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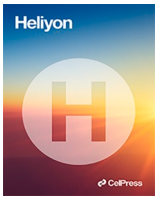

Review article

Efficacy of probiotics in hair growth and dandruff control: A systematic review and meta-analysis

Chang-Shik Yin [a,1], Trang Thi Minh Nguyen [b,1], Eun-Ji Yi [b,c], Shengdao Zheng [b,c], Arce Defeo Bellere [b], Qiwen Zheng [b], Xiangji Jin [d], Myeongju Kim [b], Sejic Park [b], Sarang Oh [b,c], Tae-Hoo Yi [b,*]

[a] *Acupuncture and Meridian Science Research Center, College of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea*
[b] *Graduate School of Biotechnology, Kyung Hee University, 1732 Deogyeong-daero, Giheung-gu, Yongin, Republic of Korea*
[c] *Snowwhitefactory Co, Ltd., 807 Nonhyeon-ro, Gangnam-gu, Seoul, 06032, Republic of Korea*
[d] *Department of Pharmacology, School of Medicine, Kyung Hee University, 23 Kyungheedae-ro, Dong-daemun, Seoul, Republic of Korea*

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ABSTRACT

Background: Probiotics are intellectually rewarding for the discovery of their potential as a source of functional food. Investigating the economic and beauty sector dynamics, this study conducted a comprehensive review of scholarly articles to evaluate the capacity of probiotics to promote hair growth and manage dandruff.

Methods: We used the PRISMA 2020 with Embase, Pubmed, ClinicalTrials.gov, Scopus, and ICTRP databases to investigate studies till May 2023. Meta-analyses utilizing the random effects model were used with odds ratios (OR) and standardized mean differences (SMD).

Result: Meta-analysis comprised eight randomized clinical trials and preclinical studies. Hair growth analysis found a non-significant improvement in hair count (SMD = 0.32, 95 % CI -0.10 to 0.75) and a significant effect on thickness (SMD = 0.92, 95 % CI 0.47 to 1.36). In preclinical studies, probiotics significantly induced hair follicle count (SMD = 3.24, 95 % CI 0.65 to 5.82) and skin thickness (SMD = 2.32, 95 % CI 0.47 to 4.17). VEGF levels increased significantly (SMD = 2.97, 95 % CI 0.80 to 5.13), while IGF-1 showed a non-significant inducement (SMD = 0.53, 95 % CI -4.40 to 5.45). For dandruff control, two studies demonstrated non-significant improvement in adherent dandruff (OR = 1.31, 95 % CI 0.13–13.65) and a significant increase in free dandruff (OR = 5.39, 95 % CI 1.50–19.43). Hair follicle count, VEGF, IGF-1, and adherent dandruff parameters were recorded with high heterogeneity. For the systematic review, probiotics have shown potential in improving hair growth and controlling dandruff through modulation of the immune pathway and gut-hair axis. The Wnt/β-catenin pathway, IGF-1 pathway, and VEGF are key molecular pathways in regulating hair follicle growth and maintenance.

Conclusions: This review found significant aspects exemplified by the properties of probiotics related to promoting hair growth and anti-dandruff effect, which serve as a roadmap for further in-depth studies to make it into pilot scales.

* Corresponding author.
E-mail address: drhoo@khu.ac.kr (T.-H. Yi).
[1] These authors contributed equally to this work.

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1. Introduction

Hair loss and dandruff are widespread conditions, with dandruff affecting nearly half of the post-pubertal population [1] and male androgenetic alopecia being the most common form of hair loss in men, impacting 80 % of males by the age of 80 [2,94]. Hair refers to the filamentous outgrowth of the skin composed of keratinized cells, typically found on the scalp, and serves various functions, including insulation, protection, and sensory perception [3]. Hair growth, also known as hair follicle development or hair cycling, refers to the natural process by which hair strands grow from the hair follicles, undergo specific stages (anagen, catagen, and telogen), and eventually shed to allow new hair to emerge [3,4]. The pathophysiology of hair loss involves complex interactions between genetic factors [5], hormonal imbalances (such as increased levels of dihydrotestosterone) [6], inflammation [6], oxidative stress [7], immune dysregulation [8], and miniaturization [9] of hair follicles. These processes can lead to progressive inflammation, disruption of hair follicle cycling, and reduced hair density and loss [6]. On the other hand, dandruff is a common scalp condition characterized by the excessive shedding of dead skin cells from the scalp. It often leads to the presence of white or yellowish flakes, itchiness, and scalp irritation [1]. Dandruff is primarily characterized by an overgrowth of the yeast-like fungus *Malassezia* [10–12], which triggers an immune response, including inflammation [1,13], leading to increased cell turnover [14] and shedding of dead skin cells from the scalp, resulting in the formation of visible flakes and scalp irritation [1].

The micro-inflammatory component, in chronic hair loss processes in particular, is localized around the bulge stem cell niche, an important area for hair follicle cycling and renewal. The release of reactive oxygen species (ROS) and inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and histamine alters the immune environment of the follicle [7,15]. Although not immediately destructive, these inflammatory processes can dysregulate the normal hair cycle dynamics and stem cell renewal over time. One crucial factor is the role of inflammatory cytokines like type 1 T helper (Th1), type 2 T helper (Th2), type 17 T helper (Th17), and immune cell signaling in the pathogenesis of hair loss [16,17]. Specifically, the expression of genes related to the Wingless-related integration site (WNT) signaling pathway, such as WNT proteins and their receptors, plays a vital role in regulating hair growth [18]. These genes influence the expression of various growth factors like insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), which are essential for initiating and maintaining the hair cycle's anagen (growth) phase [19,20]. Conversely, genes associated with the catagen (regression) phase of the hair cycle, such as transforming growth factor beta (TGF-β), IL-1, interleukin-2 (IL-2), interleukin-10 (IL-10), prostaglandin E2 (PEG-2) and TNF- α, are upregulated, leading to hair follicle apoptosis and regression [8,21]. These pro-apoptotic cytokines contribute to the premature entry of hair follicles into the catagen phase, resulting in hair shedding. Moreover, the genetic predisposition to hair loss is often influenced by hormones, such as androgens, sex hormones, prolactin, melatonin, and thyroid hormones. These hormones can bind to specific receptors in the hair follicles and modulate the expression of genes involved in hair growth and regulation [22]. Understanding the interplay between genes and proteins involved in hair loss can provide insights into potential therapeutic targets.

Recent evidence has emphasized the role of the gut-brain axis and the microbiome in hair loss and dandruff. Differences in the gut microbiome have been observed between individuals with these conditions and healthy controls, indicating their involvement in the underlying mechanisms [23]. The gut microbiome interacts with immune cells in the gastrointestinal tract, impacting the immune response [24]. Changes in the gut microbiome composition and metabolites affect T and B cell functions, influencing the severity of hair loss and dandruff in animal models [24,25]. During hair loss and dandruff onset, immunoglobulin (Ig) A + B cells from the intestine cross the blood-brain barrier, releasing antibodies that target specific bacterial strains related to these conditions [26]. This cross-reactivity may reduce neuroinflammation and alleviate symptoms. Transplanting fecal bacteria from individuals with hair loss and dandruff or healthy controls in animal models has shown symptom impact [26,27]. The disruption of miRNA-target interactions, characterized by a mismatch, results in abnormal T cell activation, impaired melanosome autophagy, and inhibited angiogenesis, ultimately contributing to hair follicle damage. The predominant metabolites produced by intestinal microbes are short-chain fatty acids (SCFAs), which play a regulatory role in T lymphocytes by influencing chromatin structure in the nucleus and promoting increased activity of gene products [28,29]. Modulating the gut microbiome and its metabolites, including SCFAs, may have the potential to prevent and treat hair loss and dandruff.

Contemporary research in hair growth and dandruff control employs diverse materials and methodologies. Regenerative approaches involve stem cell therapy [30] and the use of topicals enriched with growth factors and peptides, such as minoxidil [20], targeting hair follicle regeneration [30]. Genetic and molecular analyses aim to identify precise therapeutic targets, while convenient treatments like laser therapy [31] and microneedling [32] offer promising options. Specialized dermatologist-performed interventions include corticosteroid injections [33], hair transplants, platelet-rich plasma, and exosome treatments [34]. Prescription medications like finasteride and spironolactone provide pharmaceutical solutions, complemented by supplementation based on individual deficiencies [35]. In dandruff research, emphasis is on the scalp microbiome, anti-inflammatory agents [36], and advanced shampoo formulations with ingredients like zinc pyrithione, salicylic acid, sulfur, selenium sulfide, ketoconazole, and coal tar [37]. For severe or persistent dandruff, dermatologists may prescribe stronger shampoos or medications, considering potential underlying medical conditions such as seborrheic dermatitis, psoriasis, fungal infections, or eczema [38]. These treatments, including pharmaceutical solutions and advanced formulations, may exhibit side effects such as skin irritation, dryness, or, in the case of medications like finasteride and spironolactone, potential systemic effects that should be carefully considered and discussed with a healthcare professional [34,39], which highlight a need for a safer alternative treatment for these two problems.

Probiotics are live microorganisms that confer health benefits to the host when consumed in adequate amounts. The concept of probiotics dates back to the early 20th century when Nobel laureate Eli Metchnikoff proposed that the consumption of fermented milk products containing lactic acid bacteria could improve gut health and prolong life [40]. Colonizing the gut and enhancing the gut microbiome diversity can improve digestion, reduce inflammation, and boost the immune system [41]. Probiotics can also have

beneficial effects on other parts of the body, including the skin and hair, with produced metabolites. These include short-chain fatty acids (SCFAs) [42], bacteriocins [43], exopolysaccharides (EPS) [44], and exosomes [45]. SCFAs, such as acetic, propionic, and butyric acid, have immunomodulatory properties and can impact inflammatory responses [46]. Bacteriocins are antimicrobial peptides produced by certain probiotic strains that can inhibit the growth of harmful bacteria [43]. EPS [44] and exosomes enriched in microRNAs [45] are involved in intercellular communication and may contribute to the modulation of immune and inflammatory processes.

Moreover, there is a considerable amount of scientific research highlighting the positive effects of probiotics on issues related to hair growth and dandruff. Recent preclinical studies have shown that both single and multi-strain probiotics can improve hair growth, balance immune responses and gut microbiome in various mouse and cell models related to hair growth and dandruff [18,47,48]. Additionally, clinical trials have revealed that taking single and multi-strain probiotics can positively influence the immune and inflammatory responses of patients dealing with hair loss and dandruff problems by regulating the composition of the scalp microbiota [49,50]. However, despite these promising findings, the evidence regarding the effects of probiotics on hair growth and dandruff is still limited and unclear. There is a need for more in-depth research to determine how effective probiotics are and to understand the mechanisms behind their potential role in managing hair growth and dandruff. Previous studies have also suggested a link between hair growth and dandruff conditions and the health of the scalp skin and gut. In this context, our meta-analysis is a pioneering effort, the first quantitative assessment of how probiotics might impact hair growth and dandruff-related factors. While probiotics have shown promise for promoting hair health, hair loss, and dandruff, the limited research in this area poses several limitations to our current understanding of their potential benefits and mechanisms. Future studies should address these limitations by investigating the effects of probiotics on hair health in humans, standardizing probiotic preparations and dosages, considering potential interactions with other factors that may impact hair health, and exploring potential mechanisms beyond the skin and gut microbiome.

Despite the growing interest in the use of probiotics for hair health, there is a lack of clinical trials investigating the effectiveness of probiotics in treating hair loss and dandruff. Therefore, the research question for this systematic review and meta-analysis was set as follows:

“Can probiotic supplementation improve hair health, particularly inducing hair growth and dandruff control?”

Our review plays an important role in contributing to the understanding of the intricate relationship between probiotics and hair health. By conducting a systematic review and meta-analysis, we provide a comprehensive synthesis of existing knowledge, offering important insights into probiotics impact on hair growth and dandruff management. As the first quantitative assessment in this field, our review not only aims to clarify this important relationship but also identifies gaps and limitations in current literature. Positioned at the intersection of dermatology and microbiome science, our work serves as an important foundational resource that will play a crucial role in guiding future research, informing clinical practices, and providing evidence-based insights for individuals seeking important interventions for common hair-related concerns using probiotic products.

2. Materials and methods

2.1. Literature search

A literature search on the efficacy of probiotics on hair growth and dandruff was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 protocol to find pertinent publications published up to May 2023. The database as information sources included Excerpta Medica Database (Embase), PubMed Central (Pubmed), ClinicalTrials.gov, Scopus, and International Clinical Trials Registry Platform (ICTRP). Probiotics, Lactobacillaceae, *Lactobacillus*, hair, hair loss, hair growth, alopecia, and dandruff were used as search terms, and filters were applied as in Table 1.

Table 1
Summary of search results and filters applied in different databases.

Database	Full search term	Filters applied	Paper numbers
Embase	(’Lactobacillaceae’ OR ’*Lactobacillus*’ OR ’probiotic’) AND (’hair’ OR ’alopecia’ OR ’hair loss’ OR ’hair growth’ OR ’dandruff’)	Article Article in press	133
Pubmed	(Lactobacillaceae OR *Lactobacillus* OR probiotic) AND (hair OR alopecia OR hair loss OR hair growth OR dandruff)	English	71
ClinicalTrials.gov	Condition or disease: hair Other terms: probiotic	Completed Studies	4
Scopus	TITLE-ABS-KEY ((Lactobacillaceae) OR (*Lactobacillus*) OR probiotic) AND (hair OR alopecia OR "hair loss" OR "hair growth" OR dandruff))	Article English	125
ICTRP	Probiotic AND hair	With results only Phase 4	2

2.2. Study selection and data extraction

2.2.1. Study selection

For the human component of this meta-analysis on the efficacy of probiotics in hair growth and dandruff control, the selection criteria for randomized controlled clinical trials (RCTs) adhered to the PICO framework outlined in Table 2. The study population (P) comprised healthy adult, patients with hair loss or dandruff who underwent an intervention (I) involving probiotics, with a comparison group (C) receiving a control or placebo. The primary outcome (O) of interest was the alteration in hair growth parameters, while secondary outcomes encompassed changes in dandruff-controlling perception parameters. The effectiveness of probiotics in controlling hair dandruff and enhancing hair growth among patients with dandruff and hair loss was assessed based on these outcomes.

Regarding cell and animal studies, preclinical investigations were deemed eligible if they fulfilled the following criteria: (1) studies conducted in cells, rats, or mice with regard to dandruff or hair loss; (2) intervention involving experimental administration of probiotics; and (3) assessment of hair loss or dandruff-related parameters and/or immune, inflammatory and growth markers such as VEGF and IGF-1 in animal models of dandruff or hair loss. Studies failing to meet any of these criteria were excluded.

Duplicate articles were identified and eliminated using EndNote X9 and additional manual procedures. Following the removal of duplicates, articles were screened based on titles and abstracts in accordance with the eligibility criteria. Full texts of potentially relevant articles were subsequently assessed for eligibility, and reasons for exclusion were documented. The entire process of study inclusion was conducted independently by two investigators (Trang Thi Minh Nguyen – T.T.M.N and Chang-Shik Yin – C.S.Y.). Discrepancies were primarily resolved through discussions to achieve a consensus, and in instances where agreement could not be reached, a third investigator (Tae-Hoo Yi – T.H.Y.) was consulted for further input.

2.2.2. Data extraction

Two independent reviewers (T.T.M.N and C.S.Y.) extracted and crosschecked data from eligible studies. For clinical trials, the extracted information included participant characteristics (age, sex, medical diagnostics, and comorbidities), sample size and follow-up time, and details of the intervention (probiotic strain, dose, and delivery method). Primary outcomes are related to hair count, hair thickness, hair growth, hair follicle strength, hair quality, hair diameter, gene expression related to hair growth (e.g., VEGF, IGF-1 …), and intestinal microbiota. Secondary outcomes include dandruff-controlling perception parameters (itching perception, scaling perception (adherent dandruff), cleaning perception (free dandruff), skin biophysical parameters (pH, hydration, transepidermal water loss (TEWL), sebum), glucose and lipid profile, scalp gloss, scalp redness, single closed patch test, and repeated closed patch test). Both are recorded as mean and standard deviation (SD) data if available.

For preclinical studies, the extracted information included study design, number of subjects per group, each group number, subject age and follow-up time, and details of the intervention (probiotic strain, dose, and delivery method). Outcomes related to hair regrowth, skin thickness, hair count, hair thickness, mRNA hair growth gene expression (e.g., VEGF, IGF-1 …), hair follicle strength, hair quality, hair diameter, Th1 immune responses, hair cell proliferation, gut microbiota regulation, intestinal tissue myeloperoxidase (MPO) content parameters in mean and standard deviation complement into primary outcome related to hair growth. Meanwhile, the antimicrobial effect on *Staphylococcus aureus* (*S. aureus*), *Cutibacterium acnes* (*C. acnes*), *Candida albicans* (*C. albicans*), *Malassezia globosa* (*M. globosa*), *Malassezia restricta* (*M. restricta*), and chemical analysis of anti-fungal compounds contribute to secondary outcome. Quantitative data were extracted and included in the meta-analyses for outcomes with data available from two or more studies.

2.3. Meta-analysis

For statistically significant homogeneous studies, the fixed-effects model was applied. In case the level of heterogeneity is large ($I^2 \geq 40$ %), the random-effects model recommended by DerSimonian and Laird [51] was used. This model takes into account the presence of heterogeneity and provides a more appropriate estimation of the overall effect size. To identify a significant level of heterogeneity,

Table 2
The criteria of PICO of including and excluding studies of RCTs for meta-analysis.

	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled clinical trials published in peer-reviewed journals in English.	Observational studies, experimental studies, phase studies, case reports, reviews, abstracts, conference papers, study protocols for RCT, and studies that investigated probiotics' effect on hair growth, hair loss, and dandruff or did not report relevant outcome measures.
Population	Healthy adult human participants with ages between 18 and 60 or healthy adult human participants aged between 18 and 60 with stages of hair loss by a specific scale.	Not applicable.
Comparison	Control group or placebo group.	Not applicable.
Intervention	Probiotics, orally or topically administered, with no restriction on strains, doses, and frequency and duration of administration, provided information was reported.	Not applicable.
Outcome	Primary outcomes: changes in hair count and hair thickness measured by validated tools. Secondary outcomes: change in itchiness perception, free dandruff, and adherent dandruff measured by validated tools.	These data could not be calculated based on the information in the article such as lacking detailed data.

the I^2 statistic with a cut-off of 50 % and the chi-squared test with a *P* value < 0.10 were both utilized. For primary outcomes related to hair growth, Standardized Mean difference (SMD) was used for all parameters related to hair growth since those outcomes are measured in a variety of ways. Meanwhile, the Odd Ratio (OR) was used for effect size due to the limited number of studies on secondary outcomes. According to Cohen's general interpretation of the SMD, an SMD of 0.2 denotes a minor effect, an SMD of 0.5 denotes a medium effect, and an SMD of 0.8 or higher denotes a substantial effect [52]. Standard deviations (SD) for changes were estimated using the formula SD = SE (Standard Error) $\times \sqrt{N}$. The Review Manager version 5.4 (Revman 5.4) software was used to input each study's events, total or mean, and SD values and to perform data visualization. If the 95 % confidence interval (95 % CI) of the mean encompasses the value of 0 or the 95 % CI of the ratio encompasses the value of 1, the statistical findings would be considered non-significant [53]. Publication bias was not assessed using funnel plots due to the limited number of studies included in the meta-analyses.

2.4. Risk of bias and quality of evidence

Revman 5.4 was utilized to assess the quality of each clinical trial and preclinical studies included in the analysis. The tool evaluated seven domains of bias: Random sequence generation (selection bias); Allocation concealment (selection bias); Blinding of participants and personnel (performance bias); All outcomes, Blinding of outcome assessment (detection bias); All outcomes,

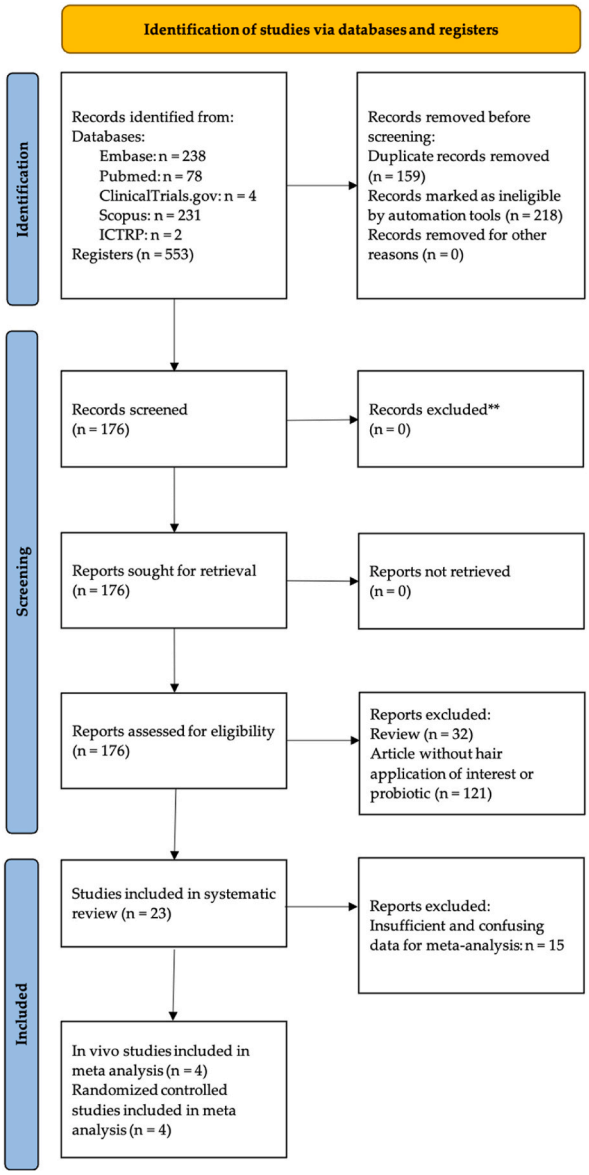

Fig. 1. PRISMA 2020 study selection flowchart for the systematic review and meta-analysis.

Table 3
Key features of clinical trial studies included hair dandruff and hair growth.

Reference	Type of patient	Gender		Age range (years)	Measurement system	Intervention	Main findings
		M	F				
Reygagne 2017, France [56]	58 healthy male, non-bald adults	58	0	40 ± 9.39 **	Itching perception Scaling perception (adherent dandruff) Cleaning perception (free dandruff)	Food supplement containing *L. paracasei* NCC2461 ST11	Signs and symptoms of moderate to severe dandruff significantly improve in 8 weeks follow-up on the treatment group ST11
Park 2020, Korea [55]	46 men with stage II to V hair loss (Hamilton–Norwood) and women with stage I to III hair loss (Ludwig)	23	23	45.35 ± 9.96	Hair count Hair thickness	80 mL of kimchi and cheonggukjang probiotic oral product containing: *-L. holzapfelii* *-Leuconostoc mesenteroides* *-Lactobacillus sakei* *-Pleuropterus multiflorus* *-Rhynchosia volubilis Lour*	Hair count and thickness significantly increased at: −1 month (90.28 ± 16.13 hairs/cm^2, 0.068 ± 0.008 mm) −4 months (91.54 ± 16.29 hairs/cm^2, 0.066 ± 0.009 mm)
Yu 2022, China [50]	26 adults presenting with hair loss and a high risk of metabolic	10	16	33.6 ± 4.5	Hair count Itching perception Skin biophysical: -pH -Glucose and lipid profile -Hydration -TEWL -Sebum	Orally twice per day sachets (1.8 g per sachet of 18.1 billion CFU) containing: *-B. lactis* Bi-07, HN019 *-L. acidophilus* NCFM *-L. rhamnosus* HN001 *-L. paracasei* Lpc- 37	After 12 weeks with probiotic supplementation: −96.2 % improved hair density, reduced hair loss −73.1 % relieved scalp itching -Increased stratum corneum hydration and pH -Decreased TEWL and sebum on scalp and facial skin -Improved glucose metabolism and lipid profile: increased HDL cholesterol, reduced glucose, HOMA-IR, total cholesterol, and non-HDL cholesterol
Yoon 2022, Korea [64]	31 adults suffering from hair loss during the 12-week test period	4	27	46.43 ± 6.92 **	Hair count Hair thickness	Inhaling L. *holzapfelii* extracellular vesicles ampoule	*L. holzapfelii* significantly improves the hair count and thickness after weeks 4th, 8th, and 12th of treatment
Liang 2022, Taiwan [54]	50 healthy adults aged above 20 years old suffered from hair loss	N/A	N/A	20 years and older	Hair growth, thickness, follicle strength Intestinal microbiota Scalp gloss, redness, health Hair diameter Dihydrotestosterone and testosterone in the blood Gene expression: SRD5A1, AR, TGF-β gene	100 mg/day of *L. plantarum* TCI999 powder	TCI999 led to: – 12-week consumption resulted in increased hair root diameter, reducing hair loss and scalp redness compared to placebo - Increased mitochondrial activity and hair cell growth - Decreased SRD5A1, AR, and TGF-β genes *in vitro*
Woo 2022, Korea [59]	56 male adults with 2, 2A, or higher (Norwood–Hamilton) or 1 or higher (Ludwig)	13	43	42.8 ± 5.21	Hair count Hair thickness Hair quality Gene expression: VEGF, IGF-1, KGF, HGF, ALP	Wash-off shampoo with *L. plantarum* KCTC 33133 fermenting *Schisandra chinensis*	Extract significantly increases the number of hairs at 8 weeks, 16 weeks, and 24 weeks compared to before product use, and a change in hair growth, a secondary efficacy evaluation variable in the clinical trial *In vitro*, hDPCs show an increase in IGF-1 gene expression in a dose-dependent manner
Alves 2023, Brazil [57]	33 adults with varying dandruff levels	16	17	32.56 ± 10.28 **	Itching perception Scaling perception (adherent dandruff) Cleaning perception (free dandruff)	1 % shampoo of Neoimuno from *B. lactis* CCT 7858	Sample makes significant positive differences between the placebo and treatment group in 4 weeks in itching perception, scaling perception,

(*continued on next page*)

Table 3 (*continued*)

Reference	Type of patient	Gender		Age range (years)	Measurement system	Intervention	Main findings
		M	F				and cleaning perception while 2 weeks has no effect
Tsai 2023, Taiwan [49]	22 healthy adults	8	14	37 ± 6.2	Scalp sebum Cleaning perception (free dandruff) Hair density Single closed patch Repeated closed patch	Twice a day base cream including heat-killed *L. plantarum*-GMNL6 (1×10^9 cells/g cream)	Sample resulted in: -Decreased dandruff and oil secretion -Increased hair growth on the human scalp -Changes in scalp microbial species: increased *M. globosa* and decreased *M. restricta* and *C. acnes*

The table includes information on participant demographics, study design, and main findings. The gender breakdown is listed as M for males and F for females with mean and standard deviation data. High-Density Lipoprotein (HDL), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). N/A: Not available. **Supplement file 1.

Incomplete outcome data (attrition bias); All outcomes, Selective reporting (reporting bias); Other bias. Each domain was assigned a risk rating of high, low, or unclear. The risk of bias assessment was conducted independently by T.M.T.N. and C.S.Y., and any disagreements were resolved through discussions and consensus with other authors. No studies were excluded based on quality ratings. The quality assessment of the included studies was conducted independently by T.M.T.N. and C.S.Y., with any disagreements resolved through discussions involving a third investigator, T.H.Y.

3. Results

3.1. Features of included studies

The search trials yielded a total of 553 records from online databases (Fig. 1). After removing 159 duplicates and filtering by automation tools, 176 articles remained, and based on the examination of titles and abstracts, 153 studies were excluded. A total of 8 clinical trial studies and 15 preclinical studies (with 2 papers including both clinical and preclinical data) were comprised for systematic analysis. Of the remaining 23 studies chosen for systematic review, 15 were excluded after assessing their full texts for meta-analysis. Ultimately, 4 RCTs and 4 preclinical studies were included for quantitative meta-analyses. The detailed process of article screening is summarized in Fig. 1.

3.2. Description of included studies

Tables 3 and 4 show the characteristics of the included studies in this systematic review and meta-analysis. Fig. 2A and B describes Korea with the most research in hair with probiotics and *Lactobacillus paracasei* (*L. paracasei*) being the most studied strain with 8 papers. Eight studies were clinical trials and were published between 2017 and 2023. The sample size ranged from 22 to 58 participants, with 322 in total, and all studies involved adult patients. Eight studies reported gender distribution (Fig. 2C) and the age range varied from 32.56 ± 10.28 to 46.43 ± 6.92 years with one paper did not report detailed data [54] (calculation being conducted in **Supplement file 1 and 2**). The intervention in the experimental group consisted of probiotics in all eight clinical trial studies. The follow-up period ranged from 2 to 24 weeks. The studies evaluated the effect of probiotics on hair health, including hair loss and dandruff. All studies used different probiotic strains, including *Bifidobacterium lactis* (*B. lactis*), *Lactobacillus plantarum* (*L. plantarum*), *Leuconostoc holzapfelii* (*L. holzapfelii*), and *Rhynchosia volubilis Lour*, among others. The measurement methods used in the included studies varied depending on the specific outcomes being evaluated. Regarding hair growth, Dr. Park in his recent study demonstrated increased hair count and thickness at 1 and 4 months [55]. A probiotic cocktail supplement improved hair density and reduced hair loss in 96.2 % of participants [50]. Furthermore, a Taiwan study by Liang in 2022 found a probiotic that boosted hair cell growth, root diameter, and overall hair quality, which showed potential influence on gene expression by reducing steroid 5α-reductase type I (SRD5A1), androgen receptor (AR), and TGF-β genes [54]. The systematic review on dandruff control yielded promising outcomes from various interventions of probiotics. *L. paracasei* NCC2461 ST11 showed significant improvements in itching perception for moderate to severe dandruff over a 4-week period [56]. *B. lactis* displayed noticeable itching improvement after 4 weeks, but not in a 2-week trial [57]. Probiotic supplementation relieved scalp itching in 73.1 % of participants over 12 weeks of treatment [50]. For scaling and cleaning perception, these parameters were suppressed by ST11 strain after 4 weeks [56], while *B. lactis* exhibited potential benefits only for scaling after 4 weeks [57]. Tsai's 2023 study [49] found decreased dandruff and oil secretion and increased hair growth with a heat-killed *L. paracasei*-containing shampoo.

For preclinical studies, 15 preclinical studies in Table 4 evaluated the effects of probiotics on hair health. The studies utilized different strains of probiotics and were published between 2012 and 2023. Various measurement systems were employed in these studies to assess the outcomes. Regarding hair growth or regrowth, various interventions showed promising results. Song et al. (2012) [58] demonstrated fermented products' effectiveness in increasing hair follicle size beyond minoxidil, a common hair-growth

Table 4
Key features of preclinical studies included hair dandruff and hair growth.

Reference	Model	Measurement system	Intervention	Main findings
Song 2012, Korea [58]	Topically treated on shaved 6-week-old C57BL/6 mice (4 groups/ each group 5 subjects)	Hair regrowth Skin thickness	G1: Normal G2: Negative control G3: Minoxidil G4: 10 % *backryeoncho* + *L. rhamnosus*	Histological evaluation showed that the essence containing fermented products markedly increased the depth and size of the hair follicles, as compared to the minoxidil in 8 days.
Papista 2012, Greece [48]	Orally treated gluten-induced coeliac-like disease 10-week-old BALB/c mice (5 groups/ each group 3 subjects)	Gene expression: IgA, COX-2, IFN, TNF-α, IL-10, IL-15, TG2	G1: gluten-free food G2: gluten-containing commercial food G3: *Saccharomyces boulardii* KK1 (10^8 CFU) G4: *L. paracasei* DC205 G5: *L. paracasei* DC412	While an increase of IgA and IgG anti-gliadin antibodies (AGA) production as well as hair loss was observed in mice 6 month post gluten diet, G3 reduced expression of IgA, COX-2, IFN, TNF-α, IL-10, IL-15, but TG2 was increased in 7 days G3 reduced epithelial cell CD71 expression and Th1 immune responses and ameliorated the histopathological features of gluten-induced enteropathy in the gluten-induced mice
Kalenova 2015, Russia [60]	Orally treated burn-injured 12-week-old BALB/c mice (4 groups/ each group 4 subjects)	Hair growth	G1: cellulose gel G2: solcoseryl G3: gel with *Bacillus cereus* IP5832 G4: gel with *Bacillus* spp. MG8 (2×10^6 CFU)	G4 recorded stronger hair regrowth in the wound healing process than G3 in 13 days
Lee 2016, Korea [63]	Orally treated LPS-induced THP-1 cell 20-week-old inbred C57BL/6 mice (3 groups/ each group 14 subjects)	Gene expression on THP-1 cells: TNF-α Hair regrowth, follicles Gene expression on mice: TNF-α, IL-10, testosterone, insulin	G1: Control G2: live *L. reuteri* BM36301 (10^6 CFU) G3: *L. reuteri* BM36304	G2 stimulated TNF-α in THP-1 cells Males mice G2 Increased testosterone levels in 20 weeks Males mice G3 experienced increased TNF-α and insulin Females mice G2 maintain lower serum TNF-α levels and higher counts of hair follicle and hair growth
Oike 2016, Japan [67]	Orally treated shaved 8-week-old C57BL/6 mice (5 groups/each group 2 subjects)	Outer hair cell, spiral ganglion neurons cell survival rate Gene expression: Bak-1, Bax	G1: Control G2: 0.05 % *Lactococcus lactis* H61	Outer hair cell, spiral ganglion neurons cell survival rate significantly increased by the intake of strain H61 in 6 months while downregulated bak1 gene
Woo 2019, Korea [47]	HDPCs cell MG-63 cell Topically treated shaved 6-week-old C57BL/6 mice (6 groups/each group 4 subjects)	Histological evaluation: - Hair growth mRNA hair growth gene expression: - VEGF - IGF-1	G1: Control G2: Hydrolysates of L. *plantarum* G3: Hydrolysates of L. *plantarum* by Alcalase G4: Hydrolysates of L. *plantarum* by bromelain G5: Hydrolysates of L. plantarum by Protamex G6: Minoxidil	G2-6 produced hair growth superior to the growth obtained with 5 % minoxidil in hair growth experiments using C57BL/6 male mice with hair growth and increasing VEGF and IGF-1 in 14 days G2, 3, 4 show no toxicity to HDPCs cell and MG-63 cell
Hai 2019, China [65]	Topically treated burn-injured 8-week-old female rats (4 groups/ each group 3 subjects)	Antioxidative and antibacterial activity Hair regrowth and skin recovery Gene expression: TNF-α, IL-1β, and IL-4	G1: Control G2: 0.9 % normal saline G3: *L. plantarum* HM218749 aloe-fermented liquid G4: Bovec skin burn cream	G3 markedly has an antioxidant effect and significantly inhibited the growth of pathogens G3 produced more eosinophils and fibroblasts and less vessel proliferation compared with G2 on the 14th day, shedding the scab and promoting hair growth, and had significantly reduced TNF-α and IL-1β and increased IL-4 G3 also regulated gut microbiota
Chae 2021, Korea [68]	*S. aureus* *C. acnes* *C. albicans* *M. globose* *M. restricta*	Indirect co-culture with LAB Plate agar overlay	G1: Cell-free supernatant of *L. plantarum* APsulloc 331261	G1, 2 inhibits viability of *S. aureus, C. acnes, C. albicans, M. globosa,* and *M. restricta* was inhibited by indirect co-culture with APsulloc 331261 or

(*continued on next page*)

Table 4 (*continued*)

Reference	Model	Measurement system	Intervention	Main findings
			G2: *L. plantarum* APsulloc 331266	APsulloc 331266 in a dose-dependent manner
Vairagkar 2021, India [11]	*Malassezia furfur* ATCC 44344 and *Malassezia furfur* 12078	Agar well diffusion Minimum Inhibitory Concentration (MIC) assay Time kill of antifungal compounds RP-HPLC and LC/HRESI-MS/MS of antifungal compounds	*Bacillus amyloliquefaciens* MTCC 10456	Sample fraction consisted of bacilysin, homologs of bacillomycin D, and members of the macrolactin family Synergism among the identified compounds was observed which enhanced the antagonistic activity against *Malassezia* spp.
Priya 2021, India [66]	*Malassezia furfur* 1374^{T}	Agar well diffusion of LAB Minimum Inhibitory Concentration (MIC) assay GC/MS analysis	G1: Positive control Climbazole (50 mg/mL) G2: Cell-free supernatant of *L. rhamnosus* G3: Cell-free supernatant of *E. faecium* G4: Cell-free supernatant of *E. faecalis* G5: Negative control (MRS broth)	G2 has a 7 mm inhibition zone against *Malassezia furfur* with a MIC value of the extracellular fraction optimized to be 100 mg/mL GC/MS analysis revealed that all three extracellular bacterial isolates had propionic acid, lactic acid, phenol, 2,4-bis (1,1-dimethyl ethyl), hexadecanoic acid, octadecanoic acid, and 3-isobutyl hexahydro pyrrolo [1,2-a] pyrazine-1,4-dione
Nam 2021, Korea [69]	HFDPC cell Orally treated shaved 7-week-old female C57BL/6 mice (3 groups/each group 6 subjects)	HFDPC proliferation HFDPC growth factor secretion Histological evaluation: - Hair follicle, skin thickness mRNA hair growth gene expression: - VEGF, IGF-1	G1: Negative control G2: Medicinal yeast (positive control) (200 mg/kg) G3: *L. paracasei* HY7015 (10^{8} CFU)	HY7015 stimulated HFDPC proliferation *in vitro* and increased their secretion of VEGF and IGF-1 Oral administration of HY7015 promoted hair growth and hair follicle maturation in the dorsal skin, increased VEGF and IGF-1 levels in mouse serum in 7 weeks
Zhang 2022, China [70]	Orally treated aspirin-induced 6-week-old BALB/c mice (10 groups/each group 4 subjects)	Intestinal tissue MPO content Gene expression: TNF-α, IL-6, intestinal tissue NF-κB p65 expression levels	G1: Control G2: Aspirin *G3:* 2000 CFU *Lactobacillus acidophilus* LA-GHB1756 G4: 10000 CFU *Lactobacillus acidophilus* LA-GHB1756	G3, 4 decreased level of MPO content, TNF-α, IL-6, intestinal tissue NF-κB p65 compared to the aspirin-induced group and improved hair growth in 8 weeks
Wang 2022, China [71]	95 healthy adults with varying dandruff levels aged 32.7 ± 7.2	Scalp and hair surface microbiota Fungal and bacterial metagenomic Co-occurrence/co-exclusion relationships network analysis	No intervention, only measure healthy scalp and hair microbiota	*L. plantarum* and *P. lactis* from the scalp inhibit *Staphylococcus epidermidis in vitro* Healthy scalp microbiota, including *Lactobacillus* and *Lactococcus*, are co-excluded with other bacterial genera and *Malassezia* sp.
Baek 2022, Korea [62]	HDPCs cell Topically treated shaved 6-week-old C57BL/6 mice (5 groups/each group 3 subjects)	HDPC proliferation Histological evaluation: skin thickness mRNA hair growth gene expression: - FGF2, FGF7, FGF10 - Wnt5a, Wnt5b, Wnt10b - VEGF A, VEGF B, IGF-1, IGF1-R	G1: Control (PBS) G2: 5 % minoxidil G3: 0 mg/mL EF-2001 in acetone + olive oil (3:1) G4: 5 mg/mL EF-2001 G5: 50 mg/mL EF-2001	*E. faecalis* EF -2001 accelerated the progression of hair regrowth in mice and promoted hair-follicle conversion from telogen to anagen, likely by increasing the expression levels of growth factors (VEGF A, VEGF B, IGF-1, IGF1-R, FGF2, FGF7, FGF10) and marker genes (Wnt5a, Wnt5b, Wnt10b) after 14 days
Lee 2022, Korea [61]	HFDPC cell NIH3T3 cell Orally treated shaved 7-week-old C57BL/6 mice (5 groups/each group 6 subjects)	HFDPC proliferation Histological evaluation: - Hair follicles, skin thickness mRNA hair growth gene expression: - VEGF, IGF-1	G1: Negative control G2: Medicinal yeast (200 mg/kg) G3: *Lycopus lucidus* – LT (100 mg/kg) G4: *L. paracasei* HY7015 (10^{8} CFU) G5: LT + HY7015 (100 mg/kg)	Oral administration of G5 promoted hair regrowth as well as hair follicle maturation in the dermal skin of C57BL/6 mice and upregulated VEGF and IGF-1 growth factor levels in mouse serum in 5 weeks

(*continued on next page*)

Table 4 (*continued*)

Reference	Model	Measurement system	Intervention	Main findings
Yoon 2022, Korea [64]	HFDPCs cell	HFDP Cell Migration and Proliferations mRNA Cisplatin-Induced HFDP Cells gene expression: CCK-8, Bcl-2, Bax, Capcase-3 mRNA hair growth gene expression: Wnt5a, Wnt10b, b-catenin, versican (VCAN), VSC, BAMBI, BMP-2, Lef1 Apoptosis and Induce Division via Control Cell Cycle in HFDP Cells	G1: Control G2: *Bifidobacterium longum* (Bl) G3: *B. animalis* G4: L. *acidophilus* *G5*: human-scalp-derived-*Leuconostoc holzapfelii* (hs-Lh) *G6: L. plantarum* (Lp)	G5 (10^{10} particles) extracellular vesicles increase cell proliferation, and migration, and regulate the cell cycle G5 modulates the mRNA expression of hair-growth-related genes *in vitro*, reduces apoptosis by modulating the cell cycle, and promotes hair growth by regulation via the Wnt/β-catenin signal transduction pathway
Tsai 2023, Taiwan [49]	Hs68 fibroblast cell B16F10 cells	Collagen synthesis mRNA gene expression Hs68 fibroblast cell: Serine palmitoyltransferase small subunit A (SPTSSA) *S. aureus* biofilm	G1: Control G2: Lipoteichoic acid from *L. paracasei* GMNL-653 G3: Peptidoglycan from L. *paracasei* GMNL-653	G2 enhanced collagen synthesis and the gene expression of SPTSSA, biofilm of *S. aureus*, and the proliferation of *C. acnes* in a dose-dependent manner

THP-1: human acute monocytic leukemia cell, HFDPC: hair follicle dermal papilla cells, C57BL/6 mice: "C: strain's origin, the Bussey Institute for Research in Applied Biology, Harvard University, in 1921; 57: number of generations of inbreeding; BL: Black coat color of the mice; 6: sixth subline or substrain derived from the original C57BL strain", HDPCs: Human dermal papilla cells, NIH3T3: embryonic mouse fibroblast cell, MG-63: human osteosarcoma cell.

substance. Woo et al. (2019) [59] also found hydrolysates of *L. plantarum* (LP) stimulated superior hair growth compared to minoxidil. The same effect goes with Kalenova et al. [60] observed stronger hair regrowth with *Bacillus* spp. MG8 gel when compared to the control group. Lee et al. [61] reported increased hair regrowth in mice treated with *L. reuteri* BM36301. For skin thickness, findings were explored by Song et al. [58] and Baek et al. [62], who suggested positive changes in skin thickness related to their interventions. For hair follicles, Lee et al. [63] showed increased follicle counts in mice treated with *L. reuteri* BM36301. Baek et al. (2022) [62] found *Enterococcus faecalis (E. faecalis)* EF-2001 may accelerate hair regrowth and follicle maturation. Lee et al. (2022) [61] observed hair regrowth and follicle maturation with *L. paracasei* HY7015 and *Lycopus lucidus Turcz.* (LT) administration. For hair growth mechanisms, gene expression changes were investigated in several studies. Cyclooxygenase-2 (COX-2), Interferon (IFN), Tumor Necrosis Factor-alpha (TNF-α), Interleukin (IL)-10 IL-15, IL-1β, CCK-8, Bcl-2, Bax, Capcase-3 are recorded to be suppressed while Transglutaminase 2 (TG2), insulin and testosterone, IL-4, growth factors (VEGF A, VEGF B, IGF-1, IGF1-R, FGF2, FGF7, FGF10) and marker genes (Wnt5a, Wnt5b, Wnt10b), b-catenin, versican (VCAN), Vascular Smooth Muscle Cell (VSC), BMP and Activin Membrane-Bound Inhibitor (BAMBI), Bone Morphogenetic Protein 2 (BMP-2), Lymphoid Enhancer-Binding Factor 1 (Lef1) are induced with probiotic treatment [48,63–65]. Yoon et al. (2022) [64] indicated gene expression modulation via the Wnt/β-catenin pathway with extracellular vesicles from *L. holzapfelii*. For dandruff control, preclinical studies in Table 4 highlight the potential of bacterial strains, especially *Lactobacillus* and *Lactococcus* species, to combat dandruff by inhibiting *Malassezia furfur* growth. Priya [66] and Vairagkar [11] found *Lactobacillus rhamnosus* (*L. rhamnosus)* and *Lactobacillus amyloliquefaciens* (*L. amyloliquefaciens)* fractions effectively inhibited *Malassezia*. These findings highlight the efficacy of these interventions in supporting scalp health and promoting hair growth.

3.3. Quality assessment of included 8 studies

Figs. 3 and 4 present a summary of the risk-of-bias assessment conducted on the included studies, both clinical trials and preclinical studies. Among them, 15 studies were classified as having a low and unclear risk of bias. However, 3 study was determined to have a high risk of bias in the Selection Bias and Incomplete outcome data domain due to the absence of baseline data in the published paper. Additional details and justifications for these judgments can be found in Supplement file 3. Additionally, for outcome assessment, approximately 50 % of the studies showed unclear risk of outcome data, suggesting a risk of detection bias. A comprehensive evaluation of study quality and risk of bias for all 23 included articles is included in Supplement file 3.

3.4. Meta-analysis of included 8 studies

3.4.1. Effect on hair growth

The primary outcomes of interest in this systematic review and meta-analysis included hair growth illustrated in Figs. 5 and 6. This outcome was assessed in both RCTs and in vivo animal studies [62,69,72,73] included in the analysis. Hair regrowth was measured using various methods, including hair count, hair thickness, hair follicle count, skin thickness, VEGF, and IGF-1 parameters. For clinical studies in Fig. 5, Yoon 2022 [64] and Woo 2022 [59] studies involving 87 participants were included in the meta-analysis of hair growth outcomes. The pooled analysis showed low heterogeneity among the RCTs studies of $I^2 = 24$ % ($P = 0.27$) and high heterogeneity in in-vivo studies with $I^2 = 68$ % and $P = 0.0005$. The standardized mean difference (SMD) for hair growth, combining hair count and thickness, was 0.32 (95 % CI -0.10 to 0.75) and 0.92 (95 % CI 0.47 to 1.36), correspondingly indicating a significant effect of the intervention of hair thickness. The CI 95 % of hair count included 0, which demonstrates a non-significant increase. Subgroup analysis for hair count and thickness was not feasible due to the limited number of studies. Heterogeneity was not observed

for hair thickness ($I^2 = 0$ %, $P = 0.62$) and for hair count ($I^2 = 0$ %, $P = 0.80$).

For preclinical studies in Fig. 6, a meta-analysis of three in vivo studies involving 40 subjects was conducted to assess the effect of the intervention on hair follicle count. The pooled analysis showed a significant induction in hair follicle count following the intervention, with a standardized mean difference (SMD) of 3.24 (95 % CI 0.65 to 5.82). Substantial heterogeneity was observed among the included studies ($I^2 = 81$ %, $P = 0.005$). Three studies with 30 subjects were included in the meta-analysis of skin thickness outcomes. The pooled analysis demonstrated a statistically significant development in skin thickness following the intervention, with an SMD of 2.32 (95 % CI 0.47 to 4.17). And heterogeneity was not notably observed among the studies ($I^2 = 48$ %, $P = 0.15$). A meta-analysis of three studies involving 30 subjects was conducted to examine the effect of the intervention on VEGF levels. The pooled analysis revealed a significant increase in VEGF levels following the intervention, with an SMD of 2.97 (95 % CI 0.80 to 5.13). Substantial heterogeneity was observed across the studies ($I^2 = 63$ %, $P = 0.07$). Two studies with 18 subjects were included in the meta-analysis of IGF-1 levels. The pooled analysis showed a moderate increase in IGF-1 levels, with an SMD of 0.53 (95 % CI -4.40 to 5.45) including 0 which demonstrated non-significant statistics. High heterogeneity was observed among the included studies ($I^2 = 90$ %, $P = 0.002$).

3.4.2. Effect on hair dandruff

The secondary outcome of this meta-analysis was dandruff control in Fig. 7. Dandruff control was evaluated through measurements such as scaling or peeling perception (adherent dandruff) and product quality cleaning perception (free dandruff). Regarding scaling perception (adherent dandruff), two studies [56,57] with 85 participants yielded an OR of 1.31 (95 % CI 0.13 to 13.65). A meta-analysis of two studies [56,57] on cleaning perception (free dandruff) included 85 participants and showed an OR of 5.39 (95 % CI 1.50 to 19.43). Adhere dandruff parameter has the Cl 95 % including 1 which indicated a non-significant increase. High heterogeneity was observed $I^2 = 78$ % with $P = 0.03$ for adherent dandruff and no heterogeneity for $I^2 = 0$ % with $P = 0.4$ of free dandruff parameter.

4. Discussions

The present systematic review and meta-analysis aimed to assess the effects of probiotics on hair health, specifically focusing on hair growth and dandruff control. The analysis included a total of four clinical studies and four preclinical studies, providing valuable insights into the potential benefits of probiotic interventions in managing hair-related conditions, within the studied probiotic strains, *L. paracasei*, *L. plantarum*, and *B. lactis* are most commonly studied. Due to the complexity of probiotic live and dead cells, or their byproducts such as SCFA, bacteriocin, and peptidoglycan, the effects on hair health (Tables 3 and 4) are difficult to attribute to any specific substance. Further research is needed to differentiate the specificity and optimal composition of probiotic interventions for various hair-related conditions. The wide range of probiotic options also highlights the challenges in ensuring quality control, while simultaneously showcasing the potential for personalized medicine in skin microbiome. In terms of hair growth, the analysis included both clinical and preclinical studies. The meta-analysis of two clinical studies showed a statistically significant effect of probiotic interventions on hair growth, as measured by hair thickness, and a non-significant increase in hair count parameters. Preclinical studies provided additional support for the positive effects of probiotics on hair health. These studies consistently demonstrated a significant induction of hair follicle count and increased skin thickness and growth factors VEGF following probiotic intervention except for IGF-1 data (Figs. 5 and 6). These findings suggest that probiotics have the potential to promote hair regrowth and improve overall hair and scalp health. However, it is important to consider the limitations of translating findings from animal studies to human populations. Three pathways involving different growth factors could be illustrated in Fig. 8.

4.1. Probiotic intervention across growth and regression phases

In the context of hair follicle regulation of the systematic review, several molecules and genes were identified, each associated with different phases of the hair growth cycle. Among the active growth stage (anagen), various growth factors (VEGF A, VEGF B, IGF-1, IGF1-R, FGF2, FGF7, FGF10, and BMP-2) and hormones (Insulin and Testosterone) were observed to increase and play essential roles in promoting hair follicle proliferation and hair growth with the intervention of probiotic [48,62,64,65]. On the other hand, the catagen phase, representing the regression stage of the hair follicle, showed the downregulation of proteins associated with hair follicle apoptosis and regression with probiotic intervention, such as Transglutaminase 2 (TG2) [48], Versican (VCAN), Vascular Smooth Muscle Cell (VSC), BMP and Activin Membrane-Bound Inhibitor (BAMBI), and Lymphoid Enhancer-Binding Factor 1 (Lef1) [64]. Moreover, the increase of the cytokine Interleukin-4 (IL-4) with probiotics was observed suggesting its potential role in orchestrating hair follicle regression [65].

4.2. Wnt/β-catenin signaling: probiotic modulation of hair follicle development and stem cell activity

During the anagen phase of the hair growth cycle, marker genes like Wnt5a, Wnt5b, and Wnt10b were identified during the anagen phase, indicating their involvement in hair follicle development and maintenance. Wnt5a, Wnt5b, and Wnt10b [64] proteins induced by probiotics are actively involved in regulating hair follicle stem cell activity and promoting hair growth [18,74]. These Wnt proteins initiate the Wnt/β-catenin pathway, which plays a crucial role in the development and maintenance of hair follicles. Activation of the Wnt/β-catenin pathway begins with the binding of Wnt proteins to their cell surface receptors, Frizzled receptors, and coreceptors such as LRP5/6. This binding event triggers a series of intracellular signaling events that ultimately lead to the stabilization and accumulation of β-catenin in the cytoplasm [75]. In the absence of Wnt activation signaling, β-catenin is targeted for degradation by a

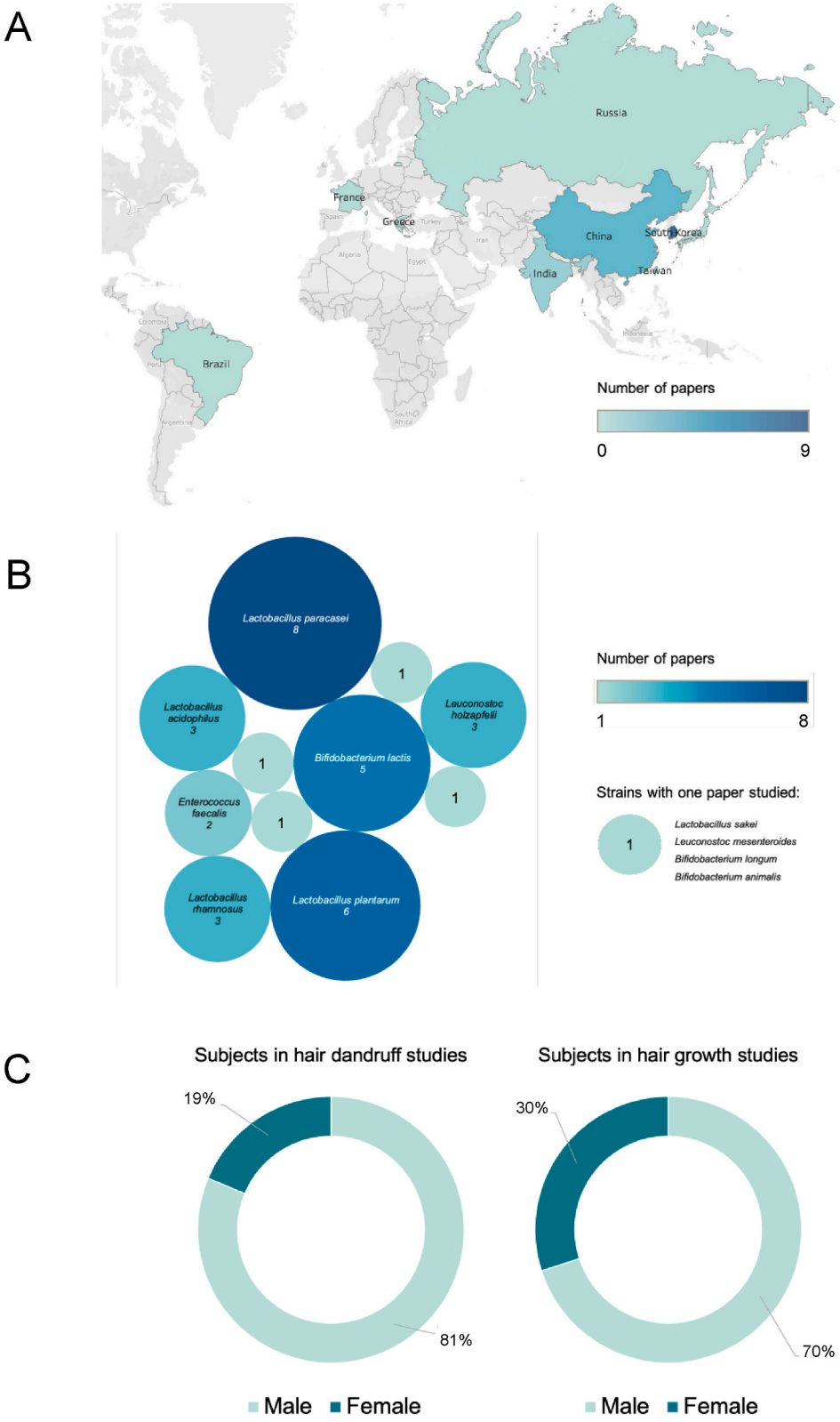

Fig. 2. Summary of data result. A. Number of included papers being conducted in different countries; B. Number of included papers being conducted on each probiotic strain; C. Gender contributions in RCTs.

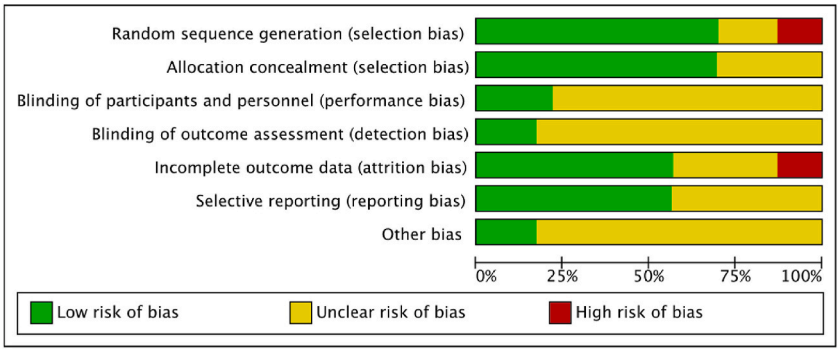

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

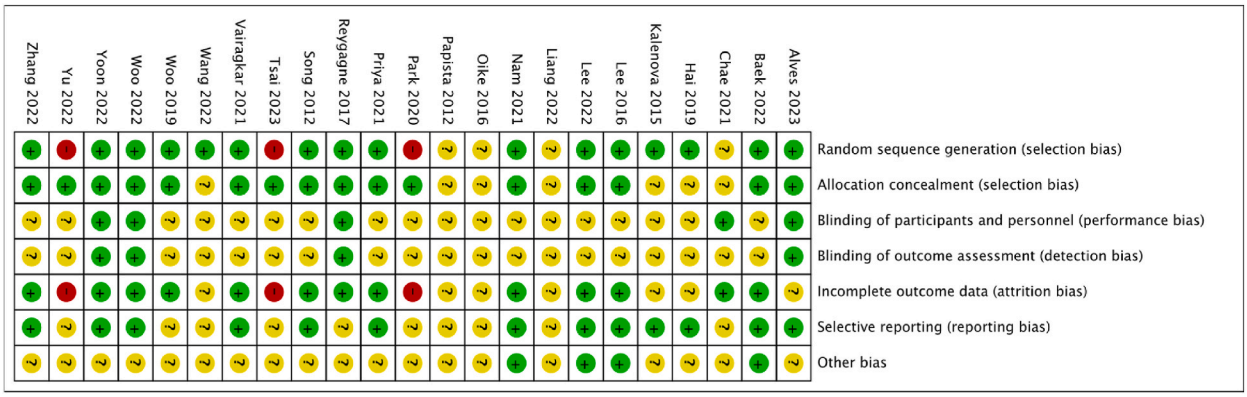

Fig. 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

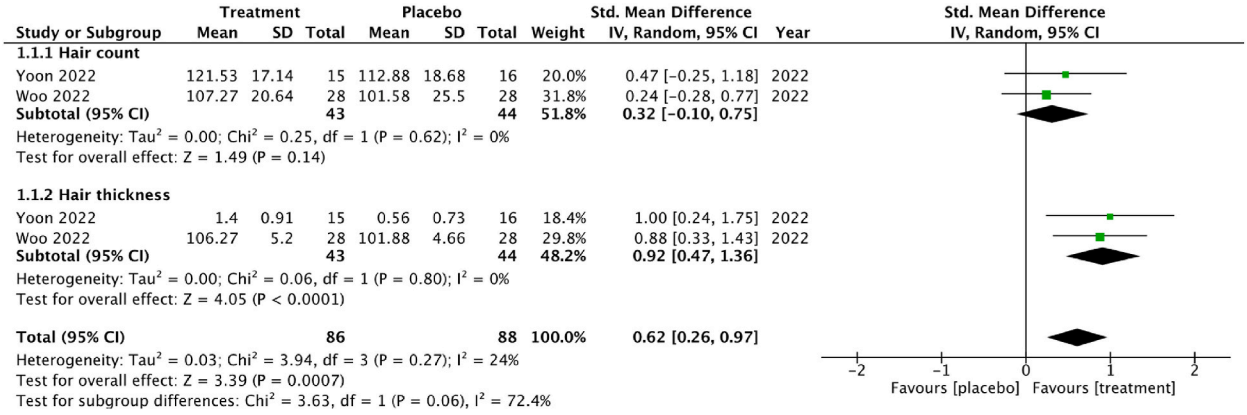

Fig. 5. Forest plot of hair growth in RCT studies.

protein complex called the destruction complex, which includes Axin, Adenomatous polyposis coli (APC), Glycogen synthase kinase-3 beta (GSK-3β), and Casein kinase 1 (CK1) [76]. This complex phosphorylates β-catenin, marking it for ubiquitination and subsequent degradation by the proteasome. However, when the Wnt/β-catenin pathway is activated by the binding of Wnt proteins, it disrupts the activity of the destruction complex [18,74,75]. This disruption prevents the phosphorylation and degradation of β-catenin, allowing it to accumulate in the cytoplasm. Accumulated β-catenin then translocates into the nucleus, where it interacts with transcription factors known as LEF/TCF (lymphoid enhancer-binding factor/T-cell factor) [77]. The binding of β-catenin to LEF/TCF proteins leads to the activation of target genes that are involved in critical cellular processes such as cell proliferation, cell differentiation, and hair follicle growth. The target genes activated by β-catenin-LEF/TCF complex can vary depending on the specific cellular context and the stage of hair follicle development. These genes include cyclin D1 [78], a key regulator of cell cycle progression, as well as other genes involved

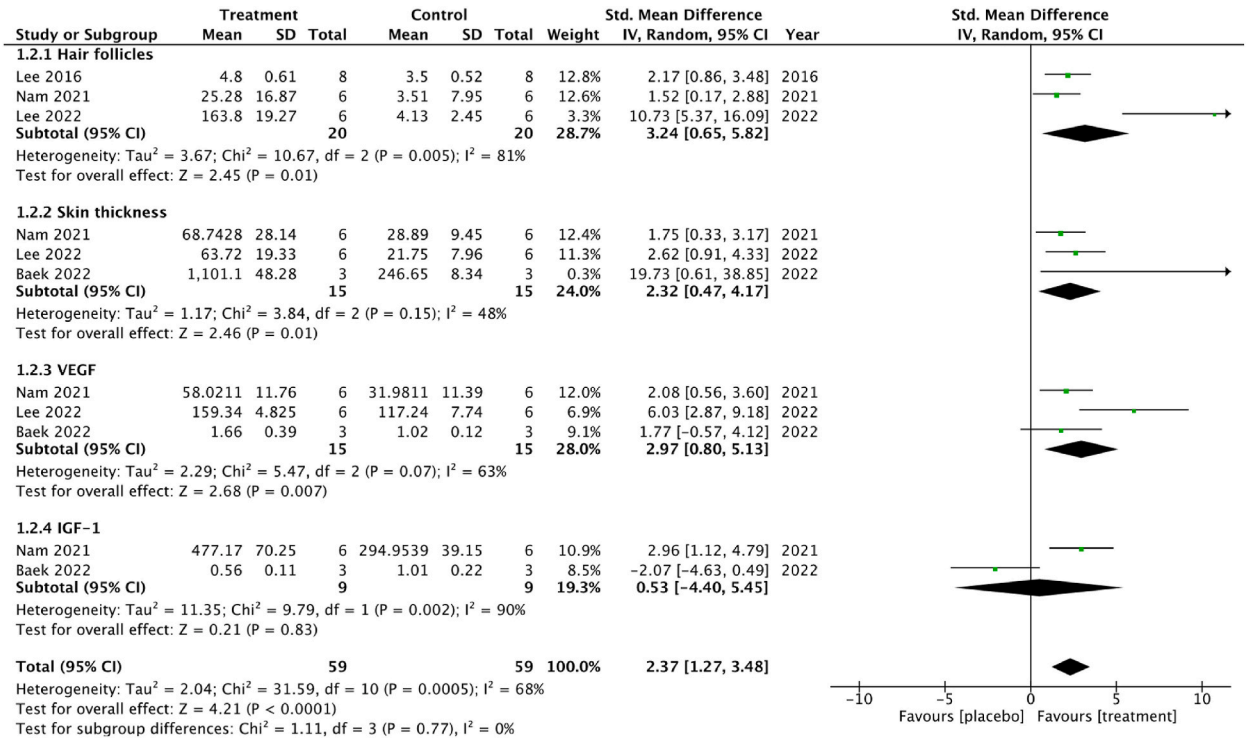

Fig. 6. Forest plot of hair growth in preclinical studies.

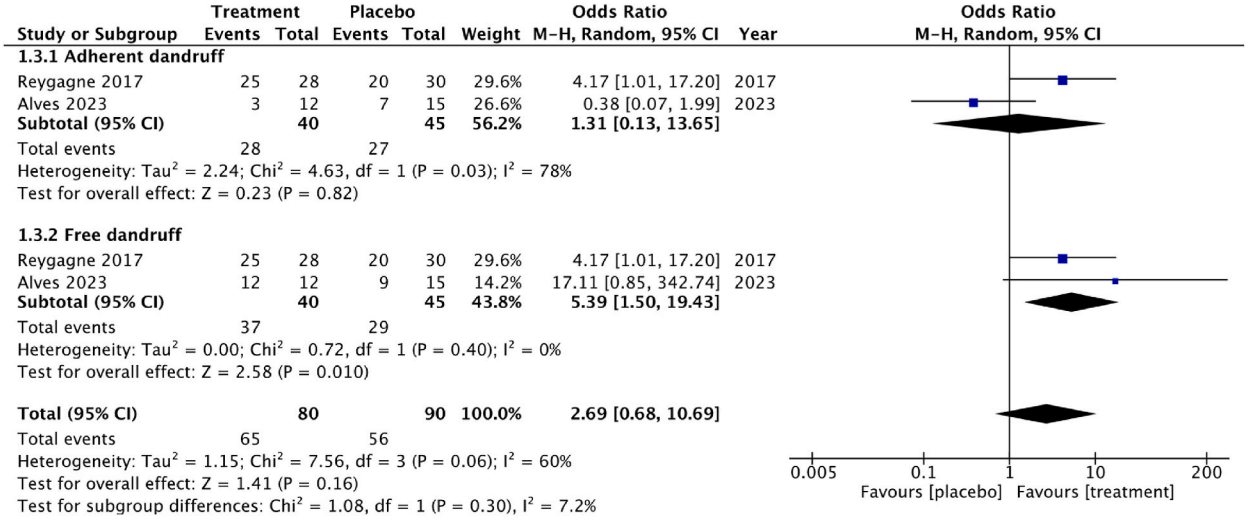

Fig. 7. Forest plot of hair dandruff perception RCTs studies.

in cell adhesion, cell signaling, and hair follicle morphogenesis.

4.3. IGF-1 pathway dynamics in hair growth: probiotic regulation of cellular energy and metabolism

The IGF-1 pathway plays a significant role in hair growth and maintenance, and it can intersect with TOR kinase and AMP kinase to regulate these processes [79]. In the context of hair growth, IGF-1, along with its receptor IGF1-R, is involved in promoting the proliferation, survival, and differentiation of hair follicle cells during the anagen and telogen phases. IGF-1 binds to IGF1-R on the surface of hair follicle cells, initiating a cascade of intracellular signaling events. Downstream of IGF1-R activation, several signaling pathways are activated, including the phosphatidylinositol 3-kinase and protein kinase B (PI3K/Akt) and mitogen-activated protein

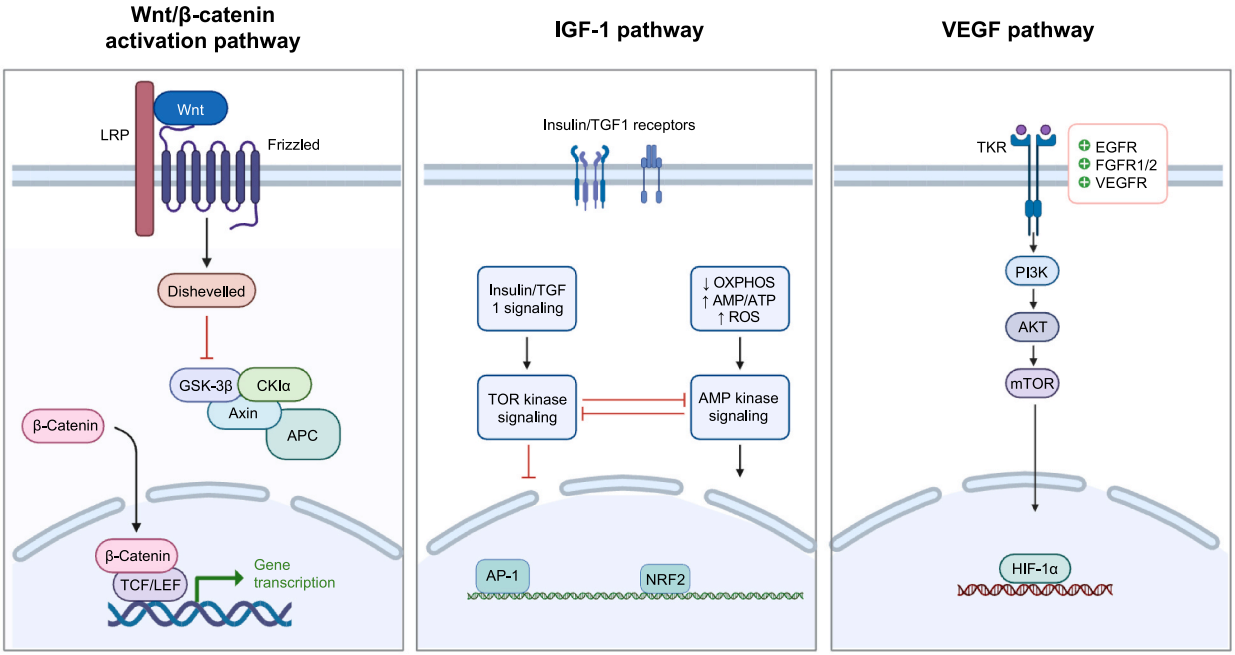

Fig. 8. Molecular diagram of hair growth pathways induced by Probiotics.

kinase and extracellular signal-regulated kinases (MAPK/ERK) pathways [80]. The PI3K/Akt pathway promotes cell survival, growth, and metabolism, while the MAPK/ERK pathway is involved in cell proliferation, differentiation, and survival. TOR kinase, as a central regulator of cellular growth and metabolism, can be influenced by the IGF-1 pathway TOR kinase activation can stimulate protein synthesis, cell cycle progression, and other cellular activities necessary for hair follicle growth [81]. Additionally, AMP kinase [81], a cellular energy sensor, can also interact with the IGF-1 pathway. Activation of AMP kinase can modulate the IGF-1 pathway by regulating cellular energy availability and metabolism. These effects contribute to the overall energy balance and metabolic adaptations necessary for hair follicle growth. activation of the IGF-1 pathway can influence OXPHOS activity, leading to increased ATP production to meet the energy demands of hair follicle growth. The interaction between the IGF-1 pathway, TOR kinase, and AMP kinase affects the AMP/ATP ratio, modulating energy balance and resource allocation [82]. Additionally, the impact of the IGF-1 pathway on Reactive oxygen species (ROS) levels may be context-dependent, involving a balance between ROS signaling and oxidative stress [83]. These interconnected processes collectively contribute to the regulation of hair follicle growth and maintenance in response to energy availability and cellular redox status.

4.4. VEGF isoforms and hair growth: probiotic modulation for angiogenesis and blood supply

During the anagen and telogen phases of the hair growth cycle, VEGF (Vascular Endothelial Growth Factor) isoforms, specifically VEGF-A and VEGF-B, play a crucial role in angiogenesis and maintaining the blood supply to the hair follicles [47,84]. VEGF promotes the formation of new blood vessels, ensuring an adequate blood flow to support the needs of the hair follicles. The VEGF pathway involves the binding of VEGF to its receptors, VEGFR1 (Vascular Endothelial Growth Factor Receptor 1) and VEGFR2 (Vascular Endothelial Growth Factor Receptor 2), located on endothelial cells of blood vessels [84]. Upon binding, the receptors initiate signaling cascades that activate several downstream molecules, including TKR (Tyrosine Kinase Receptor), PI3K, AKT, and mTOR (Mammalian Target of Rapamycin) [85]. The activation of TKR leads to the recruitment and activation of PI3K. PI3K, in turn, generates the activation of AKT. Activated AKT promotes cell survival, proliferation, and growth by modulating various cellular processes, including protein synthesis, cell cycle progression, and metabolism. Furthermore, the activation of AKT can also lead to the activation of mTOR, a key regulator of cell growth and metabolism [86]. Upon activation by the VEGF pathway and other signaling inputs, mTOR can modulate the activity of transcription factors, such as HIF-1α (hypoxia-inducible factor 1-alpha) [87], which can translocate to the nucleus and regulate the expression of specific target genes. HIF-1α is involved in the cellular response to low oxygen levels (hypoxia) and is known to regulate genes related to angiogenesis, metabolism, and cell survival. This cascade of molecular events promotes blood vessel growth, vascular permeability, and nutrient supply to the hair follicles during the anagen and telogen phases, ensuring an optimal environment for hair growth and maintenance.

4.5. Probiotics for dandruff: metabolic benefits and microbiota insights

Regarding the effect of probiotics on dandruff control, the meta-analysis of two clinical studies suggested an improvement in

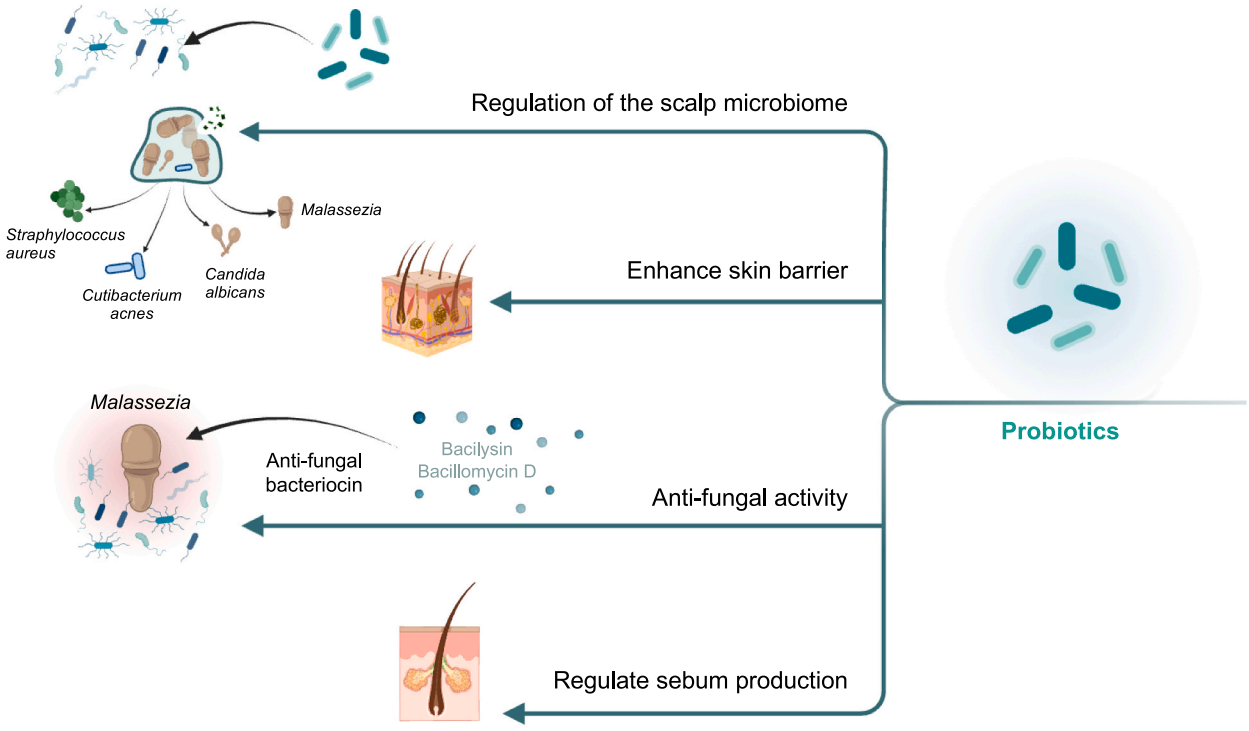

Fig. 9. Dandruff control pathways through probiotics.

scaling perception (adherent dandruff) non-significantly and cleaning perception (free dandruff) significantly in favor of the probiotic intervention (Fig. 7). These findings suggest that probiotics play a beneficial role in reducing dandruff symptoms and promoting a healthier scalp environment. Yu's 2022 study [50] revealed that probiotic supplementation over 12 weeks improved glucose and lipid profiles, suggesting potential metabolic benefits. Liang's 2022 study [54] reported changes in intestinal microbiota following TCI999 consumption, linking gut health to hair-related outcomes. Additionally, Woo and Tsai's studies [47,49] evaluated adverse events and scalp microbial species changes, providing insights into intervention safety and potential microbial effects. These findings present an exciting opportunity to explore the gut-hair axis and the potential role of probiotics in regulating scalp health and hair-related parameters. Further research in this area could lead to innovative therapeutic approaches for dandruff control, scalp health improvement, and hair growth promotion through the modulation of the gut microbiota.

4.6. Multi-pathway approach to dandruff control and scalp health by probiotics

The control of hair dandruff through probiotics may involve multiple pathways that target the underlying causes of the condition (Fig. 9). One such pathway is the modulation of the skin microbiome. The scalp harbors a diverse microbial community, and an imbalance in this ecosystem can contribute to dandruff development [88]. Probiotics, including specific strains of bacteria and fungi, have been found to restore microbial balance by inhibiting the growth of dandruff-causing fungi such as *Malassezia* [11,49,66,68]. These beneficial microorganisms produce antimicrobial peptides [89,90] and metabolites [66] that create an unfavorable environment for the growth and proliferation of dandruff-causing pathogens. Another pathway involves strengthening the skin's natural barrier function. Probiotics have been shown to enhance the production of ceramides, which are lipids that play a crucial role in maintaining the scalp's moisture balance on the skin [49,91,92]. This helps prevent dryness, flaking, and itching associated with dandruff. By improving the integrity of the skin barrier, probiotics contribute to the overall health of the scalp and reduce the occurrence of dandruff. Furthermore, probiotics can modulate the immune response, regulating the excessive production of sebum, a common factor associated with dandruff [1]. Excessive sebum production can create an environment conducive to the growth of dandruff-causing microorganisms. Probiotics have been found to reduce inflammation and rebalance sebum production, leading to a healthier scalp environment and decreased dandruff symptoms [93]. In addition to their regulatory effects on the scalp microbiome, barrier function, and immune response, probiotics produce antimicrobial compounds that display antagonistic activity against dandruff-causing pathogens. These compounds, such as bacilysin and bacillomycin D [58], inhibit the growth of *Malassezia* species biofilm [49] and contribute to the control of dandruff. By targeting these pathways, probiotics offer a promising avenue for the development of effective and sustainable treatments for hair dandruff. The ability of probiotics to restore microbial balance, enhance skin barrier function,

regulate sebum production, and produce antimicrobial compounds collectively contribute to their efficacy in controlling dandruff. However, further research is needed to optimize probiotic strains, dosages, and formulations for maximum effectiveness.

5. Limitations of study

Several limitations of this systematic review and meta-analysis should be acknowledged. Firstly, the included studies varied in terms of study design, probiotic strains used, intervention duration, and outcome measures assessed. This heterogeneity may introduce potential biases and limit the generalizability of the results. Additionally, the sample sizes and numbers of the included clinical studies were relatively small, which could impact the statistical power and precision of the findings. Furthermore, the quality assessment revealed a high risk of bias in one study due to incomplete outcome data, suggesting a need for further improvement in the reporting of study results.

Another limitation is the potential for publication bias, as the analysis relied on published studies and such studies as with negative results may have not been published. Moreover, the majority of the included studies were conducted in Korea, with only one study from Europe and one from South America. This geographical limitation raises the question of the generalizability of the findings to other populations and regions. Lastly, acknowledging the study limitation in the scarcity of papers compared to other systematic reviews, it highlights the recent surge of interest in probiotic-related studies in hair growth and dandruff, notably with the earliest identified paper dating back to 2012.

6. Conclusions

In conclusion, this systematic review and meta-analysis provide evidence supporting the potential benefits of probiotics in improving hair health, specifically in terms of dandruff control and hair growth. However, the heterogeneity among the included studies, limited sample sizes, potential publication bias, and geographical limitations should be considered when interpreting the results. Future well-designed studies including both clinical and preclinical approaches with larger sample sizes and standardized outcome measures are warranted to further investigate the effects of probiotics on hair health and to gain a better understanding of the underlying mechanisms.

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Institutional review board statement

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Informed consent statement

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Data availability statement

The data presented in this study are available in this paper.

CRediT authorship contribution statement

Chang-Shik Yin: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Trang Thi Minh Nguyen:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Eun-Ji Yi:** Resources, Methodology, Formal analysis, Data curation. **Shengdao Zheng:** Resources, Methodology, Formal analysis, Data curation. **Arce Defeo Bellere:** Software, Investigation. **Qiwen Zheng:** Visualization, Investigation, Formal analysis. **Xiangji Jin:** Visualization, Investigation, Formal analysis. **Myeongju Kim:** Visualization, Investigation. **Sejic Park:** Visualization, Investigation. **Sarang Oh:** Writing – review & editing, Resources, Data curation. **Tae-Hoo Yi:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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