et al, 2021 ¹² Biswas A et al, 2017 ¹³
Blueberries <i>Vaccinium angustifolium</i>	-phenolic compounds -anthocyanins	- high antioxidant, anti-inflammatory, antiseptic, anti-tumoral and anti-angiogenic capacity - decrease the activity of multidrug resistance protein-1 - inhibits basal and nonmitochondrial respiration of EOMA cells	- Fermented berry juice, jams, compotes, jellies; - Natural berry extract -ethanol–water extract	Johnson SA et al, 2013 ⁴⁵ Olsson M.E. et al, 2004 ⁴⁷ Sergazy S et al, 2023 ⁵⁰ Bunea A et al, 2013 ⁵¹
Black currants <i>Ribes lacustre</i>	- phenolic compounds - vitamins C, A, and E	- inhibition of pro-inflammatory molecules production, inhibition of oxidative stress, inhibition of cancer cell proliferation and increased apoptosis - neuroprotective effects, positive effects on urinary, gastrointestinal tract and cardiovascular system	- aqueous extract from the fruit or leaves - fruits and plant extracts	Misikangas M. et al, 2007 ⁴⁸ Kelly E et al, 2017 ⁴⁹ Hossain MZ et al, 2016 ⁵²

environmental stress, and they show an enhanced defense mechanism by producing increased number of polyphenolics and protecting the plants from external agents.⁵⁶ In aqueous extracts from fruit or leaves, the flavanol contents ranged between 30% and 36%, and the flavanol glycosides are in the range of 7–9%.^{57,58} The solubility of phenolics is higher in alcohols, so the ethanol–water extract may be used with higher results than the infusion.⁵⁹

Comparative analysis of several berry extracts led to the conclusion that wild blueberry and a berry mix were most effective in suppressing inducible VEGF expression and in vitro and in vivo angiogenesis.¹⁵ The blueberry and berry mix extracts had a high antioxidant function as determined by the oxygen radical absorbing capacity.¹⁵ The ORAC (oxygen radical absorbance capacity, a measure of anti-oxidant strength) values of strawberry powder and grape seed proanthocyanidin extract are higher than cranberry, elderberry, or raspberry seeds, but wild bilberry and blueberry extracts possessed the highest ORAC values.⁶⁰ The consumption of forest fruits in general should be encouraged, not only those grown in farms (such as strawberries) but as varied as possible.

Fli-1 as a Target for Antitumor Drug Development

The high expression of proto-oncogene Fli-1 in vascular tumors is much related to good prognosis and enhanced immunity, because of its action as a tumor suppressor gene. A new trend in the treatment of cancer is molecular targeted therapy, which specifically targets oncogenic sites and causes specific death of tumor cells. Recently, a group of researchers studied the traditional Chinese medicine and ethnic medicine chemical resource databases, aiming to select anti-tumor drugs from it.¹⁹ They found that the flavagline compounds A1544 and A1545, the diterpenoids A661 and A665, the chalcone derivatives C10 and ZH-254, the Cardenolides, the calcium ionophores, lumefantrine, and some others have significant inhibitor efficacy as regulators targeting Fli-1.¹⁹

Chalcone derivatives are polyphenolic flavonoid substances (phytochemicals) which contain isoflavones, with anti-tumor, antibacterial, anti-inflammatory, antiviral, and other pharmacological activities.⁶¹ Chalcones are simple chemical scaffolds belonging to the flavonoid family, found in natural plant products such as spices, vegetables, fruits, and teas. Chalcone family substances are the subject of many studies due to their biological activities like antitumoral, anti-inflammatory, antidiabetic, antioxidant, and antimicrobial activities.^{62,63} Due to their special chemical scaffolding, chalcones are useful templates for the development of novel anticancer agents. Chalcones were also documented to modulate the following steps in angiogenesis: vascular endothelial factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor- β (TGF- β) signaling pathway, or hypoxia-inducible factor-1 (HIF-1); in this way, they can be used for the treatment of hemangiomas.^{64,65} Chalcones isolated from young *Caesalpinia bonduc* (Family Caesalpiniaceae) twigs and leaves show Fli-1 agonism and regulate the expression of VEGF-1, TGF- β 2, p53, inter-cellular cell adhesion molecule-1 (ICAM-1), and MMP-1 genes, which are associated with tumor apoptosis, migration, and invasion in cancer cells.^{61,66}

Chalcones represent the core of many natural biological compounds, being found in the roots, heartwoods, buds, leaves, flowers, rhizomes, and seeds of species of genera *Angelica*, *Sophora*, *Humulus*, *Scutellaria*, *Glycyrrhiza*, *Parartocarpus*, *Ficus*, *Dorstenia*, *Morus*, and *Artocarpus*.⁶⁷ Isoliquiritigenin (ISL) is a bioactive compound with a chalcone structure isolated from licorice roots (*Glycyrrhiza glabra*, family Fabaceae). ISL has therapeutic potential against various cancers, inhibiting cancer cell migration and metastasis by suppressing cell proliferation, induces apoptosis and autophagy, arrests the cell cycle, inhibits angiogenesis, obstructs metastasis, and enhances chemosensitivity.^{68,69} Butein, is a biologically active flavonoid extracted from the bark of *Rhus verniciflua* Stokes; it exhibits significant anticancer activity and can attenuate angiogenesis, cell invasion/metastasis, and inflammation.⁷⁰

The flavagline compounds from *Dysoxylum binectariferum* (Family Meliaceae), a Chinese medicinal plant, effectively inhibit the activity of Fli-1 and consequently negatively regulate the expression of the downstream target genes C-Kit, GATA-1, and Bcl-2.²⁷ These natural compounds can represent a new strategy in the treatment of leukemia, lymphoma, and other tumors with Fli-1 overexpression.

Other Plants That Can Be Used for the Treatment of Vascular Tumors

EOMA cell proliferation could be suppressed by a sesquiterpene isolated from *Sonchus oleraceus* (family Asteraceae), a medicinal plant frequently found and used by many people as antioxidant and antidiabetic, and as a natural treatment

for many other diseases. The sesquiterpenes were isolated by the methods of column chromatography, and Western Blot assay indicated that they induced apoptosis through the Bax/caspase-3 pathway. The plant extracts elicited a moderate inhibitory effect on EOMA cells with IC50 value of 26.5 μ M.⁷¹

Grapes and grape seed extract are well-known sources of antioxidants, used for centuries in rejuvenation treatments, wound healing, inflammation, for cardiovascular disease treatment or in the fight against cancer, being known for their antiangiogenic effects. Grape seed proanthocyanidin extract (GSPE) was studied by comparison with six berries extract, and it was found that its antioxidant activity was higher than cranberry, elderberry, or raspberry seed but significantly lower than the other samples studied.⁶⁰ GSPE containing 5000 ppm resveratrol facilitates oxidant-induced VEGF expression in keratinocytes and have beneficial therapeutic effects in related skin disorders, promoting dermal wound healing or vascular tumor regression.⁷²

Nutrient mixture (NM) containing green tea (*Camellia sinensis* - Theaceae family) extract, lysine, proline, and ascorbic acid have shown significant anti-angiogenic and anti-tumor effects against a number of cancer cell lines. Using in vitro tests and a mouse hemangioendothelioma model, Roomi et al demonstrated that NM inhibited the growth of tumors by 50%. In vitro, NM induced dose-dependent apoptosis of EOMA cells.⁷³ This study concluded that NM has therapeutic potential in treating infantile HE and possibly some other cutaneous vascular tumors. Another study demonstrated that nutrient supplementation with 0.5% NM strongly suppressed tumoral growth with no adverse effects in nude mice, suggesting the nutrient combination has potential as an anticancer agent. The finding was supported by histological studies showing inhibition of MMP-9 and VEGF secretion and mitotic index (critical parameters for cancer prevention and control).⁷⁴

“Ankaferd Blood Stopper” (ABS) is a hemostatic and antimicrobial topical agent produced as a mixture of five different plant extracts (*Urtica dioica* - family Urticaceae, *Vitis vinifera* - family Vitaceae, *Glycyrrhiza glabra* - family Fabaceae, *Thymus vulgaris* - family Lamiaceae, and *Alpinia officinarum* - family Zingiberaceae). ABS is a natural hemostatic agent used in traditional Turkish medicine, well known for its rapid inhibiting effect on dental or cutaneous bleeding as well as postoperative external bleedings, and also for its antimicrobial effect.^{75,76} Annagur et al presented a seven-year-old boy with recurrent bleeding and infected hemangioma on the lower lip, successfully treated with topical ABS in terms of control of bleeding and infection.⁷⁷ ABS provides hemostasis independently from coagulation factors and the standard coagulation cascade, by forming a structural net through interaction of fibrinogen in blood and, hence, providing vital aggregation of erythrocytes.⁷⁸

Tanshen is the rhizome of *Salvia miltiorrhiza* Bunge (also known as red sage or Danshen) and is used in traditional Chinese medicine to treat hematological abnormalities, as an antioxidant and anticoagulant agent, as well as for its antibacterial and antineoplastic activities.¹¹ Its compound DHTS was much more effective than propranolol in inhibiting hemangiomas proliferation and angiogenesis and may have potential therapeutic applications for future treatment of IH.^{9,11} Water-soluble phenolic acids such as salvianolic acid B are bioactive constituents from *S. miltiorrhiza*, possessing good bioactivities like antioxidant, anti-inflammatory, anti-cancer, and other health-promoting activities.⁷⁹

The main findings of our research are centralized in Table 2.

Discussion

Vascular anomalies are a heterogeneous group of blood vessel disorders subcategorized for the first time as separate entities by Mulliken and Glowacki in 1982 (based on unique characteristics) into vascular tumors and malformations.⁸⁰ IH are the most common benign vascular tumors consisting of rapidly dividing endothelial cells. Medical and surgical options are available for the management of “problematic” hemangiomas, both options having various drawbacks. IH involving the head and neck will put patients at risk for ocular axis occlusion, amblyopia, astigmatism, tear-duct occlusion, and overall risk for ulceration and disfigurement. Therefore, when heart failure, ear disturbances, airway obstruction, nutritional disturbances, and certain cosmetic problems like disfigurement and scarring threaten to appear, a patient-specific treatment is recommended.³ Among alternatives there are propranolol, systemic or topical steroids, interferon-alpha, chemotherapeutic agents, laser therapy, and surgical excision.⁸¹ When the adverse effects are not tolerable or when the patient does not have a clear indication of standard treatment, alternative therapy based on active substances from the diet or plant extracts can be recommended for hemangiomas. Therefore, there is a great need to

Table 2 Natural Agents that Were Tested for Hemangiomas or Another Vascular Tumor Treatment

Natural Agent	Proanthocyanidins	Flavagline Compounds, Chalcone Derivatives; Isoliquiritigenin; Butein	Sesquiterpene	Nutrient Mixture (nm) Containing Green Tea Extract	Ankaferd Blood Stopper	15,16-Dihydrotanshinone I (DHTS)
The plant from which it is extracted	<i>Ribes nigrum</i> , <i>Metasequoia glyptostroboides</i> , <i>Vaccinium sect. Cyanococcus</i> , <i>Vaccinium subg. Oxycoccus</i> , <i>Vaccinium vitis-idaea</i> , <i>Vaccinium angustifolium</i> , <i>Ribes lacustre</i>	<i>Caesalpinia bonduc</i> , <i>Angelica</i> , <i>Sophora</i> , <i>Humulus</i> , <i>Scutellaria</i> , <i>Glycyrrhiza glabra</i> , <i>Parartocarpus</i> , <i>Ficus</i> , <i>Dorstenia</i> , <i>Morus</i> , <i>Artocarpus</i> ; <i>Rhus verniciflua</i> Stokes; <i>Dysoxylum binectariferum</i>	<i>Sonchus oleraceus</i>	<i>Camellia sinensis</i>	<i>Urtica dioica</i> , <i>Vitis vinifera</i> , <i>Glycyrrhiza glabra</i> , <i>Thymus vulgaris</i> , <i>Alpinia officinarum</i>	<i>Salvia miltiorrhiza</i>
Effect	Antiangiogenesis, antiproliferation, immunosuppressive, anti-inflammatory, antineoplastic activities, antidiabetic, lipid lowering and anti-obesity effects, cardio and neuroprotective effects	Antitumoral, antibacterial, anti-inflammatory, antiviral, antidiabetic, antioxidant activities; attenuate angiogenesis, cell invasion/metastasis and inflammation	Antioxidant and antidiabetic; Moderate inhibitory effect on EOMA cells	Antiangiogenic and antitumor effect; suppressed the tumoral growth with no adverse effects in nude mice	Hemostatic and antimicrobial topical agent	Antioxidant, anti-inflammatory, anti-cancer and other health-promoting activities; treatment of various cardiovascular and cerebrovascular diseases
Mode of action	Bind to VEGF and inhibit HIF-1 α translation; the decrease of VEGF expression through mediating the PI3K/Akt and mTOR/p70S6K signaling pathways; expression of adenosine deaminase and 5'ecto-nucleotidase genes was inhibited and Prostaglandin E2 receptor subtype EP4 expression was significantly decreased	Modulate the vascular endothelial factor, basic fibroblast growth factor, transforming growth factor- β signaling pathway or hypoxia-inducible factor-1; Regulate the expression of VEGF-1, TGF- β 2, p53, intercellular cell adhesion molecule-1 and MMP-1 genes	Induces apoptosis through the Bax/caspase-3 pathway	Dose-dependent apoptosis of EOMA cells; inhibition of MMP-9 and VEGF secretion and mitotic index	Provide hemostasis by forming a structural net through interaction of fibrinogen in blood and hence, providing vital aggregation of erythrocytes	DHTS could significantly decrease EOMA cells proliferation by inducing cell apoptosis; DHTS increase the expression of apoptosis-related proteins, and significantly inhibited angiogenesis, as indicated by reduced tube formation and diminished expression of vascular endothelial cell growth factor receptor 2 and matrix metalloproteinase 9
In vitro system / In vivo model	Mice model systems; in vitro system	In vitro system; In Silico Studies; Cell and Xenograft Animal Models	Western Blot assay	In vitro tests and a mouse hemangioendothelioma model; Nude mice study; Histological studies	Human tests - Prospective, randomized, controlled clinical trial	DHTS inhibit hemangiomas proliferation and angiogenesis in vitro and in vivo

(Continued)

Table 2 (Continued).

Natural Agent	Proanthocyanidins	Flavagline Compounds, Chalcone Derivatives; Isoliquiritigenin; Butein	Sesquiterpene	Nutrient Mixture (nm) Containing Green Tea Extract	Ankaferd Blood Stopper	15,16-Dihydrotanshinone I (DHTS)
Administration mode	Raw fruits; nutritional supplements; supplementation of food with 10% of freeze-dried lingonberries; Fermented berry juice, jams, compotes, jellies; aqueous extract from the fruit or leaves; ethanol–water extract	Soluble extracts administration	Column chromatography	Nutrient supplementation with 0.5% NM	Topical agent	Danshen is available in several forms, including extracts, capsules, and teas; Dripping pills (to be absorbed under the tongue) or as oral tablets
Study	Huang S et al, 2012; Yang L et al, 2018; Sano A, 2017; Yang L.-J. Et al, 2016; Afshar K et al, 2012; Wang A et al, 2016; Johnson SA et Arjmandi BH, 2013; McDougall G.J. et al, 2008; Olsson M.E. et al, 2004; Misikangas M. et al, 2007; Sergazy S et al, 2023 30–35,38–41,43	Li L. et al, 2022; Ouyang Y et al, 2021; Gao F. et al, 2020; Mirossay L. et al, 2018; Iheagwam F. N. et al, 2019; Rozmer Z. et Perjési P, 2014; Lin P.-H. et al, 2020 12,54,55,57,59,60,62	Lei M. et al, 2022 64	Roomi MW. et al, 2009; Roomi MW. Et al, 2005 64,66,67	Annagur A. et al, 2012; Meric Teker A. ett al, 2010; Tasdelen Fisgin N. et al, 2009; Goker H. et al, 2008 68–71	Duan et al, 2021; Cai et al, 2018; Wang et al, 2007; Shi et al, 2018

explore novel treatments for IH, with less side effects. Regarding vascular tumors with a risk of malignancy, huge efforts are being made by numerous teams of researchers to find those natural extracts with anti-angiogenic and anti-cancer effects, and with as few adverse effects as possible.

The use of proanthocyanidins, flavonoids, and chalcones from plant extracts is a potential therapeutic strategy to reduce inflammation and tumor angiogenesis. Chalcones play a central role in the flavonoid synthesis pathway and are frequently found in various natural products. These natural substances may also be used as therapeutics or as chemosensitizers for clinical drug resistance because they improve the pharmacokinetics of poorly absorbed chemotherapeutic cancer drugs.⁶¹ Despite medicinal applications of chalcones, their wide bioactivity spectrum represents a challenge for clinical development because used empirically or in inappropriate situations they can have adverse effects such as hepatotoxicity.^{82,83} However, more research on chalcones in marine natural products is needed and many *in vivo*, *in vitro* and clinical studies are necessary to be able to recommend the consumption of these substances as part of the treatment of some diseases, especially when it comes to children.

Natural berry extract is awarded Food and Drug Administration—Investigational New Drug for human testing against infantile hemangioma and it is proved to be very effective for treating HE in mice.^{12,13} Standardized NBE has been demonstrated to be effective in managing endothelial cell tumor *in vivo* through inhibition of MRP-1 and also in reducing cancer cell chemoresistance. An important potential role of phytochemicals as an adjunctive treatment to improve the effectiveness of chemotherapy was discovered. NBE inhibition of MRP-1 is worth consideration and more investigations are needed, as proanthocyanidins may be a notable therapeutic intervention with application for HE and other cancers with elevated MRP-1 activity. While NBE alone is effective in causing tumoral cell death, Gordillo et al demonstrated on mice with HE that the effect is significantly enhanced by cotreatment with weak XRT. Thus, a combination therapy, including weak X-ray therapy and NBE extended threefold the survival of HE-affected mice.¹² Therefore, safe natural products such as berry extracts target tumor cell mitochondria and sharply lower radiation dosage required for tumor management, warranting more clinical testing.

During their course, up to 40% of IHS may lead to certain complications, depending on localization, dimensions, and the growth rate of the lesion. The ulceration because of the mechanical trauma, infection, and bleeding or scar appearance during healing can easily be prevented or treated with plant extracts like topical ABS, a product that may be easily applied by family members. ABS is a cheap and efficient hemostatic, antimicrobial, and antineoplastic agent with no adverse effects, which stops the bleeding in a very short time in cases of external bleeding such as that seen in children with IHS.⁸⁴

Many clinical studies often confirm that the targeted therapy of cancer had an unexpectedly curative effect compared with conventional chemotherapeutic drugs, resulting in great progress in cancer management. The natural potential is extremely high, and numerous medicinal plants have already proven their effectiveness in improving and even curing numerous ailments. Every effort must be made to fully exploit this potential, for the benefit of our children and their families.

Limitation of the study: although in our review we tried to analyze as many sources of information as possible, we found very few original studies conducted on animals and even fewer conducted on human patients (clinical experience) regarding the naturopathic treatment of vascular tumors. But there are certainly other unexplored databases and case reports not included in this study, as well as reports at various conferences or preliminary results of clinical trials not yet reported, which could bring more information in the future. We need certainties, through studies based on clinical trials and randomized studies; this review only summarizes the current knowledge in the field of the beneficial actions of medicinal plants on hemangiomas and other vascular tumors.

Conclusion

Infantile hemangiomas are the most common benign vascular tumor consisting of rapidly dividing endothelial cells and may sometimes cause remarkable complications. Medical and surgical options are available for the management of “problematic” hemangiomas, both options having various drawbacks like the cost and side effects, which stop patients from adopting them. Natural extracts from plants and fruits are cost-effective and safe treatments for hemangiomas and vascular tumors, as well as for other forms of cancer, as demonstrated in our systematic review. In any case, more *in vitro* and *in vivo* experiments are needed to validate the proposed signaling pathways in tumors and confirm the improvement parameters after natural products administration. The era of personalized medicine and molecularly targeted therapy is approaching, and both naturally occurring and

synthetic substances are very useful tools for tumor treatment and prevention. Plant extract substances have strong specificity and pertinence, are non-toxic and have few side effects, and may become an emerging cancer treatment. The results of this review are encouraging, demonstrating that there is enough evidence to support the promotion of a diet rich in natural active ingredients for the management of vascular tumors; anyway, more studies based on clinical trials and randomized studies are needed to demonstrate the benefits of a medical diet.

Funding

This research received no external funding.

Disclosure

The authors report no conflicts of interest in this work.

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