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Fucoidan treatment reverses hair loss and inhibits inflammatory responses in a mouse model of androgenetic alopecia

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ABSTRACT

Androgenetic alopecia (AGA), a prevalent form of hair loss, is typically treated with minoxidil and finasteride, but their efficacy and safety are somewhat constrained. Previous studies have shown that fucoidan can regulate VEGF and Wnt signaling pathways, which are critical for hair growth. Based on bioactivity screening protocols for natural product, we hypothesized that fucoidan may exert beneficial effects on AGA, potentially through modulation of the Wnt pathway and other molecular mechanisms. This study aimed to investigate the effect of fucoidan on testosterone propionate-induced AGA in mice and explore the underlying mechanisms, providing new insights into its therapeutic potential. The results demonstrated that 2 % fucoidan significantly alleviated AGA symptoms, promoted hair growth, and increased hair density. Mechanistically, fucoidan ameliorated testosterone propionate-induced hair follicle (HF) atrophy and developmental arrest, while restoring HF pigmentation. Further analysis revealed that fucoidan regulated the Wnt/β-catenin signaling pathway, reduced cellular apoptosis, and promoted the release of vascular endothelial growth factor (VEGF). Additionally, fucoidan effectively reduced microinflammation in AGA-afflicted mice. Collectively, these findings suggest that fucoidan has potential therapeutic effects against AGA.

1. Introduction

Androgenetic alopecia (AGA) is one of the most prevalent clinical phenotype of hair loss, accounting for about 80 % of alopecia in daily life. In China, AGA is estimated to affect about 21.3 % of males and 6 % of females [1]. Despite no physical discomfort to patients typically, AGA may severely damage their appearance, sense of self, and mental health, leading to compromised quality of life, particularly for young people [2,3]. Moreover, in recent decades, AGA occurs more frequently in the younger groups due to the increasing pressure of work, life and study.

Commonly, the onset of AGA may indicate a decrease in the anagen stage of hair follicles (HFs), manifesting as the shrinkage of HFs and replacement of dense, black hair with limp, colorless hair. Eventually, there will be hair loss owing to severe atrophy of HFs. For male patients with AGA, the hair in the frontal and parietal lobes becomes sparse or even falls off completely, resulting in receding hairline and baldness [4]. Despite its name, AGA may also affect females. Unlike males, the majority of females with AGA exhibit diffuse scalp hair loss. Even without receding hairline in the frontal lobe, female patients may present with thinner hair in the scalp of the frontal lobe and parietal lobe, then sparse hair with a wider middle parting, showing a shape of "Christmas tree" [5,6]. Due to genetic and hormonal factors, males and females with AGA exhibit different performance clinically. However, both groups have major pathological characteristics, including the shortened anagen, the prolonged telogen, as well as the highly atrophied and degenerated HFs. The miniaturization of HFs is a histological indicator of AGA, and the volume of HFs may affect the diameter and color of hair shaft [7]. The miniaturization of HFs is reversible in the early stage, whereas the highly atrophic HFs will not regenerate when the arrector pili is separated from an atrophic HF. Therefore, AGA may be reversible at the early stage and irreversible at the later stage [8].

Currently, finasteride and minoxidil remain the only two approved medications for AGA treatment [9]. However, as a non-cicatricial alopecia, AGA is a multifactorial process, which cannot be managed effectively by existing drugs. Moreover, treatment using minoxidil and finasteride may trigger many adverse reactions [10–12]. It highlights the necessity of developing a new safer and better therapeutic agent for AGA.

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Natural products have been highly concerned by researchers because of their low toxicity. Numerous natural compounds have shown confirmed effect of promoting hair development, such as resveratrol [13], ginsenoside [14], Cyanidin-3-O-glucosidea [15] and Pilose antler extract [16]. In a previous study on the mechanism of various natural products in the treatment of AGA, Wu et al. summarized that the androgen pathway, Wnt/β-catenin signaling pathway, PI3K/AKT pathway, anti-inflammatory, anti-oxidation, reducing apoptosis and promoting cytokine secretion were all the main mechanisms [17]. In particular, the Wnt/β-catenin signaling pathway and vascular endothelial growth factor (VEGF) were considered as the main targets of most natural products to alleviate AGA.

Fucoidan, a natural water-soluble anionic polysaccharide, is widely distributed in macroalgae and specific invertebrate species. Its intricate and unique structural architecture endows this polysaccharide with diverse biological activities, such as anti-tumor [18], anti-oxidant [19], anti-inflammatory [20], and other bio-functions. Such multifunctional bio-activities enable its extensive applications across food science, pharmaceutical development, and cosmetic industries. Noticeably, the biological activities of fucoidan are dependent on the regulation of multiple signaling pathways [21,22]. Xu et al. has documented the regulatory role of fucoidan in the Wnt/β-catenin pathway, which could exhibit anti-lipogenic activity by up-regulating the β-catenin protein level [23]. Li et al. found that through regulating the PI3K/AKT/VEGF signaling pathway, fucoidan could promote cerebrovascular formation and alleviate brain damage in type 2 diabetes mellitus [24]. Kirindage found that fucoidan could reduce inflammation caused by 12-O-tetradecanoylphorbol 13-acetate [25]. Critically, fucoidan could also promote hair growth by stimulating the release of certain cytokines [26,27]. Furthermore, according to a method for screening the drug activity of natural products reported by Thomford et al. [28] and a method of target-based natural drug screening proposed by Najmi et al. [29], the starting point in this approach is the molecular target that is clearly involved in drug interaction, and the target is considered to be crucial in diseases. In view of the above, it is speculated that fucoidan may promote hair growth by regulating β-catenin, VEGF and other targets in the pathogenesis of AGA, which is expected to exert positive therapeutic impact on AGA. However, so far, there is still no direct and effective evidence to support the effect of fucoidan on AGA, and its mechanism of action needs to be clarified.

In this study, a mouse model of AGA was established through subcutaneous injection of testosterone propionate to determine the impact of fucoidan on AGA, to investigate its role on the pathological state in HFs, and to explore its possible mechanism by detecting the levels of related proteins and cytokines. Furthermore, immunohistochemistry (IHC) was employed to assess the effect of fucoidan on the micro-inflammation. The present study intended to investigat the effect of fucoidan on AGA and explore the underlying mechanisms, so as to promote the high-value utilization of marine resources and provide valuable ideas for AGA patients.

2. Materials and methods

2.1. Materials and reagents

Fucoidan (derived from the *Laminaria japonica*, purity 98 %, molecular weight 234.423 kDa, sulfate content 24.75 %, and additional information is provided in the supplementary materials.) was purchased from Qingdao Gene Wishdom Biology Science and Technology Development Co., Ltd. (Qingdao, China). Testosterone propionate injection was obtained from Hangzhou Animal Medicine Factory Co., Ltd. (Hangzhou, China). Anti-GSK3β antibody, Anti-p-GSK3β antibody, Anti-Cyclin D antibody, and Anti-β-catenin antibody were supplied by Wuhan Servicebio Technology Co., Ltd. (Wuhan, China). Testosterone ELISA Kit, Dihydrotestosterone ELISA Kit and Mouse VEGF-A ELISA Kit were purchased from Sangon Biotech (Shanghai, China) Co., Ltd.

2.2. Animal study design

A total of 48 male C57BL/6 mice (20 ± 2 g) were provided by Shanghai SLAC Experimental Animal Co., Ltd. (Shanghai, China). All mice were housed in a specific pathogen-free (SPF) facility under controlled conditions (23–25 °C, 60 %–70 % humidity, 12 h light-dark cycle) with free access to food and water. The animal protocol used in this study was strictly conducted following the *National Research Council's Guide for the Care and Use of Laboratory Animals* and approved by the Committee of Experimental Animals of Huaqiao University (approval number A2024010).

After a one - week acclimation period, the 48 mice were randomly assigned to six groups ($n = 8$), control group (BK), model group (MO), minoxidil group (MIN), low - concentration fucoidan group (FU50), medium - concentration fucoidan group (FU100) (FU100), and high - concentration fucoidan group (FU200). Fig. 1 showed the detailed procedures for modeling and treatment. Prior to the experiment, except for the BK group, the mice in the other five groups received subcutaneous injections of a 0.2 ml sterandryl solution (5 mg/ml) for five consecutive days. The BK group mice were injected with 0.2 ml soybean oil. On day 0, the dorsal hair of all mice was removed, followed by a 28 - days treatment phase. Starting the next day, the subcutaneous injection of testosterone propionate was continued, but administered every two days. The depilation area of mice in the BK and MO groups were topically applied with 0.2 ml of distilled water once daily. Mice in the MIN group were smeared with 0.2 ml of 2 % minoxidil once a day. The depilation areas of mice in the remaining three groups (FU50, FU100, and FU200) were treated with 0.2 ml of 0.5 %, 1 % and 2 % fucoidan solution, respectively, once daily [30–32]. Mice's hair growth status were record and evaluate every 3 days after initiating the experiment. We applied a scoring system: 0 = no growth; 1 = ≤20 % growth; 2 = 20–40 % growth; 3 = 40–70 % growth; 4 = 70–90 % growth; 5 = 90 %-to-full growth (Table 1). At the end of the 28 - day experiment, the dorsal skin of the mice was collected for further analysis [33]. On day 28, the hairs in the depilated area were removed, and their length was measured using a vernier caliper.

2.3. Histology

For histological examination, the tissues collected on the day 28 were fixed in 4 % paraformaldehyde solution. Fellowing dehydration, transparency, and embedding, they were processed into paraffin block. The blocks were sectioned into 4-μm-thick slices using a microtome (HS-3315, Feather R35 blade), and the tissue sections were mounted onto glass slides and air-dried.

After dewaxing and rehydrating, the sections were washed with PBS and stained with hematoxylin solution for 10 min. Subsequently, the slices were rinsed with tap water and counterstained with eosin for 2 min. Following staining, the sections were dehydrated through a gradient of ethanol solutions, cleared with xylene, and sealed with neutral resin. The morphological and pathological changes of HFs were observed under the microscope.

For immunohistochemistry (IHC), paraffin sections were first dewaxed and rehydrated, then washed with PBS. 0.1 % tritonX-100 was added, and the sections were permeabilized at room temperature for 10 min. After PBS washing, the sections were blocked with goat serum at room temperature for 60 min, followed by incubation with the corresponding primary antibody (1: 200) at 4 °C overnight. Following washing, the secondary antibody was added and incubated at room temperature for 1 h. After washing off the secondary antibody, DAB chromogenic solution was applied. Finally, the IHC staining section were observed under a microscope.

2.4. Determination of immune and hormone cytokines

The levels of testosterone (T), dihydrotestosterone (DHT) and VEGF

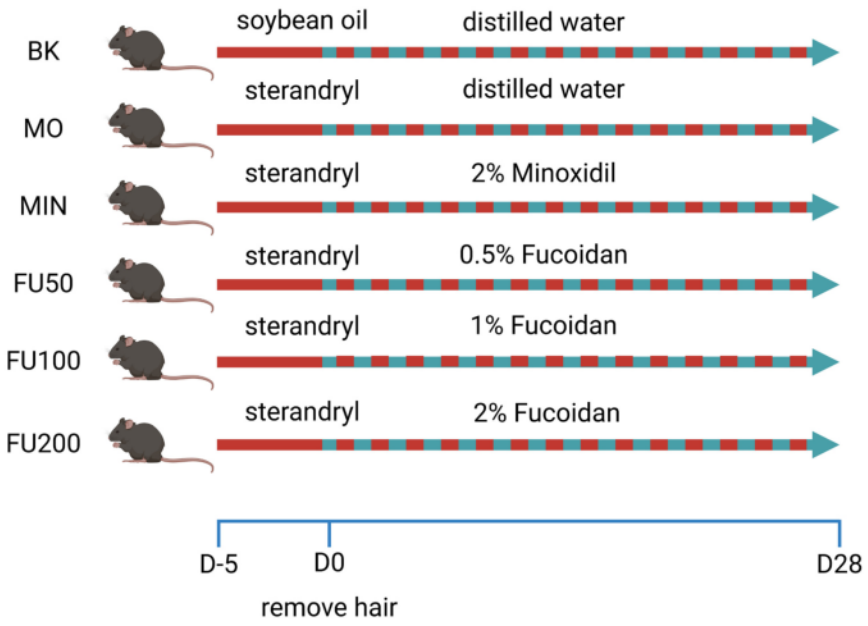

Fig. 1. Classification and progression of animal experiments (created with BioRender.com).

Table 1
The rating scale of hair growth.

score	hair regrowth area/hair removed area
0	0 %
1	0–10 %
2	20–40 %
3	40–70 %
4	70–90 %
5	90–100 %

in the sera obtained on day 28 were measured using ELISA kit, and the pecific procedure was performed following the manufacturer's instructions.

2.5. Western blotting

The skin tissue stored at −80 °C was removed, and proteins were extracted according to the protocol provided by the manufacturer of the protein extraction kit. Proteins were denatured by boiling, and the concentration of each sample was measured. Following SDS-PAGE gel separation, the samples were transferred to a polyvinylidene fluoride (PVDF) membrane at 95 V for 2 h. The PVDF membrane was then sealed with PBS and left to stand at room temperature for 2 h, followed by five washing cycles with TBST. After immersing the membrane in primary antibodies diluted with TBST, it was incubated at 4 °C overnight. The membrane was washed five times with TBST before applying the secondary antibodies, followed by shaking at room temperature for 2 h. The ECL detection kit was used for development, and finally, Image J software was employed to analyze relative protein expression.

2.6. Statistical analysis

GraphPad Prism 8.0.2 (GraphPad Software, Inc., La Jolla, California, USA) was used to statistically evaluate the data, which were presented as mean ± standard deviation (SD). A Tukey test was performed to assess statistical significance between groups. The significance threshold was set at $P < 0.05$. In the statistical graphs, data were labeled as follows: ns $P > 0.05$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

3. Results

3.1. Effect of fucoidan on hair condition of AGA model mice

The hair condition of six groups of AGA mice was shown in Fig. 2A. By day 14, the BK, MIN, and FU200 groups displayed black skin, indicating active hair follicle development. Notably, the BK group showed obvious hair regrowth by day 21, whereas, the MO group retained pink-white skin with no observable hair, confirming successful model establishment. Concurrently, the MIN group and the three fucoidan groups exhibited initial signs of hair growth. By day 28, all groups except MO showed extensive hair coverage. As depicted in Fig. 2B, the FU200 group outperformed the MIN group in hair density and pigmentation on day 28, with no significant difference from the BK group. Hair condition scores for each groups were shown in Fig. 2C. These data indicate that fucoidan alleviates androgen-induced hair growth retardation, furthermore the score of FU200 is closer to that of the BK group at the end of the experiment, which suggested that the high concentration had a better therapeutic effect. In addition, it could be seen from Fig. 2D that on the 28th day, compared with the MO group (1.55 ± 0.3 mm), FU50 group (3.26 ± 0.31 mm) and FU100 group (3.86 ± 0.42 mm), the hair of the FU200 group (4.57 ± 0.31 mm) was 3.02 mm, 1.31 mm and 0.71 mm longer, respectively, Which suggested that the hair length of mice was positively correlated with the drug concentration. In addition, we counted the number of hairs in the red circle in Fig. 2B. The result was showed in Fig. 2E, revealed that the FU200 group had 19.33 more hairs than the MO group on day 21, further confirming that fucoidan promotes hair growth in AGA mice.

AGA-affected hair follicles HFs typically exhibit retarded growth, follicular atrophy, and reduced pigmentation, leading to lighter hair color. To investigate the effect of fucoidan on HF morphology, HE staining was performed on the dorsal skin of AGA model mice. The histomorphology of HFs in different treatment groups was shown in Fig. 3A. Unlike the BK group, HFs in the MO group exhibited obvious shrinkage and widespread hypopigmentation, consistent with the characteristic features of AGA-affected HFs, conforming successfulo model establishment. After the administration of minoxidil and fucoidan, the atrophy of HFs was markedly improved, and the pigmentation of HFs with fucoidan was better than that of minoxidil. Among all the treatment groups, the FU200 group had the best effect, and the HFs in this group had entered the telogen. It suggested that fucoidan could

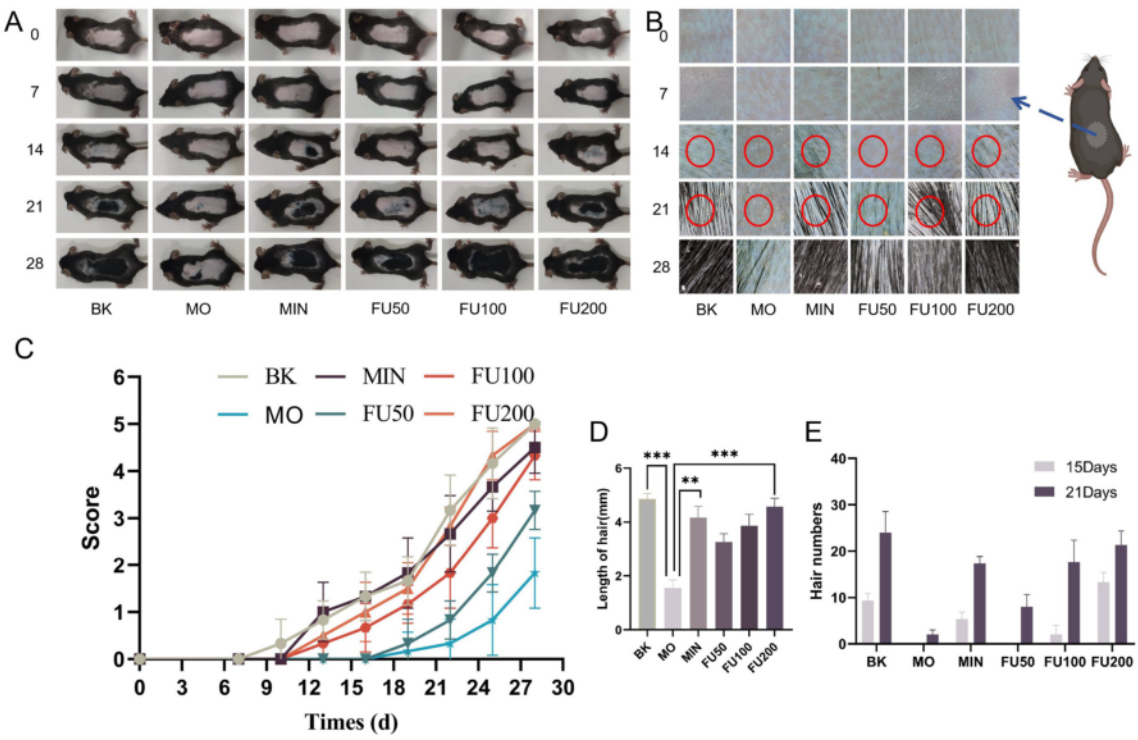

Fig. 2. Effect of fucoidan on hair condition of AGA model mice. (A) Hair condition of mice with different treatments. (B) Hair condition of mice with different treatments (1000×). (C) Score statistics for different treatment groups mice hair condition. (D) Length of hair in six groups at 28th. (E) Statistics on the number of dorsal hairs in the same area on the 15th and 21st day.

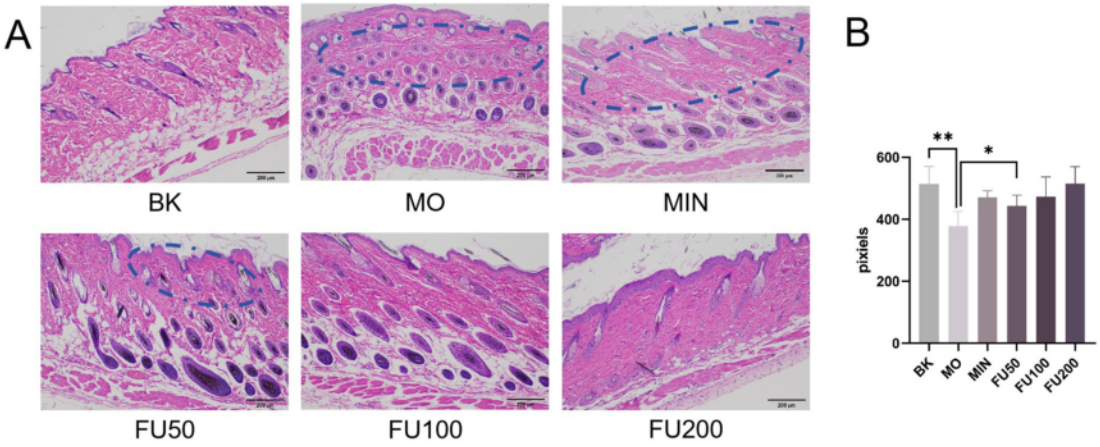

Fig. 3. Skin histology of AGA mice. (A) The dorsal skin of mice stained with HE (Blue circles were used to identify the damaged HFs). Scale bar = 200 μm. (B) Thickness of dermis of dorsal skin of mice.

alleviate the atrophy and development stagnation of HFs induced by testosterone propionate and restore the pigmentation of HFs. The dermis thickness of mice were shown in Fig. 3B. The treatment of fucoidan improved the thinning of dermal thickness of mice dorsal skin caused by TP.

3.2. Effect of fucoidan on cell proliferation of AGA model mice

Ki67 serves as a key marker for evaluate cell proliferation. The effect of fucoidan on cell proliferation in AGA mice was investigated via Ki67 staining, and the results were displayed in Fig. 4. The MO group exhibited low Ki67 positivity, consistent with its retarded HF development, whereas the MIN, FU50 and FU100 groups showed high Ki67 positivity, indicating rapid HF cell proliferating. Notably, both the BK group and FU200 group displayed low Ki67 positivity, likely because HFs in these groups had entered the late anagen or telogen. These findings demonstrated that fucoidan relieves testosterone propionate-induced inhibition of HF proliferation, and promotes HF growth and development, thereby facilitating hair growth.

3.3. Effect of fucoidan on AGA model mice's cell apoptosis

HF apoptosis was investigated by immunofluorescence staining, and the results for different treated AGA mouse groups were shown in Fig. 5. The MO group exhibited the highest fluorescence intensity, indicating the most pronounced apoptosis. Notably, minoxidil failed to alleviate apoptosis, as the fluorescence intensity in the MIN group was comparable to that in the MO group. In contrast, fucoidan administration

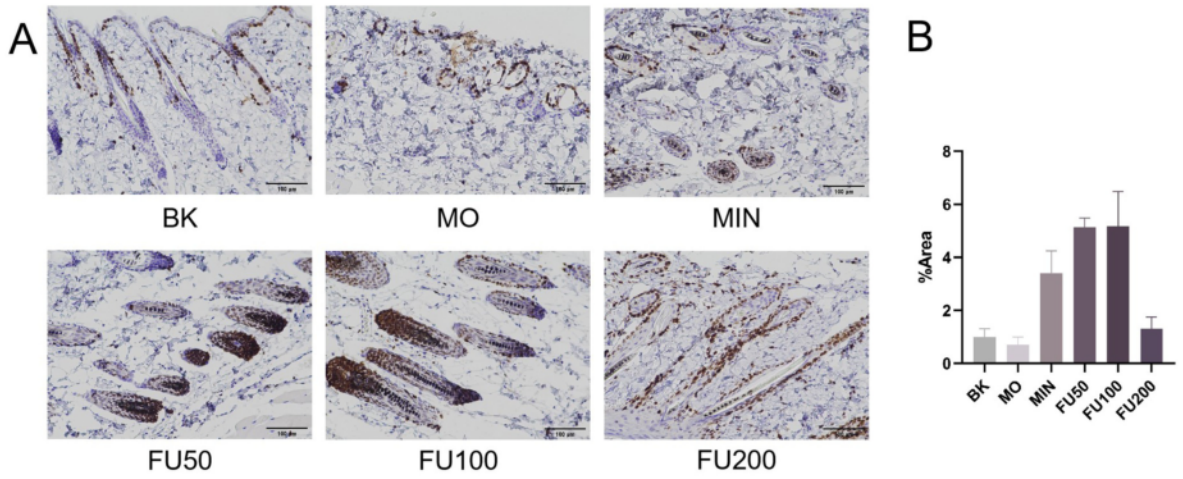

Fig. 4. Effect of fucoidan on AGA model mice's cell multiplication. (A) The dorsal skin of mice stained with Ki67. Scale bar = 100 μm. (B) Level of Ki67-positive for different treatment groups.

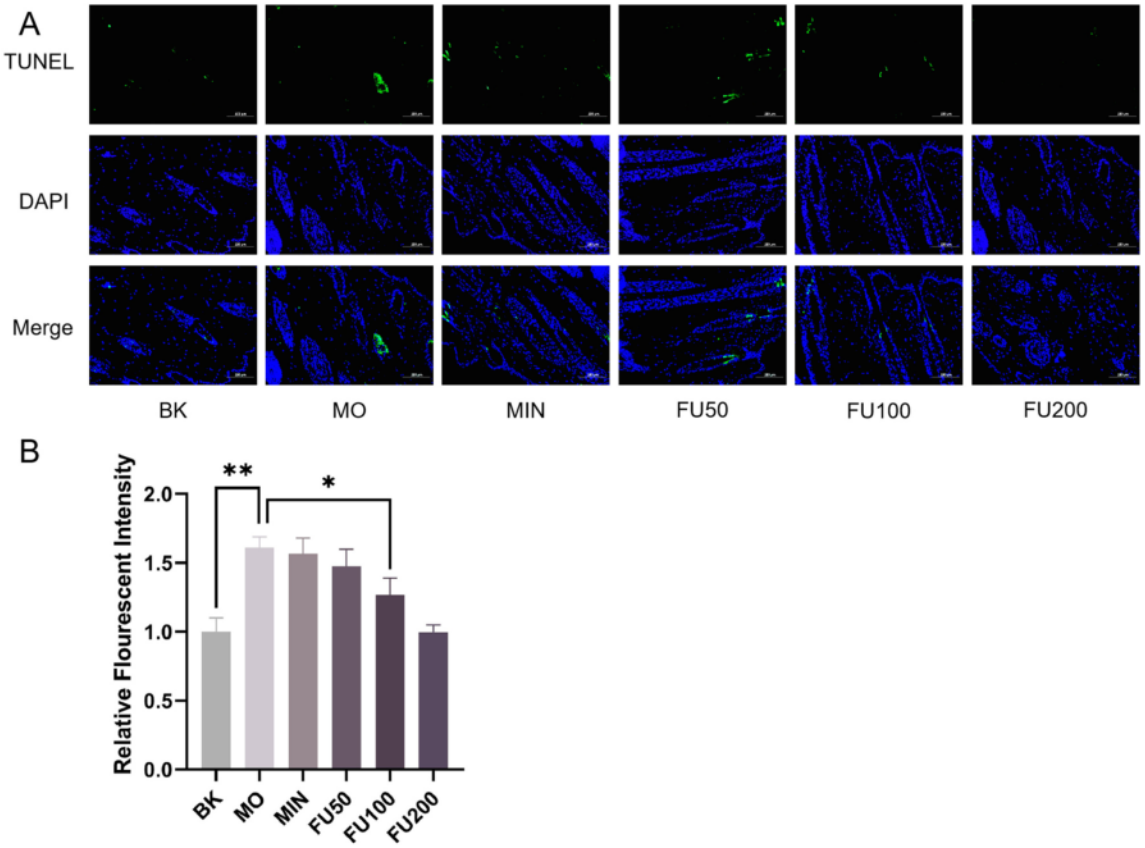

Fig. 5. Effect of fucoidan on AGA model mice's cell apoptosis. (A) The dorsal skin of mice stained with Tunel. Scale bar = 100 μm. (B) Level of TUNEL-positive for different treatment groups.

reduced apoptosis in a dose-dependent manner, with decreasing fluorescence intensity observed with increasing fucoidan concentration. There was an apparent distinction between the MO group and the dose concentration at 1 %, which indicated that fucoidan alleviated the apoptosis of cells.

3.4. *Effect of fucoidan on androgenetic and VEGF in AGA mice*

T and DHT are key regulators in the pathophysiology of AGA. DHT is transformed from T by 5α-reductase, and exhibits higher sensitive to androgen receptor (AR). ELISA was used to quantify T and DHT levels in mouse serum, and the results are shown in Fig.6A and 6B. Compared with the BK group, the MO group dispayed significantly elevated serum T and DHT levels, confirming androgen imbalance, and successful model establishment. However, administration of minoxidil and fucoidan did not significantly alter serum androgen levels, indicating that fucoidan ameliorates AGA via mechanisms independent of T/DHT regulation. The skin VEGF levels are shown in Fig. 6 C. Both fucoidan and minoxidil increasd VEGF expression, suggesting that these drugs promote HF angiogenesis to different extents. Notably, fucoidan showed a more

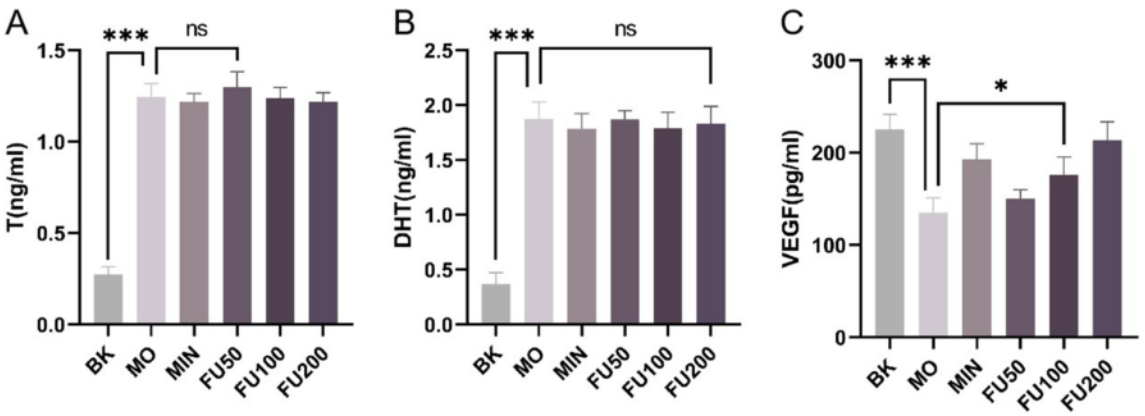

Fig. 6. Effect of fucoidan on androgenetic and VEGF in AGA mice. (A) T levels in AGA mice with various treatments. (B) DHT levels in AGA mice with various treatments. (C) VEGF levels in AGA mice with various treatments.

pronounced effect at concentration higher than 1 %, indicating that fucoidan treats AGA by enhancing VEGF secretion and regulating skin microvessels formation.

3.5. Effect of Fucoidan on Wnt/β-catenin pathway in AGA mice

The activation of the Wnt/β-catenin pathway influences both growth factor secretion and HF development. β-catenin serves as a key molecule in the Wnt pathway, and its activity is implicated in HF development [34]. GSK-3β is an enzyme responsible for phosphorylation and ubiquitination β-catenin to mediate its degradation. Cyclin D a downstream target of the Wnt/β-catenin, reflects cellular proliferative activity [35]. As shown in Fig. 7, the expression of associated proteins was examined by Western blot in order to examine the impact of fucoidan on the Wnt/β-catenin pathway. Fucoidan significantly upregulated the expression of cyclin D1, p-GSK-3β, and β-catenin. These results suggeste that fucoidan

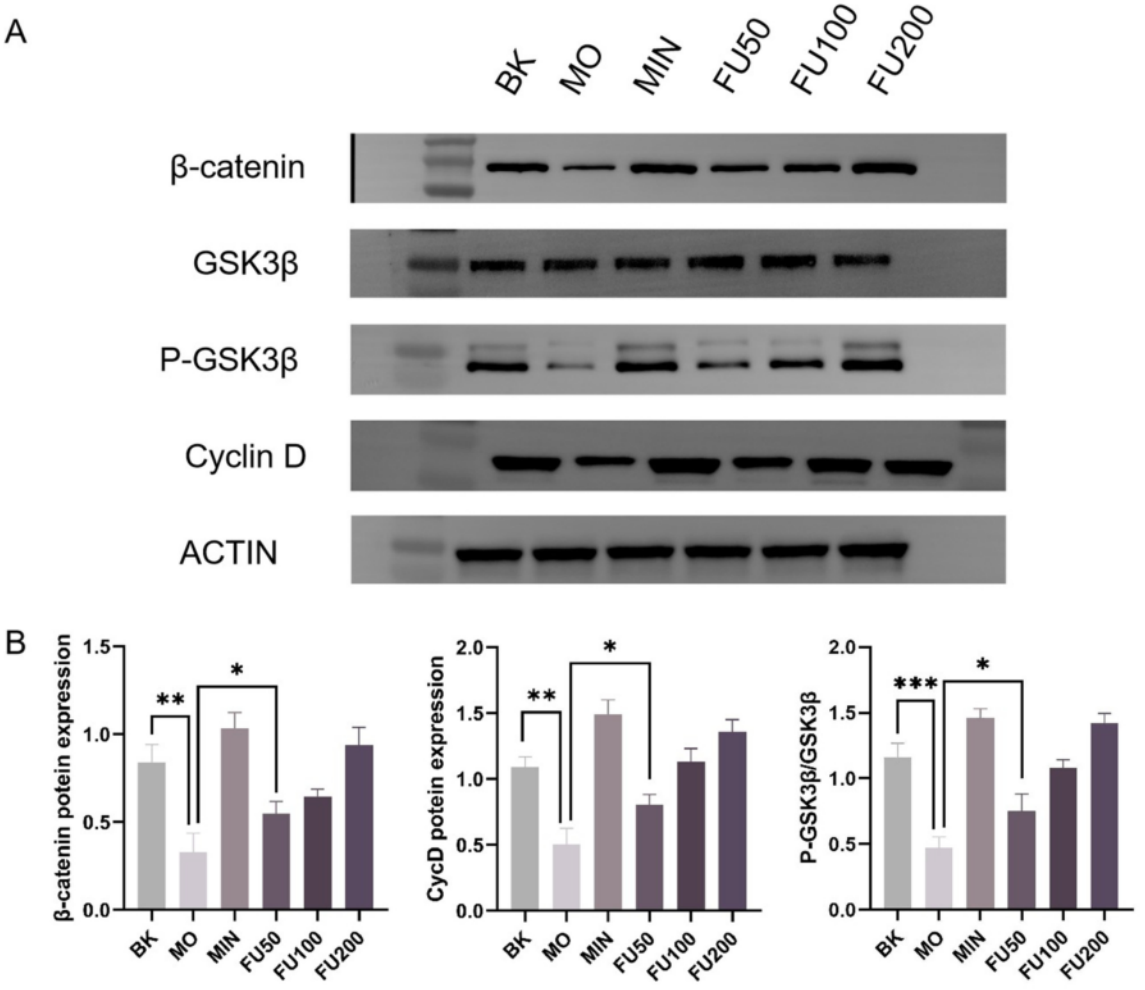

Fig. 7. Alterations in the expression of proteins in the dorsal skin of mice (A) Protein band for different treatment groups. (B) Statistical analysis of β-catenin, Cyclin D and P-GSK3β/ GSK3β.

alleviates AGA by activating the Wnt/β-catenin signaling pathway.

3.6. Effect of Fucoidan on micro-inflammation in AGA mice

Numerous studies have demonstrated that the roles of key inflammatory factors TGF-β, TNF-α, and IL-6 in AGA [36,37]. Immunohistochemical staining was performed to assess inflammatory cell infiltration in the dorsal skin of AGA model mice. The staining results are presented in Fig. 8A. In the MO group, inflammatory factors were widely expressed in the skin, with significantly higher levels than those in the BK group. Notably, inflammatory infiltration in the MIN group was not improved, but even exacerbated. This may be attributed to minoxidil's inability to resolve inflammation and the irritant effect of its solvent (propylene glycol), which aggravated the inflammatory infiltration of HFs. As shown in Fig. 8B, fucoidan administration alleviated cutaneous micro-inflammatory infiltration in AGA mice. Moreover, the anti-inflammatory effect was dose-dependent, with higher fucoidan concentrations exhibiting more pronounced inhibition. These findings indicate that reduction of skin tissue inflammatory infiltration represents an additional mechanism by which fucoidan ameliorates AGA.

4. Discussion

The incidence of AGA may be affected by multiple factors, such as genetic inheritance [38], hormone metabolism [5], stress in life, dietary habits [39,40], etc. Its common manifestations are shortened anagen, shrinking HFs, slow hair growth, black and thick terminal hair replaced by the colorless and soft mane, and finally highly atrophied and shed HFs [41]. For example, C57BL/6 mice were detected with the expression of androgen receptor (AR), with visible changes in skin color during hair growth. Meanwhile, androgen injection resulted in the shortening of HF anagen and inhibition of melanosis, leading to hair whitening, which were consistent with the histological characteristics of AGA. Accordingly, a mouse model of AGA was established by injecting androgen into the back of mice according to the modeling method proposed by Fu et al. [32]. However and significantly, the administration of fucoidan led to the restoration of the pigmentation of HFs and entering the anagen growth phase ahead of schedule. Besides, Ki67 staining revealed that fucoidan stimulated cell proliferation in HFs. All these data supported a therapeutic effect of fucoidan on AGA.

The occurrence and severity of AGA may be attributed to androgen metabolism and expression, as well as downstream cytokine release intricately. Specifically, the androgen level exerts a direct regulatory effect on the pathogenesis of AGA [42]. AGA may be triggered when the testosterone (T) and dihydrotestosterone (DHT) levels are excessively high. DHT is transformed from T by 5α-reductase, and AR is more sensitive to DHT compared with T [43]. After binding of DHT to AR, the complex enters the nucleus and recruits transcriptional coregulators to induce the secretion of downstream cytokines [44]. Similarly, Fu et al. documented a significantly altered androgen level in mice after modeling. In our study, there was no remarkable change in the levels of T and DHT in mice after fucoidan treatment, demonstrating that regulation of androgen level was not the target of fucoidan in AGA treatment. Further in-depth investigation is required to uncover the mechanism of fucoidan on AGA.

After DHT binds to AR, the complex will enter the nucleus of DP cells and stimulate DP cells to secrete tumor growth factor-β (TGF-β). It has been recognized that TGF-β may be involved in inhibiting the Wnt pathway, resulting in hair circulation disorder in AGA. Wnt/β-catenin signaling is a key mediator in the development of HFs and the growth of hair [45]. In terms of the participation of Wnt in AGA, the study of Liu employed comparative transcriptome profiling to explore the Wnt signaling pathway in AGA [46]. Consequently, the differentially expressed mRNA in AGA was mainly enriched in the Wnt/β-catenin signaling pathway. Ceruti et al. also demonstrated the interaction between androgen and Wnt in AGA, and they reported a detrimental effect of ligand-activated AR on the Wnt/β-catenin signaling pathway [47]. The suppression of Wnt/β-catenin signaling pathway may be related to androgen activation of glycogen synthase kinase-3β (GSK-3β), an enzyme responsible for phosphorylation and ubiquitination to mediate β-catenin degradation [33]. In our study, the administration of fucoidan intervened β-catenin expression, with promoted levels of Cyclin D. Therefore, the Wnt pathway may be one of the potential targets of fucoidan in the treatment of AGA, as shown in Fig. 9.

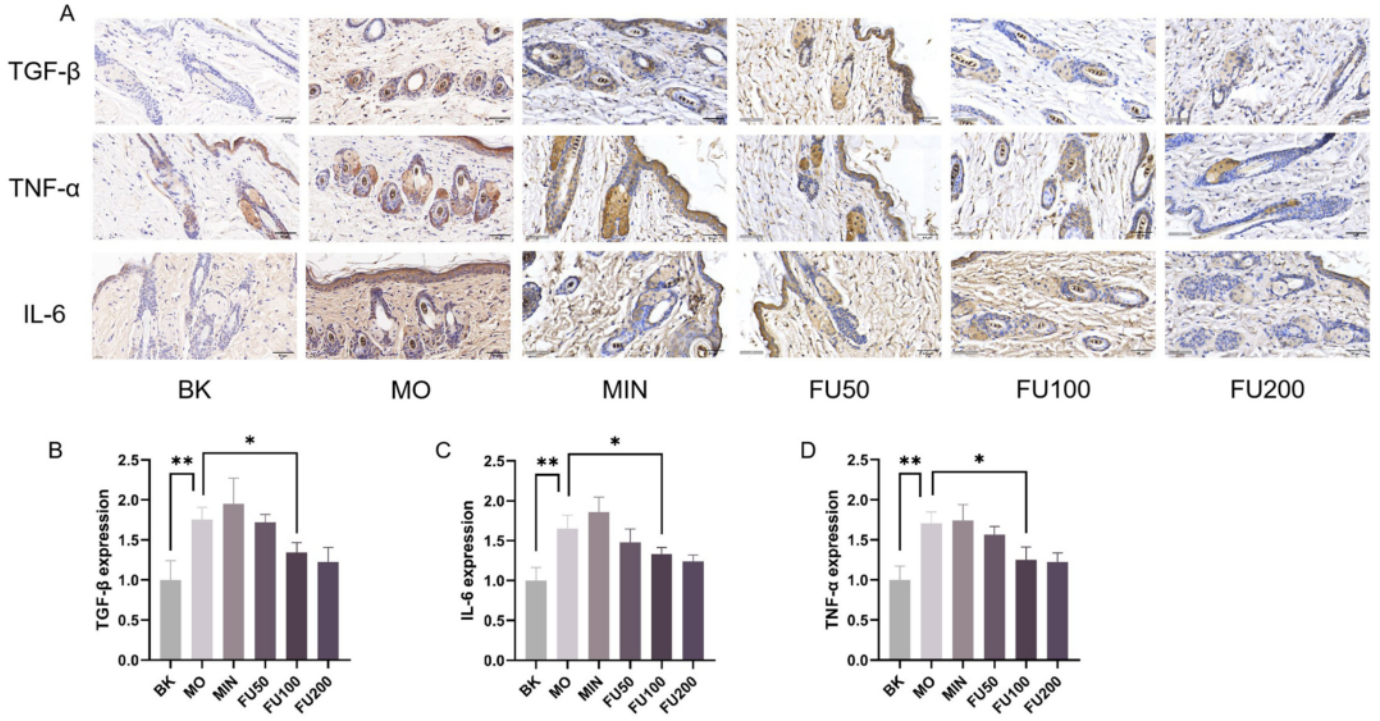

Fig. 8. Effect of Fucoidan on micro-inflammation in AGA mice. (A) IHC results, scale bar = 50 μm. (B) Level of TGF-β (C) Level of IL-6 (D) Level of TNF-α.

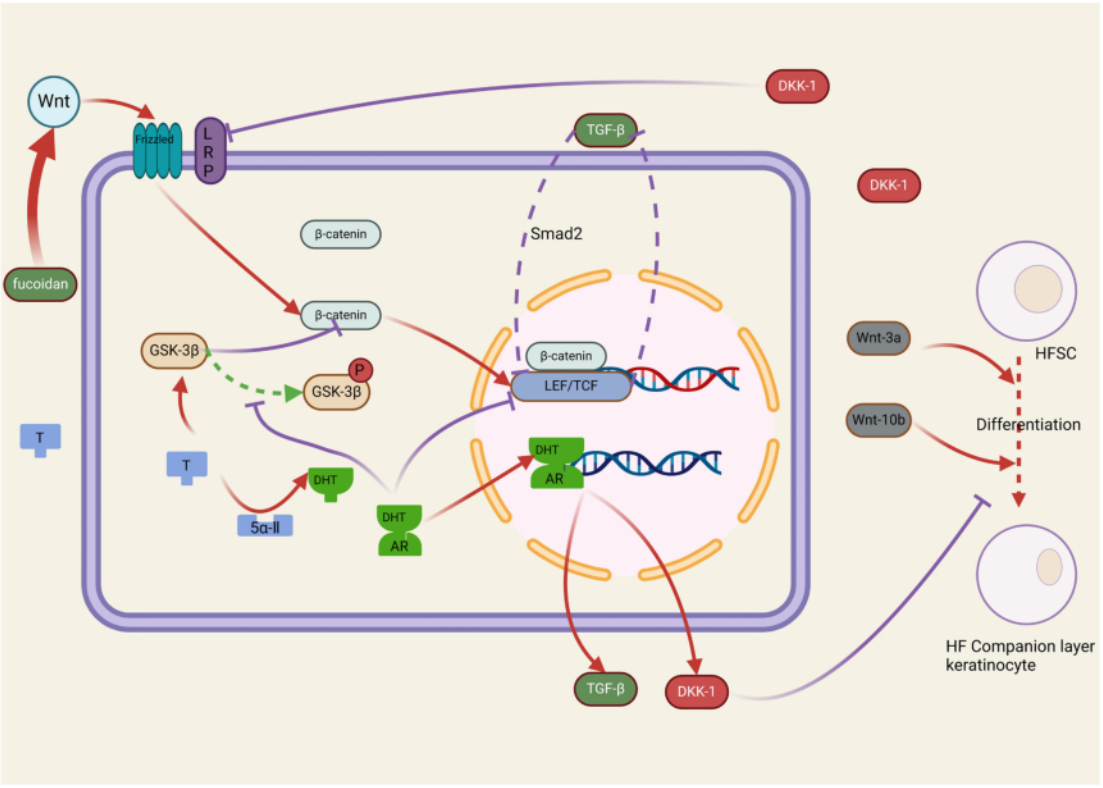

Fig. 9. Regulation of fucoidan on Wnt pathway in AGA (created with BioRender.com). T regulates the phosphorylation of GSK-3β by stimulating the complex formed by DHT and AR, this results in β-catenin degradation. Furthermore, TGF-β and DKK-1 stimulated by the complex further inhibit the Wnt pathway through the combination of the smad2 pathway and LRP, affecting the differentiation of HF stem cells, thus affecting normal hair circulation. However, the administration of fucoidan regulates the Wnt pathway and prevents the degradation of β-catenin, thus treating AGA. In the figure, the T-shaped line denotes inhibition, while the arrow line denotes promotion.

In addition to inactivating the Wnt pathway, TGF-β1 can also participate in the apoptosis of microvascular vessels in HFs. Deng et al. reported microvascular regression in AGA [48]. As indicated by IHC, the number of vascular markers decreased significantly in the alopecia scalp of AGA patient. Furthermore, there was no significant difference in normal microvascular vessels between healthy and alopecia scalps, yet accompanied by significantly reduced volume of HFs with abnormal microvessels. Hence, there may be microvascular regression in the initial phase of HF shrinkage. Furthermore, the genes of healthy and alopecia scalps of AGA patients were analyzed to understand the reasons for microvascular regression in AGA. Microvascular vessel abnormalities were found to be mainly caused by cytokines secreted by AR. Compared with healthy scalp, the TGF-β signaling pathway was considerably more active in the dermal papilla (DP) of alopecia scalp of AGA patients. Further transcription and protein analyses found that the rising TGF signal was mainly TGF-β1. Therefore, TGF-β1 was speculated to exhibit a role in endothelial cell apoptosis in the DP of AGA patients, resulting in microvascular regression. This study also examined HF apoptosis, TGF-β and VEGF levels in the skin. Fucoidan could treat AGA by reducing HF apoptosis, down-regulating TGF-β expression, and promoting VEGF secretion, as shown in Fig. 10.

Despite a common definition of noninflammatory alopecia, AGA was found to have mild inflammation in the scalp of certain AGA patients, presenting with non-inflammatory manifestation, thus it is also known as "microinflammation" [37]. AGA may also have a feature of micro-inflammation, besides the miniaturization of HFs and the disorder of HF circulation. This property of AGA results in a relatively low therapeutic effect of minoxidil on some AGA patients. As evidenced by a prior research, detection of the scalp in the hair shedding region revealed the infiltration with inflammatory cells in the scalp of about 87.9 % of AGA patients, with mild inflammation in most specimens (58.6 %) [49]. Plante et al. also noticed significant correlations of the severity of AGA with the miniaturization of HFs and the degree of inflammatory infiltration [50]. Furthermore, there was serious inflammatory infiltration around the highly miniaturized HFs. Miao et al. conducted transcriptome analysis of scalp in different parts of AGA patients and found abnormally higher TNF-α and IL-6 levels in all AGA groups [51]. Thus, using IHC, this study examined how fucoidan affected micro-inflammation in AGA. The findings showed that fucoidan decreased the infiltration of TNF-α and IL-6 in HFs. This indicates that micro-inflammation may also be the target of fucoidan on AGA, as shown in Fig. 10.

At present, the only FDA-approved drugs are minoxidil and finasteride for treating AGA. Compared with their single target mode of action, the multi-target treatment mode of fucoidan implies better effect and wider application. In addition, fucoidan, as a natural product, shows superior safety [52], which was reported to trigger no obvious adverse reactions, without inducing scalp itching, redness or sexual dysfunction to patients. Additionally, the presence of microinflammation has been demonstrated in the scalp of some patients with AGA, although this condition has long been considered a non-inflammatory form of hair loss [50,51]. Consequently, it may account for the suboptimal therapeutic efficacy of vasodilators such as minoxidil in certain AGA individuals. Currently, regulation of the hair follicle cycle and associated signaling pathways remains a major concern in most studies, without an oversight of managing microinflammation in AGA [33,53], leading to treatment failure potentially. In this study, fucoidan could reduce inflammatory factors such as TNF-α in AGA skin, indicating its effect on regulating micro-inflammation.

In summary, fucoidan can exert therapeutic effect on AGA based on its anti-apoptosis, angiogenesis promotion and anti-inflammation effects. It highlights that the effect of fucoidan on AGA is the result of

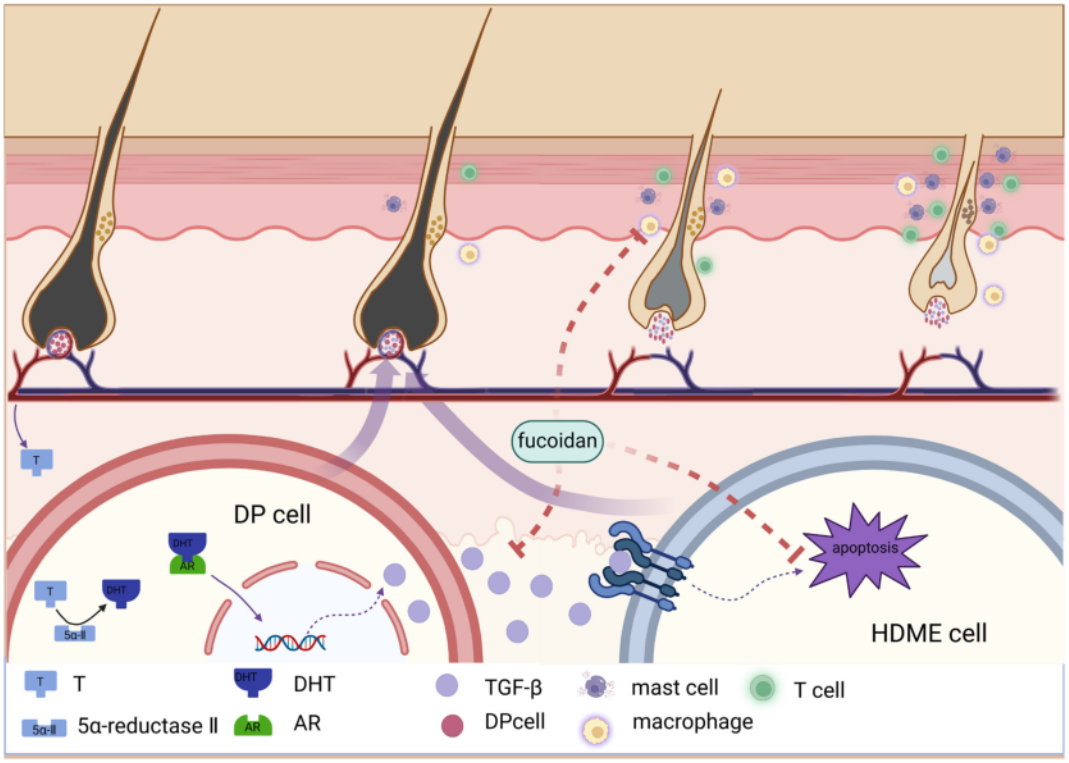

Fig. 10. Regulation of fucoidan on TGF-β and micro-inflammation in AGA (created with BioRender.com). T converted to DHT by type II 5α-reductase enters in DP cells, and then binds with androgen receptor AR to stimulate the TGF-β secreted, which leads to the apoptosis of microvascular endothelial cells and the disappearance of microvessels in the DP, what's more, the HF was miniaturization. In addition, inflammatory factors existing in the isthmus of HF also induce fibrosis of cells in the isthmus of HF, which affects the transformation of stem cells and further promotes the miniaturization of HF. After being treated with fucoidan, the level of TGF-β was inhibited, and then alleviated the regression of microvessels, and fucoidan also alleviated the infiltration of inflammatory factors, thus treating AGA. In the figure, the T-shaped line denotes inhibition, while the arrow line denotes promotion.

different therapeutic targets, rather than depending on a single target, and it also implies its preferable effect on AGA. However, this study did not investigate the effect of higher concentrations of fucoidan on AGA. In future research, an experimental group with a higher concentration will be established. Additionally, this study did not deeply explore the mechanism of action of fucoidan and the potential interactions between different targets by blocking or knocking out specific target sites. Furthermore, genomic approaches can be used to validate the target sites of fucoidan at the genetic level. These aspects will be our key research focuses in the next stage. Nonetheless, findings in the present study still support a positive effect of fucoidan on AGA.

5. Conclusion

This study suggests a positive effect of fucoidan on AGA and investigates the possible mechanism of fucoidan in treating AGA. Fucoidan can accelerate the entry of hair follicles into the anagen by stimulating the Wnt/β-catenin signaling pathway. Additionally it reduces the apoptosis of microvasculature in the hair follicles of AGA mice by enhancing the secretion of VEGF and reducing microinflammatory infiltration in hair follicles, so as to promote hair growth. These findings contribute to the high-value utilization of seaweed resources, and also provide valuable guidance for the treatment of patients with AGA.

CRediT authorship contribution statement

Zhiyan Wang: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yanbin Lai:** Methodology, Investigation, Data curation. **Bingde Zheng:** Software, Investigation, Data curation. **Na Zhang:** Writing – review & editing, Supervision, Conceptualization. **Hongjie Yang:** Software, Data curation. **Yayan Huang:** Software, Investigation, Conceptualization. **Yucheng Yang:** Methodology, Investigation, Data curation. **Xueqin Zhang:** Methodology, Investigation, Funding acquisition. **Jing Ye:** Supervision, Conceptualization. **Meitian Xiao:** Project administration, Investigation, Funding acquisition.

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Declaration of competing interest

The authors state that none of the work described in this study appears to have been influenced by any known competing financial interests or personal ties.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijbiomac.2025.146382.

Data availability

Data will be made available on request.

References

[1] T.L. Wang, C. Zhou, Y.W. Shen, X.Y. Wang, X.L. Ding, S. Tian, Y. Liu, G.H. Peng, S. Q. Xue, J.E. Zhou, R.L. Wang, X.M. Meng, G.D. Pei, Y.H. Bai, Q. Liu, H. Li, J. Z. Zhang, Prevalence of androgenetic alopecia in China: a community-based study in six cities: Prevalence of androgenetic alopecia in China, Br. J. Dermatol. 162 (2010) 843–847, https://doi.org/10.1111/j.1365-2133.2010.09640.x.

[2] M. Gonul, Comparison of quality of life in patients with androgenetic alopecia and alopecia areata, An. Bras. Dermatol. 93 (2018) 651–658, https://doi.org/10.1590/abd1806-4841.20186131.

[3] J. Griggs, B. Burroway, A. Tosti, Pediatric androgenetic alopecia: A review, J. Am. Acad. Dermatol. 85 (2021) 1267–1273, https://doi.org/10.1016/j.jaad.2019.08.018.

[4] D. Rathnayake, R. Sinclair, Male androgenetic alopecia, Expert. Opin. Pharmacother. 11 (2010) 1295–1304, https://doi.org/10.1517/14656561003752730.

[5] V.H. Price, Androgenetic Alopecia in Women, J. Investig. Dermatol. Symp. Proc. 8 (2003) 24–27, https://doi.org/10.1046/j.1523-1747.2003.12168.x.

[6] K.L. Kerkemeyer, L.T. de Carvalho, R. Jerjen, J. John, R.D. Sinclair, J. Pinczewski, B. Bhoyrul, Female pattern hair loss in men: A distinct clinical variant of androgenetic alopecia, J. Am. Acad. Dermatol. 85 (2021) 260–262, https://doi.org/10.1016/j.jaad.2020.09.042.

[7] R. Sinclair, Fortnightly review: Male pattern androgenetic alopecia, BMJ 317 (1998) 865–869, https://doi.org/10.1136/bmj.317.7162.865.

[8] K. Li, F. Liu, Y. Sun, Y. Gan, D. Zhu, H. Wang, Q. Qu, J. Wang, R. Chen, Z. Fan, B. Liu, D. Fu, Y. Miao, Z. Hu, Association of fibrosis in the bulge portion with hair follicle miniaturization in androgenetic alopecia, J. Am. Acad. Dermatol. 86 (2022) 213–215, https://doi.org/10.1016/j.jaad.2021.01.078.

[9] R. Xiao, L.N. Lee, Updated Review of Treatment of Androgenetic Alopecia, Facial Plast. Surg. Clin. North Am. 32 (2024) 417–423, https://doi.org/10.1016/j.fsc.2024.02.006.

[10] F.F.V. Santana, A.A. Lozi, R.V. Gonçalves, J. Da Silva, S.L.P. Da Matta, Comparative effects of finasteride and minoxidil on the male reproductive organs: a systematic review of in vitro and in vivo evidence, Toxicol. Appl. Pharmacol. 478 (2023) 116710, https://doi.org/10.1016/j.taap.2023.116710.

[11] F.J. Navarro-Triviño, M.D. Pegalajar-García, A. Gil-Villalba, R. Ruiz-Villaverde, Allergic Contact Dermatitis Due to Minoxidil in a Patient with Alopecia Areata, Actas Dermosifiliogr. 113 (2022) S8–S9, https://doi.org/10.1016/j.ad.2021.08.009.

[12] D.-D. Nguyen, P. Herzog, E.B. Cone, M. Labban, K.C. Zorn, B. Chughtai, S. Basaria, D.S. Elterman, Q.-D. Trinh, N. Bhojani, Disproportional signal of sexual dysfunction reports associated with finasteride use in young men with androgenetic alopecia: A pharmacovigilance analysis of VigiBase, J. Am. Acad. Dermatol. 88 (2023) 179–181, https://doi.org/10.1016/j.jaad.2022.03.037.

[13] Y. Zhang, C. Ni, Y. Huang, Y. Tang, K. Yang, X. Shi, Y. Zhang, Z. Li, J. Wang, Y. Zhu, H. Li, Y. Ma, J. Lin, J. Wang, Q. Liu, W. Wu, Hair growth-promoting effect of Resveratrol in mice, human hair follicles and dermal papilla cells CCID 14 (2021) 1805–1814, https://doi.org/10.2147/CCID.S335963.

[14] Y.H. Lee, H.-J. Choi, J.Y. Kim, J.-E. Kim, J.-H. Lee, S.-H. Cho, M.-Y. Yun, S. An, G. Y. Song, S. Bae, Ginsenoside Rg4 Enhances the Inductive Effects of Human Dermal Papilla Spheres on Hair Growth Via the AKT/GSK-3β/β-Catenin Signaling Pathway, J. Microbiol. Biotechnol. 31 (2021) 933–941, https://doi.org/10.4014/jmb.2101.01032.

[15] X. Hu, X. Li, S. Wu, X. Jiang, G. Chen, Y. Hu, J. Sun, W. Bai, Cyanidin-3-O-glucoside and its derivative vitisin A alleviate androgenetic alopecia by exerting anti-androgen effect and inhibiting dermal papilla cell apoptosis, Eur. J. Pharmacol. 963 (2024) 176237, https://doi.org/10.1016/j.ejphar.2023.176237.

[16] M. Liu, G. He, F. Wang, Y. Sun, S. Ma, Y. Hao, Y. Wang, Pilose antler extract promotes hair growth in androgenic alopecia mice by promoting the initial anagen phase, Biomed. Pharmacother. 174 (2024) 116503, https://doi.org/10.1016/j.biopha.2024.116503.

[17] S. Wu, Progress on the mechanism of natural products alleviating androgenetic alopecia, Eur. J. Med. Chem. 264 (2024) 116022, https://doi.org/10.1016/j.ejmech.2023.116022.

[18] Y. Lin, X. Qi, H. Liu, K. Xue, S. Xu, Z. Tian, The anti-cancer effects of fucoidan: a review of both in vivo and in vitro investigations, Cancer Cell Int. 20 (2020) 154, https://doi.org/10.1186/s12935-020-01233-8.

[19] H. Geun Lee, T.U. Jayawardena, N.M. Liyanage, K.-M. Song, Y.-S. Choi, Y.-J. Jeon, M.-C. Kang, Antioxidant potential of low molecular weight fucoidans from Sargassum autumnale against H2O2-induced oxidative stress in vitro and in zebrafish models based on molecular weight changes, Food Chem. 384 (2022) 132591, https://doi.org/10.1016/j.foodchem.2022.132591.

[20] H.M. Selim, W.A. Negm, M.F. Hawwal, I.A. Hussein, E. Elekhnawy, R. Ulber, A. Zayed, Fucoidan mitigates gastric ulcer injury through managing inflammation, oxidative stress, and NLRP3-mediated pyroptosis, Int. Immunopharmacol. 120 (2023) 110335, https://doi.org/10.1016/j.intimp.2023.110335.

[21] H.R. Fletcher, P. Biller, A.B. Ross, J.M.M. Adams, The seasonal variation of fucoidan within three species of brown macroalgae, Algal Res. 22 (2017) 79–86, https://doi.org/10.1016/j.algal.2016.10.015.

[22] K.S. Bittkau, S. Neupane, S. Alban, Initial evaluation of six different brown algae species as source for crude bioactive fucoidans, Algal Res. 45 (2020) 101759, https://doi.org/10.1016/j.algal.2019.101759.

[23] H. Xu, J. Wang, Y. Chang, J. Xu, Y. Wang, T. Long, C. Xue, Fucoidan from the sea cucumber Acaudina molpadioides exhibits anti-adipogenic activity by modulating the Wnt/β-catenin pathway and down-regulating the SREBP-1c expression, Food Funct. 5 (2014) 1547–1555, https://doi.org/10.1039/C3FO60716J.

[24] Z. Li, N. Wu, J. Wang, Y. Yue, L. Geng, Q. Zhang, Low molecular weight fucoidan alleviates cerebrovascular damage by promoting angiogenesis in type 2 diabetes mice, Int. J. Biol. Macromol. 217 (2022) 345–355, https://doi.org/10.1016/j.ijbiomac.2022.07.053.

[25] K.G.I.S. Kirindage, A.M.K. Jayasinghe, N.K. Cho, S.H. Cho, H.M. Yoo, K. Jung, J. S. Kim, G. Ahn, Fucoidan refined from Saccharina japonica ameliorates ambient particulate matter-induced inflammation in keratinocytes, underlying fibroblasts, and 12-O-tetradecanoylphorbol 13-acetate-induced ear edema in mice, Int. J. Biol. Macromol. 277 (2024) 134324, https://doi.org/10.1016/j.ijbiomac.2024.134324.

[26] C.-Y. Huang, C.-Y. Huang, C.-C. Yang, T.-M. Lee, J.-S. Chang, Hair growth-promoting effects of Sargassum glaucescens oligosaccharides extracts, J. Taiwan Inst. Chem. Eng. 134 (2022) 104307, https://doi.org/10.1016/j.jtice.2022.104307.

[27] K. Shin, T.-S. Kim, J. Kyung, D. Kim, D. Park, E.-K. Choi, S.-P. Lee, W.-S. Yang, M.-H. Kang, Y.-B. Kim, Effectiveness of the combinational treatment of Laminaria japonica and Cistanche tubulosa extracts in hair growth, Lab Anim Res 31 (2015) 24, https://doi.org/10.5625/lar.2015.31.1.24.

[28] N.E. Thomford, D.A. Senthebane, A. Rowe, D. Munro, P. Seele, A. Maroyi, K. Dzobo, Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Drug Discovery, IJMS 19 (2018) 1578, https://doi.org/10.3390/ijms19061578.

[29] A. Najmi, S.A. Javed, M. Al Bratty, H.A. Alhazmi, Modern approaches in the discovery and development of plant-based natural products and their analogues as potential therapeutic agents, Molecules 27 (2022) 349, https://doi.org/10.3390/molecules27020349.

[30] Z. Wang, Y. Feng, L. Ma, X. Li, W. Ding, X. Chen, Hair growth promoting effect of white wax and policosanol from white wax on the mouse model of testosterone-induced hair loss, Biomed. Pharmacother. 89 (2017) 438–446, https://doi.org/10.1016/j.biopha.2017.02.036.

[31] G. Wang, Z. Wang, J. Zhang, Y. Shen, X. Hou, L. Su, W. Chen, J. Chen, X. Guo, H. Song, Treatment of androgenetic alopecia by exosomes secreted from hair papilla cells and the intervention effect of LTF, J of Cosmetic Dermatology 22 (2023) 2996–3007, https://doi.org/10.1111/jocd.15890.

[32] D. Fu, J. Huang, K. Li, Y. Chen, Y. He, Y. Sun, Y. Guo, L. Du, Q. Qu, Y. Miao, Z. Hu, Dihydrotestosterone-induced hair regrowth inhibition by activating androgen receptor in C57BL6 mice simulates androgenetic alopecia, Biomed. Pharmacother. 137 (2021) 111247, https://doi.org/10.1016/j.biopha.2021.111247.

[33] R. Gao, Z. Yu, C. Lv, X. Geng, Y. Ren, J. Ren, H. Wang, F. Ai, B. Zhang, B. Yue, Z. Wang, W. Dou, Medicinal and edible plant Allium macrostemon Bunge for the treatment of testosterone-induced androgenetic alopecia in mice, J. Ethnopharmacol. 315 (2023) 116657, https://doi.org/10.1016/j.jep.2023.116657.

[34] Z. Wu, Y. Zhu, H. Liu, G. Liu, F. Li, Wnt10b promotes hair follicles growth and dermal papilla cells proliferation via Wnt/β-catenin signaling pathway in Rex rabbits, Biosci. Rep. 40 (2020) BSR20191248, https://doi.org/10.1042/BSR20191248.

[35] Y. Zhang, Q. Tang, B. Zeng, F. Wang, M. Luo, P. Huang, L. Chen, H. Wang, *Dendrobium officinale* polysaccharide promotes angiogenesis as well as follicle regeneration and hair growth through activation of the WNT signaling pathway, Regen. Ther. 26 (2024) 114–123, https://doi.org/10.1016/j.reth.2024.04.014.

[36] Z. Deng, M. Chen, F. Liu, Y. Wang, S. Xu, K. Sha, Q. Peng, Z. Wu, W. Xiao, T. Liu, H. Xie, J. Li, Androgen receptor-mediated paracrine signaling induces regression of blood vessels in the dermal papilla in androgenetic alopecia, J. Invest. Dermatol 142, 2022, pp. 2088–2099, https://doi.org/10.1016/j.jid.2022.01.003.

[37] J. Kong, W. Qiang, J. Jiang, X. Hu, Y. Chen, Y. Guo, H. Liu, S. Sun, H. Gao, Y. Zhang, Y. Gao, X. Liu, X. Liu, H. Li, Safflower oil body nanoparticles deliver hFGF10 to hair follicles and reduce microinflammation to accelerate hair regeneration in androgenetic alopecia, Int. J. Pharm. 616 (2022) 121537, https://doi.org/10.1016/j.ijpharm.2022.121537.

[38] W.-S. Lee, Y. Oh, J.H. Ji, J.K. Park, D.W. Kim, W.-Y. Sim, H.O. Kim, S.-W. Hwang, T.Y. Yoon, Y.C. Kye, G.S. Choi, M.-B. Kim, C.-H. Huh, B.I. Ro, S.-J. Kim, J.-H. Kim, Y. Lee, Analysis of familial factors using the basic and specific (BASP) classification in Korean patients with androgenetic alopecia, J. Am. Acad. Dermatol. 65 (2011) 40–47, https://doi.org/10.1016/j.jaad.2010.05.005.

[39] N.J. Sadgrove, The 'bald' phenotype (androgenetic alopecia) is caused by the high glycaemic, high cholesterol and low mineral 'western diet', Trends Food Sci. Technol. 116 (2021) 1170–1178, https://doi.org/10.1016/j.tifs.2021.06.056.

[40] C. Fortes, S. Mastroeni, T. Mannooranparampil, D. Abeni, A. Panebianco, Mediterranean diet: fresh herbs and fresh vegetables decrease the risk of Androgenetic Alopecia in males, Arch. Dermatol. Res. 310 (2018) 71–76, https://doi.org/10.1007/s00403-017-1799-z.

[41] D.A. Whiting, Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss, J. Am. Acad. Dermatol. 45 (2001) S81–S86, https://doi.org/10.1067/mjd.2001.117428.

[42] S. Wang, M. Li, S. Qin, R. Wang, L. Dong, S. Wang, F. Xiao, Serum lipidomic changes and sex differences in androgenetic alopecia, Heliyon 10 (2024) e26204, https://doi.org/10.1016/j.heliyon.2024.e26204.

[43] S. Inui, S. Itami, Molecular basis of androgenetic alopecia: From androgen to paracrine mediators through dermal papilla, J. Dermatol. Sci. 61 (2011) 1–6, https://doi.org/10.1016/j.jdermsci.2010.10.015.

[44] M.K. Thakur, V. Paramanik, Role of steroid hormone coregulators in health and disease, Horm. Res. Paediatr. 71 (2009) 194–200, https://doi.org/10.1159/000201107.

[45] D.W. Shin, The molecular mechanism of natural products activating Wnt/β-catenin signaling pathway for improving hair loss, Life 12 (2022) 1856, https://doi.org/10.3390/life12111856.

[46] Q. Liu, Y. Tang, Y. Huang, J. Wang, K. Yang, Y. Zhang, W. Pu, J. Liu, X. Shi, Y. Ma, C. Ni, Y. Zhang, Y. Zhu, H. Li, J. Wang, J. Lin, W. Wu, Insights into male androgenetic alopecia using comparative transcriptome profiling: hypoxia-inducible factor-1 and Wnt/β-catenin signalling pathways, Br. J. Dermatol. 187 (2022) 936–947, https://doi.org/10.1111/bjd.21783.

[47] J.M. Ceruti, G.J. Leirós, M.E. Balañá, Androgens and androgen receptor action in skin and hair follicles, Mol. Cell. Endocrinol. 465 (2018) 122–133, https://doi.org/10.1016/j.mce.2017.09.009.

[48] Z. Deng, M. Chen, F. Liu, Y. Wang, S. Xu, K. Sha, Q. Peng, Z. Wu, W. Xiao, T. Liu, H. Xie, J. Li, Androgen receptor–mediated paracrine signaling induces regression of blood vessels in the dermal papilla in androgenetic alopecia, J. Invest. Dermatol 142, 2022, pp. 2088–2099, e9, https://doi.org/10.1016/j.jid.2022.01.003.

[49] W.R. Heymann, The inflammatory component of androgenetic alopecia, J. Am. Acad. Dermatol. 86 (2022) 301–302, https://doi.org/10.1016/j.jaad.2021.11.013.

[50] J. Plante, M. Valdebran, J. Forcucci, O. Lucas, D. Elston, Perifollicular inflammation and follicular spongiosis in androgenetic alopecia, J. Am. Acad. Dermatol. 86 (2022) 437–438, https://doi.org/10.1016/j.jaad.2021.09.040.

[51] Y. Miao, W. Jiang, X.-M. Liu, P.-L. Shi, Z.-X. Fan, L.-J. Du, G.-F. Wang, X.-N. Liu, Z.-H. Guo, Y. Liu, F. Liu, Y.-R. Liu, Z.-Q. Hu, Identification of functional patterns of androgenetic alopecia using transcriptome profiling in distinct locations of hair follicles, J. Invest. Dermatol. 138 (2018) 972–975, https://doi.org/10.1016/j.jid.2017.10.027.

[52] Y. Jiang, Y. Zhao, Z. Liu, J.K.-H. Fang, K.P. Lai, R. Li, Roles and mechanisms of fucoidan against dermatitis: A review, Int. J. Biol. Macromol. 279 (2024) 135268, https://doi.org/10.1016/j.ijbiomac.2024.135268.

[53] H. Fu, W. Li, J. Liu, Q. Tang, Z. Weng, L. Zhu, B. Ding, Ellagic acid inhibits dihydrotestosterone-induced ferroptosis and promotes hair regeneration by activating the wnt/β-catenin signaling pathway, J. Ethnopharmacol. 330 (2024) 118227, https://doi.org/10.1016/j.jep.2024.118227.