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ORIGINAL RESEARCH

Berberine Inhibits Acne-Related Lipid Secretion and Inflammation by Regulating the hsa-miR-3150a-3p/TP53 Pathway

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Background: Acne is a common skin illness that damages both the appearance and mental health of sufferers.
Objective: The purpose of this study was to investigate the therapeutic value of berberine (BBR) in acne.
Methods: Firstly, TP53 was mined to be the hub gene through network pharmacology. Then, hsa-miR-3150a-3p was predicted to be the upstream miRNA of TP53 by the ENCORI/starBase database, and their expressions and targeting relationship were verified by RT-qPCR /Western blot and dual-luciferase reporter experiment, respectively. Overexpressing hsa-miR-3150a-3p and TP53 to investigate their roles in lipid secretion and inflammation of biofilm-derived *Cutibacterium acnes* (Bio-*C. acnes*)-induced sebocytes. 40 μM of BBR was used to evaluate its effect on sebocyte function. The secretion of fatty acid, triglyceride, IL-6, and IFN-γ was detected by the specific ELISA kit.
Results: Hsa-miR-3150a-3p inhibited TP53 expression by targeting its 3'UTR. BBR hindered *C. acnes* growth and biofilm formation in a concentration-dependent manner. BBR decreased the lipid secretion capacity and inflammatory response in Bio-*C. acnes*-treated sebocytes, which were synergistically enhanced by TP53 overexpression and were reversed by up-regulation of hsa-miR-3150a-3p.
Conclusion: BBR alleviated acne symptoms caused by Bio-*C. acnes* via the hsa-miR-3150a-3p/TP53 axis.
Keywords: berberine, *Cutibacterium acnes*, sebocytes, lipid secretion, inflammation

Introduction

Acne, also known as acne vulgaris, is a chronic inflammatory skin disease common in adolescent men and women. Its typical features include pustules, papules sebum overflow, etc., which can cause inflammation in the later stage.[1] Acne is caused by a variety of factors, including abnormal androgens, keratinization of perifollicle cells, increased secretion of sebaceous glands, and inflammation caused by *C. acnes*.[2,3] Based on these mechanisms, acne treatment focuses on reducing sebaceous gland secretion, inhibiting *C. acnes* growth, regulating hormone levels, and reducing inflammation.[4] Topical antibiotics are a class of drugs commonly used in the treatment of acne, but they are easy to lead to the resistance of *C. acnes*, and the formation of biofilm is an important reason for this resistance.[5]

The rhizome of *Coptidis Rhizoma* is a famous Chinese herbal medicine, which has the effect of clearing heat and drying dampness, clearing fire, and detoxifying.[6,7] According to the current reports, *Coptidis Rhizoma* has obvious anti-inflammatory and anti-bacterial functions. Its extract can inhibit the production of monocyte chemoattractant protein-1 in LPS-induced mouse macrophages and inhibit the activation of transcription factors AP-1 and NF-κB in a time- and dose-dependent manner,[8] whose low doses can hinder the biofilm formation of *Streptococcus suis*.[9] As the main active ingredient of *Coptidis Rhizoma*, the anti-inflammatory and anti-bacterial effects of BBR are self-evident. BBR treatment alleviates the infiltration of inflammatory cells in the liver of mice with non-alcoholic steatohepatitis,[10] and it could alleviate the immune cell infiltration and decrease the levels of IL-10, IL-1β, and TNF-α in the periodontal tissues of periodontitis rats by up-regulating GRP30 and inhibiting the phosphorylation of p38 MAPK and NF-κB.[11] BBR has been shown to exhibit activity against methicillin-resistant *Staphylococcus aureus* by impairing the integrity of cell membranes.[12] Sun et al reported the obvious growth

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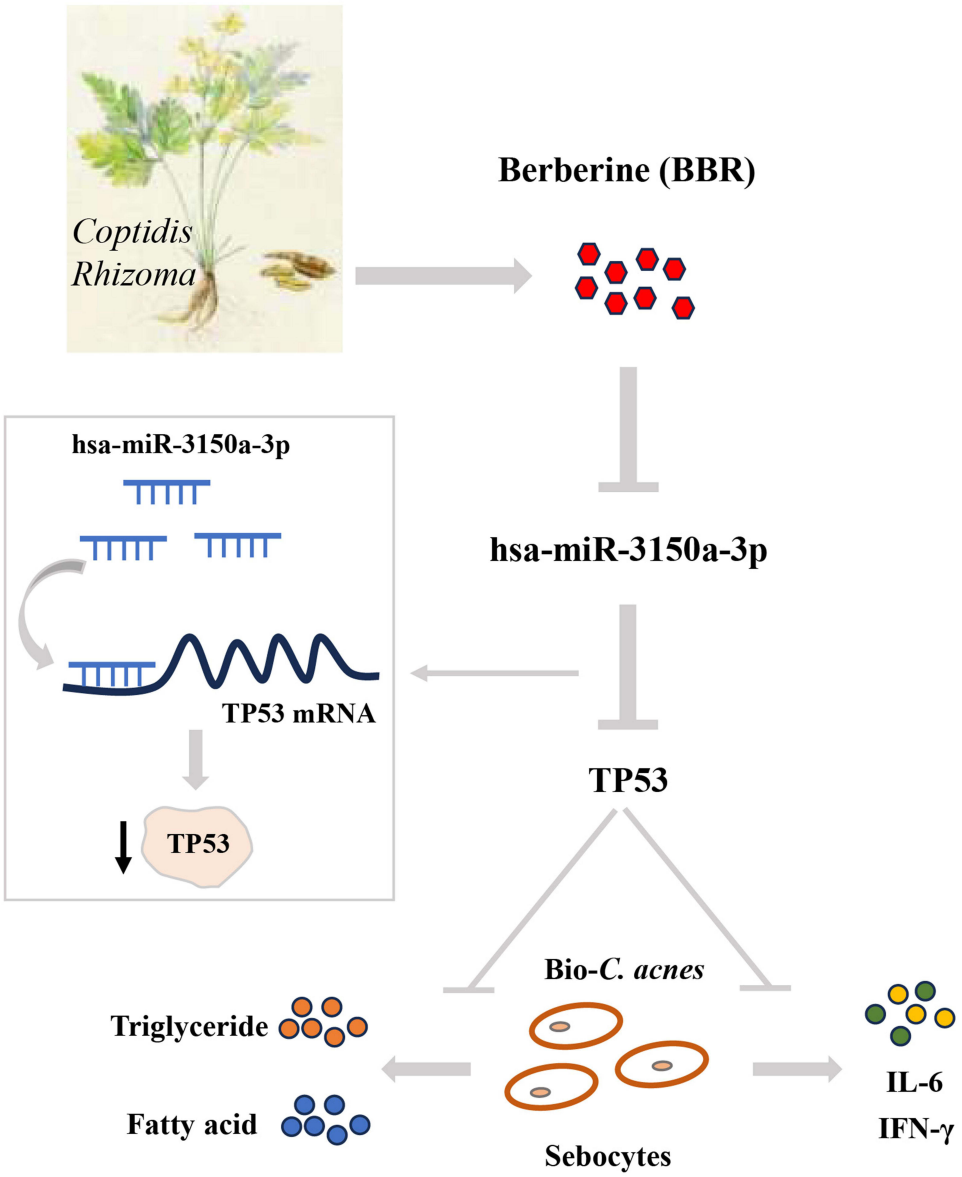
Graphical Abstract



inhibition effect of BBR on different strains of *C. acnes*. BBR can reduce the number of *C. acnes* colonized in the ears of mice and decrease the production of IL-1β, IL-6, and TNF-α in the ear tissues.[13] However, the molecular mechanism of BBR in treating acne caused by *C. acnes* remains to be explored.

Based on the above background, this study aims to explore the specific mechanism of BBR in the treatment of acne. Here, we identified TP53 as a potential target that BBR might regulate in acne by using network pharmacology methods and predicted hsa-miR-3150a-3p as an upstream molecule regulating TP53 by using bioinformatics methods. Through relevant experimental verification, we elucidated a novel mechanism by which BBR influences the lipid secretion function and inflammation of *C. acnes*-induced sebocytes by regulating the hsa-miR-3150a-3p/TP53 axis.

Materials and Methods

Network Pharmacology

The TCMSP 2.0 database (https://www.tcmsp-e.com) was used to screen the active components of *C. acnes*. The screening conditions were oral bioavailability (OB) ≥ 30%, drug-likeness (DL) ≥ 0.18, Caco-2 ≥ −0.4. The targets for these components were retrieved through the HERB database (http://herb.ac.cn). The STRING database (https://cn.string-db.org/) was applied to construct the protein–protein interaction (PPI) network, and the herb-ingredient-target network was constructed using Cytoscape software.

Bioinformatics Analysis

The public dataset GSE212605 was downloaded from the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/). The ENCORI/starBase database (https://rnasysu.com/encori/index.php) was used to predict the upstream miRNAs of TP53 and the binding sites of hsa-miR-3150a-3p targeting TP53. According to Article 32 of the "Measures for the Ethical Review of Life Science and Medical Research Involving the Human Body" issued by China on February 18, 2023, if the following circumstances of life science and medical research involving the human body are conducted using human information data or biological samples and do not cause harm to the human body, do not involve sensitive personal information or commercial interests, ethical review may be exempted: (1) Conducting research by using publicly available data obtained through legal means or by observing data that does not interfere with public behavior; (2) Conducting research using anonymized information data. Therefore, the ethical review of this study was exempted by the Ethics Committee of Hebei Medical University Third Hospital.

Reagents and Materials

Immortalized human sebocytes (SZ95) were purchased from BLUEFBIO company (CHN). BBR and hsa-miR-3150a-3p mimic were from MedChemExpress (USA). The dual-luciferase vector was commissioned to be constructed by GENE CREATE (CHN). The Lipo6000™ Transfection Reagent from Beyotime (CHN) was used for the transfection of cells.

Cell Culture and Treatment

SZ95 cells were maintained in a sebomed medium (Sigma-Aldrich, USA) in a 37°C-incubator containing 5% CO_2. SZ95 cells were exposed to 40 μM of BBR for 24 hours to explore BBR's effect on cell function.

RT-qPCR

Total RNA was extracted using RNAiso Plus (Takara Bio, JPN) and cDNA was synthesized according to the manufacturer's instructions. Quantitative PCR was performed in the Bio-Rad CFX96 system (Bio-Rad, USA) using a fluorescent quantitative PCR kit (Biosharp, CHN). The internal reference gene for quantification of mRNA was GAPDH, and U6 was for miRNA. The relative expression of miRNA or mRNA was measured by $2^{-\Delta\Delta Ct}$.

Dual-Luciferase Reporter Assay

Hsa-miR-3150a-3p mimic or negative control (NC) was co-transfected into SZ95 cells with the luciferase vector containing wild-type/mutant TP53 fragment, respectively. After 48 hours, luciferase activity was assessed using a dual luciferase reporter assay kit (Promega, USA) according to the manufacturer's instructions.

Western Blot

Total protein was extracted using RIPA lysate (Solarbio, CHN) containing protease inhibitor and quantified with BCA kit (Solarbio). The protein (50 μg protein/pore) was isolated with 10% SDS polyacrylamide gel and transferred to the PVDF membrane. The membrane was incubated in 5% skim milk at room temperature (RT) for 2 hours and incubated with primary antibody at 4°C overnight subsequently. The membrane was then incubated with the secondary antibody (Immunoway, UK) under RT for 1.5 hours, and the protein signal was detected using the Ultra High Sensitivity ECL Kit (GLPBIO, USA).

Determination of *C. acnes* Growth and Biofilm Formation

C. acnes (ATCC 6919) were suspended in the reinforced clostridial medium (RCM, J&K Scientific, CHN) and grew at 37°C. *C. acnes* were exposed to the RCM containing different concentrations of BBR. The optical density value of each group was measured using a spectrophotometer 24 hours later, to evaluate the influence of BBR on *C. acnes* growth. A bacterial suspension of 1×10^7 CFU/mL was inoculated into a 48-well plate. *C. acnes* were treated with different concentrations of BBR for 24 hours. After the suspended cells were removed, the adherent cells were washed with sterile water and then fixed with 100% methanol for 30 minutes. After being stained for 30 minutes using crystal violet solution, the biofilm was washed to remove excess dye. Finally, the stain on the biofilm was dissolved with a solution of 20% methanol and 5% acetic acid. A spectrophotometer was used for quantification at 595 nm.

Bio-*C. acnes* Acquisition

The sterile cell culture caps (13 mm) were inserted into the 24-well plate. Five hundred microliters *C. acnes* suspension (1×10^8 CFU/mL) was added to each well. After 8 days of anaerobic culture at 37°C, the biofilm was scraped from the culture plate to re-suspended in PBS buffer and oscillated on a shaker to fully disperse the cells. *C. acnes* suspension with a cell density of 2×10^8 CFU/mL was treated with SZ95 cells after heat treatment at 80°C for 30 minutes.

Detection of Lipid Secretion

The secretory function of sebocytes was evaluated by measuring fatty acid and triglyceride content in cell culture using an ELISA kit (FineTest, USA).

Detection of Inflammation

The inflammatory response was measured by detecting the production of IL-6 and IFN-γ and the expression of NF-κB. The ELISA kits for IL-6 and IFN-γ were purchased from Abcam Bio (UK).

Mouse Acne Model

A total of 18 BALB/c mice were purchased from Cyagen Biotech (CHN). After adapting for 5 days in our laboratory, they were randomly divided into three groups: The CTR group (injected with normal saline), the *C. acnes* group (injected with 2×10^8 CFU *C. acnes* at the ear), and the *C. acnes* + BBR group (injected with 2×10^8 CFU *C. acnes* and wet compress with 40 μM BBR). After 24 hours, the mice were euthanized, and the skin tissues from their ears were harvested for analysis. All the experimental procedures followed the principles set by the Animal Care and Use Committee of Hebei Medical University Third Hospital.

Statistical Analysis

All statistical analyses were performed in GraphPad Prism 5 software. Student's *t*-test was used to analyze the difference between the two groups. For multiple comparisons, the one-way ANOVA analysis was performed. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ were considered statistically significant.

Results

Screening of Hub Gene and Plant Component

The active components of *Coptidis Rhizoma* were obtained by the TCMSP 2.0 database, and the targets of these components were retrieved by the HERB database. Then, a PPI network was constructed in the STRING database based on these target proteins, and a visual network diagram was made using Cytoscape software (Supplementary Figure 1A). The top 10 nodes in the network were screened by calculating the node degree value, including TP53 (46), AKT1 (32), JUN (29), TNF (27), IL6 (24), ESR1 (21), MAPK3 (21), IL1B (20), MAPK1 (20), and MYC (19). As shown in the Venn diagram in Supplementary Figure 1B, these nodes are the genes associated with acne vulgaris, with TP53 showing the highest nodal degree value. The herb-ingredient-target network shows that TP53 is the target of BBR (Figure 1). BBR is the main active component of *Coptidis Rhizoma*, so it was selected as the component of interest to us, and TP53 was identified as the hub gene.

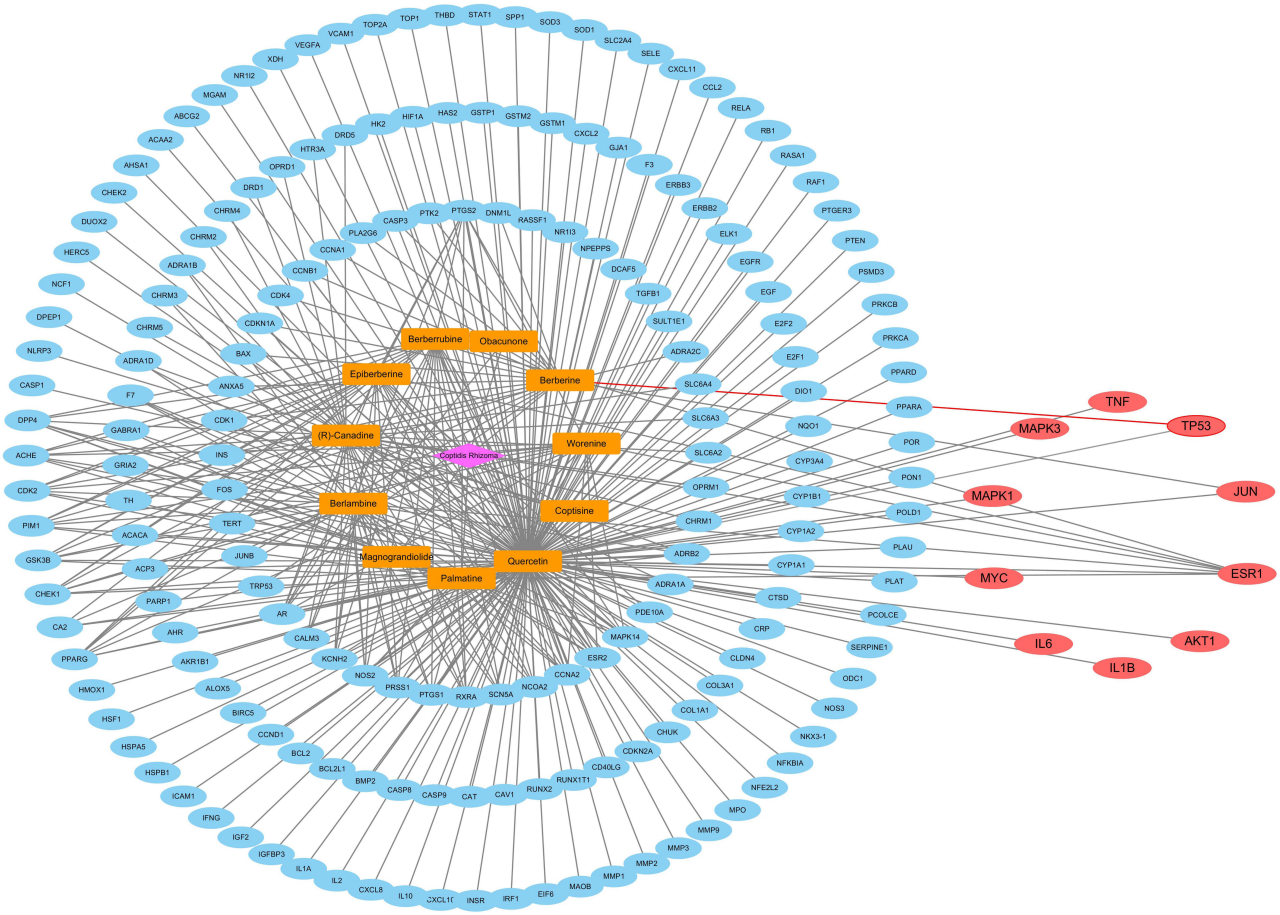


Figure 1 The network of *Coptidis Rhizoma*-ingredient-target.

Exploration of the Molecular Mechanism of Acne Occurrence

To further explore the molecular mechanism of acne occurrence, the miRNAs targeting TP53 were predicted by the ENCORI/starBase database. By analyzing the public dataset GSE212605, a total of 181 miRNAs were identified to be high-expressed in acne lesions. There were 11 miRNAs which were the intersection of these miRNAs (Figure 2A), and their expressions were shown in Figure 2B. Since the fold change of hsa-miR-3150a-3p was the most obvious ($\log_2$FC = 4.27), it was chosen to be our study object. The sequence of hsa-miR-3150a-3p targeting TP53 3'UTR was obtained by the ENCORI/starBase database (Figure 2C). The mimic and inhibitor of hsa-miR-3150a-3p were introduced to explore its regulatory effect on TP53. Transfection of the mimic significantly up-regulated the hsa-miR-3150a-3p level, and its inhibitor restrained hsa-miR-3150a-3p expression obviously (Supplementary Figure 2A and B). Based on the target sites of hsa-miR-3150a-3p, the luciferase vector containing wild-type (wt) or mutant (mut) TP53 fragment was constructed. The miR-3150a-3p mimic suppressed the luciferase activity of cells with wt-TP53 vector transfection but did not affect the cells transfected with mut-TP53 vector (Figure 2D), proving the targeting relationship of hsa-miR-3150a-3p to TP53. The up-regulation of hsa-miR-3150a-3p inhibited TP53 expression, which was promoted by hsa-miR-3150a-3p inhibitor (Figure 2E), indicating that hsa-miR-3150a-3p negatively regulated TP53.

Increased sebaceous lipid secretion is an important factor causing acne. The TP53 plasmid (p-TP53) was introduced for mechanism study. The expression level of TP53 increased after p-TP53 transfection (Supplementary Figure 2C). FASN is a fatty acid synthetase. DGAT1 is a diacylglycerol o-acyltransferase, which is a key enzyme in the synthesis of triglycerides. Transfection of hsa-miR-3150a-3p mimic promoted the expressions of FASN and DGAT1, which was down-regulated by TP53 overexpression. The co-transfection of p-TP53 reversed the positive regulation of FASN/DGAT1 expression by hsa-miR-3150a-3p mimic (Figure 2F–G). Furthermore, overexpression of TP53 reversed the

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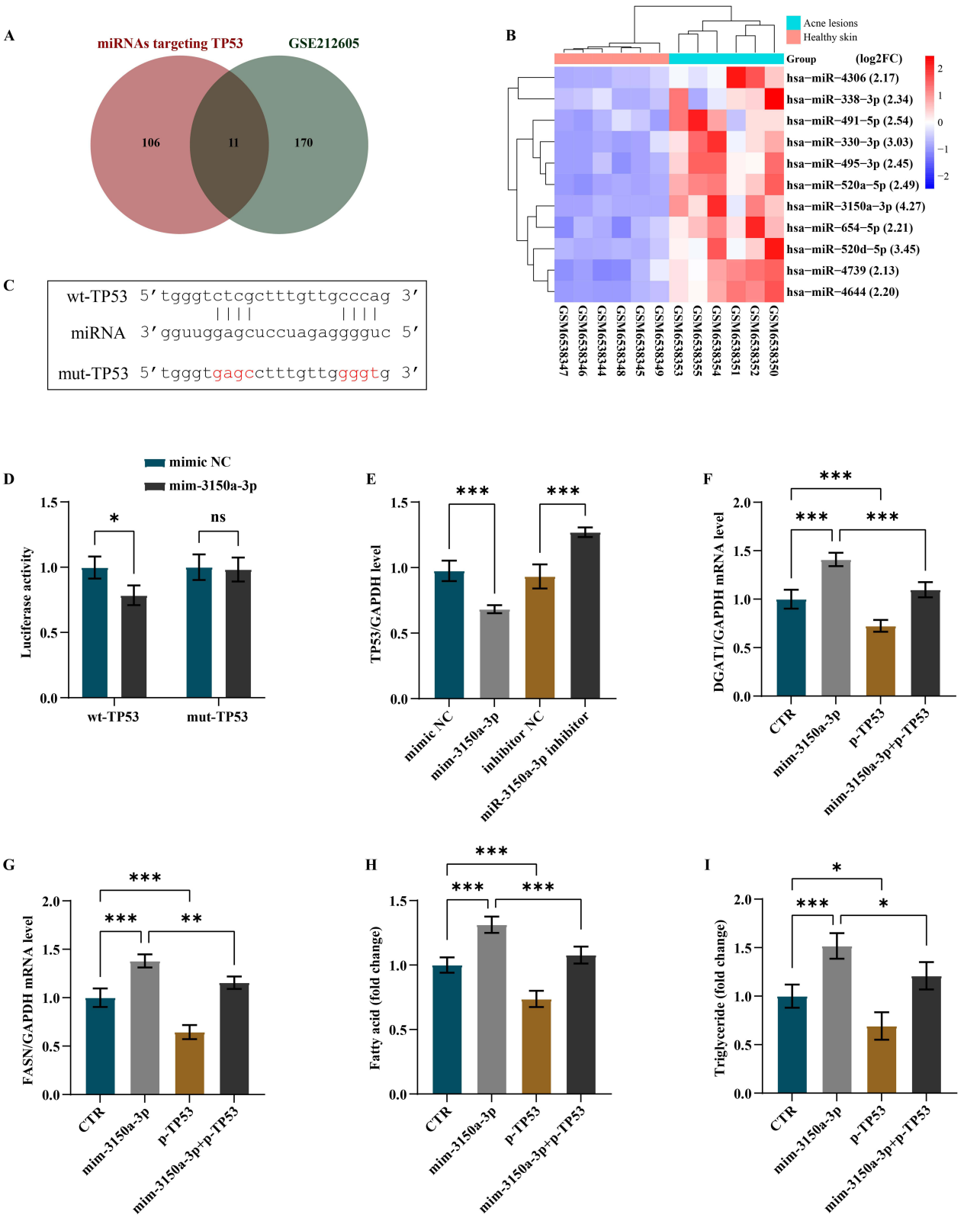

Figure 2 BBR regulated the expression of hsa-miR-3150a-3p/TP53 axis. (**A**) Venn diagram between the miRNAs targeting TP53 and the high-expressed miRNAs in acne lesions. (**B**) Expression map of 11 miRNAs in GSE212605 dataset. (**C**) Binding sites of hsa-miR-3150a-3p to TP53 3'UTR. (**D**) Targeting effect of hsa-miR-3150a-3p on TP53. (**E**) Regulation of TP53 expression by hsa-miR-3150a-3p. (**F** and **G**) Regulation of FASN/DGAT1 expression by the hsa-miR-3150a-3p/TP53 axis. (**H** and **I**) Effect of hsa-miR -3150a-3p/TP53 axis on fatty acid and triglyceride secretion. ns, no significant difference. *p < 0.05, **p < 0.01, ***p < 0.001.

increased secretion of fatty acid and triglyceride caused by hsa-miR-3150a-3p upregulation in SZ95 cells (Figure 2H–I), suggesting that the hsa-miR-3150a-3p/TP53 axis plays an important role in the progression of acne.

The Potential of BBR in Treating Acne

C. acnes colonization is the key pathogenic factors of acne.[14]

The Anti-Bacterial Effect of BBR

Different concentrations of BBR were used to treat *C. acnes*. A low concentration of BBR (10 μM) inhibited the growth of *C. acnes*, and with the increase of the concentration, its inhibitory effect on *C. acnes* growth was more significant (Figure 3A). Biofilm formation is an important virulence characteristic of *C. acnes*. Our results show that BBR restrained the biofilm formation ability of *C. acnes* in a concentration-dependent manner (Figure 3B). These findings reveal the significant inhibitory effect of BBR on *C. acnes* and suggest its potential in treating acne.

Since 40 μM BBR significantly inhibited the growth and biofilm formation of *C. acnes* and caused no obvious damage to sebocyte viability (Supplementary Figure 3), this concentration of the drug was chosen for the subsequent cell experiments.

BBR Inhibited Lipid Hypersecretion in *C. acnes*-Stimulated Sebocytes by Regulating the hsa-miR-3150a-3p/TP53 Axis

In sebocytes, after Bio-*C. acnes* induction, the expressions of FASN and DGAT1 increased, and the secretion levels of fatty acid and triglyceride elevated. BBR mitigated the enhanced secretory function of SZ95 cells induced by Bio-*C. acnes* (Figure 4A–D). In these respects, overexpressing TP53 played a synergistic role with BBR, while transfection of hsa-miR-3150a-3p mimic attenuated the effects of BBR (Figure 4A–D). BBR treatment reduced the cellular level of hsa-miR-3150a-3p (Figure 4E). Inversely, BBR promoted TP53 expression, which was reversed by the miR-3150a-3p mimic (Figure 4F). These results prove that BBR promoted TP53 expression by inhibiting hsa-miR-3150a-3p. These findings manifest that BBR restrained the *C. acnes*-stimulated sebocyte secretion function by regulating hsa-miR-3150a-3p/TP53 axis.

BBR Alleviated *C. acnes*-Induced Inflammation via the hsa-miR-3150a-3p/TP53 Axis

ELISA analysis displayed that BBR hindered the increased production of pro-inflammatory factors IL-6 and IFN-γ in Bio-*C. acnes*-induced SZ95 cells. These effects of BBR were reversed by transfection of hsa-miR-3150a-3p mimic and further enhanced by TP53 overexpression, and co-transfection of p-TP53 weakened the function of hsa-miR-3150a-3p mimic (Figure 5A and B). What's more, upregulation of hsa-miR-3150a-3p reversed the inhibitory effect of BBR on NF-κB expression in Bio-*C. acnes*-treated cells, which was reversed by TP53 overexpression (Figure 5C). These data suggest that BBR inhibited NF-κB pathway-mediated inflammatory responses via the hsa-miR-3150a-3p/TP53 axis. In the acne mouse model induced by *C. acnes*, BBR treatment significantly reduced the production of pro-inflammatory factors in their skin tissue (Figure 5D), which further demonstrated the anti-inflammatory effect of BBR. Moreover, *C. acnes*

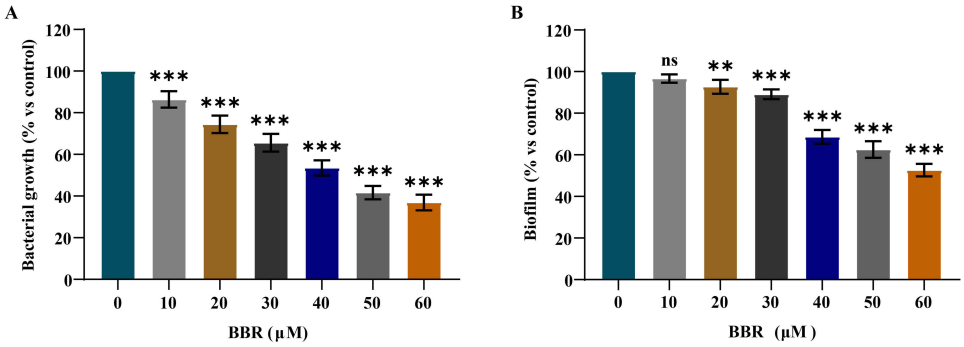

Figure 3 The anti-bacterial effect of BBR. (**A** and **B**) Inhibition of different concentrations of BBR on growth and biofilm formation of *C. acnes*. ns, no significant difference. $^{**}p < 0.01$, $^{***}p < 0.001$.

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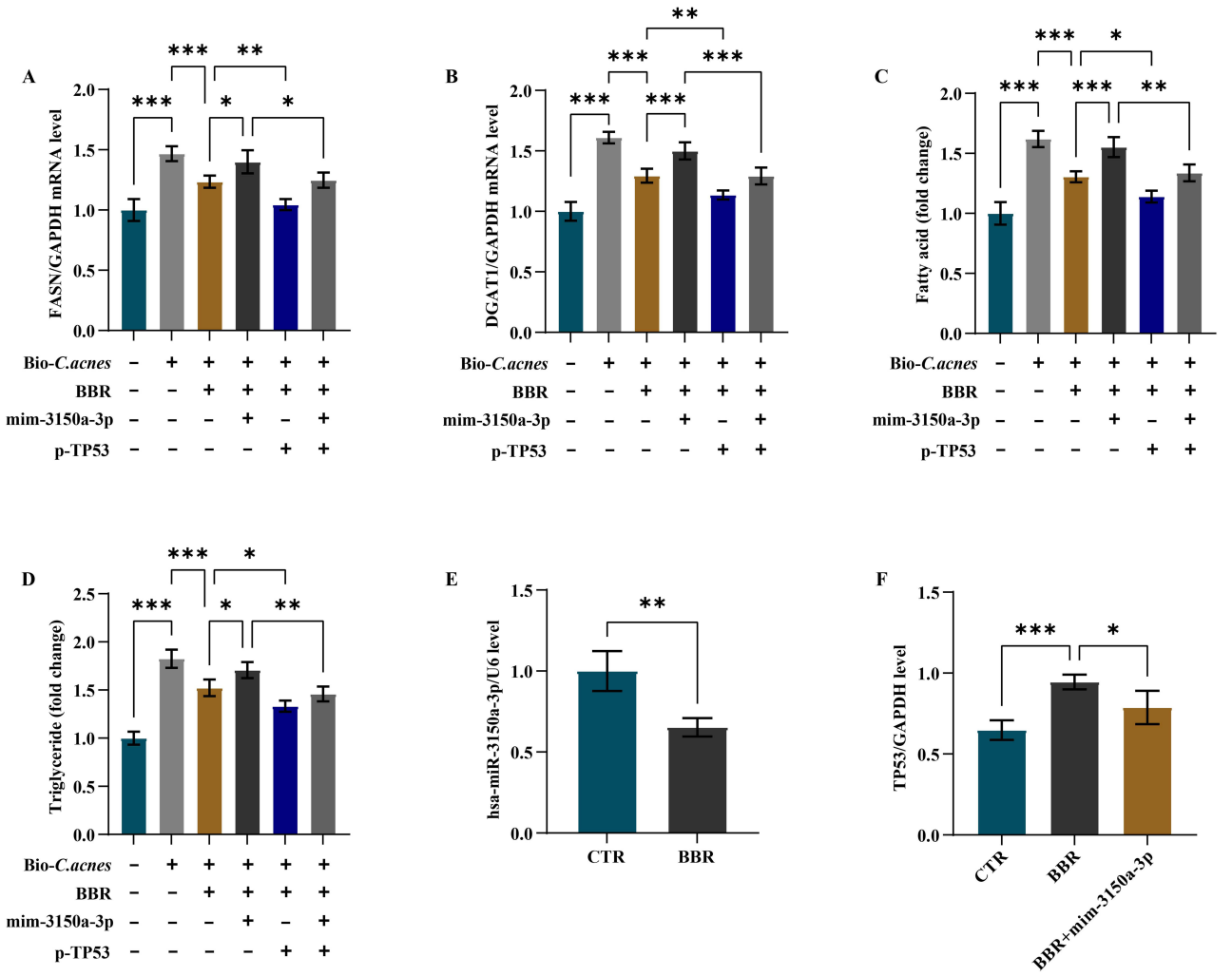

Figure 4 Effect of BBR on secretion function of sebocytes. (**A** and **B**) Effects of BBR on the expressions of FASN and DGAT1 in Bio-*C. acnes* induced sebocytes. (**C** and **D**) BBR affected the secretion of fatty acid and triglyceride in sebocytes. (**E**) Changes of hsa-miR-3150a-3p expression after BBR treatment. (**F**) Regulation of BBR on TP53 expression. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

induced high expression of hsa-miR-3150a-3p and low expression of TP53 (Figure 5E and F). BBR treatment inhibited this inducing effect of *C. acnes* (Figure 5E and F), which further confirmed the regulation of hsa-miR-3150a-3p/TP53 by BBR in the treatment of acne.

Discussion

C. acnes colonization, increased sebaceous lipid secretion, and inflammation are the key pathogenic factors of acne.[14] Based on the anti-inflammatory and antibacterial effects of *Coptidis Rhizoma*, we consider it a potential herb for acne treatment. We first constructed a PPI network and an herb-ingredient-target network based on its active ingredients and the targets of these ingredients. TP53 was screened as a hub gene, and BBR was identified as the key active ingredient. Multiple studies have shown that BBR has extensive anti-inflammatory activities.[15–18] It is worth noting that BBR has the potential to inhibit the growth and colonization of *C. acnes*.[12,13] Our evidence shows that BBR inhibited the growth of *C. acnes* and the formation of their biofilms in a concentration-dependent manner, suggesting the potential of BBR in treating acne. Our further research found that Bio-*C. acnes* can lead to an increase in the secretion of lipids and inflammatory factors in sebocytes. BBR significantly promoted TP53 expression by down-regulating hsa-miR-3150a-3p, thereby reducing the secretion of fatty acid/triglyceride in *C. acnes*-stimulated sebocytes and relieving the inflammation in vitro and in vivo.

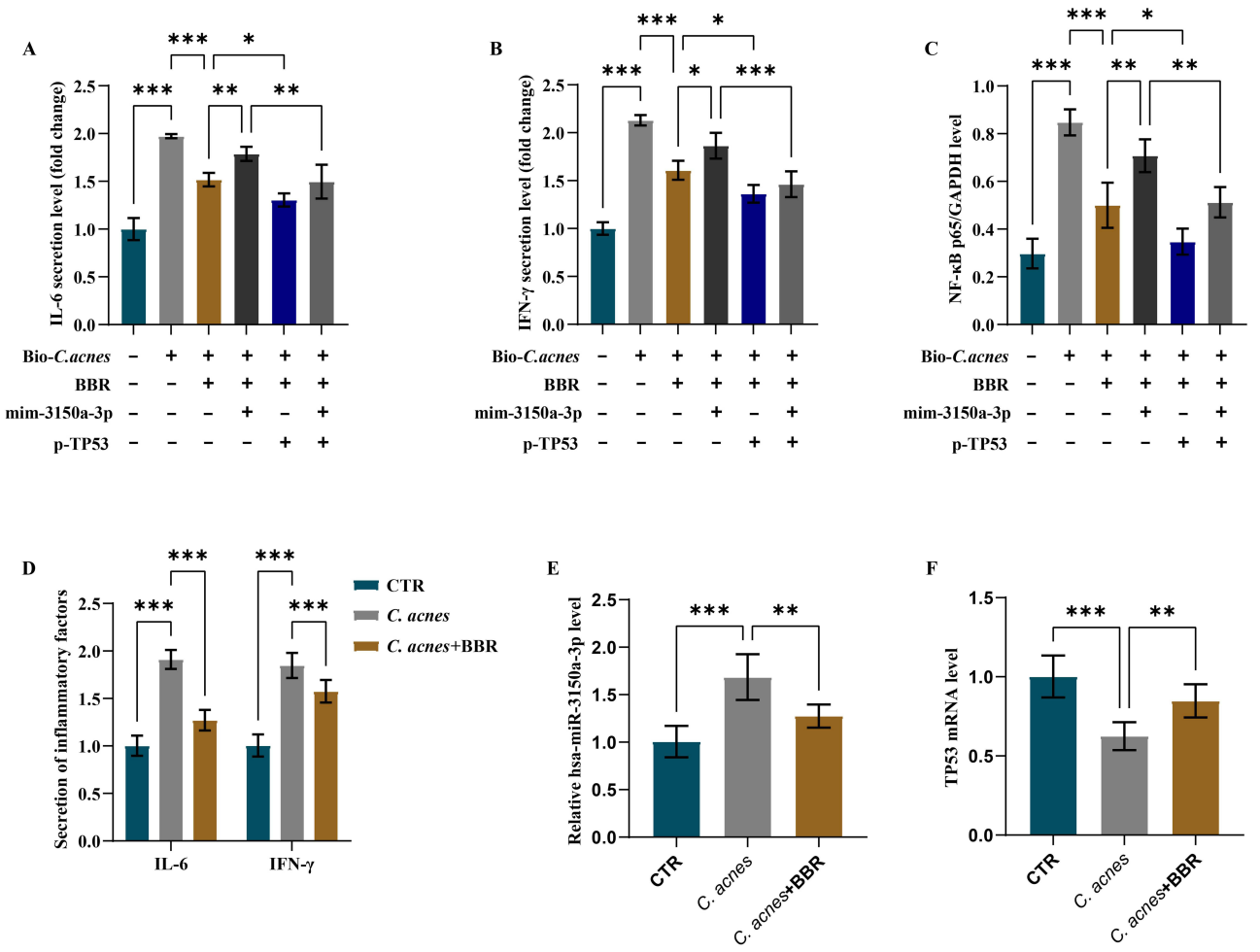

Figure 5 BBR alleviated Bio-*C. acnes*-induced inflammation. (**A** and **B**) Effect of BBR on IL-6 and IFN-γ production. (**C**) BBR regulated NF-κB expression. (**D**) BBR treatment alleviated the inflammation of mouse skin tissue caused by *C. acnes*. (**E** and **F**) Effect of BBR treatment on the expression of hsa-miR-3150a-3p and TP53 in mouse skin tissue. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

MiR-3150a-3p is a significantly upregulated miRNA in human-degraded intervertebral disc samples, which slows the progression of disc degeneration by reducing ACAN expression in nucleus pulposus cells.[19] Overexpression of miR-3150a-3p promotes the growth of prostate cancer (PCa) cells and induces their anti-apoptosis. LINC01679 can sponge miR-3150a-3p to up-regulate SLC17A9, inhibiting PCa progression.[20] MiR-3150a-3p is reported to be a potential protective factor of diabetic foot ulcer (DFU), which is down-regulated in the DFU tissues and is the target of circ_072697. Circ_072697 can promote KDM2A expression to mediate DFU occurrence by adsorption of miR-3150a-3p.[21] So far, the role of miR-3150a-3p in acne has not been explored.

TP53 is also known as P53, and it has been proposed that its polymorphism is related to the morbidity of acne.[22] Agamia et al revealed: TP53 is upregulated in the sebaceous glands and skin of acne patients after isotretinoin treatment. Its expression level is negatively correlated with the severity of acne.[23] MiRNAs are a class of non-coding RNAs with gene expression regulation functions, which can induce the degradation of target mRNA by binding to its 3'UTR sequence. We found that hsa-miR-3150a-3p has sequences targeting TP53 mRNA and participated in the regulation of sebocyte function by negatively regulating TP53 expression.

Topical medication is the first choice for patients with mild or moderate acne. The common topical drugs mainly include retinoic acid and anti-bacterial drugs. Retinoic acid drugs are more irritating to the skin, and patients are prone to symptoms such as redness, swelling, itching, and pain after use. The main drawback of antibacterial drugs is that they are easy to cause resistance. Therefore, gentle traditional Chinese medicine therapy is considered a potential strategy for acne

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relief. Jinhuang ointment (JHO) is composed of 10 kinds of traditional Chinese medicine, such as *Trichosanthis Radix, Radix Rhei Et Rhizome, Phellodendri Chinrnsis Cortex, Curcumaelongae Rhizoma*, A. *Dahurica (Fisch). Benth. Et Hook*, etc. It has the effect of clearing heat and removing dampness, detoxifying, eliminating stasis and phlegm, and is widely used in the prevention and treatment of inflammatory skin diseases. The network pharmacological analysis of JHO shows that the target genes of its active ingredients contain 12 differentially expressed genes in acne skin, and these genes were enriched in bacteria and inflammatory responses.[24] The herbal ball is a traditional Thai treatment made from traditional Chinese herbs such as *Centella Asiatica* and *Andrographis Herba*, etc. In the study of Jantarat et al, the gel preparation of herbal ball extract has anti-*C. acnes* efficacy, revealing the potential of topical gel preparation for acne treatment.[25] BBR is a natural active ingredient from *Coptidis Rhizoma*. In this study, we highlighted the role of BBR in alleviating the increased lipid secretion and inflammatory response induced by *C. acnes* in sebocytes, which were mediated through the regulation of the hsa-miR-3150a-3p/TP53 axis. Notably, our evidence shows that low concentration of BBR (40 μM) was both bacteriostatic and non-damaging to sebocyte viability, which demonstrates certain safety. This research will provide a theoretical basis for the inclusion of BBR in acne topical drugs.

Conclusion

This study reveals that BBR can promote the expression of TP53 by inhibiting hsa-miR-3150a-3p, thereby reducing the secretion of lipids and inflammatory factors in sebocytes caused by Bio-*C. acnes*. However, our results can only serve as theoretical support for BBR in treating acne, and its practical application value still needs to be further investigated in clinical practice.

Disclosure

The author(s) report no conflicts of interest in this work.

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