Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: www.tandfonline.com/journals/ijdt20

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To cite this article: Chaimae El Ammari, Ana María García-Muñoz, Rubén Zapata-Pérez, Rubén Rabadán-Ros, Carmen Lucas-Abellán, Rebeca González-Louzao & Desirée Victoria-Montesinos (2026) Efficacy of polyphenolic compounds for hair regeneration: a systematic review and meta-analysis of randomized controlled trials, Journal of Dermatological Treatment, 37:1, 2654112, DOI: 10.1080/09546634.2026.2654112

To link to this article: https://doi.org/10.1080/09546634.2026.2654112

JOURNAL OF DERMATOLOGICAL TREATMENT
2026, VOL. 37, NO. 1, 2654112
https://doi.org/10.1080/09546634.2026.2654112

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REVIEW ARTICLE

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Efficacy of polyphenolic compounds for hair regeneration: a systematic review and meta-analysis of randomized controlled trials

Chaimae El Ammari[a,b], Ana María García-Muñoz[c], Rubén Zapata-Pérez[a,b], Rubén Rabadán-Ros[a,b], Carmen Lucas-Abellán[c], Rebeca González-Louzao[c] and Desirée Victoria-Montesinos[c]

[a]UCAM HiTech Sport & Health Innovation Hub, Universidad Católica de Murcia, Murcia, Spain; [b]Group of Metabolism and Gene Regulation, UCAM HiTech Sport & Health Innovation Hub, Universidad Católica de Murcia, Murcia, Spain; [c]Faculty of Pharmacy and Nutrition, UCAM Universidad Católica San Antonio de Murcia, Murcia, Spain

ABSTRACT

Background: Non-scarring alopecia, including androgenetic alopecia, alopecia areata, and telogen effluvium, is highly prevalent and often associated with significant psychosocial burden. Although treatments such as minoxidil and finasteride are available, variability in response and tolerability concerns have increased interest in alternative therapeutic approaches. Polyphenolic compounds have attracted attention due to their antioxidant, anti-inflammatory, and immunomodulatory properties.

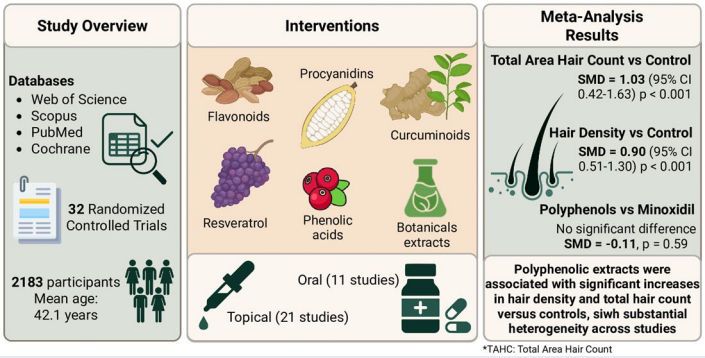
Objectives: This systematic review and meta-analysis evaluated the efficacy of oral and topical polyphenolic interventions for hair regeneration in adults with non-scarring alopecia.

Methods: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, and Cochrane CENTRAL was conducted according to PRISMA 2020 guidelines (PROSPERO: CRD420251230149). Randomized, blinded controlled trials were included. Primary outcomes were objective trichoscopic measures, including hair density and total area hair count.

Results: Thirty-two randomized controlled trials involving 2,183 participants were analyzed. Compared with controls, polyphenolic interventions significantly improved hair density (SMD 0.90; 95% CI 0.51–1.30) and total area hair count (SMD 1.03; 95% CI 0.42–1.63), although substantial heterogeneity was observed. Direct comparisons with minoxidil did not show significant differences in overall hair count outcomes.

Conclusions: Current evidence suggests that selected polyphenolic formulations may represent a potential adjunctive therapeutic approach in non-scarring alopecia, though further standardized and long-term trials are warranted.

GRAPHICAL ABSTRACT



ARTICLE HISTORY

Received 16 February 2026
Accepted 28 March 2026

KEYWORDS

Polyphenols; androgenetic alopecia; hair density; botanical extracts; randomized controlled trials; meta-analysis

1. Introduction

Alopecia is a prevalent condition frequently associated with diminished quality of life and increased psychological distress (1,2). Its pathology is broadly categorized into scarring (permanent) and non-scarring (reversible) types (3). While scarring alopecia results in the irreversible destruction of the follicle, non-scarring varieties, such as androgenetic alopecia, alopecia areata, and telogen effluvium, are driven by cyclical aberrations (3,4). In these instances, the preservation of the hair follicle enables the possibility of physiological restoration, making hair regeneration a critical area of dermatological study.

CONTACT Desirée Victoria-Montesinos dvictoria@ucam.edu Faculty of Pharmacy and Nutrition, UCAM Universidad Católica de Murcia, 30107 Murcia, Spain.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/09546634.2026.2654112.

Current FDA-approved pharmacotherapies for alopecia remain limited in scope and efficacy. Finasteride, a type II 5α-reductase inhibitor, targets the conversion of testosterone to dihydrotestosterone (DHT); while traditionally administered orally at 1 mg/day, its topical application is under increasing investigation to mitigate systemic side effects (5). Concurrently, Minoxidil is utilized topically (2–5%) as a vasodilator that promotes hair regeneration through potassium channel activation, modulating in this way the follicular microenvironment (6). Despite these options, variable clinical outcomes and potential adverse effects need for the exploration of novel compounds to promote hair regeneration. In this sense, there is significant interest in plant-derived polyphenolic compounds. These bioactive molecules offer a multi-targeted approach through their documented antioxidant, anti-inflammatory, and immunomodulatory properties, providing a potential safer profile for long-term hair follicle modulation (5,6).

Despite the proliferation of studies on botanical interventions, a comprehensive quantitative synthesis of their efficacy across diverse alopecia phenotypes has been lacking. This systematic review and meta-analysis aims to evaluate the efficacy of polyphenolic compounds in the treatment of non-scarring alopecia, including androgenetic alopecia (AGA), alopecia areata (AA), and telogen effluvium. Formulated according to the PICOS framework, the eligibility criteria were restricted to blinded, randomized controlled trials (RCTs) involving adults to mitigate the high risk of bias inherent in subjective hair-growth assessments. By systematically evaluating 32 randomized controlled trials involving 2183 participants, this study seeks to clarify the therapeutic potential of various polyphenolic subclasses. The investigation encompasses a range of oral and topical interventions, including pure compounds, as well as standardized extracts. Ultimately, this meta-analysis aims to provide a high-level evidence base to guide clinical decision-making and identify future directions for the development of standardized, plant-derived hair regeneration therapies.

2. Materials and methods

2.1. Protocol and registration

This systematic review and meta-analysis was performed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (7). The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) prior to study selection to ensure methodological transparency and to prevent reporting bias (Registration ID: CRD420251230149).

2.2. Research question and eligibility criteria

This review evaluated the efficacy and safety of polyphenolic compounds for the treatment of non-scarring alopecia, including androgenetic alopecia (AGA), alopecia areata (AA) and telogen effluvium. The research question was defined using the PICOS framework. Only randomized controlled trials (RCTs) with control groups were included, requiring blinding of participants, outcome assessors, or both; open-label trials were excluded due to the high risk of bias associated with subjective and patient-reported outcomes.

Eligible participants were adult men and women (≥18 years), either healthy volunteers or patients with alopecia of any etiology except chemotherapy-induced hair loss. Pediatric populations and secondary alopecias were excluded unless the intervention specifically targeted polyphenol-related effects on primary alopecia. Interventions comprised oral or topical administration of isolated polyphenols or standardized polyphenol-rich extracts, including procyanidins, catechins, resveratrol, quercetin, curcumin, genistein, caffeic and cinnamic acids, as well as extracts from green tea, rosemary oil, pumpkin seed oil, Annurca apple and onion juice. Trials in which polyphenols were not the main active component, their effects could not be isolated, or dietary interventions lacked standardized polyphenol content were excluded.

Comparators included placebo, no treatment, or approved pharmacological therapies such as minoxidil, finasteride or corticosteroids; head-to-head comparisons between polyphenolic compounds were also eligible. Primary outcomes for quantitative synthesis were objective trichoscopic measures of hair growth, namely hair density, total area hair count (TAHC) and terminal hair count. Additional outcomes were synthesized narratively due to methodological heterogeneity.

Only trials with a minimum intervention duration of four weeks were included, as shorter studies are insufficient to detect physiologically meaningful changes across the hair growth cycle.

2.3. Information sources and search strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science Core Collection and Cochrane CENTRAL from database inception to November 2025. Searches were performed between August and November 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to polyphenols and hair loss, linked using Boolean operators. Truncation and controlled vocabulary were applied where appropriate. Full search strategies for all databases are provided in Table S1.

Backward citation tracking of included studies was also performed, but no additional eligible studies were identified.

2.4. Study selection process

All records were imported into Rayyan (Qatar Computing Research Institute, Doha, Qatar) for systematic screening and duplicate removal. Two independent reviewers, D.V.-M. and A.M.G.-M., screened titles and abstracts to identify potentially eligible studies based on the predefined inclusion criteria. Full texts of selected articles were then reviewed in detail. Any disagreements were resolved by discussion or by consulting a third reviewer (R.G.-L.). Inter-rater agreement was calculated using Cohen's kappa coefficient to quantify consistency between reviewers.

A PRISMA 2020 flow diagram illustrates the number of records identified, screened, excluded (with reasons), and finally included in the qualitative and quantitative syntheses.

2.5. Data extraction and management

Data were extracted independently by two reviewers (D.V.-M. and A.M.G.-M.) using a standardized, piloted extraction form in Microsoft Excel. Extracted data included study characteristics, participant characteristics, intervention and comparator details, outcomes, and main results.

To ensure comparability across studies and suitability for meta-analysis, outcome data were standardized to absolute change from baseline with corresponding means and standard deviations. When standard errors of the mean (SEM) were reported, standard deviations (SDs) were calculated according to the Cochrane Handbook recommendations (8).

When data were missing or incompletely reported, study authors were contacted to obtain the required information. For outcomes reported only graphically, numerical estimates were extracted using WebPlotDigitizer software (v4.8; A. Rohatgi, Automeris LLC). All extracted data were independently verified by a third reviewer to ensure accuracy and data integrity.

2.6. Risk of bias assessment

As all included studies were randomized controlled trials, methodological quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool (9). Studies were classified according to their primary analysis approach as intention-to-treat (ITT) or per-protocol (PP). Risk of bias assessments were conducted independently by two reviewers, with disagreements resolved by consensus. Sensitivity analyses were planned to evaluate the influence of studies at high risk of bias on the meta-analysis results.

2.7. Data synthesis and meta-analysis

A qualitative synthesis was first performed to describe the characteristics and findings of all included RCTs, grouped by type of polyphenol, route of administration, and alopecia subtype. Quantitative synthesis (meta-analysis) was subsequently carried out for outcomes reported by at least two studies.

For continuous variables (e.g. hair density, total area hair count, and terminal area hair count), standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using Hedges' g. Analyses were initially performed using a fixed-effect model. Heterogeneity was assessed *via* Cochran's Q and the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. In cases where heterogeneity was statistically significant (Q test $p < 0.05$), the corresponding models were re-estimated using a random-effects approach (DerSimonian-Laird).

To explore the potential impact of clinical heterogeneity related to differences in alopecia subtype, sensitivity analyses were additionally performed by restricting the meta-analyses to studies including only patients with AGA. These analyses were conducted for outcomes in which the primary pooled estimates included mixed alopecia populations. No additional sensitivity analysis was undertaken when all studies contributing to a given outcome were already limited to AGA.

Subgroup analyses were performed based solely on the route of administration (topical vs. oral) to explore potential differences in treatment effects. Publication bias was assessed through visual inspection of funnel plots and Egger's test for funnel plot asymmetry ($p < 0.05$ indicating potential bias). These evaluations were performed only for outcomes with at least three studies, as funnel plots and asymmetry tests are not reliable when fewer studies are available. Funnel plots and the corresponding Egger's test statistics are presented within the respective figures. All analyses were conducted using Stata (version 16.1; StataCorp, College Station, TX, USA).

3. Results

3.1. Study selection

The systematic database search identified a total of 738 records. After removal of duplicates, 459 titles and abstracts were screened for eligibility. Following detailed full-text review, 52 full-text articles were assessed against predefined inclusion criteria, including the requirement for a control group (placebo, active comparator, or standard care). A total of 20 studies were excluded at the full-text screening stage for the following reasons: non-polyphenolic interventions ($n = 10$), open-label design ($n = 4$), pediatric population ($n = 2$), chemotherapy-induced alopecia ($n = 1$), hirsutism population ($n = 1$), non-scalp (axillary) hair outcomes ($n = 1$), and intervention duration shorter than eligibility criteria ($n = 1$). Ultimately, 32 randomized controlled trials met all inclusion criteria and were included in this systematic review and meta-analysis (Table 1). The PRISMA 2020 flow diagram (Figure 1) illustrates the study selection process with reasons for exclusion at each stage. Detailed exclusion reasons for each individual study are provided in Table S2.

3.2. Study characteristics

3.2.1. General study features

The 32 randomized controlled trials included were published between 2001 and 2025, with a striking acceleration in publication frequency over the past five years (22 studies published between 2020 and 2025), underscoring intensifying research interest in botanical and polyphenolic interventions for alopecia. Studies were conducted across diverse geographical locations. Asian countries included South Korea (17–19,21,23,24), Thailand (16,27,33,37,39), China (14,25,28), Japan (35,36), India (34), Malaysia (11), and Iran (30). European studies originated from Italy (13,38), Turkey (31,41), Germany (15,40), Spain (32), France (26), Greece (22), and Russia (29). North American research was conducted in the United States (10,12,20). This geographic diversity reflects global research engagement with polyphenolic interventions for alopecia. Study designs were predominantly double-blind, randomized, placebo-controlled trials ($n = 26$) (10–15,17–26,29,32–36,38–41). Active-controlled designs were used in four studies comparing botanical interventions with minoxidil (16,27,28,30,37), while one study employed a mixed placebo–active design (37). Single-blind or assessor-blinded designs were used in one study (31).

3.2.2. Population characteristics

Androgenetic alopecia was the most frequently investigated condition, addressed in 23 trials (10–12,14,16,18–20,22–24,26,27,30,33–41). Alopecia areata (28) and telogen effluvium (21), were each investigated in one study, with additional representation in mixed cohorts (31,32). Five studies used nonspecific descriptors such as hair thinning or diffuse hair loss and were classified as undefined alopecia (13,15,17,25,29). Across all studies, 2183 participants were included, with sample sizes ranging from 20 to 250. The mean age was 42.1 years, and the mean proportion of women was 37.8%.

3.2.3. Intervention characteristics

The included trials investigated a wide range of polyphenolic compounds, botanical sources, and delivery formats. Procyanidins and proanthocyanidins were among the most frequently studied subclasses, appearing in seven trials (13,14,25,32,35,38,41). Curcuminoids were evaluated in five studies, primarily as oral supplements (10,12,21), while topical Curcuma aeruginosa was assessed in a separate trial (33); an additional study examined a topical curcumin–capsaicin–piperine formulation (28). Flavonoids and flavonoid-rich extracts were investigated in nine trials using diverse botanical sources (15–17,22–24,26,27,37). Other phenolic compounds,

Table 1. Characteristics of included trials.

Author, Year	Study Design	Sample Size (n)	Mean age	Women (%)	Polyphenol Extract/Active Ingredient	Polyphenol Type/Class	Duration (months)	Type of Alopecia	Route	Primary Outcome Measure	Main Results
Ablon et al. 2018 (10)	RCT, double-blind, placebo-controlled	40	50	100	Nutrafol® Women (curcumin, ashwagandha, saw palmetto, tocotrienols)	Multiple (curcuminoids, polyphenols from saw palmetto)	6	Female pattern hair loss	Oral	Terminal and vellus hair count	Terminal + vellus hair increased at 90d and 180d
Amini et al. 2025 (11)	RCT, double-blind, pilot	20	NR	0	ECPE (Ecklonia cava + Thuja orientalis) with exosomes	Phlorotannins, fucoidans (marine brown alga)	4	Male AGA (Norwood 2–3)	Intradermal (injection)	Hair density (count/0.5 cm^2)	ECPE group significantly increased hair count; large effect size
Bhatia et al. 2025 (12)	RCT, double-blind, placebo-controlled	85	40,6	0	Nutrafol Men (saw palmetto, ashwagandha, vitamin E, curcumin)	Multiple (polyphenols from saw palmetto)	6	Male pattern hair thinning	Oral	Blinded investigator global assessment (hair growth and quality)	79% active group rated improved hair growth vs 51% placebo at 6 months
Biasio et al. 2023 (13)	RCT, double-blind, placebo-controlled	40	44	50	Annurca apple extract + red grape extract + amino acids + vitamins/minerals	Multiple (Annurca apple, grape seed)	6	Female hair thinning	Oral	Hair count, thickness	Increased hair density and diameter
Cai et al. 2023 (14)	RCT, double-blind, placebo-controlled	60	54	100	Grape seed proanthocyanidin extract (GSPE)	Proanthocyanidins	6	AGA	Oral	Hair density and thickness	GSPE increased hair density and thickness significantly vs placebo
Campiche et al. 2022 (15)	RCT, double-blind, placebo-controlled	60	44,5	88,3	Leontopodium alpinum (Edelweiss) extract 0.001%	Flavonoids/leontopodin acid	5	Undefined / nonspecific hair loss	Topical	Hair density, anagen/catagen ratio	Increased hair density; improved anagen/catagen ratio vs placebo
Cheyasak et al. 2024 (16)	RCT, double-blind, controlled	60	51,2	50	Dihydroquercetin glucoside, epigallocatechin gallate glucoside, zinc, glycine	Flavonoids (DHQG + EGCG2)	6	AGA	Topical	Total hair count, hair mass index	Total hair count: +10 hairs/cm^2 (herbal) vs +23 hairs/cm^2 (minoxidil)
Cho et al. 2014 (17)	RCT, double-blind, placebo-controlled	40	46,2	0	Red ginseng oil + fermented grape extract	Multiple (ginsenosides + anthocyanins/resveratrol)	6	Pattern hair loss	Topical	Hair density and diameter	Increased hair density and diameter at 6 months
Choi et al. 2015 (18)	RCT, double-blind, placebo-controlled	50	42,0	44	Rice bran supercritical CO2 extract (RB-SCE) 0.5%	Polyphenol-rich rice extract	4	Alopecia (male and female pattern hair loss)	Topical	Hair count, diameter, density (Folliscope)	RB-SCE significantly increased hair diameter in males
Do et al. 2021 (19)	RCT, single-blind, placebo-controlled	100	48,3	0	Six plant extracts (Jerusalem artichoke, quinoa seeds, hazelnut, goldenberry, Paeonia radix, Pleuropterus multiflorus)	Multiple (polyphenols/ phytochemicals from 6 plants)	4	AGA	Topical	Hair shaft thickness, hair density, hair cortisol, DHT concentrations	Increased hair thickness and density; DHT concentration decreased
Greenberg et al. 1996 (20)	RCT, double-blind, placebo-controlled	24	43,1	0	7.5% herbal extract (fennel, polygonum, mint, chamomile, thuja, hibiscus)	Multiple (mixed polyphenols/flavonoids)	12	AGA (Hamilton-Norwood III-IV)	Topical	Total hair count, terminal hair count	Total hair count +77% vs +3% placebo; Terminal hair +169% vs +33% placebo
Ham et al. 2023 (21)	RCT, double-blind, placebo-controlled	40	38,8	61,4	Persimmon leaf extract + green tea catechins + Sophora extract	Polyphenols (catechins, flavonoids)	6	Telogen effluvium	Oral	Hair density, diameter, anagen/telogen ratio	BLH308 increased hair density (+15.3% vs −0.8% placebo) and thickness.

(*Continued*)

Table 1. Continued.

Author, Year	Study Design	Sample Size (n)	Mean age	Women (%)	Polyphenol Extract/Active Ingredient	Polyphenol Type/Class	Duration (months)	Type of Alopecia	Route	Primary Outcome Measure	Main Results
Katoulis et al. 2020 (22)	RCT, double-blind, placebo-controlled	50	44,7	100	White grape extract (polyphenol-rich)	Mixed polyphenols (flavonoids, phenolic acids)	6	Female androgenetic alopecia	Oral	Hair density change	Hair density increase +48.5% active vs +24.9% placebo
Lee et al. 2025 (a) (23)	RCT, double-blind, placebo-controlled	105	44,7	74,4	Flavonoid-rich plant extract	Flavonoids	6	Pattern hair loss	Topical	Hair density, thickness	Significant improvement in hair parameters
Lee et al. 2025 (b) (24)	RCT, double-blind, placebo-controlled	84	39,9	18	Flavonoid-rich extract	Flavonoids	6	Pattern hair loss	Topical	Hair count, thickness	Significant hair count and thickness improvements
Liang et al. 2023 (25)	RCT, double-blind, placebo-controlled	50	NR	86	Banana flower extract	Anthocyanins, catechins, gallic acid	3	Hair loss	Oral	Hair root diameter, hair loss reduction	Hair loss decreased, hair density increased, scalp redness reduced
Loing et al. 2013 (26)	RCT, placebo-controlled	30	NR	NR	Trifolium pratense extract + acetyl tetrapeptide-3	Isoflavones (biochanin A)	4	Male pattern hair loss	Topical	Anagen hair increase, telogen decrease, A/T ratio	Anagen +13%, telogen −29%, A/T ratio +46% active vs placebo
Lueangarun et al. 2020 (27)	RCT, triple-blind, controlled	32	41,3	50	Biochanin A, acetyl tetrapeptide-3, ginseng extracts	Isoflavones (biochanin A) + peptide + polyphenols	6	AGA (Norwood III-IV, Ludwig I-II)	Topical	Terminal hair count, hair mass index	Herbal treatment similar efficacy to minoxidil; comparable terminal hair count improvement
Mao et al. 2021 (28)	RCT, double-blind, active-controlled	60	43,3	66,7	Curcumin + capsaicin + piperine	Curcuminoid + capsaicinoids	3	Alopecia areata	Topical	SALT score, effective rate, dermoscopy	Effective rate 63.33% mixed preparation vs 70% minoxidil; both effective
Mayer et al. 2023 (29)	RCT, double-blind, placebo + caffeine-controlled	154	42	44,2	Fermented papaya + fermented mangosteen + caffeine	Multiple (polyphenols from fermented fruits)	3	Androgenic or diffuse alopecia	Topical	Hair loss inhibition, hair density/ thickness, hair follicle structure	Significantly inhibited hair loss, increased hair density/ thickness vs placebo and caffeine; normalized microbiota pattern
Panahi et al. 2015 (30)	RCT, double-blind, active-controlled	100	24,1	0	Rosemary oil vs Minoxidil 2%	Phenolic diterpenes (carnosic acid, rosmarinic acid)	6	AGA	Topical	Hair count and coverage (vs minoxidil)	Similar efficacy to minoxidil 2% in hair count improvement
Pekmezci et al. 2018 (31)	RCT, single-blind, placebo-controlled	120	36	50	Herbal extract mixture (Urtica urens, Urtica dioica, Matricaria chamomilla, Achillea millefolium, Ceratonia siliqua, Equisetum arvense)	Multiple (flavonoids, phenolic compounds)	6	AGA and telogen effluvium	Topical	Pull test, phototrichogram (anagen/telogen ratio)	Active formulations more effective than placebo; anagen/telogen ratios improved

(*Continued*)

Table 1. Continued.

Author, Year	Study Design	Sample Size (n)	Mean age	Women (%)	Polyphenol Extract/Active Ingredient	Polyphenol Type/Class	Duration (months)	Type of Alopecia	Route	Primary Outcome Measure	Main Results
Piquero-Casals et al. 2024 (32)	RCT, double-blind, placebo-controlled	60	35,5	50	L-Cysteine + Serenoa repens + Cucurbita pepo + Pygeum africanum	Multiple (polyphenols from saw palmetto, phytosterols)	6	Chronic TE and AGA	Oral	Hair count at 90 and 180 days	Increased hair count at 90d (+11.3%) and 180d (+17.8%) vs placebo
Pumthong et al. 2012 (33)	RCT, double-blind, placebo-controlled	30	38	0	Curcuma aeruginosa extract 5%	Curcuminoids	6	AGA	Topical	Hair growth by phototrichogram	5% Curcuma extract increased anagen hair and improved visual density
Revathi and Suhav, 2025 (34)	RCT, double-blind, placebo-controlled	50	39	0	Amaranthus extract cream 10% (betalains, phenolic acids, flavonoids)	Betalains + phenolic acids + flavonoids	3	MPHL (Norwood III-V)	Topical	Terminal hair density, anagen hair density, A/T ratio (Trichoscan)	Terminal hair density +28.2% vs +15.2% placebo; Anagen hair density +54% vs +17.5% placebo; A/T ratio +155% vs +21% placebo
Takahashi et al. 2001 (35)	RCT, double-blind, placebo-controlled	43	46	0	Procyanidin B2 (1% topical)	Procyanidin	4	Male AGA	Topical	Hair growth efficacy	1% procyanidin B2 increased terminal hair significantly
Takahashi et al. 2016 (36)	RCT, double-blind, placebo-controlled	73	42,4	0	Sophora flavescens Aiton extract 0.5%	Pterocarpans (L-maackiain, medicarpin)	6	AGA (Hamilton-Norwood II-VI)	Topical	Alopecia score (Hamilton-Norwood classification)	Improved alopecia score vs placebo; significant improvement with lotion + extract
Tanuphol et al. 2024 (37)	RCT, double-blind, placebo-controlled	61	41,9	0	Teak leaf extract (Tectona grandis) 1%	Flavonoids (quercetin, kaempferol)	6	AGA	Topical	Hair density, thickness	Teak extract increased hair density (+30.3%) and reduced telogen hair
Tenore et al. 2018 (38)	RCT, double-blind, placebo-controlled	250	43	53,6	AppleMets (annurca apple extract with procyanidin B2)	Procyanidins (especially B2)	2	AGA	Oral	Hair weight, hair growth rate	Increased hair weight by 125%, hair number by 56% vs placebo
Vichit and Saewan 2024 (39)	RCT, double-blind, placebo-controlled	60	NR	85	Resveratrol-rich peanut callus extract	Resveratrol (stilbene)	3	Hair loss	Topical	Hair shedding reduction, anagen/telogen ratio	Reduced hair shedding (67% reduction), increased anagen/telogen ratio

(*Continued*)

Table 1. Continued.

Author, Year	Study Design	Sample Size (n)	Mean age	Women (%)	Polyphenol Extract/Active Ingredient	Polyphenol Type/Class	Duration (months)	Type of Alopecia	Route	Primary Outcome Measure	Main Results
Welzel et al. 2022 (40)	RCT, double-blind, vehicle-controlled	62	42	0	Foam with nicotinic acid hexyl ester, polyphenols, zinc, glycine, caffeine	Multiple polyphenols	6	AGA (men)	Topical	Telogen rate reduction, hair density increase	Telogen rate reduced significantly in verum vs vehicle; hair density increased both groups
Yeniay and Arca, 2022 (41)	RCT, double-blind, placebo-controlled	40	33,3	0	Procyanidin B2 1% dimer (from apple) + biotin + dexpanthenol	Procyanidins (oligomeric flavonoids)	4	AGA (Hamilton-Norwood II-V)	Topical	Total hair count, anagen hair count (trichoscan)	Increased total hair count and anagen hair; expert improvement assessment

Abbreviations: A/T ratio, anagen-to-telogen ratio; AGA, androgenetic alopecia; DHT, dihydrotestosterone; ECPE, *Ecklonia cava* and *Thuja orientalis* extract; GSPE, grape seed proanthocyanidin extract; MPHL, male pattern hair loss; NR, not reported; RB-SCE, rice bran supercritical CO_2 extract; RCT, randomized controlled trial; SALT, Severity of Alopecia Tool; TE, telogen effluvium.

including phenolic acids, diterpenes, stilbenes, and mixed polyphenolic formulations, were evaluated across seven studies (11,18,20,29–31,34,39,40), reflecting substantial heterogeneity of interventions.

Regarding administration routes, 11 studies evaluated oral supplementation (10,12–14,19,21,22,24,25,32,38), 21 investigated topical formulations (11,15–18,20,23,27–31,33–37,39–41), and one combined both approaches (31). Intervention durations ranged from 8 weeks to 12 months, with most studies lasting 3–6 months.

3.2.4. Comparator groups

Placebo controls were used in 26 studies, while active comparators (primarily minoxidil) were employed in four trials (16,27,28,30). Mixed designs including both placebo and active comparators were reported in two studies (29,37). One study used single-blind or assessor-blinded methodology (31). No trial included a true no-treatment control group.

3.2.5. Risk of bias assessment

RoB 2.0 tool was used to evaluate 32 RCTs, of which 7 were rated as having a "low risk" of bias (12,16,20,21,32,34,37), and 25 as having "some concerns" of bias (10,11,13–15,17–19,22–31,33,35,36,38–41) (see Figure S1).

3.3. Quantitative synthesis

3.3.1. Hair density: Polyphenolic extract vs. control

Seven studies compared polyphenolic extracts with control groups for changes in hair density. The pooled analysis showed a significant increase in hair density favoring polyphenolic interventions (SMD 0.90, 95% CI 0.51–1.30; $z = 4.44$, $p < 0.001$; Figure 2). Substantial heterogeneity was observed (I^2 = 78.61%, τ^2 = 0.23; Q(6) = 25.65, $p < 0.001$). When the analysis was restricted to studies including only patients with AGA, the pooled effect remained statistically significant and continued to favor polyphenolic interventions over control (SMD 1.04, 95% CI 0.24–1.83; $z = 2.56$, $p < 0.01$). However, substantial heterogeneity persisted (I^2 = 80.51%, τ^2 = 0.26; Q(1) = 5.13, $p < 0.02$; Figure S2A).

Subgroup analysis by route of administration did not reveal significant differences between oral and topical interventions (Qb(1) = 0.00, $p = 0.99$). The pooled effect size was similar for oral interventions (SMD 0.91, 95% CI 0.55–1.27; I^2 = 67.20%; Q(4) = 12.08, $p < 0.02$) and topical interventions (SMD 0.91, 95% CI − 0.61–2.44; I^2 = 92.54%; Q(1) = 13.41, $p < 0.001$). Detailed forest plots are shown in Figure S3A.

3.3.2. Total area hair count (TAHC): polyphenolic extract vs. control

Five studies evaluated changes in TAHC. Meta-analysis demonstrated a significant improvement in TAHC among participants treated with polyphenolic extracts compared with controls (SMD 1.03, 95% CI 0.42–1.63; $z = 3.32$, $p < 0.001$; Figure 3). Between-study heterogeneity was substantial (I^2 = 78.64%, τ^2 = 0.37; Q(4) = 19.21, $p < 0.001$). A similar pattern was observed when the analysis was limited to studies involving only patients with AGA. In this restricted model, polyphenolic interventions continued to show a significant benefit over control (SMD 0.85, 95% CI 0.21–1.50; $z = 2.61$, $p < 0.01$), although considerable between-study heterogeneity remained (I^2 = 76.37%, τ^2 = 0.33; Q(3) = 12.29, $p < 0.01$; Figure S2B).

Subgroup analysis indicated a significant pooled effect for topical interventions (SMD 0.90, 95% CI 0.21–1.60; I^2 = 81.16%; Q(3) =

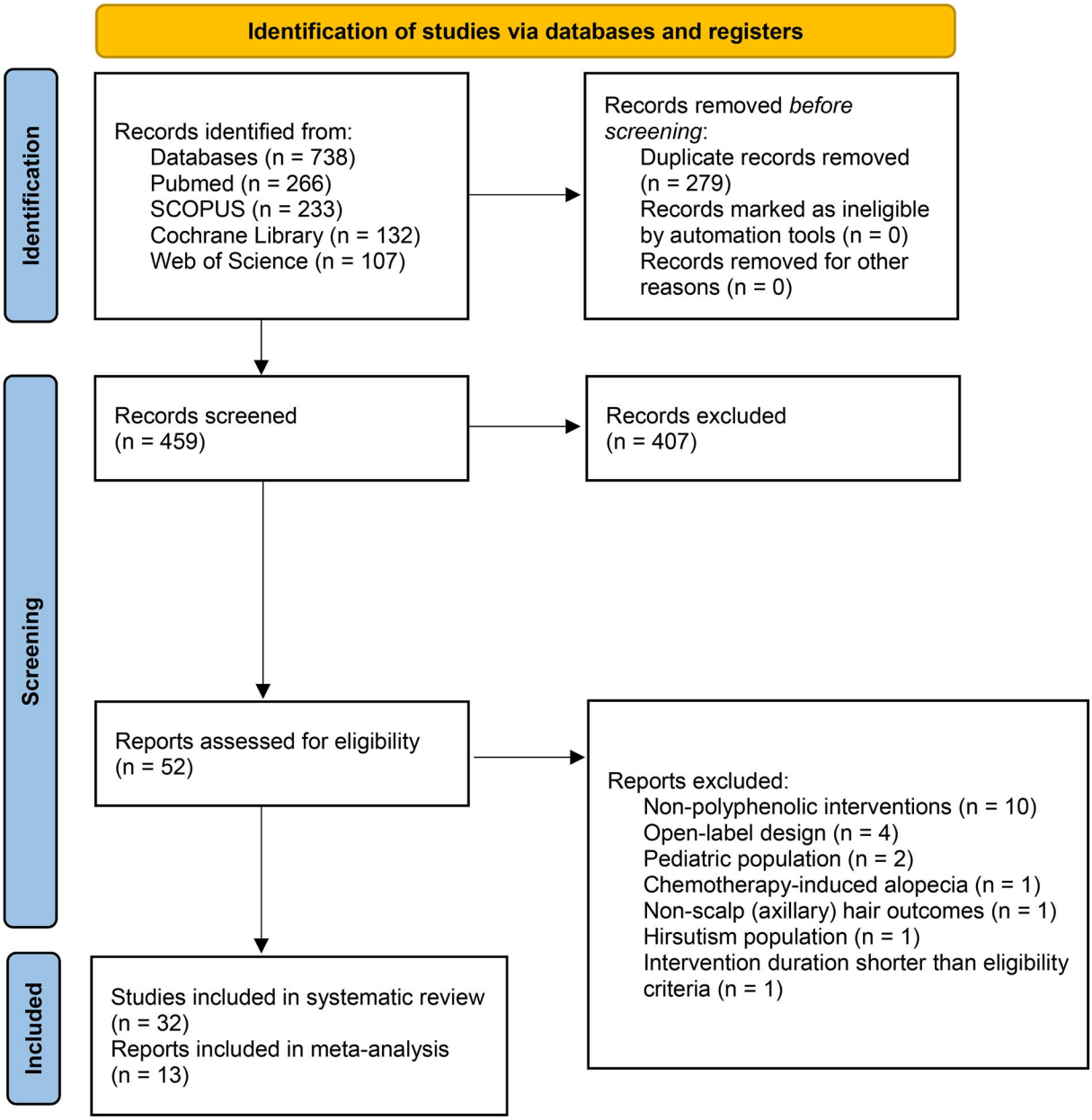


Figure 1. PRISMA flow diagram of study selection.

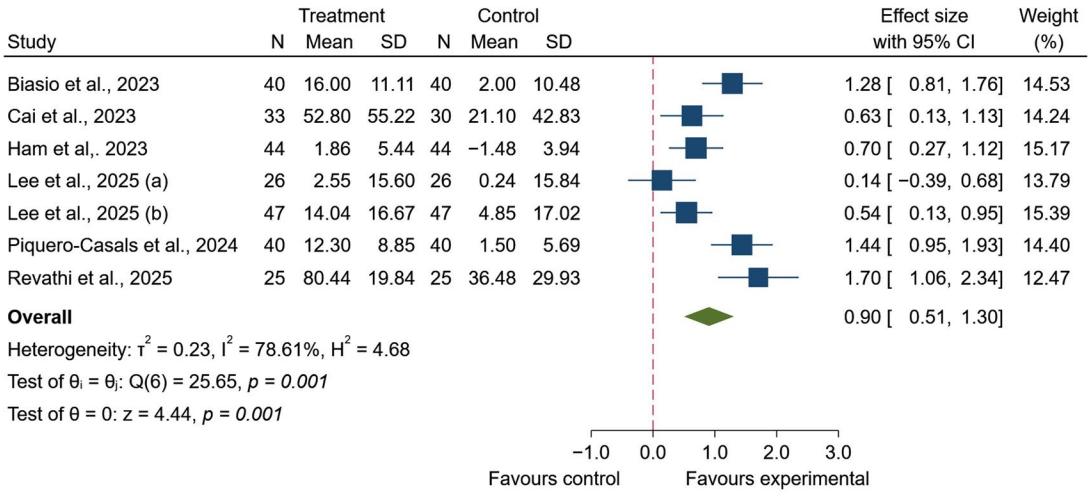


Figure 2. Forest plot of the effect of polyphenolic compounds on hair density.

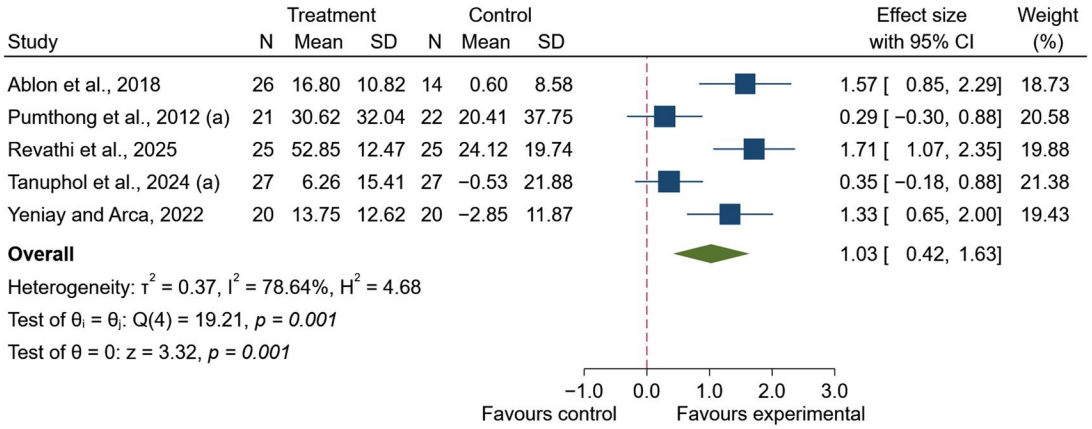


Figure 3. Forest plot of the effect of polyphenolic compounds on total area hair count (TAHC).

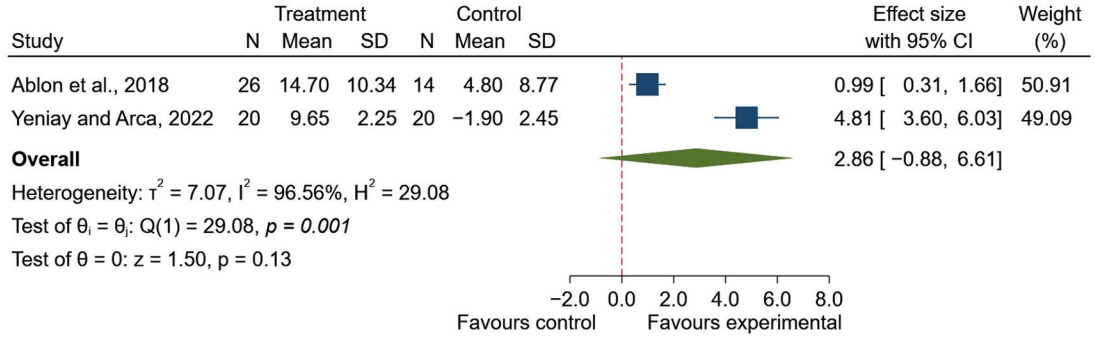


Figure 4. Forest plot of the effect of polyphenolic compounds on Terminal Area Hair Count (TAHCt).

15.77, $p < 0.001$). However, no statistically significant differences were observed between oral and topical routes (Qb (1) = 1.69, $p = 0.19$), and this comparison should be interpreted cautiously due to the limited number of oral studies ($n = 1$). Subgroup forest plots are presented in Figure S3B.

3.3.3. Terminal area hair count: Polyphenolic extract vs. control

Two studies assessed terminal area hair count (TAHCt). The pooled estimate suggested a potential increase with polyphenolic extracts (SMD 2.86, 95% CI −0.88 to 6.61; $z = 1.50$, $p = 0.13$; Figure 4). Between-study heterogeneity was extremely high (I^2 = 96.56%, τ^2 = 7.07; Q(1) = 29.08, $p < 0.001$), indicating substantial uncertainty around the pooled effect. Notably, all studies included in this analysis were conducted exclusively in patients with AGA.

3.3.4. Total area hair count: Polyphenolic extract vs. minoxidil

Two studies directly compared polyphenolic extracts with topical minoxidil. No statistically significant difference between treatments was observed (SMD − 0.11, 95% CI − 0.50 to 0.28; z=− 0.54, $p = 0.59$; Figure S3C). No heterogeneity was detected (I^2 = 0.00%; Q(1) = 0.17, $p = 0.68$).

3.3.5. Terminal area hair count: Polyphenolic extract vs. minoxidil

Two studies compared polyphenolic extracts with minoxidil for TAHCt. Individual trials yielded inconsistent results, with one study favoring minoxidil markedly and the other showing no significant difference. The pooled effect did not reach statistical significance (SMD −0.87, 95% CI −2.31 to 0.57; z = −1.18, $p = 0.24$; Figure S3D), and heterogeneity was substantial (I^2 = 90.50%, τ^2 = 0.98; Q(1) = 10.52, $p < 0.001$).

3.4. Publication bias assessment

Publication bias was assessed for the primary meta-analyses using funnel plot inspection and Egger's regression test (Figure S4). For hair density versus control (seven studies; Figure S4A), the funnel plot showed no clear asymmetry, and Egger's test did not indicate significant small-study effects (β = 6.34, SE = 5.62, $p = 0.2680$), despite the presence of substantial heterogeneity.

For TAHC versus control (Figure S4B), funnel plot inspection did not reveal obvious asymmetry; however, Egger's regression test suggested potential small-study effects (β = 14.91, SE = 5.85, $p < 0.0108$).

Publication bias was not assessed for terminal area hair count (TAHCt) or for comparisons between polyphenolic extracts and minoxidil, as these analyses included only two studies each, and funnel plot–based methods are not considered reliable with such limited numbers of studies. The reporting structure of this systematic review and meta-analysis followed the PRISMA 2020 recommendations, and the completed PRISMA checklist is provided in Figure S5.

4. Discussion

The therapeutic landscape for alopecia is currently dominated by a limited number of FDA-approved pharmacological interventions, primarily topical minoxidil and oral finasteride (42). While these agents are effective for a significant proportion of patients, their clinical utility is hampered by factors including adverse effect profiles, narrow mechanistic focus, and the perception of natural or plant derived alternatives as compounds with superior safety profiles and fewer systemic risks (43) minoxidil). Due to their natural

origin and diverse pharmacological profiles, polyphenolic compounds provide a multi-targeted approach that makes them promising candidates for treating hair loss. This systematic review provides, for the first time, a rigorous evaluation of the efficacy and safety of polyphenolic compounds across diverse forms of alopecia, with a predominant focus on androgenetic alopecia, which was the most represented phenotype.

Among the 32 studies included in this analysis, flavonoids constituted the most frequently investigated subclass of polyphenols, likely reflecting their well-established antioxidant, anti-inflammatory, and vasodilatory properties (44). Procyanidins and proanthocyanidins were the second most consistently studied group. These polyphenols are of particular interest in trichology due to their ability to promote the transition of hair follicles from the telogen to the anagen phase, potentially *via* modulation of protein kinase C–dependent signaling pathways (45). Curcuminoids and phenolic acids were also prominently represented across the included trials, highlighting a growing emphasis on targeting the microinflammatory milieu of the hair follicle (46). While heterogeneity in formulations and outcome measures limits direct comparison between individual compounds, the convergence of positive effects across these polyphenolic classes supports their collective therapeutic potential in the management of non-scarring alopecia.

The meta-analysis of seven RCTs revealed that the application of polyphenolic extracts significantly increases hair density compared with placebo, with a pooled effect size in the large range (SMD = 0.90, 95% CI 0.51–1.30). Notably, despite substantial heterogeneity, the overall effect remained highly significant (I^2 = 78.61%; Q(6) = 25.65, $p < 0.001$), suggesting that variability across trials influence the magnitude of benefit more than the direction of effect. Such heterogeneity is expected, given the differences in polyphenolic subclass and composition, alopecia phenotype and severity, and variation in trichoscopic methods and reporting formats.

Similarly, five studies contributed to the meta-analysis for total area hair count (TAHC), again demonstrating a statistically significant improvement with polyphenolic extracts relative to control (SMD = 1.03, 95% CI 0.42–1.63), with a magnitude of effect also within the large range. As with density, heterogeneity was substantial (I^2 = 78.64%; Q(4) = 19.21, $p < 0.001$), indicating marked variability across studies, which could be amplified because count is especially sensitive to methodological differences and hair count may respond differently depending on whether an intervention primarily drives anagen induction versus shaft thickness. In contrast to these results, head-to-head comparisons with topical minoxidil showed no statistically significant difference in TAHC (SMD = −0.11, 95% CI −0.50 to 0.28), with the small numerical advantage observed for minoxidil unlikely to be clinically meaningful. Notably, heterogeneity was absent in this comparison (I^2 = 0%), indicating consistent findings across the two available trials and supporting a comparable effect of polyphenolic extracts and minoxidil on this outcome.

In contrast to the more consistent findings observed for hair density and total area hair count, evidence for terminal area hair count (TAHCt) was limited and less stable. Only two studies comparing polyphenolic extracts with control interventions were available, yielding an imprecise pooled estimate that did not reach statistical significance (SMD = 2.86, 95% CI 0.88–6.61; $p = 0.13$). Although the point estimate suggested a potentially large effect, interpretation is constrained by the wide confidence interval and extreme heterogeneity (I^2 = 96.56%; Q(1) = 29.08, $p < 0.001$), which precludes clear differentiation between true treatment effects, methodological variability, and random error. Similarly, head-to-head comparisons with topical minoxidil also failed to demonstrate a statistically significant difference in TAHCt (SMD = −0.87, 95% CI −2.31 to 0.57), despite both studies numerically favoring minoxidil. The substantial heterogeneity observed in this analysis (I^2 = 90.50%) further limits definitive conclusions and indicates that, while polyphenolic extracts may approach minoxidil in overall hair count outcomes, current evidence is insufficient to support comparable effects on terminal hair regrowth.

In addition to evaluating overall efficacy, we also examined the route of administration as a potential contributor to differences in treatment effects. Although the route of administration may influence drug delivery and biological response, subgroup analyses did not identify significant differences between oral and topical polyphenolic interventions for either hair density or total area hair count, suggesting that route alone does not appear to be a primary determinant of efficacy. In fact, oral and topical formulations yielded identical pooled effect sizes (SMD = 0.91) for hair density, and formal testing confirmed the absence of between-group differences. A similar pattern was observed for total area hair count. While the topical subgroup demonstrated a statistically significant pooled effect (SMD = 0.90) and accounted for the majority of available studies, formal comparison between routes did not reveal a significant difference, although these results should be interpreted with caution, as the number of oral studies available was very limited.

5. Conclusion

Overall, the findings of this systematic review and meta-analysis support polyphenolic compounds as promising interventions for non-scarring alopecia, particularly androgenetic alopecia. Across placebo-controlled trials, polyphenolic extracts were associated with significant and clinically relevant improvements in hair density and total area hair counts, with large pooled effect sizes despite substantial heterogeneity. Head-to-head comparisons with minoxidil further suggest that selected polyphenolic formulations may achieve comparable benefits in overall hair count, although evidence remains insufficient to establish equivalence for terminal hair regrowth, a key marker of follicular terminalization. Notably, no meaningful differences in efficacy were observed between oral or topical application of the compounds, indicating that the route of administration alone is unlikely to be a major determinant of treatment response. Interpretation of these findings is nevertheless limited by variability in polyphenolic composition, dosing, intervention duration, and outcome assessment, as well as by the relatively small number of direct comparative and long-term studies. Future research should prioritize adequately powered randomized controlled trials with standardized trichoscopic endpoints, longer follow-up periods, and detailed characterization of polyphenol formulations to better define their comparative efficacy.

Authors' contributions

CRediT: **Chaimae El Ammari**: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing; **Ana María García-Muñoz**: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing; **Rubén Zapata-Pérez**: Writing – review & editing; **Rubén Rabadán-Ros**: Writing – review & editing; **Carmen Lucas-Abellán**: Writing – review & editing; **Rebeca**

González-Louzao: Writing – review & editing; **Desirée Victoria-Montesinos**: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Chaimae El Ammari belongs to the 'Programa de Doctorado en Ciencias de la Salud' from the Catholic University of Murcia (UCAM). Work in Rubén Rabadán-Ros and Rubén Zapata-Pérez group is supported by a grant from Ministerio de Ciencia, Innovación y Universidades – Proyectos de Generación de Conocimiento 2023 (PID2023-147560OA-I00). Rubén Rabadán-Ros is supported by a grant from Fundación Séneca – Agencia de Ciencia y Tecnología de la Región de Murcia (22524/JLI/24, Ayudas a Proyectos para la Generación de Nuevo Liderazgo Científico Jóvenes Líderes en Investigación 2024).

ORCID

Chaimae El Ammari http://orcid.org/0009-0006-1130-970X
Ana María García-Muñoz http://orcid.org/0000-0002-1021-5385
Rubén Zapata-Pérez http://orcid.org/0000-0003-4432-9652
Rubén Rabadán-Ros http://orcid.org/0000-0003-2990-4620
Carmen Lucas-Abellán http://orcid.org/0000-0002-8655-4156
Rebeca González-Louzao http://orcid.org/0000-0003-3540-9095
Desirée Victoria-Montesinos http://orcid.org/0000-0003-3968-9477

Data availability statement

No new primary data were generated in this study. All data analyzed in this systematic review and meta-analysis are derived from previously published studies and are available within the article and its supplementary material.

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