ORIGINAL ARTICLE

The potential use of phenolic compounds in the treatment of hair loss: A literature review

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ABSTRACT

Hair loss is a condition that affects both men and women, causing psychological and physical suffering. This literature review aimed to bring together *in vivo* studies and clinical trials related to the use of phenolic compounds, mainly tannins, flavonoids, and metabolites from the phenolic acid class to combat hair loss. The bibliographic search was carried out in the PubMed/MEDLINE and Scopus databases, using keywords such as "flavonoids", "tannins", "phenolic acid" and "hair loss". Regarding the clinical trials included, three types of study were used (randomized, double-blind, and placebo control). All the compounds evaluated were obtained from medicinal plants, three tannins and one flavonoid. The formulations evaluated were three hair tonics and one lotion, and phenolic compounds from procyanidin class were present in almost all articles (n=3). The use of these compounds was related to the reported potent antioxidant and anti-inflammatory activity, which favor the anagen phase of hair, reducing reactive oxygen species and inflammation of hair follicles. Therefore, more studies are needed to promote and discuss the use of phenolic compounds for hair loss, mainly through randomized clinical trials. To contribute to the research and development of new medicines, polyphenols have several benefits and have a similar action to conventional medicines.

Keywords: Alopecia, Clinical trial, Medicinal plants, Polyphenols, Review.

INTRODUCTION

Hair loss is a common disorder that does not threaten life, but generates anguish and affects the life quality of those who suffer from it, in both sexes, since hair acts as a thermal protector, as well as playing an important role in social and sexual communication (Lourith and Kanlayavattanakul 2013). This change is detected by the daily increase in hair loss (effluvium) or the lack of visible hair (alopecia), as well as by the decrease in the growth of new hair (Wolff et al. 2016). It occurs preferentially in women Caucasians after menopause and men up to 50 years of age (Vujovic and Marmol 2014).

There are several causes for hair loss, as well as intrinsic factors, such as androgenic hormones, which act as modulators and promote hair loss. Among the extrinsic factors, general health problems such as vitamin deficiency, history of chronic diseases, menstrual cycle, exacerbated exposure to UV radiation, tanning lamps, trauma to the scalp stand out. Stress, smoking, and excessive alcohol consumption are aggravating factors (Piraccini 2015; Cho and Kim 2020).

The treatment of hair loss is based on the inhibition of the 5α-reductase enzyme associated with active ingredients that promote hair growth (Lourith and Kanlayavattanakul 2013). The main treatments available to reverse this condition

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include the use of topical medications, such as minoxidil, and oral solutions, including finasteride and dutasteride. However, this medications have adverse effects, such as reversible loss of libido and erectile dysfunction for minoxidil, and increased risk of prostate cancer, breast cancer, and infertility for finasteride. Dutasteride has more side effects, such as impotence and ejaculatory disorders, despite having an action similar to finasteride (Wolff et al. 2016; Rose 2021).

Medicinal plants have been used in the treatment and prevention of diseases since ancient times, being the first intervention option for several generations (Abbasi et al. 2010). Brazilian biodiversity represents a vast national heritage, contributing to the country's research and development, and the pharmaceutical industry, a sector in constant evolution and innovation (Oliveira et al. 2019).

Several plant extracts are used in cosmetic formulations, due to the presence of phytochemical active ingredients (Cho and Kim 2020). Among the secondary metabolites are phenolic substances from the class of flavonoids, tannins, phenolic acids, coumarins, among others (Arnoso et al. 2019). Such compounds are present in several plant species, being stored in flowers, leaves, stems, roots, and seeds. Phenolic compounds have antioxidant activity, acting to reduce free radicals and inflammation. In this way, they can play a fundamental role in hair loss through the regeneration of the hair follicle, inducing the anagen phase of the hair cycle and other activities (Simões et al. 2010; Kumar and Goel 2019).

Currently, on the pharmaceutical market, there are no specific medications to combat hair loss, minoxidil, finasteride and dutasteride are the main active ingredients used. For hair growth to occur, it is necessary to administer these medications for months, and when stopping treatment, hair loss returns, in addition to possible adverse effects and health risks (Banka et al. 2013; York et al. 2020).

In this context, the use of medicinal plants to combat hair loss, including those rich in tannins, flavonoids, and phenolic acids, can promote the regeneration of the hair follicle, contributing to improved blood circulation, reducing inflammation, and inducing hair growth on the scalp (Škulj et al. 2019; Sun et al. 2020), which justifies this literature review work. This work aimed to carry out a literature review to evaluate the use of phenolic compounds, from natural products, for the treatment of hair loss, in particular, non-scarring alopecias, such as androgenetic alopecia (AGA), alopecia areata (AA), telogen effluvium (TE), and trichotillomania (TT).

METHODS

This literature review included a bibliographic search for scientific articles, carried out in the PubMed/MEDLINE and Scopus databases on November 4, 2022. There were no time or language restrictions.

To develop the search strategy, descriptors related to phenolic compounds were considered, such as "flavonoids", "flavones", "flavonols", "anthocyanins", "anthocyanidin", "chalcone", "isoflavones", "proanthocyanidin", "flavan-3-ol", "tannins", "hydrolyzable tannins", "condensed tannins", "phenolic acid", "coumaric acids", "hydroxycinnamic acid", "hydroxybenzoic acid", and related to hair loss such as "hair growth", "hair regrowth", "hair loss", "alopecia", "baldness".

The inclusion criteria used were: clinical trials or *in vivo* studies that evaluated the exclusive use of phenolic compounds in the treatment of hair loss. Literature review, systematic, and scope studies, in addition to articles that investigated formulations with various secondary metabolites and use of the crude extract, as well as treatments designed for other disorders, exemplifying hair hypopigmentation, *Tinea capitis* infection, and other complications were considered excluded in the study selection process.

The process of selecting the included studies involved reading the titles and abstracts of the studies retrieved from the databases, followed by reading the full text. Data extraction was carried out using standardized forms in *Microsoft Excel*®, to facilitate data manipulation and interpretation. Data analysis was carried out qualitatively (descriptively).

RESULTS AND DISCUSSION

In total, 239 studies were identified after removing duplicates. During the screening stage (reading the title and abstract), 146 studies were excluded, resulting in 93 studies for the full reading stage. Of these, 15 met the inclusion criteria and were considered eligible, as shown in the flowchart (Figure 1).

Among the studies included, 11 were *in vivo* (Takahashi et al. 1998; Takahashi et al. 1999a; Takahashi et al. 2000; Takahashi 2001; Kamimura and Takahashi 2002; Wikramanayake et al. 2012; Shin et al. 2014; Kim et al. 2016; Su et al. 2016; Xing et al. 2017; Jung et al. 2022) and four studies were clinical trials (Kamimura et al. 2000; Takahashi et al. 2001; Takahashi et al. 2005; Nagasawa et al. 2016).

In vivo studies

Among the *in vivo* studies, sixteen phenolic compounds were evaluated in mice, among them five studies highlighted the use of procyanidins. Only six compounds were extracted from plant extracts and another six were standards. The difference in

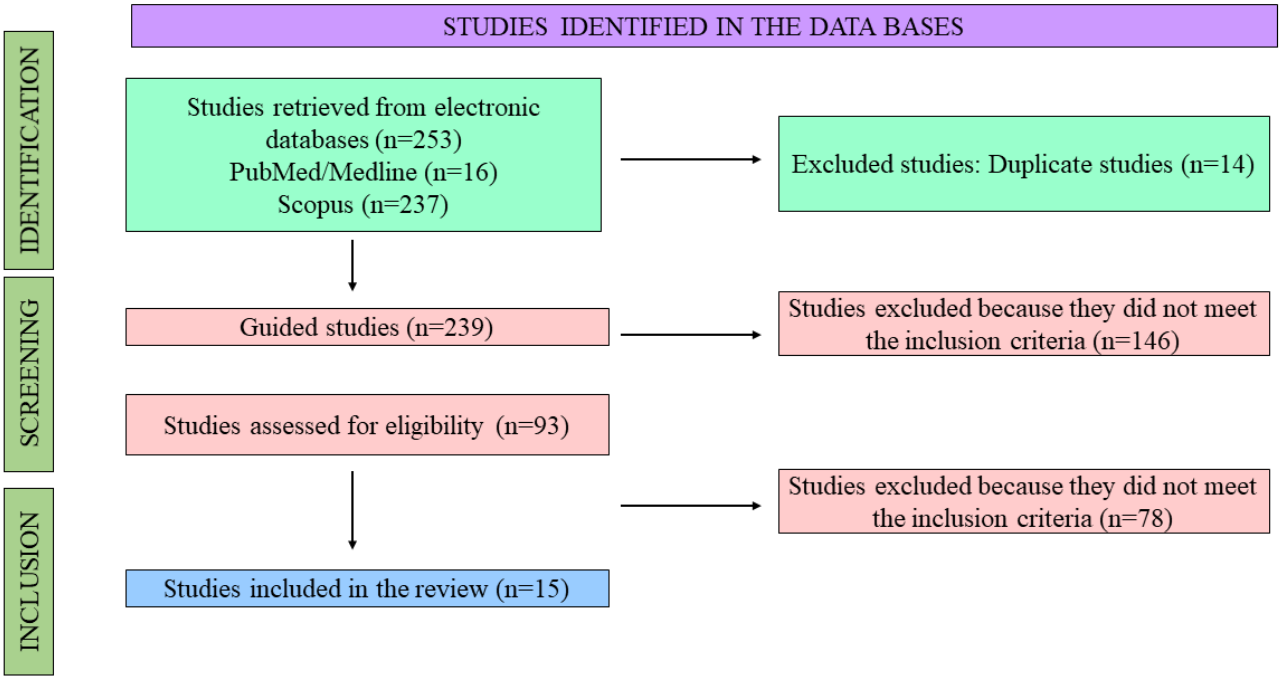

Figure 1. Flowchart of the study selection process. **Source:** Own authorship

the origin of the compounds is explained by the use of the same extract to obtain different polyphenols. The main characteristics related to the compounds evaluated are available in Table 1.

Table 2 shows the characteristics related to the animal model, such as type of animal, age, gender, route of administration, and negative control. The positive control, percentage (%) and micromolar (μ*M*) treatment were demonstrated in Tables 3 and 4, respectively. Furthermore, the main outcomes obtained from *in vivo* studies are shown in Table 5.

Table 1. Compounds, sources, and classes of polyphenols used from the included *in vivo* studies.

Author/ Year	Country	Class	Compounds (chemical strucutre)	Source	n	Lineage
Takahashi et al. 1998	Japan	Tannin	Proanthocyanidins	Grape Seed Extract (Chardonnay variety)	12	C3H/HeS1c
Takahashi et al. 1999	Japan	Tannin	Procyanidin B2 (**1**) Procyanidin B3 (**2**) Procyanidin C1 (**3**)	PB2 and PC1: Juice of *Malus pumila* Miller var. *domestica* Schneider PB3: Shells of *Hordeum vulgare* L. var. *distichon* Alefeld	21	C3H/HeS1c
Takahashi et al. 2000	Japan	Tannin	Procyanidin B2 (**1**) Procyanidin B5 (**4**) Procyanidin trimer	Juice of *Malus pumila* Miller var. domestica Schneider	16	C3H
Takahashi 2001	Japan	Tannin	Procyanidin B2 (**1**) Procyanidin C1 (**3**)	Extract of *Malus pumila* Miller var. domestica Schneider immature	13	C3H/HeSlc
Kamimura and Takahashi 2002	Japan	Tannin	Procyanidin B3 (**2**)	Extract from seed shells of *Hordeum vulgare* L. var. distichon Alefeld	16	C3H/HeSlc
Wikramanayake et al. 2012	USA	Flavonoid	Quercetin (**5**)	Sigma-Aldrich	16 50	C3H/HeJ

Continue...

Table 1. Continuation

Author/ Year	Country	Class	Compounds (chemical strucutre)	Source	n	Lineage
Shin et al. 2014	South Korea	Flavonoid	Baicalin (**6**)	Sigma-Aldrich	15	C57BL/6
Kim et al. 2016	South Korea	Flavonoid	3-Deoxysappanchalcone (**7**)	AK Scientific	8	C57BL
Su et al. 2016	China	Flavonoid	Icariin (**8**)	Sigma-Aldrich	10	C57BL/6
Xing et al. 2017	China	Flavonoid	Baicalin (6)	Chengdu Must Bio-Technology	45	BALB/c-nu
Jung et al. 2022	South Korea	Tannin	Cyanidin-3-*O*-arabinoside (**9**)	Cayman Chemical	15	C57BL/6

n= Number of mice used in the study; PB2= Procyanidin B2; PB3= Procyanidin B3; PC1= Procyanidin C1

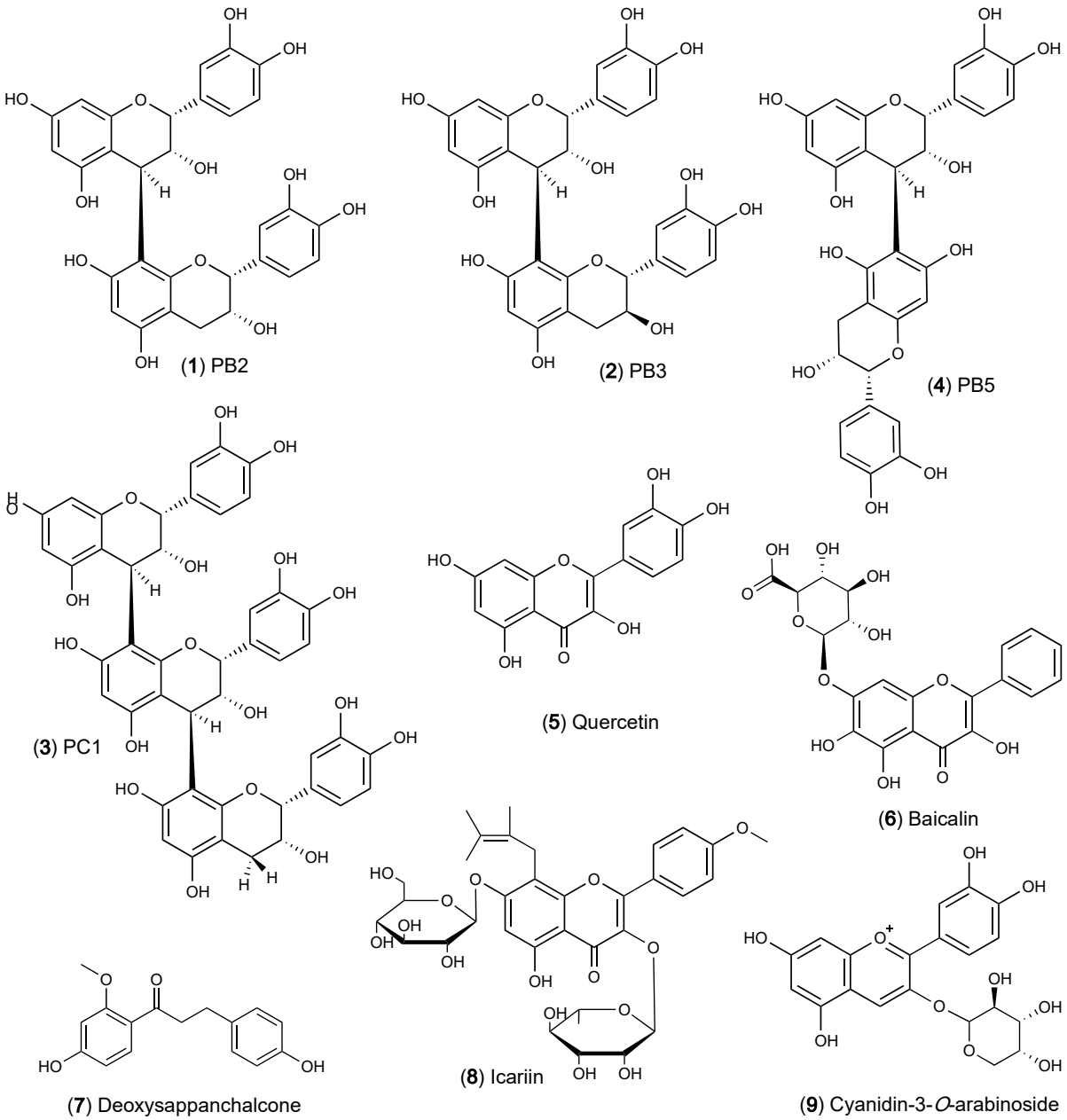

Figure 1. Compounds from table 1, sources, and classes of polyphenols used in the *in vivo* studies.

Table 2. Animals and age, negative control, and route of administration used from the included *in vivo* studies.

Author/ Year	Hair loss category	Animal/ Age	Gender	Route of administration	Negative control
Takahashi et al. 1998	NR	Mice 8 weeks	Male	Topic	14 g of ethyl alcohol, 2 g of 1,3-butylene glycol, 0.1 g of N-acetylglutamine-isostearyl, 0.05 g of polyox-yethylen and glyceryl monopyroglutamate monoisostearate, and 3.65 g of pure water
Takahashi et al. 1999	NR	Mice 8 weeks	Male	Topic	14 g of ethyl alcohol, 2 g of 1,3-butylene glycol, 0.1 g of N-acetylglutamine-isostearyl, 0.05 g of polyox-yethylen, and 3.65 g of pure water
Takahashi et al. 2000	NR	Mice 8_weeks	Male	Topic	70% ethyl alcohol, 10% 1,3-butylene glycol, 0.5% N-acetylglutamine-isostearyl ester, 0.25% polyox-yethylen
Takahashi 2001	NR	Mice 8 weeks	Male	Topic	70% ethyl alcohol, 10% 1,3-butylene glycol, and 0.5% N-acetylglutamine-isostearyl ester
Kamimura and Takahashi 2002	NR	Mice 8 weeks	Male	Topic	70% ethyl alcohol, 10% 1,3-butylene glycol, and 0.5% N-acetylglutamine-isostearyl ester
Wikramanayake et al. 2012	Alopecia areata	Mice 24 weeks	Female	Subcutaneous Intraperitoneal	10% DMSO in PBS
Shin et al. 2014	NR	Mice 8 weeks	Female	Topic	50% ethanol
Kim et al. 2016	NR	Mice 7 weeks	Female	Topic	50% ethanol
Su et al. 2016	Alopecia androgenetic	Mice 16 weeks	Female	Gavage	50% saline and 50% DMSO
Xing et al. 2017	NR	Mice 6 weeks	Female	Topic	50% ethanol in PBS

DMSO= dimethyl sulfoxide; NR= Not reported; PBS= Phophate-Buffered Saline

Table 3. Percentage of phenolic compounds used in the treatment and positive control of the included *in vivo* studies.

Author/Year	Treatment (%)	Positive control (%)
Takahashi et al. 1998	1 (Proanthocyanidins)	3 (minoxidil)
Takahashi et al. 1999	1 (PB2, PB3, and PC1)	1 (minoxidil)
Takahashi et al. 2000	1 (PB5 and procyanidin trimer)	NR
Takahashi 2001	1 (PB2, PC1)	NR
Kamimura and Takahashi 2002	1, 5 and 8 (PB3)	NR
Wikramanayake et al. 2012	1* (Quercetin)	NR
Su et al. 2016	1 (Icarina)	NR

NR= Not reported; PB2= Procyanidin B2; PB3= Procyanidin B3; PC1= Procyanidin C1; PB5= Procyanidin B5; *Value obtained after conversion to percentage.

Table 4. Treatment with phenolic compounds and positive control used by the authors of the included *in vivo* studies.

Author/Year	Treatment (µ*M*)	Positive control (µ*M*)
Shin et al. 2014	50 and 100 (Baicalin)	NR
Kim et al. 2016	3 (3-DSC)	NR
Xing et al. 2017	50 and 100 (Baicalin)	10 (minoxidil)
Jung et al. 2022	500 (C3A)	NR

NR= Not reported; 3-DSC= 3-Deoxysappanchalcone; C3A= Cyanidin-3-*O*-arabinoside

Table 5. Main results obtained and other activities described by the authors of the included *in vivo* studies.

Author/Year	Treatment time (days)	Main outcomes	Other pharmacological activities
Takahashi et al. 1998	19	Induced the anagen phase	Promote the proliferation of hair follicular cells
Takahashi et al. 1999	19	Induced the anagen phase of the hair cycle	Showed growth of capillary epithelial cells
Takahashi et al. 2000	19	Induced the anagen phase	Hair epithelial cell growth
Takahashi 2001	19	Induced the anagen phase of the hair cycle	NR
Kamimura and Takahashi 2002	19	Induced the anagen phase of the hair cycle	NR
Wikramanayake et al. 2012	42	Demonstrated hair growth in mice with AA and did not progress to severe alopecia	NR
Shin et al. 2014	35	Anagen phase, dose-dependent	Wnt /ß-catenin signaling
Kim et al. 2016	15	Promoted intense hair growth, increased diameter and depth of hair follicles	Wnt /ß- catenin signaling. Inhibits STAT-mediated quiescence of hair follicular cells
Su et al. 2016	20	anagen phase and enlarged the hair follicle	Proliferation of keratinocytes in follicles. Increased expression of IGF-1
Xing et al. 2017	14	Promoted hair growth, in the same way as the positive control.	Increased protein levels of Wnt3a, Wnt5a, β-catenin and LEF1
Jung et al. 2022	19	Decreases the activity of DHT, promotes hair growth, and inhibits the senescence of dermal papillae.	ROS levels, as well as senescence. Inhibits intracellular calcium accumulation

NR= Not reported; AA= Alopecia areata; IGF-1= Insulin-like growth factor type 1; LEF-1= Lymphoid enhancer-binding factor 1; DHT= dihydrotestosterone; ROS= Reactive oxygen species; STAT= signal transducer and activator of transcription

The *in vivo* assays were governed by the synchronized capillary cycle of the animal, and the mice were stipulated for all studies, given that until the 2nd week of life, the animals are in the first anagen phase and the 4th to 4.5th week are in the second anagen phase, which is responsible for the hair growth. The first telogen stage is between the 2.5th to 3.5th week and the second phase is from the 5th to 14th week, being responsible for the hair strand reduction (Takahashi et al. 1998). After the delimitation of the growth stages, the hair of the dorsal region of each mouse was shaved with a shaver in order not to injure and stimulate the skin. In general, just twelve used animals at 4 to 10 weeks, and three studies used animals above 14 weeks. It is evident that the animals are in the telogenic phase and the application of polyphenols induced hair growth.

In the study of Takahashi et al. (1998) formulations containing proanthocyanidins (condensed tannins) extracted from the grape seed of the Chardonnay variety were used. The formulations were applied topically in 16 mice for

19 days. It was verified the growth of 80 to 90% of hair strands in the scraped area in the treated group, and the positive control, Minoxidil, obtained equivalent results of 90 to 100%, and the negative control obtained growth of about 30 to 40%.

According to the authors, the possible mechanism of action of proanthocyanidins present in grape seeds is related to the prevention of cell differentiation for the telogen phase of the capillary cycle, since the cells of the outer sheath of the capillary root, as well as the bulb cells convert the telogen phase to the anagen phase. The study confirms that catechin did not have an anti-hair loss action, suggesting that capillary growth depends on oligomeric structures, as well as present in proanthocyanidins (Takahashi et al. 1998).

In the study by Takahashi et al. (1999a) a formulation was developed with procyanidin B2 and C1 extracted from the commercial juice of *Malus pumila* Miller var. *domestica* Schneider, popularly known as "Fuji Apple", for topical application in 21 mice. The authors also used procyanidin B3 purified from barley husk extract, specifically *Hordeum vulgare* L. var. *distichon* Alefeld. The growth results obtained were: 69% of the shaved dorsal area was covered with hair from the group treated with PB2, 80% of the area treated wiith PB3, and 88% of the region treated with PC1, that is, the substances induced the anagen phase of the hair cycle, thus as the positive control (Minoxidil) demonstrated growth of 80%.

In the study by Takahashi et al. (2000), three different formulations containing 1% procyanidin B2 (1), 1% procyanidin B5 (2), and 1% procyanidin trimer (3) extracted from *M. pumila* were applied topically in 16 mice. In addition, the negative control, whose composition is described in Table 2, was applied for 19 days. Mice treated with PB2 achieved greater growth (93.6%) than the negative control (29.5%). However, PB5 (62.4%) and the procyanidin trimer (37.9%) demonstrated less growth when compared to PB2.

Takahashi (2001) also developed two different formulations for topical application in 13 mice for 19 days. The main active ingredients were 1% procyanidin B2 and 1% procyanidin C1, extracted from *M. pumila*. The group treated with PB2 (n=4) resulted in 69.6% growth in the dorsal area and the group treated with PC1 (n=4) demonstrated 78.3% growth. When comparing them with the negative control group (n=5), a growth of 41.7% was found.

Toxicological studies were carried out to verify the safety of using procyanidin B2. PB2 was considered non-toxic, non-mutagenic, and does not cause skin irritation and inflammation, except at the injection site, with a lethal dose greater than 2,000 mg/kg (Takahashi et al. 1999b).

Kamimura and Takahashi (2002) evaluated the hair-growing activity of a purified fraction rich in procianidin B3, obtained from *H. vulgare* shell seed extract. It was applied three fraction concentrations, 1, 5, ad 8%. The results obtained demonstrated that the 1% fraction (n=4) achieved 49.7% growth, the 5% fraction (n=4) resulted in 76.6%, and the 8% fraction (n=4) achieved 89.5% growth. Confirming that the phenolic compond content directly influences anti-alopecia activity. The authors reported that the supposed mechanism of action of PB3 would be related to germ cells. From them, the hair originates and extends out of the hair follicle, thus inducing the anagen phase of the hair cycle. In addition, PB3 has anti-inflammatory and antioxidant activity, promoting cellular growth and proliferation activity of the outer root sheath, in a way contributing to the formation of hair follicles. (Kamimura and Takahashi 2002).

Wikramanayake and colleagues (2012) selected 6-month-old animals to spontaneously develop alopecia areata. They then received quercetin subcutaneously to treat the hair loss and all of them showed hair growth in the injured area after around 6 weeks, while no mice in the negative control group showed growth in the area. In histological analysis, lymphocytes were present in and around the hair follicles of mice with alopecia. Another study coducted by the same authors demonstrated that of the 50 mice treated with quercetin, administered intraperitoneally, none developed severe alopecia, only two developed focal alopecia, and 48 showed no apparent hair loss (Wikramanayake et al. 2012). No adverse effects were reported for quercetin after oral administration of 1,000 mg/day for 12 weeks (Harwood et al. 2007).

Alopecia areata is an autoimmune disease that shares the same genes as other autoimmune disorders, such as type 1 diabetes mellitus. The region of the human leukocyte antigen that encodes key regulatory factors in humans and the major histocompatibility complexes has been identified as an important genetic contributor to the disease phenotype (Simakou et al. 2019). However, alopecia androgenetic occurs due to a dysfunction of hormonal and genetic factors, but the causative genes have not been fully elucidated. Effluvium Telogen occurs after a specific cause such as stress, infections and other disorders (Gordon and Tosti, 2011; Pereira, 2018).

Shin et al. (2014) evaluated the activity of baicalin, a flavonoid isolated from *Scutellaria baicalensis* Georgi, with antioxidant, anti-inflammatory, anti-ischemic, and antimutagenic activity reported in the literature. The formulation containing baicalin, at concentrations of 50 and 100 µ*M*, was applied topically to the dorsal area of 15 mice for five weeks. It was noted that the conversion

from telogen to anagen phase was faster than when compared to the control group.

In the study conducted by Xing et al. (2017), 45 albino hairless mice (BALB/c-nu, six weeks old) were used. They were grafted in the dorsal region with dermal and epidermal cells isolated from 1 day old mice (C57BL/6). The treatment was started two weeks after grafting, when hair growth was noticed. Baicalin was administered at concentrations of 50 and 100 µ*M* in the dorsal area of the animals. Through biopsy, an increase in the number and size of hair follicles was observed in the group treated with baicalin and minoxidil. Furthermore, levels of alkaline phosphatase (ALP), a marker present in dermal papilla cells, increased considerably in the treated groups when compared to the negative control.

Due to its intense anti-inflammatory activity, baicalin reduces scalp inflammation and induces hair regeneration, in addition to inhibiting the enzyme 5α-reductase, modulates the expression of genes involved in hair growth, and protects hair cells from apoptosis. However, further studies are required to fully understand the mechanism of action of this compound in the treatment of alopecia (Chen et al. 2022).

There are few studies on the toxicity of baicalin. However, experiments carried out on animals that received this compound showed no abnormalities in behavior or toxicity. Therefore, an oral dose of 2,000 mg/kg/day is considered safe for mice, according to a study carried out by Dinda et al. (2017).

Kim et al. (2016) verified the activity of 3-deoxysappanchalcone (3-DSC), a flavonoid isolated from *Caesalpinia sappan* L., used to reduce inflammation and improve blood circulation. The study developed a formulation with a concentration of 3 µ*M* of 3-DSC, for topical application in animals over a 15-day period. The treatment resulted in rapid and intense hair growth. histopathological analysis revelead that the diameter and depth of hair follicles were significantly greater in the treatment group compared to the control group. The activities of 3-DSC were associated with dermal papilla cells proliferation and stimulation of hair growth through the activation of Wnt/ß-catenin signaling and inhibition of STAT-mediated quiescence (Kim et al. 2016).

Su et al. (2016) evaluated the effect of icarin, a major flavonoid in *Epimedium koreanum* Nakai, with 5α-reductase inhibitory activity. The treatment group exhibited accelerated hair growth compared to the negative control, and histological analysis revelead increased depth and size of hair follicles compared to the control group. The potential mechanism of action of icarin is based on the increase of insulin-like growth factor-1 (IGF-1) in dermal papilla cells. This factor is known to stimulate the hair follicles growth by promoting cell proliferation and differentiation. Additionally, Wnt/β-catenin signaling is also activated, playing a crucial role in hair growth regulating (Su et al. 2016).

In a clinical trial conduced by Brown et al. (2019), the safety of icarin was evaluated. Results demonstrated that the compound was well tolerated, with no serious adverse event reported. Mild symptoms such as nausea, diarrhea, abdominal pain, headache, and dizziness were reported by volunteers but were similar to the placebo group, suggesting that these complications were not related to the icarin use.

Jung et al. (2022) injected dihydrotestosterone (DHT) into seven mice and treated them with cyanidin-3-*O*-arabinoside (C3A) topically for 20 days. Results showed that C3A induced the anagen phase and restored hair growth rate due to the inhibition of dermal papilla cell senescence. Furthermore, while DHT-injected mice exhibited decreased hair thickness, C3A treatment reversed this effect..

C3A, a cyanidin responsible for various activities such as anticancer, anti-inflammatory, neuroprotective, cardioprotective, and anti-aging, is responsible for the pigmentation of various fruits, vegetables, and flowers (Putta et al. 2018). Chemically, C3A is a cyanidin conjugated with an arabinoside sugar at the C3 position of the C ring, possessing stronge antioxidant activity (Bräunlich et al. 2013; Jung et al. 2022).

The proposed mechanism of action of cyanidin-3-*O*-arabinoside involves the modulation of the p38-dependent signaling pathway associated with endoplasmic reticulum (ER)-mitochondria contact sites, which is involved in the regulation of oxidative stress and cellular senescence. ER-mitochondria contact are essential for energy supply and the regulation of oxidative stress in cells. Exposure to DHT can lead to an increase oxidative stress and cellular aging, and the study suggests that C3A can modulate this pathway, reducing oxidative stress and suppressing DHT-induced senescence of dermal papilla cells (Jung et al. 2022).

Clinical trials

In clinical trials, three types of study designs were used, all with male patients, and in all studies, participants were treated with phenolic compounds isolated from plant extracts (Tables 6 and 7). The main results obtained in clinical trials are shown in Table 8.

Table 6. Types of clinical trials and their variables used by the authors.

Author/year	Country	Type of clinical trial	n	Treaties	Placebo	Gender	Age (years)	Alopecia category
Kamimura et al. 2000	Japan	Placebo control	30	19	10	Masculine	30 to 57	Androgenetic alopecia
Takahashi et al. 2001	Japan	Randomized Double-blind Placebo control	30	19	10	Masculine	30 to 57	Androgenetic alopecia
Takahashi et al. 2005	Japan	Double-blind	49	21	22	Masculine	25 to 58	Androgenetic alopecia
Nagasawa et al. 2016	Japan	Randomized Double-blind Placebo control	84	31	19	Masculine	20 to 60	Androgenetic alopecia

N= number of participants in the study.

Table 7. Compounds and formulations used in clinical trials.

Author/Year	Phenolic compound class	Compounds	Origin of the compound	Formulation concentration (%)	Formulation type
Kamimura et al. 2000	Tannin	Procyanidin B2	*Malus pumila* Miller var. *domestica* Schneider juice	1	Hair tonic
Takahashi et al. 2001	Tannin	Procyanidin B2	*Malus pumila* Miller var. *domestica* Schneider juice	1	Hair tonic
Takahashi et al. 2005	Tannin	Procyanidin oligomers	*Malus pumila* Miller var. *domestica* Schneider immature extract	0.7	Hair tonic
Nagasawa et al. 2016	Flavonoid	*trans* -3,4′-Dimetil-3-hidroxiflavanone (t- flavanone)	*Hypericum perforatum* L. extract	0.1 - 0.3	Lotion

Table 8. Main results obtained in the included clinical trials.

Author/ Year	Placebo formulation	Route of administration/ location	Treatment time (weeks)	Main outcomes	Other pharmacological activities
Kamimura et al. 2000	10% 1,3-butylene glycol, 0.5% N-acetylglutamine-isostearyl ester, 0.25% polyoxyethylene monoisostearate glyceryl monopyroglutamate, 0.1% *dl*-α-tocopherol, 0.05% *d*-biotin, 0.1% ascorbyl palmitate, 0.001% β-carotene, 0.1% sodium citrate, and 17.899% purified water	Topical/scalp	24	Increased capillary density, as well as stimulated terminal strands	NR
Takahashi et al. 2001	10% 1,3-butylene glycol, 0.5% N-acetylglutamine-isostearyl ester, 0.25% polyoxyethylene monoisostearate glyceryl monopyroglutamate, 0.1 % *dl*-α-tocopherol, 0.05% *d*-biotin, 0.1% ascorbyl palmitate, 0.001% β-carotene, 0.1% sodium citrate, and 17.899% purified water	Topical/scalp	16	Increased the diameter and density of the wires. Improves hair quality and appearance and reduces dandruff	NR

Continue...

Table 8. Continuation

Author/ Year	Placebo formulation	Route of administration/ location	Treatment time (weeks)	Main outcomes	Other pharmacological activities
Takahashi et al. 2005	70% ethanol, 3% 1,3-butylene glycol, 0.15% (w/w) N-acetylglutamine isostearyl ester, 0.067% citrate-sodium citrate, buffer, 0.05% sodium bisulfite, and purified water (remaining)	Topical/scalp	48	Increased hair density	NR
Nagasawa et al. 2016	57.5% alcohol/water and 0.15% L-menthol	Topical/scalp	30	Induced hair growth, increased the tenacity and diameter of the hair	Increased expression levels of DSG1, DSG2, and DSG3.

NR= Not reported; DSG1= Desmoglein type 1; DSG2= Desmoglein type 2; DSG3= Desmoglein type 3

Procyanidin B2 has shown excellent results in combating hair loss. Kamimura et al. (2000) and Takahashi et al. (2001) developed a hair tonic based on PB2 extracted from apple juice, specifically *M. pumila*, at a concentration of 1%. For the study, 30 men aged 30 to 57 were selected to apply the tonic containing PB2 to the scalp. The gold standard of clinical trials is double-blind studies, that allow random selection with or without treatment, without generating distrust in the conclusions, reducing the influence and increasing the credibility of the results. However, the placebo control group receives the medication randomly, but the placebo group is identified by the team, providing good results but can generate interference.

Kamimura et al. (2000) obtained as a result an increase in hair density in individuals treated with PB2 (6.68 cm^2) and the control group (0.08 cm^2). Hair density is responsible for the significant increase in hair growth in a given area. There was also a noticeable increase in terminal hairs, which presented a thick, long and pigmented appearance, when compared to the placebo group. These same effects were observed after the administration of Minoxidil and Finasteride for 12 months due to the anti-alopecia effects (Kreindler 1987).

Takahashi et al. (2001) obtained similar results. After 4 months of treatment, the hair diameter in individuals treated with PB2 was (78.9%) larger than the control group (40%). Similarly, hair density was significantly higher in the treated group (84.2%), while no significant difference was observed in the placebo group.

During this period, no allergic reactions, irritation, or inflammation were reported, nor did participants complain of itching, pain, dryness, or scaling of the scalp in both studies. However, an unintended beneficial effect was described in Takahashi et al. (2001), due a 47.4% decrease in dandruff in the treated group, while only 20% of the placebo group obtained this result. Thus, a large-scale clinical trial with procyanidin B2 over a longer period of time could provide more information regarding the use of this compound in the treatment of baldness.

Another trial conduced by Takahashi et al. (2005) used a hair tonic containing procyanidin oligomers, perticularly procyanidin B1, B2, and C1, from the extract of *M. pumila*. For this study, the hair tonic was applied directly to the scalp at a concentration of 0.7% procyanidin, in 49 male volunteers, aged 25 to 58 years, for 12 months. No adverse effects were recorded during the study period.

According to Takahashi et al. (2005) the haircapillary density obtained for the treated group after 6 months of treatment was relatively higher (3.3 cm^2) compared to the placebo group (-3.6 cm^2). However, after 12 months of treatment, the increase in hair count was considerable (11.5 cm^2), highlighting that the results for hair density was time-dependent. The continuous use of this formulation for 12 months promoted growth of 23 hairs/cm^2. Similar results were obtained after the application of 2% Minoxidil, promoting growth of 49 hairs/cm^2 and Finasteride provided growth of 16.9 hairs/cm^2, obtaining positive results against baldness (Kaufman et al. 1998). The level of efficacy of the formulation with 0.7% procyanidin oligomeris favorably comparable to therapy with minoxidil and finasteride(Takahashi et al. 2005).

The authors suggest that the possible mechanism of action of procyanidin B2 is related to its intense antioxidant activity, suppressing inflammation in the hair follicle, as well as the inhibitory activity of transforming growth factor

beta (TGF-β), which is responsible for inducing the catagen phase of the hair cycle. Hair growth activity may depend on more than one of the numerous physiological functions of this compound (Takahashi et al. 2005).

Nagasawa et al. (2016) developed a lotion with t-flavanone, a compound extracted from *H. perforatum*, at concentrations of 0.1 and 0.3% for application to the scalp of 84 male volunteers aged 20 to 60 years. The hair diameter in the group treated with t-flavanone was thicker in a dose-dependent manner. The tenacity test was performed in this study, which is defined as the elasticity of the hair. The treated group performed better and was stronger than the placebo group. Nagasawa et al. (2016) hypothesize that hair diameter is correlated with tenacity, as hairs with the same diameter treated with 0.3% t-flavanone obtained better results.

The composition of the hair lotion produced by Nagasawa et al. is described as an aqueous formulation, without any lipophilic active ingredient, thus ensuring less absorption in the epidermis where the hair follicles are located. However, the hair tonic by Takahashi et al. (2005), contains a agent in addition to the active ingredient, a moisturizing agent that ensures the lipophilicity of the formulation and increases penetration into the follicles.

Limitations

This literature review presented some limitations, such as the lack of standardization of studies that used the same plant species, for example, such as the articles that described the use of *M. pumila*. Some studies reported the use of immature apples for the preparation of the extract, while other studies used commercial apple juice. Thus, there was no standardization regarding the use of extracts from this species.

In addition, in the studies that used grape seeds, the species was not described, only the grape variety. Likewise, few *in vivo* studies evaluated positive control, which could facilitate a misinterpretation of the results obtained. In the clinical study of Takahashi et al. (2005), it was reported that the placebo group obtained a negative hair density value, however, there is no explanation of how to interpret this result and compare it to the treated group. Finally, the authors of *in vivo* studies using female mice failed to provide a rationale for their choice or to describe the differences in testing between the two genders.

CONCLUSION

In this review, tannins, mainly procyanidins, were identified as the major class of phenolic compound due to their excellent antioxidant and anti-inflammatory activity, promoting hair growth. However, the mechanism of action of these compounds is not fully elucidated. Flavonoids have also achieved excellent results in combating hair loss, inducing the anagen phase and preventing severe alopecia, thus contributing to hair therapies. However, no studies have evaluated the specific use of phenolic acids. The use of extracts from *M. pumila*, also known as “Fuji Apple”, was evidenced in almost all studies, given that it was a source of phenolic compounds.

Therefore, it can be concluded that phenolic compounds are being increasingly studied for various purposes, including alopecia. The results suggest the possibility of replacing conventional medicines used to treat hair loss with active ingredients from plant extracts, aiming for a less abrasive and safer therapy for the patient. However, more clinical and toxicological studies using polyphenols are needed. This promising approach could revolutionize the way the population deals with hair disorders, as well as encourage the use of natural resources in health treatments.

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AUTHOR’S CONTRIBUTIONS

Contextualization, APBC, JCPM; methodology, APBC, DCOT, and NCG; writing/ reviewing and editing, APBC, DCOT, NCG; MNP, and CBL; supervision, DC, NCG, and JCPM.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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