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The Role of Botanical Products in the Treatment of Alopecia

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Abstract

Alopecia, which is defined as the loss of hair from the body, encompasses a wide range of hair loss disorders, including alopecia areata and androgenetic alopecia. There is a growing use of botanical sources in dermatology. Accordingly the interest in the use of botanical and natural products for the treatment of alopecia is growing. Here we present a systematic review of natural and botanical products that have been examined as potential treatment options for alopecia. Our results yielded 13 studies that examined 11 different natural and botanical products for the potential treatment of alopecia areata. Studies pertaining to alopecia areata and androgenetic alopecia were found. These results are promising as they signal increasing investigation into the use of natural and botanical products for the treatment of alopecia.

Keywords: Alopecia; Alopecia areata; Androgenetic; Male pattern baldness; Botanical; Plant; Extract; Phytochemical

Introduction

Hair is characteristic of mammals. In humans, it can be an integral part of personal appearance and self-image. Alopecia is the loss or absence of hair on the body and can have a negative psychological impact, especially when the hair loss is from the scalp.

Hair is comprised of two parts, the hair follicle that is found in the dermis and the hair shaft that extends outward above the skin surface [1]. The hair follicle is involved in the regulation of hair growth. The papilla, or the central structure of the hair follicle, contains mesenchymal stem cells and influence the thickness and the length of the hair, while the cells of the epidermal bulge are involved in the generation of new hair [2,3]. Hair grows in a cycle with three different phases: anagen, catagen, and telogen. The anagen phase is characterized by growth of 1 cm per month and its duration is multifactorial including the influence of genes and hormones [1,4]. The catagen phase marks the end of hair growth and lasts 2-3 weeks [1]. The telogen phase lasts approximately 3 months and is characterized by shedding of the hair [1].

Alopecia encompasses a wide range of hair loss disorders. This is typically divided as scarring and non-scarring alopecias. Scarring alopecia lead to destruction of the hair follicle with associated loss of the sebaceous glands. The hair loss is typically irreversible. In non-scarring alopecia, there is loss of the hair with preservation of the pilosebaceous unit and the growth of hair can potentially recur. The use of botanical sources in dermatology is increasing [5,6] and there is increasing interest on the role of botanical and natural products for use in the treatment of alopecia. Here we present a systematic review of natural and botanical products that have been examined as potential treatment options for alopecia.

Methods

A systematic search was conducted of MEDLINE and EMBASE databases in April 2015 for published clinical data regarding the use of botanical and natural products in the treatment of alopecia. The MEDLINE database was searched using the following MESH terms: "alopecia areata," "natural products and biological products," "phytochemicals," "botanical or plant," "medicinal plant," "plant extracts," and "Chinese herbal drugs." The EMBASE database was searched using Emtree search terms "alopecia," "natural products," "biologic products," "Chinese drug," "medicinal plant," "plant extract," which included subcategories "phytochemicals" and "alopecia areata." The following terms were not included in the MEDLINE MESH or EMBASE Emtree databases and were included as key words: "androgenetic alopecia," "male pattern baldness," "female pattern baldness," "scarring alopecia," "cicatricial alopecia," "lichen planopilaris," "central centrifugal cicatricial alopecia" and "botanical extracts." Inclusion criteria were limited to articles that were of clinical trials, case reports, and published in English. The two authors viewed the search results independently and then any discrepancies were discussed.

Results

The MEDLINE search yielded 19 results, where 11 met our inclusion criteria and 8 were excluded. Our EMBASE search yielded 25 results, where 3 met our inclusion criteria and 22 were excluded. The bibliographies of review articles from both searches were assessed for other valid studies and yielded 1 additional publication that met our inclusion criteria. There were 2 duplicate findings from the two databases, which were consolidated. Another study was suggested by reviewers that met inclusion criteria. There were 14 studies included for final review. A summary of the results is found in Tables 1 and 2.

Androgenetic Alopecia

Our search results found several studies that investigated the use of botanical products for the treatment of Androgenetic alopecia (Table 1). However, all studies reviewed pertained to male pattern baldness and none pertained to female pattern baldness.

In a randomized double blind controlled trial Procyanidin-B2 polyphenol was evaluated as a potential treatment for male pattern baldness. Procyanidin-B2 polyphenol is an active component found in apples and had been found to act as a hair-growing factor in murine hair epithelial cells and in *in vivo* murine models prior to initiation of this study [7]. This study found that twice daily topical treatment with procyanidin-B2 polyphenol in an ethanol based solution lead to an average of 6.68 more hairs in the area of the scalp elected for hair

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counting, including terminal hairs after 6 months, compared to an average of 0.08 more hairs in the area assessed after treatment with an ethanol based solution alone [7]. A 1 cm area on the vertex of the scalp near the edge of the affected area was selected for total hair counting for each individual.

In a follow up study, researchers continued to investigate Procyanidin-B2 polyphenol as a potential treatment for male pattern baldness. Twice daily treatment to the affected area with 0.7% (w/w) procyanidin in an ethanol based solvent resulted in an average increase

Author, year	Agent and Frequency of Application	Control Group	Methodology	Major findings	Notes
Pumthong et al., 2012 [12] Male pattern baldness	Hair tonic base containing either: 1) 5% *Curcuma aeruginosa* (hexane extract) + 5% minoxidil or 2) 5% *Curcuma aeruginosa* (hexane extract) 3) 5% minoxidil, applied twice/day	Hair tonic base (not described in more detail)	RCT, double blind	Significantly higher hair growth score with combination *Curcuma aeruginosa* and minoxidil treatment after 6 months. *Adverse effects:* One subject in the combination treatment group experienced pruritus that subsided after 1 week of abstinence from the treatment.	Score assigned using 7-point scale to assess global photograph.
Kessels, et al., 1991 [9]	8% Dabao (Chinese herb preparation), Solution containing 50% ethanol, 42% water, applied topically twice/day	Solution containing 50% ethanol, 48% water, 2% coloring and odor agents	RCT, double blind	Increased number of nonvellus hairs with Dabao treatment after 6 months. *Adverse effects:* One subject in the Dabao group developed contact dermatitis after 3 months. An unspecified number of patients developed isolated inflamed follicles.	
Kamimura, et al., 2000 [7]	Procyanidin- B2 polyphenol in ethanol based solution applied topically twice/daily	Ethanol based solution without Procyanidin- B2	RCT, double blind	Significantly increased number of hairs, including terminal hairs with procyanidin- B2 treatment after 6 months. *Adverse effects:* None	
Takahashi, et al., 2005 [8]	0.7% (w/w) procyanidin in basal solvent containing 70% (w/w) of ethanol, 3% (w/w) of, 1,3-butylene glycol, 0.15% (w/w) of Nacetylglutamine isostearyl ester, 0.067% of citrate-sodium citrate buffer, 0.05% (w/w) of sodium bisulfite, and purified water. Solution was applied to the affected area twice daily for 12 months for the treatment group and 6 months for the control group.	Vehicle control	RCT	Significant increase in the number of total hairs, with procyanidin- B2 treatment after 6 and 12 months compared to control. *Adverse effects:* None.	Follow-up study to Kamimura, Takahashi, and Watanabe, 2000
Prager et al., 2002 [10]	Liposterolic *Serenoa repens* extract, 200 mg + ß-sitosterol, 50 mg, taken orally twice/day	Soybean oil 540 mg	RCT, double blind	Improvement in hair based on subject assessment with liposterolic *Sernoa repens* extract and ß-sitosterol treatment after 4.6-5.4 months of treatment. *Adverse effects:* Three subjects in treatment group experienced GI symptoms (loss of appetite, flatulence, and diarrhea). Three subjects in the placebo group each had one of the following: frequent urination, lightheadedness with a bowel movement, and heightened sense of heartbeat.	No quantitative measurements of measuring improvement of hair growth. Not clear why soybean oil was chosen as control for study agent.
Rossi et al., 2012 [11]	*Serenoa repens* 320 mg/day	Finasteride 1 mg/day	RCT	Found that finasteride group had a higher rate of hair regrowth compared to *Serenoa repens* group. *Adverse effects:* None	
Liong et al., 2013	5% *Trifolium pretense* flower extract and acetyl tetrapeptide lotion applied topically once/day	Lotion containing 80% water 20% alcohol	RCT	Increased anagen hair numbers and a reduction in telogen hair numbers after 4 months of *Trifolium pretense* flower extract and acetyl tetrapeptide treatment. *Adverse effects:* Not reported	

RCT: Randomized Controlled Trial.

Table 1: Summary of Studies for androgenetic alopecia.

Author, year	Agent and Frequency of Application	Control Group	Methodology	Major findings	Notes
Ehansi et al., 2009	Capsaicin ointment, 0.35-0.63 mg capsaicin/gram ointment applied topically once/day for 2 weeks then twice/day for 4 weeks	Clobetasol ointment 0.05% applied topically once/day	RCT	Significantly more vellus and non-cosmetic hair growth with capsaicin ointment treatment. *Adverse effects:* 1 subject in treatment group experienced an eczematous transient reaction in week 6.	The authors do not define "cosmetic" and "non-cosmetic" hairs
Swanson et al., 1981 [16]	Croton oil 5-30% in hydrophilic ointment applied topically every 1-3 days. and dintrochlorobenzene	Dintrochlorobenzene (DNCB) 0.01-1% in hydrophilic ointment applied topically every 5-7 days	RCT, double blind	DCNB treatment resulted in significant hair regrowth after 6 months while croton oil did not. *Adverse effects:* 100% of subjects in both groups experience pruritus. Five subjects in control group had autoeczematization. One subject of the control group had transient uticaria necessitating a 2 week discontinuation of therapy.	
Hajheydari, et al., 2007 [18]	Garlic gel 5% + bethamethasone cream 0.1% in isopropyl alcohol applied topically twice/day	Bethamethasone cream 0.1% in isopropyl alcohol applied topically twice/day	RCT	Significantly more total and terminal hairs in the garlic gel group after 3 months. *Adverse effects:* None.	Both groups received betamethasone cream
Yang et al., 2012 [17]	Total glucosides of Peony capsules, 600 mg taken orally three times/day + 10 mg of B12 taken orally twice/day	Glycyrrhizin 50 mg tablet taken orally three times/day + 10 mg of B12 taken orally twice/day	RCT	Study found similar improvement for both groups as seen in effectiveness and cure rates. *Adverse effects:* Treatment group: 4.5% abdominal pain, 13.6% loose stool, and 9.1%, increased stool frequency. Control group: 4.8% hypokalemia, 6.8% increased blood pressure, 11.4% edema, 4.5% weight gain, 2.3% decreased muscle strength.	
Sharquie and Al-Obaidi [20]	Crude onion juice applied twice daily	Tap water applied twice daily	RCT	Found higher rate of hair regrowth in the treatment group after 8 weeks of treatment compared to the control group. *Adverse effects:* 14 subjects or 60.8% of the treatment group experienced mild erythema.	Control was not well defined as to why tap water was chosen

RCT: Randomized Controlled Trial.

Table 2: Summary of studies for alopecia areata.

of 3.3 hairs in a 0.5 cm^2 area of the scalp selected for counting after 6 months of treatment, and an average increase of 11.5 hairs in the same area of the scalp after 12 months [8]. Conversely, treatment with vehicle alone resulted in an average decrease of 3.6 hairs after treatment for 6 months [8].

In another study researchers investigated the use of Dabao, a mixture of different Chinese herbs as a possible treatment for Androgenetic alopecia, specifically male pattern baldness. Previous non-controlled clinical studies and one randomized controlled trial with a 109 nine participants had found increases in hair growth with Dabao treatment [9]. This double blind randomized control trial that compared the efficacy of twice daily topical treatment with an ethanol based solution containing Dabao to that without Dabao, found that there was an overall increase in the number of non-vellus hairs in the Dabao treatment group after 6 months with an average increase of 135 hairs per 5 cm^2 compared to an average increase of 110 hairs per 5 cm^2 in the control group [9]. One of the major advantages of this study was that it was significantly larger than other studies encountered in this review as 273 out of the original 396 men enrolled in the study completed the study [9].

One study examined the potential use of *Trifolium pretense*, or red clover extract, and acetyl tetra peptide as a treatment for male pattern baldness. In a randomized control investigation, a 13% increase in the number of anagen hairs and an average reduction of 29% in the number of telogen hairs was seen in the group treated once daily with a 5% topical *Trifolium pretense* acetyl tetra peptide lotion after 4 months [1]. One advantage of this study was that hair density was measured utilizing TrichoScan™ instrumental measurements, so that human error

was reduced from the hair counting process. In addition to the clinical endpoint, the effects of *Trifolium pretense* extract and acetyl tetra peptide was also tested on the 5-α reductase, immunomodulatory, and ECM protein expression. Results indicated that a mixture of *Trifolium pretense* and acetyl tetra peptide inhibited 5-α reductase activity, limited the expression of inflammatory signals, and stimulated the expression of ECM proteins, including collagens III and VII and laminin [1].

The use of liposterolic *Serenoa repens, or* saw palmetto berry extract, and ß-sitosterol, a plant phytosterol, as a potential treatment option for male pattern baldness as both serve to inhibit 5-α reductase [10]. After a minimum of 4.6 months and a maximum of 5.4 months of twice daily treatment with an oral softgel containing 200 mg of liposterolic *Serenoa repens* extract and 50 mg of ß-sitosterol, 60% of subjects in the treatment group rated their hair as improved at the end of the study [10]. Conversely, 11% of subjects in the control group rated their hair as improved following twice-daily ingestion of a sofgel containing 540 mg of soybean oil [10]. One major disadvantage of this study is that results were measured based on dermatologist scores on 7 point grading scale and subject self-assessment scores. Assessments did not include more objective measurements, such as hair counting. Moreover, it was unclear why soybean oil was chosen as a control for the study.

In another study investigating the potential of *Serenoa repens* as a possible treatment for male pattern baldness, a randomized controlled trial was conducted comparing the efficacy of treatment with 320 mg of *Serenoa repens* taken orally once daily to 1 mg of finasteride taken orally once daily. Results demonstrate that an average of 38% of subjects in the *Serenoa repens* group had a score greater than 0, indicating increased hair density compared to baseline while an average of 68% of subjects in the finasteride group had a score greater than 0 [11]. Scores based on a 7-point scale were assigned after assessment of a global photograph. A disadvantage of this study was that this study utilized a subjective measure as the endpoint rather than an objective measure such as hair thickness or hair counts.

The potential use of *Curcuma aeruginosa* has been evaluated for the treatment of male pattern baldness. *Curcuma aeruginosa* is a plant native to Southeast Asia and previous in-vitro studies have indicated that it inhibits 5-α reductase [12]. In a double blind randomized controlled trial investigators found that twice daily topical treatment for 6 months with a hair tonic containing 5% *Curcuma aeruginosa* and 5% minoxidil resulted in an average increase of 32.6 hairs [12]. However, the treatment with 5% *Curcuma aeruginosa* only or 5% minoxidil only resulted in an average increase of 30.6 hairs and 31.3 hairs [12]. On the other hand, subjects in the control group who received twice daily application with hair tonic alone had an average increase of 20.4 hairs [12]. Moreover, 77% of subjects in the combination treatment group were rated as moderately or minimally improved based on global photographic review after 6 months of treatment, which was significantly higher than the control group [12]. Therefore, there does not seem to be a synergistic benefit to using both *Curcuma aeruginosa* and minoxidil, and this is not surprising since both acts as 5-α reductase inhibitors. The use of either minoxidil or *Curcuma aeruginosa* alone appears to be similarly effective. However, further studies are needed to better assess how this may be utilized in women.

In a case report, Kwon and colleagues investigated the potential use of epigallocatechin-3-gallate (EGCG) as a treatment for androgenetic alopecia. EGCG is a major constituent polyphenol of green tea and has been found to have 5α-reductase activity [13]. In order to investigate the effect of EGCG on human dermal papilla cells in vivo, researchers obtained scalp samples of three patients who were treated twice daily with 10% EGCG in ethanol for 4 days. Results of western blot analysis of these scalp samples demonstrated an increased phosphorylation of ERK and Akt, as well as an increased Bcl-2/Bax ratio with ECGC treatment [13]. Results of cultured human dermal papilla cells treated with EGCG demonstrated similar results with an increase in phosphorylation of ERK and Akt, as well as an increase in Bcl-2/Bax ratio with EGCG concentrations ranging from 0.01-0.5 μM [13]. EGCG may therefore mediate growth of dermal papilla cells through proliferative and anti-apoptotic effects. However, based on these results it is difficult to determine whether or not EGCG does prolong the anagen stage of hair growth as the authors suggest. A clinical evaluation is necessary for evaluation of EGCG on hair growth.

Alopecia Areata

Several studies have evaluated the use of botanical products for the treatment of alopecia areata (Table 2). In a randomized controlled trial, the use of capsaicin as a potential treatment for alopecia areata was evaluated. Capsaicin has been shown to stimulate hair growth [14]. It is suspected that this effect is mediated through the depletion of neuronal substance P and calcitonin gene-related peptide, both neuropeptides involved in the pathogenesis of alopecia areata, after repeated stimulation by capsaicin [14]. Results of this trial demonstrated that 33.3% of patients in the capsaicin group who received treatment with a capsaicin ointment (0.35-0.63 mg capsaicin/gram ointment) for 6 weeks had vellus hair compared to 4.5% of patients in the clobetasol group who received treatment with 0.05% clobetasol ointment [14]. However, when comparing cosmetically significant hair growth, neither capsaicin nor clobetasol had any effect. In a case report, researchers examined the use of capsaicin as a potential treatment for alopecia areata as well as the effect of capsaicin on perifollicular nerves. Two patients applied 0.075% capsaicin cream to the scalp for three weeks. Both patients experienced vellus hair growth within 21 days of initiation of treatment [15]. Immunohistochemistry results of scalp biopsies taken from both patients demonstrated increased neuropeptide SP expression in the follicle and decreased neuropeptide SP and pan-neuronal protein gene product 9.5 (PGP 9.5) in nerves of the epidermis following capsaicin treatment for 21 days [15]. Taken together, capsaicin application is associated with greater vellus hair growth, but it is not clear what role capsaicin has in therapy since cosmetically significant hairs do not seem to be improved.

A double blind randomized controlled study investigated the use of croton oil and dintrochlorobenzene (DNCB) as treatment options for alopecia areata. As croton oil contains phorbol ester, an irritant, it was hypothesized that it would induce hair growth through irritation like DNCB, a known contact sensitizer [16]. All patients were initially sensitized to DNCB for 1 week. Patients were then treated with either 5-30% of croton oil in a hydrophilic ointment topically applied every 1-3 days or 0.01-1% DNCB in hydrophilic ointment topically applied to induce allergic contact dermatitis. After 6 months of treatment, 3 patients treated with croton oil and one patient treated with DNCB experienced hair growth away from the site of application that lasted for longer than 6 months after cessation of treatment [16]. Of the remaining patients, 63.3% of those treated with DNCB experienced hair regrowth in the treatment area while no patients treated with croton oil experienced regrowth in the treatment area [16]. As the only patients who experienced hair regrowth following croton oil treatment did so in an area of the scalp outside the treatment area, it is difficult to assess the true effect of croton oil on hair growth. It appears that croton oil did not have efficacy for the treatment of alopecia areata.

Yang et al., studied the effects of total glucosides of peony as well

as glycyrrhizin on hair growth as potential treatments for alopecia areata. Total glucosides of peony are a group of glycoside substances found in Radix Paeoniae, or peonies, which has been shown to have immunomodulatory and anti-inflammatory effects [17]. Glycyrrhizin is used to treat alopecia and has also been shown to have immunomodulatory, anti-inflammatory and steroid like effects [17]. Treatment effectiveness in this randomized controlled trial was assessed using a 4-point scale (cured, markedly effective, effective, and failed) based on percentage of hair growth obtained as 100%, 70%, 30%, and less than 30%, respectively. The cured and markedly effective rates for the group treated with total glucosides of peony 600 mg capsules taken orally three times a day was 68.18% after 3 months compared to the cured and markedly effective rate of 71.43% in the control group treated with glycyrrhizin 50 mg tablets taken orally three times a day [17]. Notably, the authors did not compare either treatment against a non-active placebo, making any conclusions regarding efficacy difficult.

Garlic has been evaluated in its ability to promote hair growth. A randomized double-blind controlled trial showed that after 3 months of treatment the combination of 5% garlic gel and 0.1% bethamethasone cream had statistically significant more terminal hairs than treatment with 0.1% betamethasone cream alone [18]. The authors utilized a 12 point scoring system that incorporated size of hairless area, number of terminal hairs, and the total number of hairs. Although both treatment groups had a statistical increase in the score over baseline, the authors did not report the baseline score [18]. Also, it was not clear if the garlic/betamethasone score was different from the betamethasone score. Altogether, garlic showed promise as an adjuvant with topical betamethasone. However, it not known how garlic compares to betamethasone and future studies should look the isolated effects of garlic. Although no side effects were noted in this study, garlic has been reported to cause contact allergy [19] and should be utilized with caution.

As garlic has been used a topical treatment for alopecia areata and garlic and onions have many similar chemical properties it was hypothesized that crude onion juice may have hair regrowth effects [20]. In this randomized controlled trial, the effect of topical crude onion juice was found to stimulate hair growth in 86.9% of subjects with alopecia totalis while 13% of patient treated with tap water alone saw hair growth [20]. The choice of tap water as a control was not well described and it is unclear how this may or may not serve as an appropriate control for the onion juice.

The result of our systematic review of published data examining the use of natural and botanical products for the treatment of alopecia reveal that there is limited data pertaining to this topic. Moreover, although it was our intent to review the literature encompassing various forms of alopecia, such as alopecia areata, androgenetic alopecia, and scarring alopecias, we only found published studies examining the role of botanical and natural products for the treatment of alopecia areata and androgenetic alopecia. More specifically, our search of studies pertaining to androgenetic alopecia only yielded studies that investigated the use of male pattern baldness, as no studies included female participants.

Conclusion

Apart from having a limited scope for the different types of alopecia, the results of our review demonstrate that the majority of studies conducted in this area of alopecia treatment our either pilot studies or small scale clinical trials. Only two of the studies reviewed included 100 or more individuals [9,11]. Conversely, five of the studies that we reviewed included fewer than 30 individuals who completed the study [1,7,10,16,20].

Regardless of the limitations of our review, the results indicate increasing interest into botanicals and natural products for the treatment of alopecia. This increasing interest is especially pertinent when taking commonly used treatment options into account. As there is no cure or definitive treatment for either alopecia areata or androgenetic alopecia, there are a wide range of current therapies with various mechanisms of stimulating hair growth. Some examples for the treatment of alopecia areata include topical and systemic corticosteroids, minoxidil, biologics, and calcineurin inhibitors. A less common example includes antidepressants to treat comorbid stress thought to be involved in the pathogenesis of alopecia areata [21]. No randomized controlled trials have found complete regrowth with any of these treatment options [21]. Moreover, several of these treatments, such as corticosteroids, can have serious side effects [22]. Current treatment options for androgenetic alopecia include medical options, such as 5 alpha reductase inhibitors, spironolactone and other anti-androgens, minoxidil, and non-medical treatments such as surgical treatment and light treatment [22]. Although some of these treatment options are effective for the androgenetic alopecia, many undesired and potentially serious side effects [22].

There is a need for novel treatment options for alopecia. Botanicals and natural products can potentially serve this unmet need. With the increasing number of studies investigating the potential use of these products for the treatment of alopecia, the evidence will continue to grow and establish which therapies are effective and which are not.

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