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RESEARCH

Lacticaseibacillus Paracasei CCFM1350 Demonstrates Potentials in Hair Growth and Treating Alopecia in Mice

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Abstract
Alopecia, a prevalent condition characterized by patterned or complete hair loss, significantly impacts quality of life. Effective treatments require modulation of underlying biological pathways rather than addressing superficial damage to skin or hair follicles. This study investigates *Lacticaseibacillus paracasei* CCFM1350 live bacteria as a potential intervention for promoting hair growth and treating alopecia. Through a series of animal experiments and biochemical assays, we demonstrate that CCFM1350 live bacteria significantly enhance hair growth via the Wnt/β-catenin signaling pathway. Specifically, the administration of CCFM1350 resulted in a 3.464-fold increase in hair growth compared to the control group. This effect was associated with a 243% increase in Wnt10b expression and a 35.56% increase in β-catenin expression. Additionally, significant alterations in the gut microbiota were observed in the CCFM1350-treated group, including changes in the abundance of Verrucomicrobia and Bacteroidetes at the phylum level and *Akkermansia* at the genus level. These findings suggest that *L. paracasei* CCFM1350 could serve as a viable probiotic treatment for alopecia, providing a natural alternative to conventional drugs like Finasteride.

Keywords Alopecia · Probiotics · Lacticaseibacillus paracasei · Wnt/β-cateinin pathway · Hair growth

Introduction

Alopecia encompasses various forms of hair loss disorders such as Alopecia areata (AA), Androgenic alopecia (AGA), and Telogen effluvium (TE). These conditions can result from genetic predispositions, autoimmune disorders, psychological stress, and nutritional deficiencies [1]. The involvement of diverse genetic loci in these diseases offers therapeutic potential for targeting specific hair loss pathways, as many loci present promising targets for pharmacological regulation. Heilmann et al. identified twelve distinct risk loci, including two within the Wnt family [2]. In Alopecia Areata (AA), hair follicles normally function as immune-privileged sites, preventing immune system activation against them. Within this protected microenvironment, autoimmune reactions are suppressed and immune cell infiltration is inhibited. Consequently, autoimmune disorders causing aberrant interleukin expression and dysregulation of CD4 + and CD8 + T-cells can induce hair loss through distinct mechanisms [3, 4]. Androgenic alopecia (AGA) primarily caused by 5α-reductase type II-induced hair follicle miniaturization, is not significantly affected by autoimmune disorders. In contrast, Telogen effluvium (TE) can be triggered by abnormal immune cell activity. Therefore, despite differences in pathogenesis, these subtypes share common pathways and symptoms. Hair follicle development occurs in three phases: anagen (growth), catagen (regression), and telogen (rest) [5]. The anagen phase is critical for hair growth and is the primary focus for alopecic treatment [5, 6] and Wnt10 in the Wnt family is one of the most important gene that regulate hair growth. The cell apoptosis pathway

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was mostly regulated during catagen. Dermal papilla cell plays a pivotal role in hair follicle development and are regulated by key cell proliferation and differentiation pathways during these phases [7].

Various treatment strategies have been explored for alopecia. FDA-approved drugs like Finasteride have been developed to address hair loss; however, they can cause adverse effects even at prescribed dosages [8, 9]. Plant extract have also been investigated due to their natural origin and lower likelihood of causing adverse events. Studies have shown that Annurca Apple Extract and *Cacumen platyclade* (the dried branch and leaf of *Platycladus orientalis*can) promote hair growth. Although more effective in comparison to Finasteride, Cacumen platyclade extract showed greater effectiveness in promoting hair growth, though only at higher concentrations [10, 11]. Coffee bean residue extract also indicated a higher relative cell vitality and a higher ATP production compared to Minoxidil, and determined to be effective in regulating hair follicle development through multiple signaling pathways [12]. These natural products offer promising alternatives for alopecia treatment.

Probiotics have emerged as another potential treatment for alopecia due to their beneficial effects on health without significant adverse reactions. Previous studies have shown that certain lactobacilli strains can promote hair growth. For instance, *L. curvatus* have been reported to enhance hair regeneration in mice [13], and various bacteria from Kimchi and Cheonggukjang could promote hair growth and reverse hair loss without associated adverse effects such as diarrhea [14]. *Lacticaseibacillus paracasei*, previously known as *Lactobacillus paracasei*, have been reported to treat hair regrowth disorders by increasing VEGF and IGF-1 levels [15]. Additionally, biotransformation of *Cacumen platyclade* with specific strains of *Lactiplantibacillus plantarum* has shown effectiveness in treating alopecia. The combination of probiotics and bioactive plant extracts demonstrates therapeutic potential for alopecia, mediated by metabolites generated during fermentation [16]. This study aims to evaluate the effects of *L. paracasei* CCFM1350 on hair coverage in mice by examining the gene expression and protein concentrations related to hair development signaling pathways.

The Wnt/β-catenin signaling pathway is an important signaling pathway that regulates cell differentiation, development, and proliferation. Many previous studies regarding hair regeneration include regulating gene expressions and proteins on this pathway to promote hair growth, and the results aligns with the findings in this study. The binding of Wnt ligands to Frizzled receptor (Fzd) and LRP5/6 co-receptors at the upper stream forms a complex involving β-catenin, Axin, APC, and GSK3, leading to β-catenin accumulation in cells. During activation, the β-catenin was not decomposed by phosphorylation inhibitors like TLE in binding to LEF/TCF, forming a transcriptional complex that stimulates target gene transcription, promoting cell growth, differentiation, and skin tissue restoration. Conversely, pathway inactivation leads to β-catenin phosphorylation and proteasomal degradation, while the LEF/TCF complex recruits transcriptional repressors to block downstream gene expression [17–19]. Among Wnt-related hair loss genes, Wnt10b is a pivotal regulator of the Wnt/β-catenin signaling cascade and consequently modulates the hair follicle cycle [20].

Materials and Methods

Chemicals and Reagents

Primers for RT-qPCR were obtained from Sangon Biotech (Shanghai, China). Kits for RNA extraction, reverse transcription, and fluorescent quantification were purchased from Vazyme (Nanjing, China). ELISA kits for β-catenin, Ki67, VEGF, TGF-β1, and IGF-1 concentration were sourced from Senbeijia Biotechnology (Nanjing, China); Finasteride (Fin) was procured from Shanghai Macklin Biochemical (Shanghai, China). All other chemicals were purchased from Sinopharm Chemical Reagent (Shanghai, China), unless otherwise specified.

Probiotic and Postbiotic Bacteria Samples

L. paracasei CCFM1350 was sourced from the Culture Collection of Food Microorganisms of Jiangnan University. The strain was activated and then inoculated at 2% v/v into liquid MRS (de Man, Rogosa and Sharpe) medium, where it was cultured for 18 h at 37°C, resulting in a viable count of 5×10^9 CFU/mL. The culture was centrifuged at 8000r/min for 20 min at 4°C, and the bacteria pellet was washed twice with sterilized 0.85% saline twice and stored at 4°C for subsequent experiments. For the postbiotic group, the bacteria were inactivated by thermal treatment at 65°C for 30 min.

Animal Experiment

Hair Loss Mice Model Establishment

Twenty-four C57BL/6J mice (male, aged 6 weeks, body weight 20±2 g) were obtained from Vital River (Beijing, China). This study adhered to Directive 2010/63/EU and was approved by the Ethics Committee of Jiangnan University, China (JN.No.20230415c1440605). After a one-week acclimatization period, the dorsal hair of the mice was

shaved using an electrical clipper (Codos, Wuxi, China), followed by the application of hair removal cream (Veet, Shanghai, China) to ensure complete hair removal. The pink coloration of the skin indicated that the hair had entered the telogen phase.

Trial Grouping

The mice were divided into four groups as outlined in Table 1. The control group received 0.85% saline, while the positive control group received 10 mg/Kg of Finasteride. The live bacteria group received 0.2mL of CCFM1350 live bacteria at a concentration of 5×10^9 CFU/mL. The dead bacteria group received CCFM1350 postbiotics at 500 mg/Kg in MRS medium, prepared as described in Sect. 2.2. Each group received a daily administration of 0.2 mL for 21 days. The administration concentration was referred to Tang et al.'s study [16].

Immunohistochemistry

To observe morphological changes in hair follicles, mice were sacrificed on day 21, and dorsal skin samples were fixed in 4% (v/v) formaldehyde, embedded in paraffin, sectioned into 5 µm thick and stained with Hematoxylin-eosin stain (Servicebio, Wuhan, China). The stained sections were examined using CaseViewer 2.4 (Fig. 1c).

Biochemical Assays

Post-sacrifice, 30 mg of the mice dorsal skin was homogenized in 270 µL of PBS, and the supernatant was collected after of centrifuge at 3000 g for 20 min. Fecal samples were collected before sacrifice and both skin and fecal samples were stored at −80℃ for further analysis.

Protein Concentration Measurement Via ELISA

The concentrations of β-catenin, VEGF, TGF-β1, Ki67, and IGF-1 in skin samples were measured using ELISA kits according to the manufacturer's instruction.

Table 1 Trial grouping and administration

Groups	Abbreviations	Administration
Blank control	Control	0.85% saline
Positive control	Fin	10 mg/kg finasteride
CCFM 1350 live bacteria	1350-L	1×10^9 CFU/mL CCFM 1350 (live bacteria)
CCFM 1350 postbiotics	1350-D	500 mg/kg CCFM 1350 self-fermented in MRS medium, inactivated

Real-Time Quantitative qPCR Analysis

RNA was extracted from skin samples using Trizol and reverse-transcribed into cDNA using a reverse transcription kit. mRNA expression levels of Wnt5a, Wnt10b, Bcl-2, BAX, and IGF-1 were quantified by RT-qPCR) using the ChamQ Universal SYBR qPCR Master Mix on a Bio-Rad system (1708882). Primer sequences are listed in Table 2.

DNA Sequencing for Microbiota

DNA from fecal samples was extracted using the FastDNA Spin Kit for Feces (Mp Biomedical, CA, USA), amplified by PCR targeting the V3-V4 region of the 16 S rRNA gene, purified via agarose gel electrophoresis, quantified using Nanodrop and Qubit assays, and sequenced on an Illumina MiSeq platform [21]. Sequencing in this study was performed by Majorbio (Shanghai, China).

Data Analysis

Biochemical assay data were analyzed using GraphPad Prism 9.0 and presented as mean ± standard deviation. Statistical significance was determined by one-way ANOVA with $P < 0.05$. Microbiota analysis followed QIIME2 protocols for 16 S rRNA gene sequencing as described by Hall et al. [22].

Results

Effects of *L. Paracasei* CCFM1350 on Hair Growth in Mice

The initiation of the anagen phase was marked by the emergence of new hair on the shaved skin of mice. Hair growth was monitored and recorded on the 7th, 14th, and 21 st days post-administration. Photographs were taken under anesthesia to ensure consistent imaging conditions. On the 21 st day, hair coverage percentages were quantified using ImageJ software. The CCFM1350 dead bacteria group (1350-D) showed negligible differences compared to the control group. However, the CCFM1350 live bacteria group (1350-L) demonstrated a substantial increase in hair coverage, averaging 70.51% which is a 3.464-fold increase compared to the control group ($p<0.0001$). This increase surpassed that of the positive control group (Finasteride), which showed a 68.3% hair coverage, a 3.25-fold increase over the control group (Fig. 1a and b).

Histological analysis of dorsal skin sections demonstrated significant differences in hair follicle development

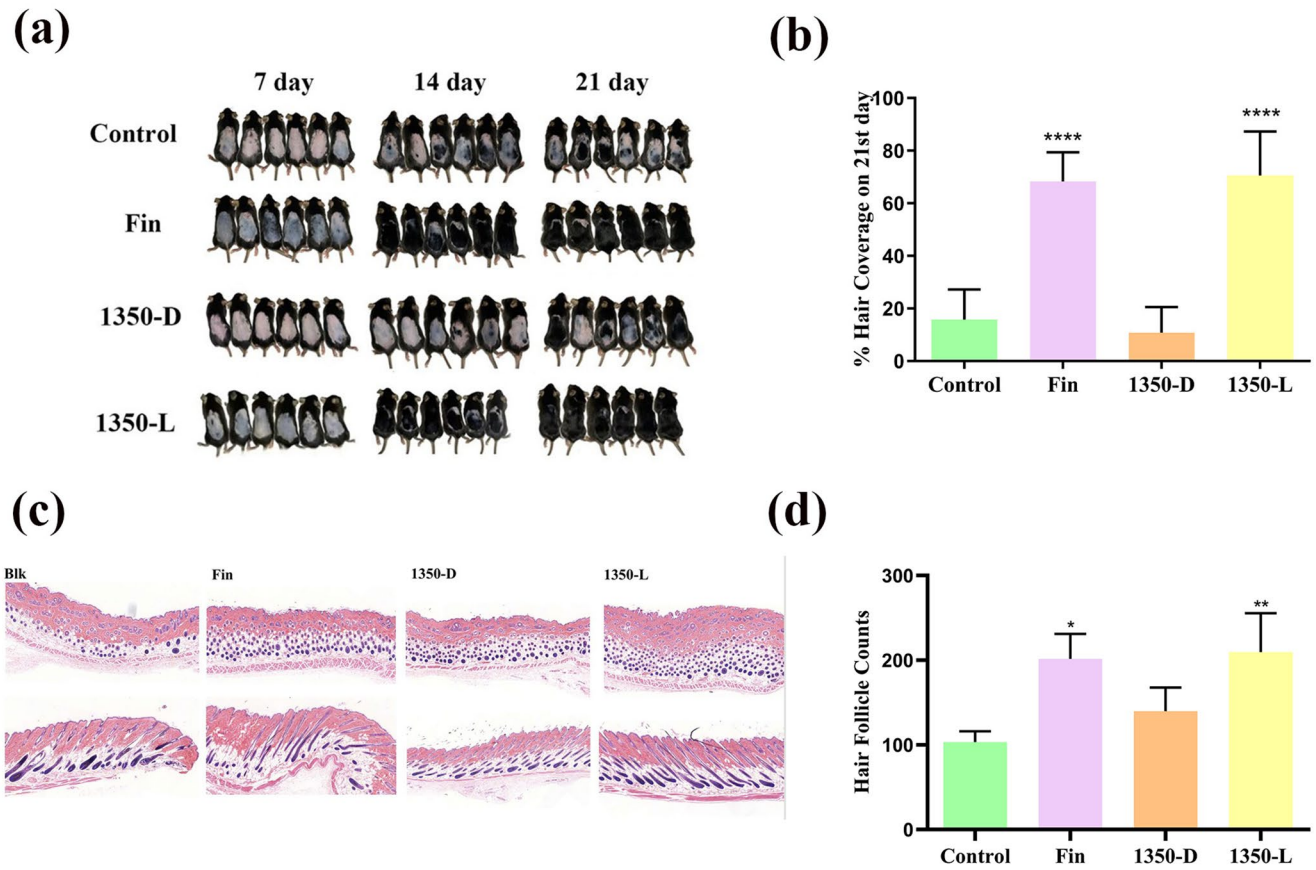

Fig. 1 Effect of *L. paracasei* CCFM1350 intervention on the hair conditions of mice. (**a**) Hair growth on the back of mice on the 7th, 14th, and 21 st day. (**b**) Hair coverage on the 21 st day. (**c**) Horizontal (top) and vertical (bottom) paraffin sections of the mice dorsal skin. (d) Hair follicle counts on the 21 st day. ****, $p<0.0001$; **, $p<0.01$; *, $p<0.05$. The data are shown as the mean ± SD ($n=6$)

across the groups (Fig. 1c). Both the Finasteride ($p<0.05$) and 1350-L groups ($p<0.01$) exhibited significantly higher hair follicle counts compared to the control group, with the 1350-L group showing a 2.03-fold increase in follicle density.

Table 2 Primers used in the study for the reverse transcription

Primer	Sequence(5'−3')
GADPH	F: AGGTCGGTGTGAACGGATTTG
	R: TGTAGACCATGTAGTTGAGGTCA
Wnt5α	F: CAACTGGCAGGACTTTCTCAA
	R: CCTTCTCCAATGTACTGCATGTG
Wnt10b	F: GCGGGTCTCCTGTTCTTGG
	R: CCGGGAAGTTTAAGGCCCAG
LEF1	F: TGTTTATCCCATCACGGGTGG
	R: CATGGAAGTGTCGCCTGACAG
Bcl-2	F: GTCGCTACCGTCGTGACTTC
	R: CAGACATGCACCTACCCAGC
BAX	F: TGAAGACAGGGGCCTTTTTG
	R: AATTCGCCGGAGACACTCG
IGF-1	F: GCTCTTCAGTTCGTGTGTGGA
	R: GCCTCCTTAGATCACAGCTCC

Effects of CCFM1350 Probiotic and Postbiotic on the Wnt/β-catenin Pathway

The result of β-catenin/Wnt pathway related expressions are indicated in Fig. 2. The Wnt protein family (Wnt5a and Wnt10b), β-Catenin, and LEF1 play crucial roles in regulating hair growth via the Wnt/β-catenin signaling pathway. RT-qPCR revealed that Wnt10b expression in the 1350-L group increased by 3.43-fold ($p<0.001$), while Wnt5a expression was downregulated in both the 1350-L and 1350-D groups. β-catenin concentration measured using ELISA, showed a 35.56% in 1350-L group ($p<0.01$). LEF1 mRNA expression did not exhibit significant changes compared to the control group.

Effects of CCFM1350 on Cell Apoptosis Pathway and Growth Factors

Apoptosis is a key regulatory pathway for cell death during the catagen phase in hair growth disorders. Immunohistochemical analysis revealed that Ki67, a proliferation

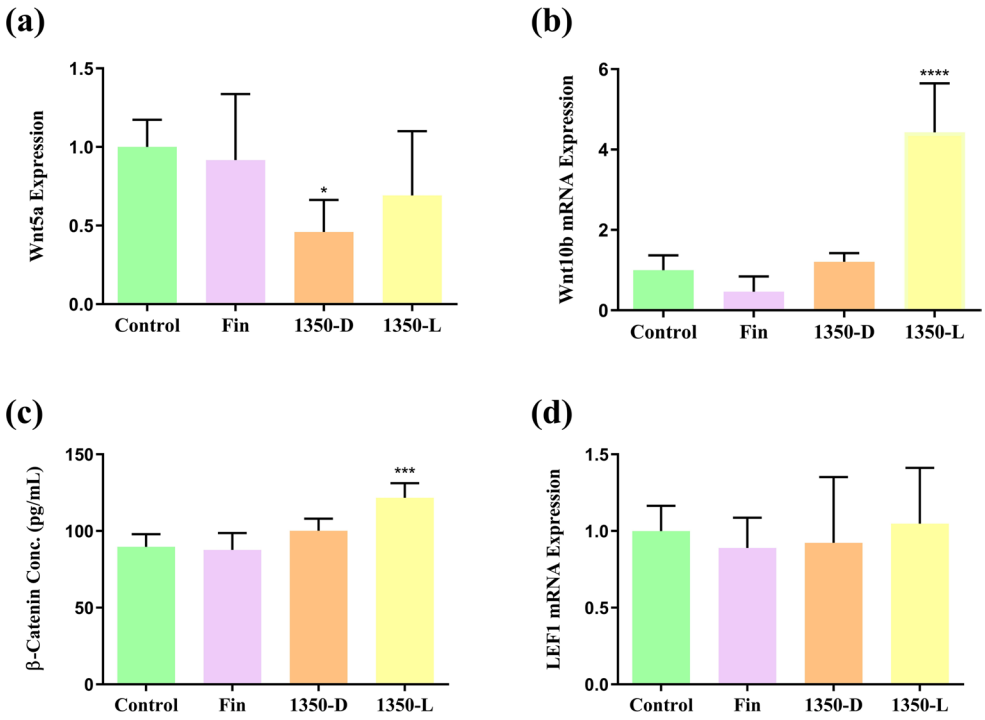

Fig. 2 Effect of *L. paracasei* CCFM1350 intervention on the expressions of related genes in the Wnt/β-catenin pathway. (**a**) Wnt5a expression. (**b**) Wnt10b expression. (**c**) β-catenin concentration. (**d**) LEF 1 expression. ****, $p<0.0001$; **, $p<0.01$; *, $p<0.05$. The data are shown as the mean ± SD ($n=6$)

marker, showed an 18.36% in the 1350-D group ($p<0.05$) and a 13.61% increase in the 1350-L group (Fig. 3a), though the latter was not statistically significant. We also examined expression patterns of apoptosis-related markers: Bcl-2 (an apoptosis suppressor) and BAX (an apoptosis promotor). BAX mRNA expression decreased by 59.2% in the Finasteride group and by 41.1% in the 1350-D group, while Bcl-2 expression remained unchanged (Fig. 3b and c).

Other growth factors such as VEGF and IGF-1, which regulate hair follicle development via the PI3K-AKT signaling pathway, were also analyzed. VEGF expression increased by 11.8% in the 1350-D group and by 10.6% in the 1350-L group (Fig. 3d), though these changes were not statistically significant. IGF-1 levels, both mRNA and protein concentrations, showed no significant changes in either treatment group (Fig. 3e and f). TGF-β1, which inhibits hair follicle development via the Hedgehog pathway, showed a slight increase in concentration (7.68% in the 1350-D group and 1.37% in the 1350-L group), but TGF-β2 mRNA expression did not change significantly (Fig. 3g and h).

Overall, while CCFM1350 live bacteria exhibited significant effects on hair growth through the Wnt/β-catenin pathway, its impact on cell apoptosis markers and other growth factors was limited.

Effect of CCFM1350 Administrations on Intestinal Microbiota

The sequencing results indicate significant alteration in the gut microbiota following the administration of both live and inactivated *L. paracasei* CCFM1350, with the 1350-D group showing more pronounced deviations. The α-diversity indices (Fig. 4a and b) and β-diversity indices (Fig. 4c and d) reveal that the microbial environment of the 1350-D group underwent substantial changes post-administration, while the 1350-L group also exhibited increased diversity. The relative abundance at both phylum and genus levels, presented as percentage stacked bar charts (Fig. 5a and b), demonstrates shifts in microbiota composition. At the phylum level, inactivated CCFM1350 increased the abundance of Firmicutes and decreased Bacteroides, whereas live bacteria enhanced Verrucomicrobia and reduced Bacteroides. At the genus level, the 1350-D group elevated Lactobacillus and decreased an unknown genus of Muribaculaceae. The correlation analysis between biomarkers and bacterial genera, illustrated in a heatmap (Fig. 5c), highlights positive correlations between key biomarkers (Wnt10b and β-catenin) and specific genera such as *Clostridium* sensu stricto 1, *Lactobacillus*, *Candidatus Saccharimonas*, and *Lacnoclostridium*. Among these, *Clostridium sensu* stricto 1 exhibited strong positive correlation with Wnt10b and β-catenin.

Discussion

L. paracasei CCFM1350 modulates multiple biomarkers across key signaling pathways involved in hair regeneration and alopecia treatment. Our findings demonstrate that live CCFM1350 bacteria significantly enhance hair growth through Wnt/β-catenin pathway activation, exhibiting

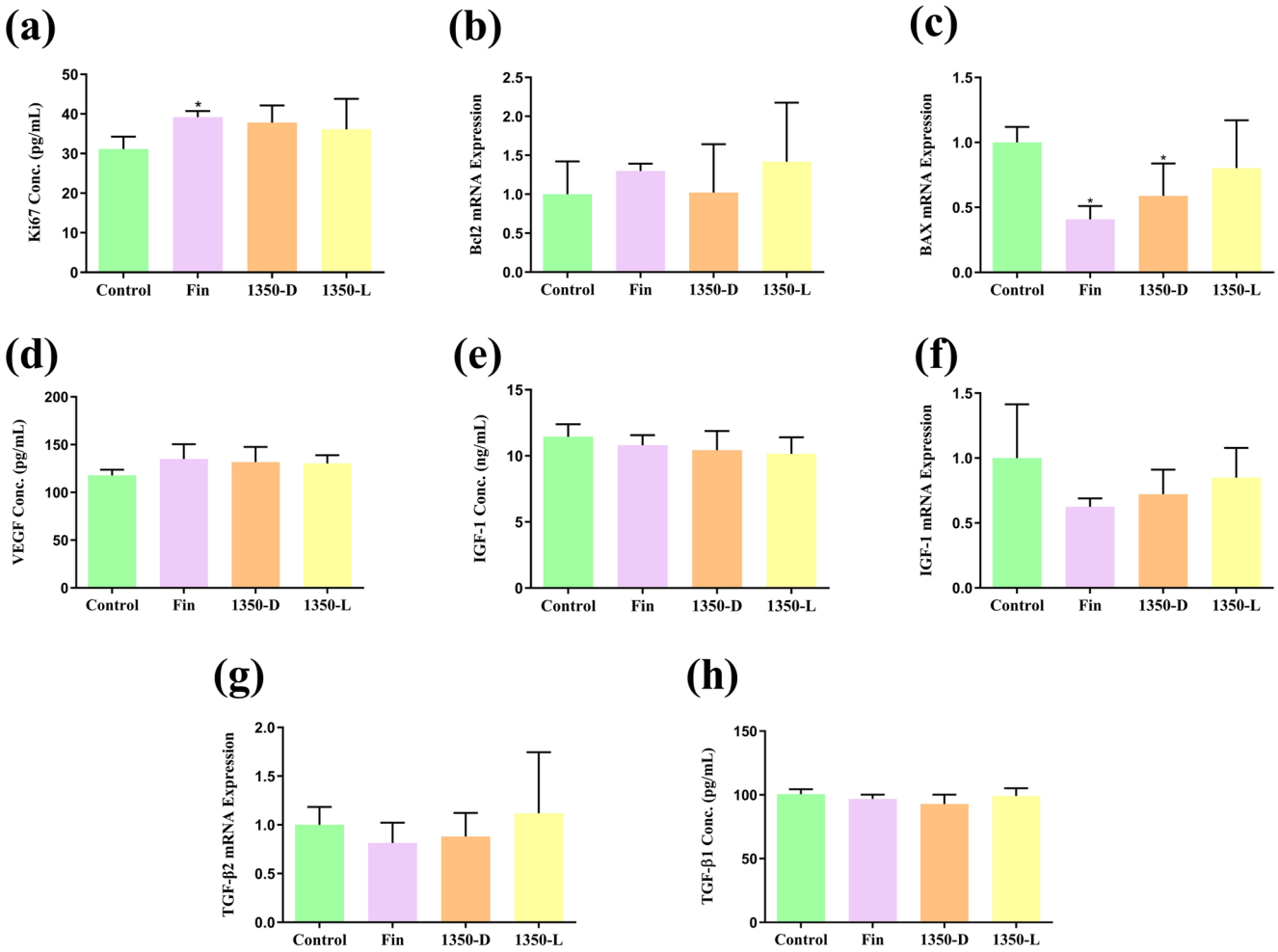

Fig. 3 Effect of *L. paracasei* CCFM1350 intervention on the biochemical index in cell apoptosis pathway and various growth factors in the PI3K-Akt and Hedgehog signaling pathway. (**a**) Ki67 concentration. (**b**) Bcl-2 mRNA expression. (**c**) BAX mRNA expression. (**d**) VEGF concentration. (**e**) IGF-1 concentration. (**f**) IGF-1 mRNA concentration. (**g**) TGF-β2 mRNA expression. (**h**) TGF-β1 concentration. *, $p<0.05$. The data are shown as the mean ± SD ($n=6$)

superior efficacy to Finasteride (the positive control) in mice models. Finasteride, an FDA-approved treatment for androgenic alopecia, acts by inhibiting type II 5α-reducatase and suppressing dihydrotestosterone production via testosterone dehydrogenation [8]. As the current gold standard for alopecia treatment, finasteride serves as a benchmark comparator in studies [23]. Notably, CCFM1350 live bacteria showed more effective than Finasteride in the mice hair loss model.

The Wnt/β-catenin pathway is crucial for cell differentiation, development, and proliferation. Previous studies by Fu et al. and Song et al. have reported similar hair growth-promoting effects through Wnt10b and β-catenin mRNA using plant extract [11, 13]. The 1350-L group showed significant upregulation of Wnt10b mRNA and β-catenin protein expression, facilitating hair growth. In contrast, Finasteride did not affect these specific pathway markers, consistent with previous studies. Thus, live CCFM1350 bacteria enhance hair growth through the Wnt/β-catenin pathway by increasing Wnt10b and β-catenin expression.

CCFM1350 live bacteria treatment showed no significant regulatory effects on biomarkers associated with the apoptotic pathway, which plays a crucial role in hair follicle cycling through characteristic morphological shrinkage during programmed cell death [24]. While Ki67 serves as a well-established proliferation marker for assessing cellular regeneration [25], neither live nor inactivated bacteria significantly influenced its expression levels. In the intrinsic apoptosis pathway, Bcl-2 functions as an anti-apoptotic regulator whereas BAX acts as a pro-apoptotic effector [26]. Previous study demonstrates that Finasteride administration differentially modulates these markers across tissues-upregulating BAX while downregulating Bcl-2 in hepatic and serum, but exhibiting paradoxical effects in cutaneous tissue (BAX downregulation with Bcl-2 upregulation)

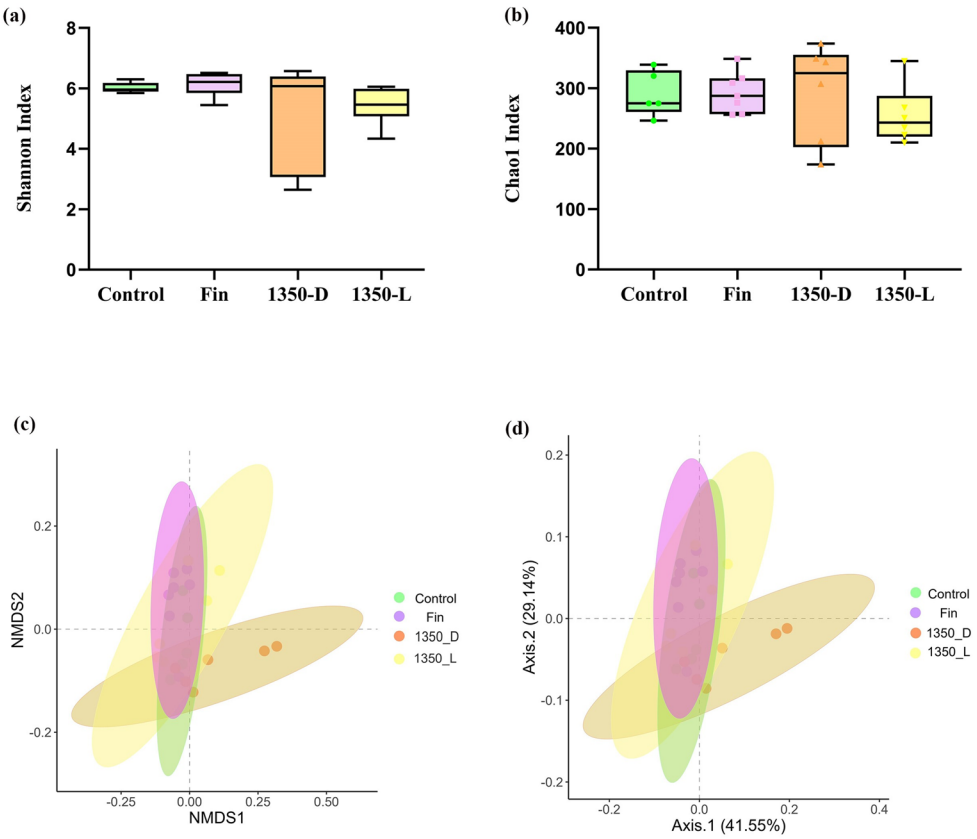

Fig. 4 Effect of *L. paracasei* CCFM1350 intervention on α and β diversity of gut microbiota (**a**) Shannon index. (**b**) Chao1 index. (**c**) NMDS analysis, with a stress = 0.081. (**d**) PCoA analysis

[27]. Our findings align with the dermal regulation patterns observed by Ayatollahi et al. in skin flap models [28]. Notably, although the 1350-D group showed BAX downregulation, it demonstrated inferior hair growth promotion compared to the 1350-L group.

Furthermore, our results indicate that CCFM1350 live bacteria do not mediate hair growth through growth factor modulation. VEGF and IGF-1, which function through the PI3K-Akt pathway, normally stimulate epidermal cell growth by upregulating associated growth factors [29]. IGF-1 additionally activates β-catenin via LEF/TCF-dependent activation, with eleveted expression of these proteins serving as a hallmark of anagen phase initiation [30]. During active hair growth, VEGF secretion increases significantly [31], while sustained IGF-1 expression represents another reliable anagen phase marker [32]. Transforming Growth Factor-β (TGF-β) inhibits hair follicle development through multiple pathways, including Hedgehog signaling inhibition [33]. Sonic Hedgehog (Shh) pathway shares regulatory compounds with the Wnt/β-catenin pathway, enabling coregulation of hair growth [34]. In this study, the levels of these growth factors were similar across all groups, suggesting that CCFM1350's hair growth-promoting effects occur independently of these pathways. This finding aligns with established hair loss pathophysiology, where elevated TGF-β family protein expression contributes to follicular regression, and TGF-β inhibition has demonstrated therapeutic potential [27, 35].

The gut microbiota of mice showed significant changes following the administration of *L. paracasei* CCFM1350. α-diversity analysis using the Shannon index and Chao1 indicated that both live and dead CCFM1350 bacteria altered the microbiota composition. Lactobacillus emerged as one of the most abundant genera and is considered a crucial probiotic in traditional fermented foods [15]. The heatmap analysis (Fig. 5c) revealed a positive correlation between Lactobacillus abundance and Wnt/β-catenin pathway biomarkers. This finding parallels observations by Ding et al. in broiler chickens with intestinal mucosal damage [36]. Previous research byTyagi et al. demonstrated that *Lactobacillus rahmosus GG* (LGG) upregulates Wnt10b expression in Treg cell, subsequently increasing bone mass in mice [37]. Notably, LGG has also shown therapeutic efficacy against neonatal inflammatory intestinal diseases [38]. Our study identified a significant association between *Lactobacillus* and Wnt10b expression, but there was no direct evidence to show *Lactobacillus* can increase the Wnt10b expression.

No other abundant genera demonstrated significant correlations with the measured biomarkers. Previous research has shown that *Akkermansia muciniphila* secretes proteins that activate the Wnt/β-catenin signaling pathway, thereby enhancing gut health through intestinal stem cell regulation

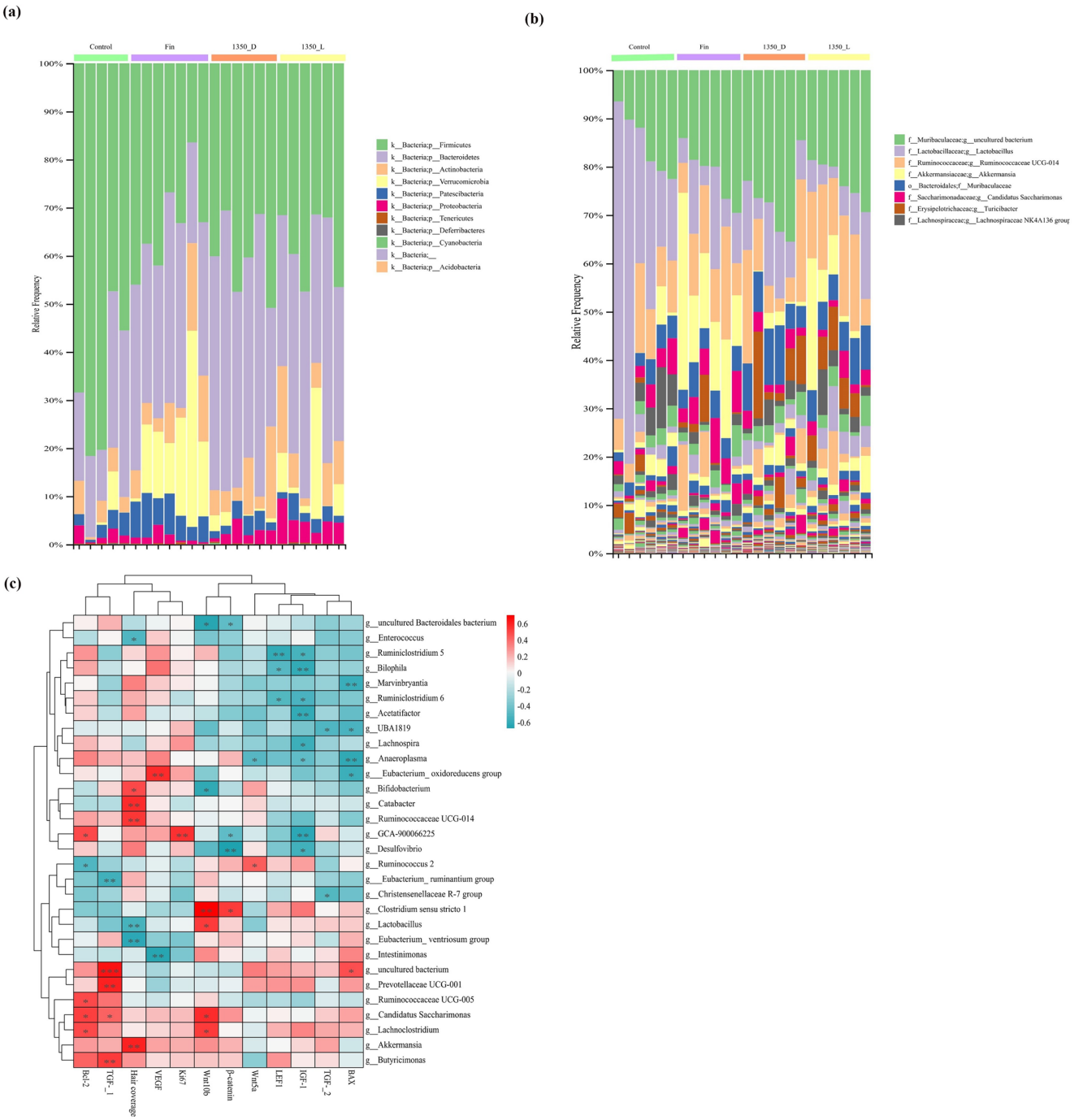

Fig. 5 Relative abundance of each experiment groups and correlation between functional genes and bacteria (**a**) percentage stacked bar chart of relative abundance at phylum level; (**b**) percentage stacked bar chart of relative abundance at genus level; (**c**) correlation heatmap between the biomarker bacteria at the genus level and the hair-loss related genes and proteins

[39]. Although CCFM1350 live bacteria increased *Akkermansia* abundance, this change did not correlate with Wnt10b and β-catenin levels in the context of hair growth. Muribaculaceae, a common and vital family in gut microbiota, plays roles in immune regulation and metabolic processes [40]. Both live and dead CCFM1350 reduced Muribaculaceae abundance, though no association with hair regeneration biomarkers was observed. *Clostridium senus* stricto 1, though not highly abundant, exhibited the strongest correlation with Wnt10b expression. This finding contrasts with Deng et al.'s report that Clostridium inhibits Wnt/β-catenin signaling to suppress tumorigenesis [41].

Conclusion

L. paracasei CCFM1350 live bacteria significantly promote hair follicle development and hair growth. Our results demonstrate that CCFM1350 regulates hair regeneration primarily through Wnt/β-catenin pathway activation, specifically by elevating Wnt10b and β-catenin expression. CCFM1350 live bacteria administration achieved comparable efficacy to Finasteride, the current clinical standard for oral alopecia treatment. Although gut microbiota composition changed following intervention, these alterations showed limited correlation with Wnt pathway biomarker levels.

Given the close relationship with gut microbiota (established gut-microbiota-skin axis), future cohort studies should establish optimal dosing regimens for clinical applications and develop personalized treatment strategies. Future research should focus on: (1) identifying the active bacterial components or metabolites responsible for pathway regulation, and (2) investigating potential synergistic effects between CCFM1350 and plant-derived compounds for hair loss therapy.

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Author Contributions S.C. and X.T. conceived and designed this study. Y.G. and T.Z. performed the experiments and wrote the draft manuscript. X.T. and Q.Z. analyzed and interpreted the data. B.M., J.Z. and S.C. revised the article. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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