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Review Article

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Do Non-Prescription Products Help in Managing Androgenic Alopecia?

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Keywords
Androgenetic alopecia · Complementary medicine · Alternative medicine · Natural products · Non-prescription drugs

Abstract
Background: Androgenetic alopecia (AGA) is the most common cause of hair loss. Currently, approved medications for AGA are topical minoxidil and oral finasteride, both of which are prescription medications which may cause side effects. Non-prescription products such as herbal extracts and over-the-counter medications have limited evidence regarding safety and efficacy; however, they may be an alternative for patients unable or unwilling to use prescription medication. ***Summary:*** This article reviews investigator-blinded, controlled clinical trials assessing the efficacy of non-prescription monotherapies in treating AGA. A total of 13 studies were included using procyanidin, cetirizine, caffeine, *Oryza sativa* bran, pumpkin seed oil, rosemary oil, saw palmetto, and watercress. The available data demonstrate considerable improvements in one or more parameters: total hair density, terminal hair density and hair diameter. Procyanidin and cetirizine were investigated in more investigator-blinded, randomized controlled trials than other agents. Minimal adverse events were observed; however, more robust clinical trial and long-term safety and efficacy data are warranted. ***Key Message:*** Additional investigations through the conduct of high quality randomized, controlled trials with larger numbers of patients will help determine the effectiveness and safety of this class of compounds, either as monotherapy or as an addition to current pharmacological interventions.

Introduction

The leading cause of hair loss worldwide is androgenetic alopecia (AGA), affecting both males and females [1, 2]. Elevated levels of dihydrotestosterone (DHT) are thought of as the main cause of AGA [2]. DHT is converted from testosterone by the 5α-reductase enzyme. DHT then acts on hair follicles, promoting miniaturization and hair loss [2]. We review the efficacy and safety of selected non-prescription products in the management of AGA. The US FDA approved treatments for AGA are topical minoxidil for men and women, and oral finasteride for males [3]. Oral finasteride has been used off-label in postmenopausal women.

Many patients seek alternatives when they are reluctant to use prescribed medications, or have experienced poor efficacy or side effects from their prescribed medications. These natural products and over-the-counter (OTC) drugs may be complementary therapies for the treatment of AGA along with currently prescribed

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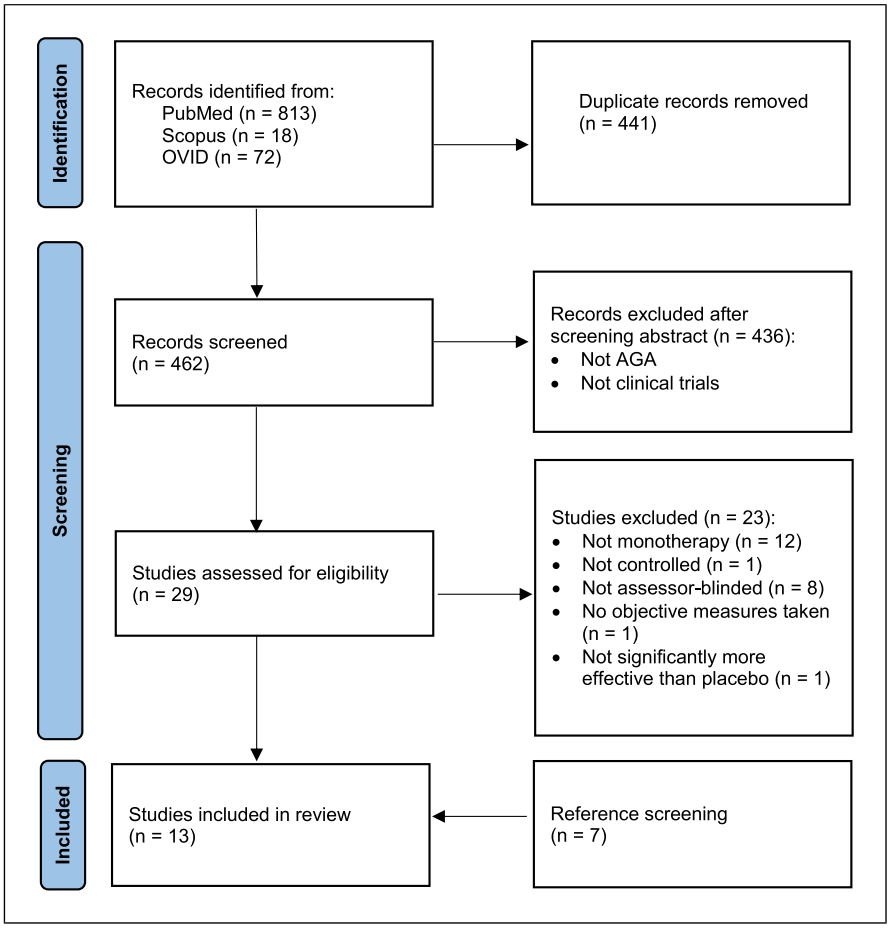

Fig. 1. Overview of systematic search.

medications [4]. This article reviews monotherapy clinical trials (randomized controlled trials [RCTs]) on the following natural compounds: procyanidin (4 RCTs), caffeine (1 RCT), *Oryza sativa* bran (OSB) (1 RCT), pumpkin seed oil (PSO) (1 RCT), rosemary oil (1 RCT), saw palmetto (1 RCT) and watercress (1 RCT), well as the OTC drug cetirizine (3 RCTs).

Methods

We conducted a systematic search in PubMed, Scopus, and EMBASE (Ovid) on September 30, 2024, using various keywords and MeSH terms for androgenetic alopecia, androgenic alopecia, AGA, natural products, botanical products, and alternative therapies. The search identified 903 articles. Rayyan was used to process the systemic search and remove duplicates and conduct initial screening. In addition, we hand-searched bibliographies of selected review articles to identify relevant clinical studies (shown in Fig. 1).

This review includes clinical studies investigating the efficacy of various monotherapy non-prescription products (natural and OTC off-label treatments) for both male and female AGA. Trials without investigator blinding or without a comparator arm were excluded. Trials that did not focus solely on AGA were excluded. Trials which examined a combination treatment of multiple products or compounds were excluded (shown in online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000542880). Compounds were included based on whether they had a minimum of one investigator-blinded RCT which took objective measurements of efficacy (i.e., hair density, terminal hair density, hair diameter, hair-pull test). Selection criteria have concluded with 14 relevant clinical review articles. Evidence quality was rated using the Oxford Centre for Evidence Based Medicine, 2011 Levels of Evidence table (Table 1). Compounds are listed in descending order of the number of total RCTs. For articles in which a baseline and final value is not reported for any of the parameters (i.e., presented visually

Table 1. Summary of natural and OTC products for AGA and quality assessment of the included studies

Agent	Mechanism of action	Potential efficacy	RCTs, *N*	Quality of evidence[a]	Relative search volume in 2020 and 2024 ytd[b] (% increase)
Procyanidin	Antioxidative, anti-inflammatory, and growth-promoting action on hair epithelial cells [4, 5]	Increased total hair density, terminal hair density and hair width compared to placebo [5–8] No comparisons in the literature to minoxidil or finasteride	4	2	Insufficient data
Cetirizine	PGD2 inhibitor, PGE2 stimulator [9]	Combination therapy with minoxidil 5% not more effective than minoxidil alone [10] Improves hair density and diameter but not to the extent of minoxidil 5% [11] Regrows hair and improves hair density [12]	3	2	Insufficient data
Caffeine	Promotes expression of insulin-like growth factor-1 and inhibits testosterone-induced TGF-β1 [13, 14]	Reduced hair loss when compared to control [15] No comparisons made to minoxidil or finasteride	1	2	7.85 in 2020 28.6% in 2024 (264%)
OSB	5α-reductase enzyme inhibition [16]	Increased total hair density and hair diameter in male and female patients [17] No comparisons made to minoxidil or finasteride	1	2	Insufficient data
PSO	5α-reductase enzyme inhibition [18]; antioxidant, anti-inflammatory	Increased hair count compared to placebo, did not increase hair width when compared to control [19] No comparisons made to minoxidil or finasteride	1	2	0.94 in 2020 33.4 in 2024 (654.4%)
Rosemary oil	Antioxidant, antimicrobial, antispasmodic action on smooth muscles [20]	Increased total hair density to a similar extent as minoxidil 2% [20]	1	2	10.5 in 2020 68.6 in 2024 (551.3%)
Saw palmetto	5α-reductase enzyme inhibition [21]	Increased hair density, terminal hair density, and hair diameter [22] No comparisons made to minoxidil or finasteride	1	2	14.6 in 2020 22.2 in 2024 (52.3%)
Watercress extract	RSPO1 upregulation, DKK1 inhibitor [23]	Increased hair density and hair diameter [23] No comparisons made to minoxidil or finasteride	1	2	Insufficient data

[a]Quality defined by the Oxford Centre for Evidence Based Medicine, 2011 [24]: Level 1: systematic review (not included in this analysis). Level 2: randomized clinical trial, observational study with substantial effect, inception cohort study. Level 3: cohort study, nonrandomized controlled cohort with follow-up study. Level 4: case series, case control, poor quality prognostic cohort study, or historically controlled studies (not included in this analysis). Level 5: mechanism-based reasoning (not included in this analysis).
[b]Google Trends accessed September 30 – October 3, 2024.

Table 2. Summary of clinical efficacy as per trichoscopy assessment

Study	AGA severity	Intervention, *N*	Regimen	Follow-up	Total hair density, /cm^2, mean (SD)		Terminal hair density, /cm^2, mean (SD)		Hair diameter, μm, mean (SD)	
					baseline	F/U	baseline	F/U	baseline	F/U
Procyanidin										
Yeniay 2022 [6]	NH II-IV	Procyanidin B2 1% (20)	1.8 mL topical spray BID for 16 weeks	Week 16	141.7 (16.2)	155.4 (21.0)	51.6 (6.8)	67.2 (9.0)[a]	NR	
Randomized, double-blinded, controlled		Placebo (20)	1.8 mL topical spray BID for 16 weeks		145.4 (17.1)	142.5 (19.6)	60.8 (7.1)	58.9 (9.6)	NR	
Kamimura 2000 [5]	Ogata I-IV	Procyanidin B2 1% (19)	15 mg topical BID for 6 months	Month 6	127.2 Calc	153.9[a,b] Calc	27.3 Calc	35.3[a,b] Calc	NR	
Randomized, double-blinded, controlled		Placebo (10)	1.8 mL topical BID for 6 months		138.0 Calc	138.3 Calc	40.8 Calc	37.5[a,b] Calc	NR	
Takahashi 2001 [7]	Ogata II-IV	Procyanidin B2 1% (19)	15 mg topical BID for 6 months	Month 4	127 Calc Est	142 Calc Est	NR		Δ 2.7 (4.7)	
Randomized, double-blinded, controlled		Placebo (10)	1.8 mL topical BID for 6 months		138 Calc Est	127 Calc Est	NR		Δ −1.1 (6.8)	
Takahashi 2005 [8]	Ogata I-IV	Procyanidin 0.7% (21)	9.35 mg topical BID for 6 months	Month 6	Δ 6.6 (26.0)[b]		NR		NR	
Randomized, double-blinded, controlled		Placebo (22)	2 mL topical BID for 6 months		Δ −7.2 (16.2)		NR		NR	
Cetirizine										
Bassiouny 2023 [10]	Sinclair II-IV	Cetirizine 1% and minoxidil 5% (26)	1 mL cetirizine, 1 mL minoxidil QD for 24 weeks	Week 24	NR		97.6 (32.9)	177.4 (43.2)[b]	42.29 (10.06)	42.37 (7.97)
Randomized, double-blinded, controlled		Placebo and minoxidil 5% (27)	1 mL placebo, 1 mL minoxidil QD for 24 weeks		NR		107.9 (28.6)	197.4 (43.1)[a]	46.05 (8.93)	45.12 (9.35)
Mostafa 2021 [11]	AGA II-IV	Cetirizine 1% (18)	1 mL topical BID for 16 weeks	Week 16	102 Est	124[a] Est	NR		65 Est	70 Est
Randomized, double-blinded, controlled		Minoxidil 5% (12)	1 mL topical BID for 16 weeks		113 Est	148[a] Est	NR		68 Est	74 Est

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Table 2 (continued)

Study	AGA severity	Intervention, *N*	Regimen	Follow-up	Total hair density, /cm^2, mean (SD)		Terminal hair density, /cm^2, mean (SD)		Hair diameter, μm, mean (SD)	
					baseline	F/U	baseline	F/U	baseline	F/U
Caffeine										
Bussoletti 2020 [15]	Ludwig 0–2	Phyto-caffeine shampoo (70)	7 mL QD topical for 6 months. Rinsed off after 2 min	Month 6	*Hair-pull test:* significant reduction in hair loss (21.4±2.4–18.3±2.3)					
Randomized, double-blinded, placebo-controlled		Placebo shampoo (70)	7 mL QD topical for 6 months. Rinsed off after 2 min		*Hair-pull test:* no significant change in hair loss (21.3±2.3–20.7±2.3)					
OSB										
Choi 2015 [17]	HN (22)	Rice bran extract 0.5% (M: 12, F: 13)	4 mL topical BID for 16 weeks	Week 16	M: 93.5 (11.8) F: 82.0 (13.6)	M: 103.2 (10.1)[a,b] F: 95.6 (8.4)[a]	NR		M: 57 (18) F: 72 (15)	M: 75 (16)[a] F: 89 (14)[a]
Randomized, double-blinded, controlled	Ludwig (21) Grades NR	Placebo (M: 16, F: 9)	4 mL topical BID for 16 weeks		M: 88.2 (23.4) F: 70.6 (11.1)	M: 90.9 (17.5) F: 80.9 (10.0)[a]	NR		M: 59 (17) F: 62 (14)	M: 69 (16) F: 74 (11)[a]
PSO										
Cho 2014 [19]	HN II-V	PSO (37)	Two 100 mg oral BID for 24 weeks	Week 24	Δ 6.2 (6.5)[b,c]		NR		Δ 0.34 (0.03)[c]	
Randomized, double-blinded, controlled		Placebo (39)	Two 100 mg oral BID for 24 weeks		Δ 1.8 (6.2)[c]		NR		Δ 0.34 (0.02)[‡]	
Rosemary oil										
Panahi 2015 [20]	HN (vertex) II-IV	Rosemary oil (50)	1 mL topical BID for 6 months	Month 6	122.8 (48.9)	129.6 (51.2)[a]	NR		NR	
Randomized, investigator-blinded, controlled		Minoxidil 2% (50)	1 mL topical BID for 6 months		138.4 (38)[‡]	140.7 (38.5)[a,b]	NR		NR	
Saw palmetto										
Sudeep 2023 [22]	HN II-IV (male)	Saw palmetto oral (18)	400 mg oral QD for 16 weeks	Week 16	222.6 (46.8)	234.1 (37.7)[a,b]	NR		16.9 (3.5)	19.6 (3.3)[a]
		Placebo oral (19)	400 mg oral QD for 16 weeks		215.2 (29.1)	208.3 (29.2)[a]	NR		17.2 (2.6)	17.5 (3.5)

Table 2 (continued)

Study	AGA severity	Intervention, *N*	Regimen	Follow-up	Total hair density, /cm^2, mean (SD)		Terminal hair density, /cm^2, mean (SD)		Hair diameter, μm, mean (SD)	
					baseline	F/U	baseline	F/U	baseline	F/U
Randomized, double-blinded, controlled	Sinclair II-IV (female)	Saw palmetto topical (18)	5 mL topical QD for 16 weeks		205.7 (34.3)	221.3 (37.6)[a,b]	NR		16.5 (4.4)	17.4 (3.7)
		Placebo topical (18)	5 mL topical QD for 16 weeks		230.2 (47.2)	221.8 (45.9)[a]	NR		16.6 (3.89)	16.6 (3.4)
Watercress extract										
Hashimoto 2022 [23]	3–6 extended Norwood and Ludwig	Watercress extract lotion (19)	1.2 g lotion topical BID for 6 months	Month 6	147 Est	160[a] Est	NR		47 Est	61[a] Est
Randomized, double-blind, controlled		Placebo lotion (19)	1.2 g lotion topical BID for 6 months		145 Est	145 Est	NR		49 Est	44 Est

HN and Ogata grade used to assess male AGA severity. Ludwing or Sinclair grade used to assess female AGA severity. BID, twice daily; F, female; F/U, follow-up; HN, Hamilton-Norwood; M, male; QD, once daily. [a]Significantly ($p < 0.05$) changed from baseline. [b]Significantly ($p < 0.05$) different from other treatment group (placebo/monotherapy/other drug). [c]Units unspecified. Δ = reported change from baseline, no baseline, or F/U values reported. Calc., when baseline or final values are not reported, average values were calculated based on available individual data points from graphs or tables. Est., when baseline or final values are not reported, values were estimated based on available graphs or tables.

in graphs) in Table 2, a value was estimated using PlotDigitizer. If no mean values were reported and individual values were available, the mean was calculated from individual values and reported as such.

A Google Trends search was done to assess current interest in a specific compound (Table 1). Data were taken from Google Trends between September 30 and October 4, 2024, and the weekly relative search volume was taken and averaged for January–December 2020 and January–September 2024. If fewer than 3 years over a 5-year period showed peaks in relative search volume, data were not collected and reported as insufficient.

Results and Discussion

An overview of the agents with an assessment of evidence quality is presented in Table 1. Clinical efficacy of the identified agents – as per total hair density, terminal hair density and hair diameter – is summarized in Table 2. Reported adverse events, either deemed drug-related or otherwise, are summarized in Table 3.

Procyanidin

Procyanidins may prevent TGF-β1- and TGF-β2-induced apoptosis in dermal papilla cells and thus promote hair growth (Table 1) [4]. It may also stimulate other hair growth-promoting pathways and inhibit inflammatory pathways in hair follicles [25]. Procyanidin has the potential to be an effective and well-tolerated agent to treat AGA, with efficacy in increasing hair density [5–8]. Procyanidin may lack the side effects of 5α-reductase inhibition, and may target a different pathway than both minoxidil and finasteride, thereby being a possible agent to treat AGA (Table 1).

Clinical Evidence

Yeniay and Arca conducted a randomized double-blind, placebo-controlled study with 40 male patients with AGA [6]. For 16 weeks, participants applied either procyanidin B2 1% or placebo topical spray (1.8 mL/day) twice daily. Procyanidin significantly improved both hair density and terminal hair density in the treatment group after 16 weeks (155.40 ± 21.01 hairs/cm^2, 67.20 ± 9.04 hairs/cm^2) compared to baseline (141.65 ± 16.18 hairs/cm^2, 51.55 ± 6.70 hairs/cm^2) ($p < 0.05$). The placebo arm saw reduced terminal hair density (baseline:

Table 3. Reported adverse events

Intervention	AE
Procyanidin	Mild erythema and scaling [6] None reported [5, 7, 8]
Cetirizine	None reported for cetirizine monotherapy [10–12]
Caffeine	None reported [15]
OSB	None reported [17]
PSO	Pruritus, mild abdominal discomfort [19]
Rosemary oil	Scalp itching [20]
Saw palmetto	Common cold and headaches [22]
Watercress	None reported [23]

60.80 ± 7.12 hairs/cm^2, 16 weeks: 58.90 ± 9.57 hairs/cm^2) and total hair density (baseline: 145.35 ± 17.13 hairs/cm^2, 16 weeks: 142.50 ± 19.64 hairs/cm^2); however, the reduction was not significant ($p > 0.05$) (Table 2).

Kamimura et al. [5] conducted a randomized, double-blind, placebo-controlled study with 29 male patients with AGA. Participants applied either procyanidin B2 1% (30 mg/day) or placebo topically to affected areas. After 4 months of treatment, the treatment arm had significantly increased total and terminal hair densities from baseline (+26.72 ± 22.1 hairs/cm^2, 7.69 ± 10.32 hairs/cm^2), while the control arm had no significant change in both densities (+0.32 ± 18.24 hairs/cm^2, −3.28 ± 13.6 hairs/cm^2), this difference from the treatment arm was significant ($p < 0.005$, $p < 0.02$) (Table 2).

Takahashi et al. [7] in 2001 repeated the study and assessed hair density and hair diameter in response to the same procyanidin B2 1% treatment. The study was double-blinded and placebo-controlled, with the same treatment schedule as previously. After 4 months, procyanidin treatment increased hair density (mean change: +14.68 ± 16.36 hairs/cm^2) in 84.2% of the treatment arm, whereas only 20.0% of the control arm had increased hair density (mean change: −10.16 ± 16.00 hairs/cm^2) ($p < 0.002$). As well, 78.9% of the treatment arm had increased hair diameters (mean change: +2.68 ± 4.68 μm) compared to 30.0% of placebo group (mean change −1.08 ± 6.77 μm) ($p < 0.02$). There was significantly increased ratio of terminal hairs (treatment: 8.04 ± 13.75% vs. placebo: −4.32 ± 18.31%, $p < 0.05$) (Table 2).

The same group in 2005 conducted a randomized, double-blind, placebo-controlled study with 43 participants over 6 months of treatment [8]. Participants applied either 2 mL of procyanidin 0.7% (18.7 mg/day) or placebo twice daily for 6 months. There were significant increases in hair counts at 6 months (mean change: +6.6 ± 26.0 hairs/cm^2) in procyanidin compared to placebo (−7.2 ± 16.2 hairs/cm^2) ($p < 0.001$) (Table 2).

Safety

Yeniay and Arca reported mild erythema and scaling in 3 patients, but did not conclude that the reaction was drug-related (Table 3) [6]. Kamimura et al. [5], Takahashi et al. [7], and Takahashi et al. [8] assessed side effects and conducted dermatologic analyses of the scalp post-treatment; no adverse-events were reported.

Cetirizine

Cetirizine (available OTC) is a selective second-generation antihistamine and a H1 antagonist that modulates the release of prostaglandins (Table 1) [9]. It reduces the release of prostaglandin D2(PGD2) and stimulates the release of prostaglandin E2(PGE2). PGD2 is highly expressed in men with AGA, where it inhibits hair growth [9]. In contrast, PGE2 was reduced in subjects with AGA in the bald areas compared to haired areas; thus, the stimulation of PGE2 by cetirizine may upregulate hair growth [26]. There currently exist three double-blinded, controlled, randomized control trials studying the effect of cetirizine in AGA patients; however, indications of efficacy maintain that cetirizine should be considered an alternative or supplemental treatment for AGA.

Clinical Evidence

Bassiouny et al. [10] conducted a randomized, double-blinded, placebo-controlled study comparing the efficacy of a combination therapy of topical cetirizine with topical minoxidil against the efficacy of minoxidil alone in treating females with AGA. In the double-blind study, 53 female patients with AGA applied 1 mL of topical minoxidil 5%

once daily, and then also 1 mL of topical cetirizine 1% or 1 mL of placebo for 24 weeks. Both the treatment arms had significantly improved terminal hair density and vellus hair density in the vertex at 12 weeks ($p < 0.0005$). The combination of topical cetirizine and topical minoxidil changed vertex terminal hair density from 97.62 ± 32.89 hairs/cm^2 at baseline to 177.43 ± 43.15 hairs/cm^2 at 24 weeks in the frontal region, while minoxidil alone changed frontal area terminal hair density from 107.87 ± 28.63 hairs/cm^2 to 197.36 ± 43.07 hairs/cm^2 ($p < 0.0005$) (Table 2).

Mostafa et al. [11] conducted a study assessing the efficacy of topical cetirizine 1% compared with topical minoxidil 5% in a randomized, investigator-blinded clinical study. The participants (forty men) applied either 1 mL of cetirizine 1% or 1 mL of minoxidil 5% topically on the scalp daily for 16 weeks. After 16 weeks, the participants received a placebo solution for the next 8 weeks. Total hair density at 16 weeks was significantly increased in both the cetirizine and minoxidil groups ($p < 0.01$) (Table 2). A non-significant increase in terminal hair density was observed. At week 16, the minoxidil treated group had significantly higher hair density than the cetirizine group ($p < 0.05$) but not at 24 weeks following placebo treatment in both groups.

Zaky et al. [12] conducted a randomized double-blinded placebo-controlled study with 60 male patients with AGA. Participants applied 1 mL 1% topical cetirizine lotion daily for 6 months. There was a significant difference between cetirizine 1% and placebo groups, where 10 participants (33.3%) showed photographic improvement, whereas no participants in placebo showed improvement ($p < 0.001$). Significantly more patients in the treatment arm had regrowing hairs compared to placebo (13 vs. 0, $p < 0.001$).

Safety

Oral cetirizine causes primarily somnolence and headaches. No drug-related side effects were observed with topical cetirizine [12]. In the Mostafa et al. study, which reviewed the efficacy of cetirizine in comparison with minoxidil, the minoxidil group experienced mild pruritus (15%) and scaling (10%), whereas the cetirizine group experienced no side effects (Table 3) [11]. In addition, combination treatment with both cetirizine and minoxidil or minoxidil only both showed similar levels of reported side effects (itching, dry hair, dandruff, and initial hair loss), all of which are known side effects of minoxidil, with the treatment group receiving both cetirizine and minoxidil showing no increase in side effects compared with the group receiving only minoxidil [10].

Caffeine

Caffeine is a stimulator of hair growth and may rescue testosterone/DHT-induced hair loss and hair follicle miniaturization [13]. Caffeine also promotes increased expression of insulin-like growth factor-1, a promoter of hair growth, and inhibits the expression of testosterone-induced TGF-β1, a hair growth inhibitor [14]. While elevated caffeine intake may not increase hair growth, caffeine is readily absorbed by the scalp and penetrates hair follicles in response to topical lotion and shampoo applications with limited side effects (Table 1) [27]. Few studies have been conducted on topical caffeine formulations as a monotherapy in treatment of AGA; however, it has been used in various combination therapies and is an ingredient in commercial alternative AGA treatments [28, 29].

Clinical Evidence

Bussoletti et al. [15] conducted a randomized, double-blind placebo-controlled study using a phyto-caffeine shampoo on 140 female subjects with AGA over a 6-month period. At month 6, participants in the phyto-caffeine shampoo group had significantly reduced hair loss (baseline: 21.4 ± 2.4, 6 months: 18.3 ± 2.3, $p < 0.001$) as assessed by a hair-pull test when compared to placebo (baseline: 21.3 ± 2.3, 6 months: 20.7 ± 2.3) (Table 2). Patient satisfaction was more pronounced in subjects receiving the caffeine shampoo.

Safety

No adverse events were reported (Table 3) [15].

Oryza Sativa Bran

OSB, or rice bran, has been classified as 5α-reductase enzyme inhibitor, indicating its use as a potential therapy for AGA, as the 5α-reductase enzyme is culpable in hair loss and miniaturization [16]. OSB has specifically been found in vivo to be as effective of an inhibitor of 5α-reductase I as finasteride [16]. Topical OSB may be an effective alternative for those wishing to avoid the systemic side effects associated with oral 5α-alpha reductase inhibitors (Table 1).

Clinical Evidence

Choi et al. [17] conducted a 16-week randomized double-blind, placebo-controlled trial which assessed the efficacy OSB extract in treating 28 male and 22 female AGA patients. The participants applied 4 mL of a liquid topical OSB extract twice daily for 16 weeks. The OSB treated group showed significantly improved hair density, the baseline for male patients was 93.50 ± 11.8 hairs/cm^2 and was increased to 103.22 ± 10.1 hairs/cm^2 at 16 weeks ($p < 0.0001$); the baseline for female patients was 81.96 ± 13.6 1 hairs/cm^2

and increased to 95.59 ± 8.4 hairs/cm^2 at 16 weeks (p = 0.006). In the placebo group, hair density was significantly increased only in female participants, from baseline 70.56 ± 11.1 hairs/cm^2 to 80.94 ± 10.0 hairs/cm^2 at 16 weeks (p = 0.039). Hair diameter was significantly increased for both male and female patients in response to OSB treatment from baseline (male: 57 ± 18 μm; female: 72 ± 15 μm) compared to at 16 weeks (male: 75 ± 16 μm; female: 89 ± 14 μm) (p = 0.001). Only female placebo patients had a significant increase in hair diameter (baseline: 62 ± 14 μm; placebo: 74 ± 11 μm; p = 0.027) (Table 2).

Safety

No adverse reactions were reported in the study participants (Table 3) [17]. Despite this, OSB has the potential as a 5α-reductase inhibitor, and while it may be used topically, oral intake of OSB may require the same safety precautions needed for women and pregnant women as other 5α-reductase inhibitors such as finasteride. In addition, rice and rice by-products may carry a risk of high heavy metal levels; as such, products containing OSB should be assessed for safety and purity from such contaminants.

Pumpkin Seed Oil

PSO consists of various fatty acids including β-sitosterol and linolenic acid, both of which are inhibitors of the 5α-reductase enzyme [30]. Furthermore, PSO also has antioxidant and anti-inflammatory properties which may further promote hair growth and reduce hair loss [30]. While PSO may not be as effective as topical minoxidil, it may still be a safe and effective consideration for those unwilling or unable to take pharmaceutical interventions (Table 1) [18].

Clinical Evidence

Cho et al. [19] conducted a controlled randomized, double-blinded, placebo-controlled study on the effect of PSO in 76 male patients with AGA. Participants took 400 mg of PSO per day for 24 weeks. The PSO treatment group had significantly higher increases in hair count change when compared to placebo at 24 weeks (+6.2 ± 6.5 hairs [40% increase] versus +1.8 ± 6.2 [10% increase]; p = 0.004) in a ×60 lens frame (Table 2). There was no change in hair diameter between the two groups. Investigator evaluations judged that 44.1% of PSO treated participants showed slight to moderate improvements compared to only 7.7% of placebo (p = 0.002).

Safety

Most subjects did not report adverse symptoms throughout treatment, with uncommon reports of pruritus (n = 1) and mild abdominal discomfort (n = 1) (Table 3) [19]. No changes in liver function markers were observed. Serum-free testosterone levels were also unchanged from baseline [19]. In general, studies have shown that PSO is generally well tolerated with few side effects; however, potential 5α-reductase inhibition related adverse effects need to be ruled out.

Rosemary Oil

Rosemary (*Rosmarinus officinalis*) contains antioxidant, anti-inflammatory, and antimicrobial compounds. A study done in vivo found that rosemary extract contains, 12-methoxycarnosic acid, which functions as a 5α-reductase enzyme inhibitor and therefore may be effective at treating AGA [31]. Rosemary oil is an ingredient in many hair growth cosmetic products, and a clinical study treating AGA rosemary oil alone was comparable in efficacy to minoxidil 2% (Table 1) [20, 32, 33].

Clinical Evidence

Panahi et al. [20] conducted a 6-month randomized, investigator-blinded clinical trial comparing the efficacy of rosemary oil lotion (3.7 mg 1,8-cineol per mL lotion) to minoxidil 2%. The study assessed one hundred men with AGA and participants applied 1 mL of either solution twice daily to the frontoparietal and vertex areas of the scalp for 6 months. At 6 months, hair counts in both the rosemary lotion and minoxidil 2% group were significantly increased from 122.8 ± 48.9 hairs and 138.4 ± 38.0 hairs, respectively, at baseline to 129.6 ± 51.2 hairs and 140.7 ± 38.5 hairs, respectively ($p < 0.05$) (Table 2). The size and location of hair count area was not reported. There was no significant difference between the rosemary lotion and minoxidil 2% group at 6 months.

Safety

Rosemary oil treatment did not significantly increase frequency in hair dryness, greasiness, or dandruff. It may increase frequency of scalp itching; however, the reported frequency of scalp itching was lower in the rosemary group in comparison to minoxidil treatment. No other adverse effects were reported (Table 3) [20]. To our knowledge, there are no reports of rosemary oil toxicity when applied topically; however, contact dermatitis may uncommonly occur [34].

Saw Palmetto

Saw palmetto (*Serona repens*) extract (SPE) has been used to treat benign prostatic hyperplasia. Due to the similarities between the pathogenesis of AGA and benign prostatic hyperplasia, SPE has been considered for the treatment of AGA [21]. Saw palmetto may be an effective

inhibitor of 5α-reductase types I and II. Many commercial hair-growth botanical compounds contain SPE [35–37].

Clinical studies indicate that SPE at 200–300 mg/day may promote hair growth or prevent hair loss in AGA. The long-term safety and efficacy of SPE is unclear; no studies have reported on the potential teratogenic effect. SPE may be less effective than oral finasteride; however, it is often considered a possible option by those unwilling or unable to take oral finasteride (Table 1).

Clinical Evidence

Sudeep et al. [22] conducted a randomized, double-blind, placebo-controlled clinical study investigating AGA, and enrolled eighty male and female participants. Patients were randomized to receive either SPE 100 mg in oral capsules or SPE 20% in 5 mL lotion. At 16 weeks, both oral and topical SPE significantly increased hair density (234.06 ± 37.74 hairs/cm^2; 221.33 ± 37.61 hairs/cm^2) from baseline (222.56 ± 46.81 hairs/cm^2; 205.67 ± 34.34 hairs/cm^2) compared to placebo ($p < 0.05$) (Table 2). The authors found a significant increase in hair caliber at 16 weeks, but only in the oral SPE group.

Safety

No major adverse events were reported by study participants [22]. Sudeep et al. [23] also assessed liver toxicity and found that neither oral nor topical applications of SPE affected markers of liver function. All observed side effects were reversible upon discontinuation.

While reported to be generally tolerable, SPE is still a 5-alpha-reductase inhibitor and may have sexual side effects seen with other 5-alpha-reductase inhibitors. More investigations into the long-term safety of SPE should be conducted to rule out potential teratogenic side effects.

Watercress Extract

Watercress extract is predicted to function by upregulating R-spondin 1, a hair growth promoter, and inhibiting Dickkopf-1 (DKK-1), a hair growth suppressor (Table 1). DKK-1 induces catagen in hair cycling, leading to the premature loss of hair and in vivo DKK-1 inhibition resulted in increased hair length [38]. This proposed mechanism differs from the one used by finasteride and minoxidil and be an effective treatment when used in combination with prescription drugs.

Clinical Evidence

Hashimoto et al. [23] conducted a double-blinded, randomized, controlled clinical trial assessing the efficacy of WCE 2% lotion in treating AGA. Forty-four male participants with AGA were given either WCE 2% lotion or placebo applied topically (1.2 g lotion) twice daily for 6 months. The treatment arm showed significant improvement in hair diameter from baseline when compared to placebo (+13.53 ± 0.879 vs. −4.98 ± 1.44 μm/hair, $p < 0.01$) and hair density (+2.8 ± 5.83 hairs/cm^2 vs. −0.130 ± 6.62 hairs/cm^2, $p < 0.05$) at 6 months (Table 2).

Safety

No adverse reactions were reported by Hashimoto et al. [23] (Table 3). The reports of watercress extract safety in the literature are limited, so further studies should be conducted on its safety for WCE to be considered a safe therapy.

Limitations

While clinical studies exist for other natural compounds such as ginseng and cannabidiol, none indicated that they were investigator-blinded. Other commercial supplements (e.g., Nutrafol, Viviscal) which do have blinded control trials were not included in this review due to their ingredients consisting of multiple natural compounds and therefore would be categorized as combination therapies (online suppl. Table 1). To our knowledge, the included natural compounds do not have studies investigating the long-term safety and effects of continuous use for over 1-year, and the sample sizes may not be sufficient to identify uncommon or rare adverse events. In addition, the mechanisms of action and pathways for some compounds may require more robust in vitro mechanistic analyses.

Conclusions

We reviewed natural/OTC agents for the treatment of AGA that have been independently assessed in investigator-blinded, controlled trials that have been found to be significantly more effective than placebo treatments. Overall, there are few adverse events reported, most of which resolved upon treatment discontinuation, suggesting a favorable tolerability profile.

Comparatively, topical procyanidin and topical cetirizine were the two agents with more robust evidence, having been investigated in 4 RCTs and 3 RCTs, respectively. Topical administration of procyanidin demonstrated significant improvements in hair density and diameter up to 6 months. Cetirizine and rosemary oil had demonstrated efficacies comparable to that of minoxidil. Based on available studies, these products show promise as treatments for promoting hair growth and treating AGA; however, none were shown to be more effective than topical minoxidil or oral finasteride and the volume

of available studies is lacking. Clinicians should exercise caution when recommending alternative treatments for AGA as some agents could lead to adverse effects as 5α-reductase inhibitors or other unintended effects. Future trials are warranted to elucidate the efficacy and safety of these agents as monotherapy or in combination therapy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The conceptualization of project and supervision were done by Aditya K. Gupta. Visualization, original draft preparation, and data curation were done by Honglin Wang. Reviewing and editing were done by Aditya K. Gupta, Tong Wang, and Mesbah Talukder.

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