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Original Article

Anti-inflammatory effects of banana (*Musa balbisiana*) peel extract on acne vulgaris: *In vivo* and *in silico* study

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الملخص

أهداف البحث: حب الشباب الشائع مشكلة شائعة، مع معدل حدوث مرتفع نسبيا بين الآسيويين. بالمناسبة، تم إثبات الخصائص المحتملة المضادة للميكروبات والمضادة للالتهابات لقشور الموز في دراسات سابقة؛ ومع ذلك، لم يتم دراستها في حالة حب الشباب. هدفت الدراسة الحالية إلى معرفة التأثيرات الوقائية لمستخلص قشر الموز (موسى بالبيسانا) بسبب حب الشباب.

طريقة البحث: تم تقسيم ثلاثين جرذا إلى خمس مجموعات (عدد = 6 فئران في كل مجموعة): مجموعة حب الشباب، مجموعة حب الشباب الشائع المعالجة بـ 0.15 ٪ قشر الموز (موسى بالبيسانا) ، مجموعة حب الشباب الشائع المعالجة بنسبة 0.30 ٪ قشر الموز (موسى بالبيسانا)، مجموعة حب الشباب الشائع المعالجة 0.60 ٪ قشر الموز (موسى بالبيسانا)، وحب الشباب الشائع المجموعة التي تم إعطاؤها الكليندامايسين كدواء قياسي. قمنا بتقييم حجم العقيدات وعدد البكتيريا وعلم الأنسجة ومستويات السيتوكين (انترليوكن-1، وانتر فيرون جاما، وعامل نخر العظم-ألفا، انترليوكن-8). تم استخدام المقايسات المناعية المرتبطة بالإنزيم لقياس مستويات السيتوكين. بالإضافة إلى ذلك، أجرينا دراسات الالتحام الجزيئي لتحديد التفاعلات بين المواد الكيميائية النباتية (تريغونيلين، الفانيلين، حمض الفيروليك، حمض الأيزوفانيليك، الروتين، والسالسولينول) عبر مسارات المستقبل الشبيه بالتول-2 والعامل النووي – كابا ب.

النتائج: أدت جميع جرعات قشر الموز (موسى بالبيسانا) إلى تثبيط نمو البكتيريا وإنتاج السيتوكينات المنشطة للالتهابات مقارنة بمجموعة حب الشباب، بالإضافة إلى علاج التهاب الأنسجة. تم قمع حجم العقدة بشكل معنوي بأعلى جرعتين من قشر الموز (موسى بالبيسانا) مقارنة بمجموعة حب الشباب. ومع ذلك، يظل تأثيره الدوائي أدنى من تأثير الكليندامايسين. أظهرت دراسات الالتحام أن المركب النباتي ذو الطاقة التفاعلية الأكثر سلبية مع المستقبل الشبيه بالتول-2 والعامل النووي – كابا ب كان روتيني.

الاستنتاجات: تشير هذه النتائج إلى أن مستخلص قشر الموز (موسى بالبيسانا) يعمل كعامل مضاد للالتهابات ضد حب الشباب الشائع، عن طريق قمع تكوينات العقيدات، وتثبيط نمو البكتيريا، وتقليل إنتاج السيتوكينات المسببة للالتهابات.

الكلمات المفتاحية: موسى بالبيسانا؛ في الجسم الحي؛ في السيليكو؛ مضاد للبكتيريا؛ مضاد للإلتهاب

Abstract

Objective: Acne vulgaris (AV) is a common problem with a relatively high incidence rate among Asian people. The potential antimicrobial and anti-inflammatory properties

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of banana peels have been demonstrated in previous studies but have not been studied in cases of AV. Therefore, this study was aimed at investigating the protective effects of banana (*Musa balbisiana*) peel extract (MBPE) against AV.

Methods: Thirty rats were divided into five groups (n = 6 rats per group): an AV group, AV group treated with 0.15% MBPE, AV group administered 0.30% MBPE, AV group administered 0.60% MBPE, and AV group administered clindamycin (the standard drug treatment). We assessed nodule size, bacterial count, histopathology, and cytokine levels (IL-1α, IFN-γ, tumor necrosis factor (TNF)-α, and IL-8). Enzyme linked immunoassays were used to measure the cytokine levels. In addition, we performed molecular docking studies to determine the interactions between phytochemicals (trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol) via the Toll-like receptor 2 (TLR2) and nuclear factor-kappa B (NF-κB) pathways.

Results: All MBPE treatment groups, compared with the AV group, showed suppression of both bacterial growth and proinflammatory cytokine production, as well as resolved tissue inflammation. The nodule size was significantly suppressed in the groups receiving the two highest doses of MBPE, compared with the AV group. However, the pharmacological action of MBPE remained inferior to that of clindamycin. Docking studies demonstrated that rutin was the phytocompound with the most negative interaction energy with TLR2 or NF-κB.

Conclusions: Our results indicated that MBPE has anti-inflammatory effects against AV, by suppressing nodule formation, inhibiting bacterial growth, and decreasing proinflammatory cytokine production.

Keywords: Anti-inflammation; Antibacterial; *In silico*; *In vivo*; *Musa balbisiana*

Introduction

Acne vulgaris (AV) is a sebaceous gland and hair follicle condition that affects the face, back, shoulders, and chest. These sites contain the most oil glands, which participate in sebum excretion, comedogenesis, bacterial growth, and inflammation. AV is a hereditary environment disease that affects people of all ages, cultures, and ethnicities.[1–3] Studies in the United States and other countries have shown that the incidence of AV is higher among people of Asian descent than people of White or other races. In addition, Asian skin is more pigmented; therefore, it is at risk of acne sequelae.[4]

Inflammation is the body's response to several damaging stimuli, including infection. An excessive inflammatory reaction might cause tissue damage.[5] The complicated interaction between *Propionibacterium acnes* (*P. acnes*) infection and innate immunity results in AV inflammation via the generation of cytokines, chemokines, and antimicrobial peptides in the epidermis and immune cells. Infection with *P. acnes* causes hyperkeratinization and innate immune activation. Severe acne lesions develop if the irritation persists. Cytokines are inflammatory chemicals found in uninfected sebocytes. Cytokine levels increase during infection. In addition, inflammatory mediators affect hyperkeratinization, the first stage of microcomedo formation.[6]

Conventional AV treatment is based on the type of acne and focuses on symptoms; this treatment not only may trigger resistance to antibacterial agents and uncontrollable adverse effects, but also is expensive.[7,8] Topical antibiotics may trigger irritation, redness, skin dryness, and hypopigmentation. Oral antibiotics may trigger gastrointestinal disorders and increase the risk of venous thromboembolism.[9] In contrast, a new approach involving treating AV with herbs has been associated with fewer adverse effects and better patient compliance.[10]

Bananas originated in South Asia around the year 650 AD. This plant belongs to the Musaceae family and is divided into three genera: *Musa*, *Ensette*, and *Musella*.[11,12] In 2019. Indonesia overtook India and China as the third-largest banana producer.[12] The fruit produces waste in the form of peels, which account for 30% of the fruit weight. This waste is high in fiber and low in tannins, and it typically is disposed of in the environment without being processed or is used as animal feed.[13,14] Banana peels are rich in fiber, protein, essential amino acids, polyunsaturated fatty acids, potassium, and phenolic compounds.[11,15]

Banana peels have been used for biotechnological purposes, for example, as a source of enzymes, in the food industry, and for energy production.[12,16–18] Pharmacological applications are beginning to be developed, such as dietary supplements for acute liver disease and the treatment of hypercholesterolemia.[11,19,20] The potential antimicrobial and anti-inflammatory properties of banana peels have been demonstrated in previous studies[21,22]; however, they have not been studied in cases of AV. Therefore, this study was aimed at investigating the *in silico* and *in vivo* effects of banana (*Musa balbisiana*) peel extract (MBPE) on AV inflammation.

Materials and Methods

Rat experimental groups

Thirty female, hairless strain Sprague–Dawley rats were divided into five study groups (n = 6 each): an AV group; AV group administered an MBPE dose of 0.15% (MBPE1); an AV group administered an MBPE dose of 0.30% (MBPE2); an AV group administered an MBPE dose of 0.60% (MBPE3); and an AV group administered clindamycin, a standard drug treatment. The experimental animals were acclimated through colony rearing for 7 days. The environment was maintained at a room temperature of 22–24 °C, 50–60% humidity, and 12/12 h light/dark cycles. Food and water were provided ad libitum.

Extraction

Ripe, fresh and, disease-free bananas (*M. balbisiana*) were purchased from the Klojen traditional market in Malang City, East Java, Indonesia. The banana peels were washed with tap water to remove dust and dirt. Surface water adhering to the skin was removed, and the skin was cut into 2 cm × 2 cm sections and dried at 50 ± 5 °C in a dryer. The dried skin was ground into flour with a grinder.[23,24] The banana peel powder was dissolved in 70% ethanol for 5 days. Mixing and maceration were performed in triplicate samples. The solution was then filtered through filter paper. A rotary evaporator was used to remove the solvent. Condensation after the evaporation process was performed with the freeze drying method.[25,26] The dry extract was used to prepare a transfersome gel.

Models for acne

Acclimated rats were induced with the *P. acnes* ATCC® 6919™ strain via intradermal injection on both sides of back. The strains of *P. acnes* were cultured in *Brucella* agar supplemented with hemin (5 µg/ml; Sigma, St. Louis, MO), vitamin K1 (1 µg/ml; Sigma, St. Louis, MO), and lysed horse blood (5% v/v; Shanghai, China) at 37 °C in an anaerobic atmosphere with MGC Anaeropack systems (Mitsubishi, Gas Chemical Co., Inc., Japan). *P. acnes* was cultured to the exponential phase for 2 days and to the stationary phase for 3–4 days, then resuspended in 0.9% saline (5×10^8 colony forming units/ml).[27] The bacterial strain was obtained from post-log phase culture in brain-heart Infusion medium. Bacteria were heated at 95 °C for 5 min and lyophilized (freeze dried) before injection. Bacterial suspensions were prepared at 10^8 and 10^9 colony forming units/µL, and 20 µL was injected into both sides of each rat's back. Intradermal injection was performed with a 30-gauge needle.

Sample isolation

On day 14, the rats were anesthetized to isolate back skin samples. Back skin tissue was homogenized with a tissue grinder in 0.9% salt solution. The supernatant was then centrifuged at 2000×*g* for 10 min to separate the clear liquid. The cytokine levels were measured.

Cytokine analysis

Enzyme-linked immunosorbent assays were used to analyze IL-1α, IFN-γ, TNF-α, and IL-8 in the supernatant. A mouse IL1A/IL-1 alpha (sandwich) ELISA kit (catalog No. LS-F24824-1), mouse TNF alpha (sandwich) ELISA kit (catalog No. LS-F54858-1), mouse IL8 (sandwich) ELISA kit (catalog No. LS-F54858-1) and mouse IFN gamma (sandwich) ELISA kit (catalog No. LS-F3414-1) were purchased from LS Bio (Seattle, WA, USA). The analysis was performed in accordance with the manufacturer's protocol.

Histopathological analysis

After model establishment and treatment, the skin was excised and immersed in 10% formaldehyde solution. Tissues were dehydrated with a graded ethanol series from 80% to 100%, and embedded in paraffin. The wax block was cut to a thickness of 3–5 µm and stained with hematoxylin and eosin (Sigma) for histopathological examination under an optical microscope (BX53, Olympus, scale × 200).

In silico studies

In silico studies included searching for amino acids in the Toll-like receptor-2/nuclear factor-kappa B (TLR2/NF-κB) pathway and the structure of the active compound; protein 3D structure modeling; protein-ligand docking and visualization; and analysis of the binding interaction. We previously demonstrated that the phytochemical composition of MBPE includes trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol, by using liquid chromatography-high resolution mass spectrometry[28,29] Subsequently, we performed an *in silico* study of TLR-2 and NF-κβ signals with molecular docking. The amino acid composition of the protein in the TLR2/NF-κβ pathway was obtained from the National Center for Biotechnology Information, United States National Library of Medicine, National Institutes of Health (http://www.ncbi.nlm.nih.gov). The 3D structure of the protein in the TLR2/NF-κβ pathway was obtained in *.sdf file format and was converted into a *.pdb file with OpenBabel software.[30] The 3D structure of the active compound components of the MBPE was obtained from the PubChem Open Chemistry Database, according to our previous study.[31,32] The structure was in *.sdf file format and was converted into a *.pdb file with OpenBabel software.[33] The 3D structures of the target proteins were predicted with the SWISS-MODEL webserver with the homology modeling method. The 3D structures of the protein were then validated with Ramachandran plot analysis.[34,35] Docking simulations between the active compound and target proteins were performed with HEX 8.0 software.[36] The docking protocol consisted of three visualization stages: minimization of rigid-body energy, semi-flexible repair, and finishing refinement in an explicit solvent. The docking results were then visualized with Chimera 1.6.2 and Discovery Studio 4.1 software. The docking analysis results were visualized with Discovery Studio 4.1, LigPlot+, and LigandScout 3.1 software.[34,35] The interactions between proteins and ligands were analyzed to determine the numbers and types of bonds and interactions formed, such as hydrogen bonds, hydrophobic interactions, and van der Waals interactions.

Statistical analysis

The collected data were tabulated and analyzed in Microsoft Excel and subjected to ANOVA and post hoc tests. A statistical value of $p < 0.05$ was considered significantly different. Statistical analyses were performed in SPSS software version 16.

Results

Figure 1 shows the IL-1α levels in the various study groups. The IL-1α levels were significantly lower in the three MBPE groups than the AV group ($p < 0.05$) but did not reach levels comparable to those in the clindamycin group ($p < 0.05$).

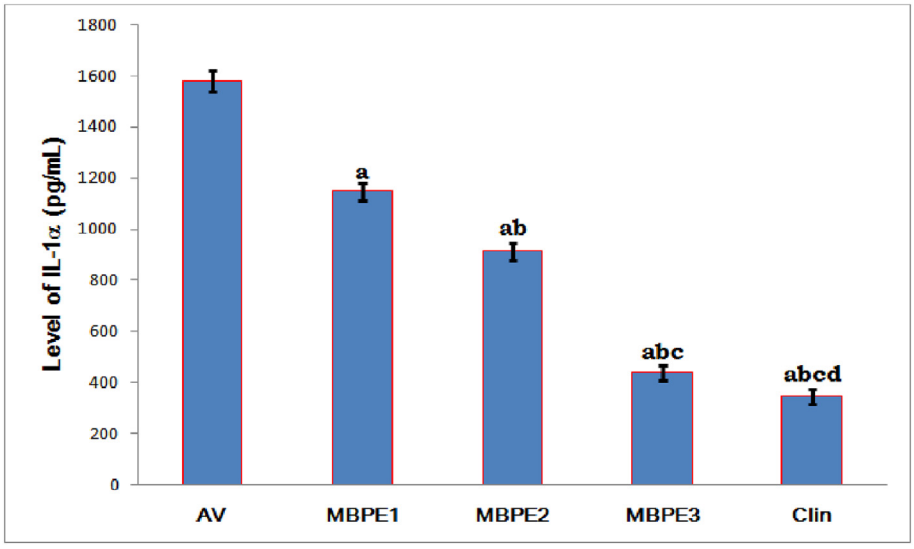

Figure 1: IL-1α levels in various groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); d: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

The IL-8 levels in the various study groups are shown in Figure 2. The IL-8 levels in the MBPE groups were significantly lower than those in the AV group ($p < 0.05$). In addition, the IL-8 level in the MBPE2 group was significantly lower than that in the MBPE3 group ($p < 0.05$). The IL-8 levels in the 0.60% MBPE group were significantly lower than those in the 0.30% MBPE group ($p < 0.05$). The IL-8 levels in the clindamycin group were significantly lower than those in the three MBPE groups ($p < 0.05$).

Figure 3 shows the differences in TNF-α levels in the various study groups. TNF-α levels in the three groups receiving MBPE were significantly lower than those in the AV group ($p < 0.05$). Moreover, the TNF-α levels were significantly lower in the MBPE2 group than the MBPE3

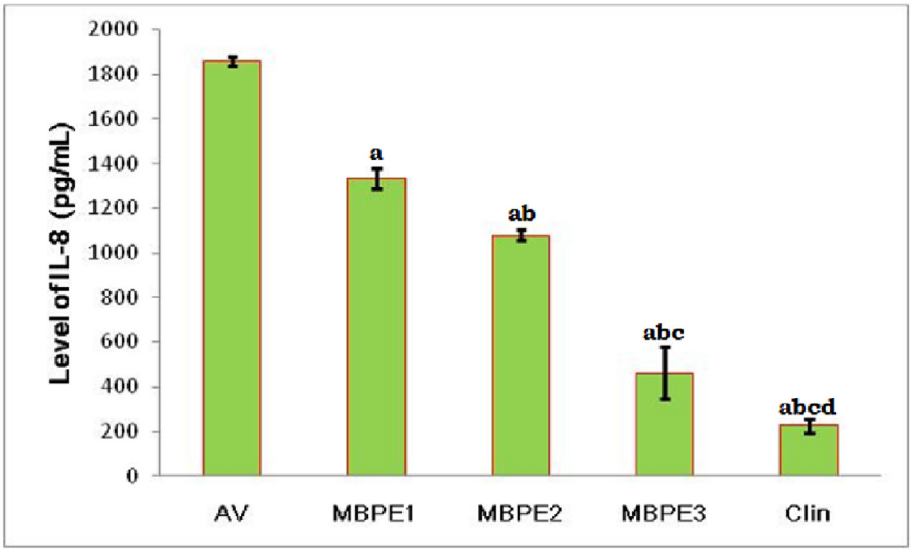

Figure 2: IL-8 levels in various groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); d: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

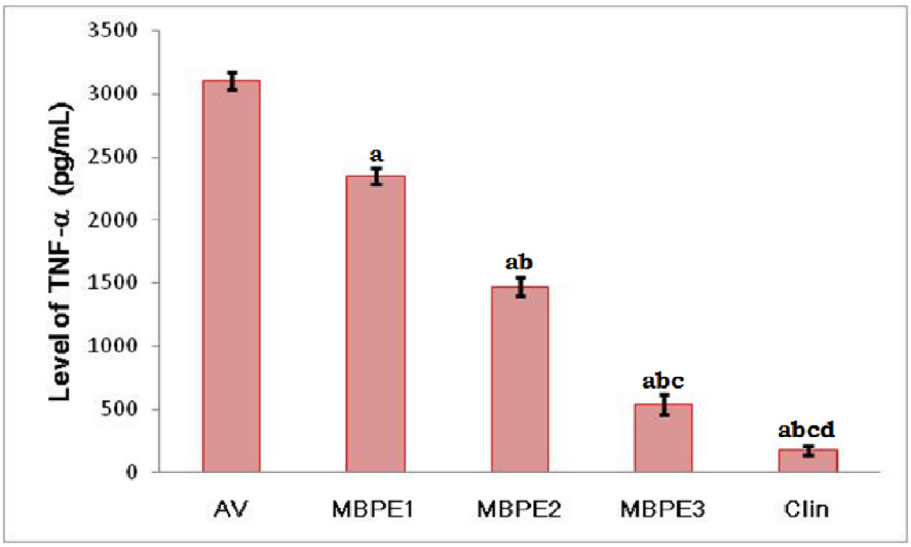

Figure 3: TNF-α levels in various groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); [d]: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

group ($p < 0.05$), and in the MBPE3 group than the MBPE 2 group ($p < 0.05$). TNF-α levels were significantly lower in the clindamycin group than all three MBPE groups ($p < 0.05$).

Figure 4 shows the IFN-γ levels in the various study groups. The IFN-γ levels were significantly lower in the three MBPE groups than the AV group ($p < 0.05$) but did not reach levels comparable to those in the clindamycin group ($p < 0.05$). The higher the dose of MBPE, the lower the IFN-γ level.

Figure 5 shows the differences in nodule thickness between the groups. In the three MBPE groups, the mean nodule thickness was significantly lower than that in the AV group ($p < 0.05$). however, no differences in mean nodule thickness were observed between the MBPE1,

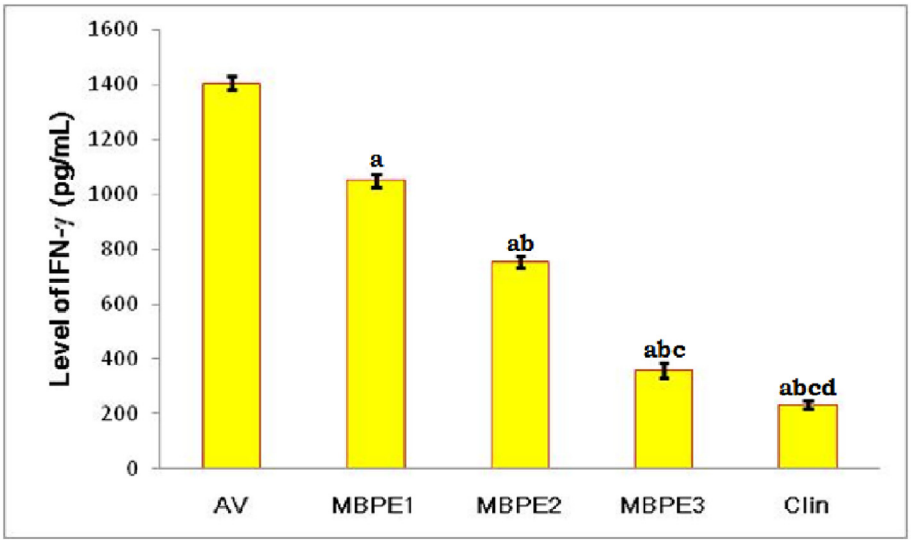

Figure 4: IFN-γ levels in various groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); d: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

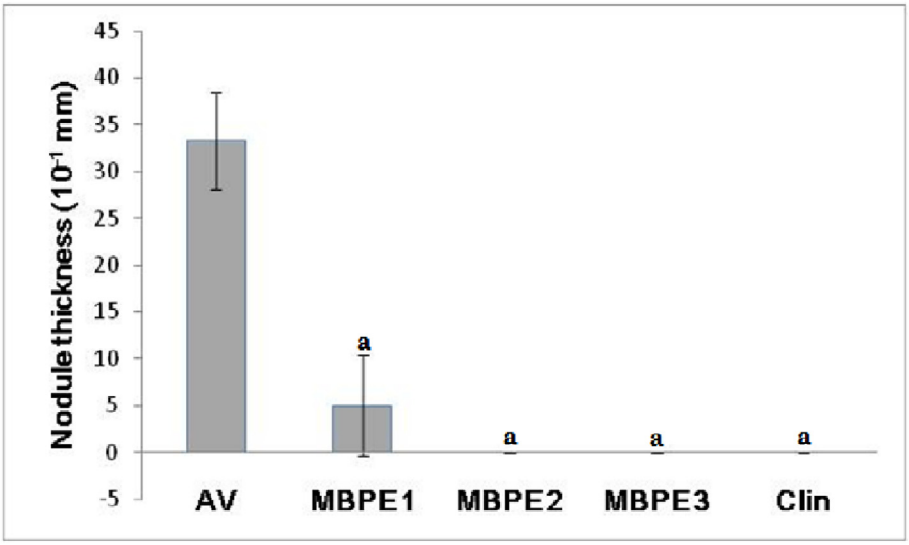

Figure 5: Nodule thickness in various groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); d: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: mm: millimeter; AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

MBPE2, or MBPE3 group and the clindamycin group ($p > 0.05$).

The average numbers of bacterial colonies in the various groups is shown in Figure 6. The number of colonies in the three MBPE groups was significantly lower than that in the AV group ($p < 0.05$). No significant difference was observed in the number of bacterial colonies between the MBP3 and clindamycin group ($p > 0.05$).

Figure 7 shows the histopathological results of acne lesions in the various groups. In the AV group, we observed severe inflammation characterized by abundant inflammatory cells, such as neutrophils, lymphocytes, and histiocytes, in the dermis to the subcutis, and in the epidermis, where abscesses formed. Mild inflammation was observed in the MBPE1 and MBPE2 groups, whereas resolution of inflammation was observed in the MBPE3

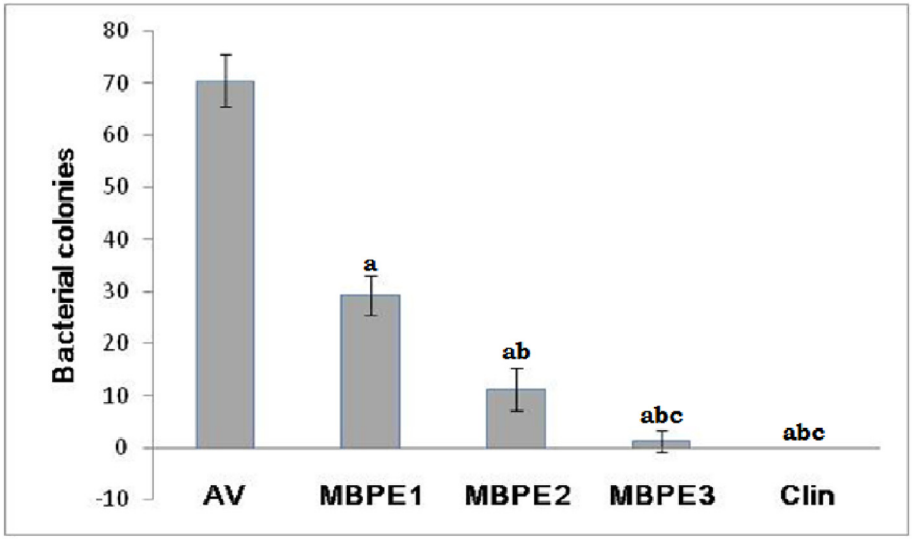

Figure 6: Number of bacterial colonies from various observation groups. a: significant difference with respect to the acne vulgaris group (negative control); b: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.15% (MBPE1); c: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.30% (MBPE2); d: significant difference with respect to the acne vulgaris group administered MBPE at a dose of 0.60% (MBPE3). Note: AV: acne vulgaris group; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

group. These pathological features were similar to those in the clindamycin group.

The phytochemical interaction energies between the TLR2 protein and trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol were −4.810 kJ/mol, −5.212 kJ/mol, −6.102 kJ/mol, −5.479 kJ/mol, −10.080 kJ/mol, and −6.103 kJ/mol, respectively. The compound with the most negative interaction energy was rutin. The results of the docking analysis of rutin and TLR2 are shown in Figure 8. The interaction map between rutin and TLR2 indicated van der Waals interactions involving amino acids ASN A33, SER A56, ALA A80, ASP B233, ASP B235, LYS B260, THR B262, ASP B263, LEU B289, and SER B291; conventional hydrogen bonds involving amino acids LYS A55, ASP A58, GLN A79, GLU A103, ILE B261, GLN B288, and LYS B290; and carbon-hydrogen bonds involving LYS A37. Hydrophobic interactions involved Pi alkyl groups in ILE A35 and unfavorable donors in HIS A104.

The phytochemical interaction energies between NF-κβ and trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol were −3.897 kJ/mol, −4.386 kJ/mol, −4.856 kJ/mol, −4.735 kJ/mol, −7.354 kJ/mol, and −4.984 kJ/mol, respectively. The compound with the most negative interaction energy was rutin. The docking analysis results for rutin and NF-κβ are presented in Figure 9. The interaction map between rutin and NF-κβ inducing kinase indicated van der Waals interactions involving the amino acids PRO A488, ASP A490, ASN A591, PRO A619, PROA624, GLN A657, LYS A662, and SER A663; and conventional hydrogen bonds involving CYS A486, LEU A487, GLU A489, LEU A590, SER A621, and LYS A670. The hydrophobic interactions involved Pi anions, Pi sigma in ALA A621 and Pi alkyl groups in VAL A658.

The phytochemical interaction energies between the NF-κβ p50 homodimer and trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol were −4.503 kJ/mol, −4.695 kJ/mol, −5.678 kJ/mol, −5.227 kJ/mol, −7.446 kJ/mol, and −5.539 kJ/mol, respectively. The compound with the most negative interaction energy was rutin. Figure 10 shows the docking analysis results between rutin and the NF-κβ p50 homodimer. The interaction map between rutin and the NF-κβ p50 homodimer revealed conventional hydrogen bonds involving the amino acids VAL A58, SER A63, GLY A65, ASN A136, and ARG A154, and hydrogen carbon bonds involving PRO A62 and GLY A113. Hydrophobic interactions involved Pi sigma and Pi alkyl groups in VAL A112, and LEU A140, respectively.

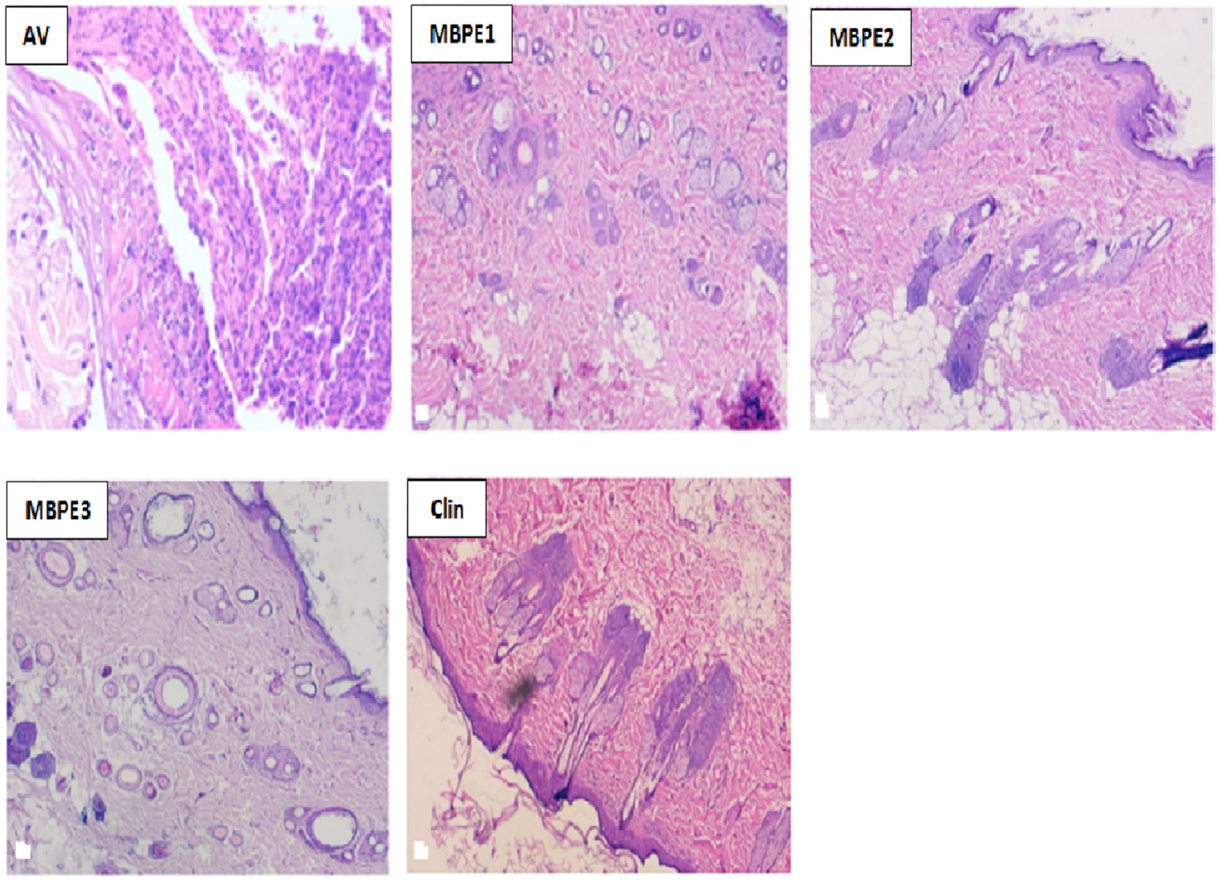

Figure 7: Histopathology of acne lesions in various groups. Note: AV: acne vulgaris group as a positive control; MBPE: banana (*Musa balbisiana*) peel extract; Clin: acne vulgaris group given the standard drug clindamycin.

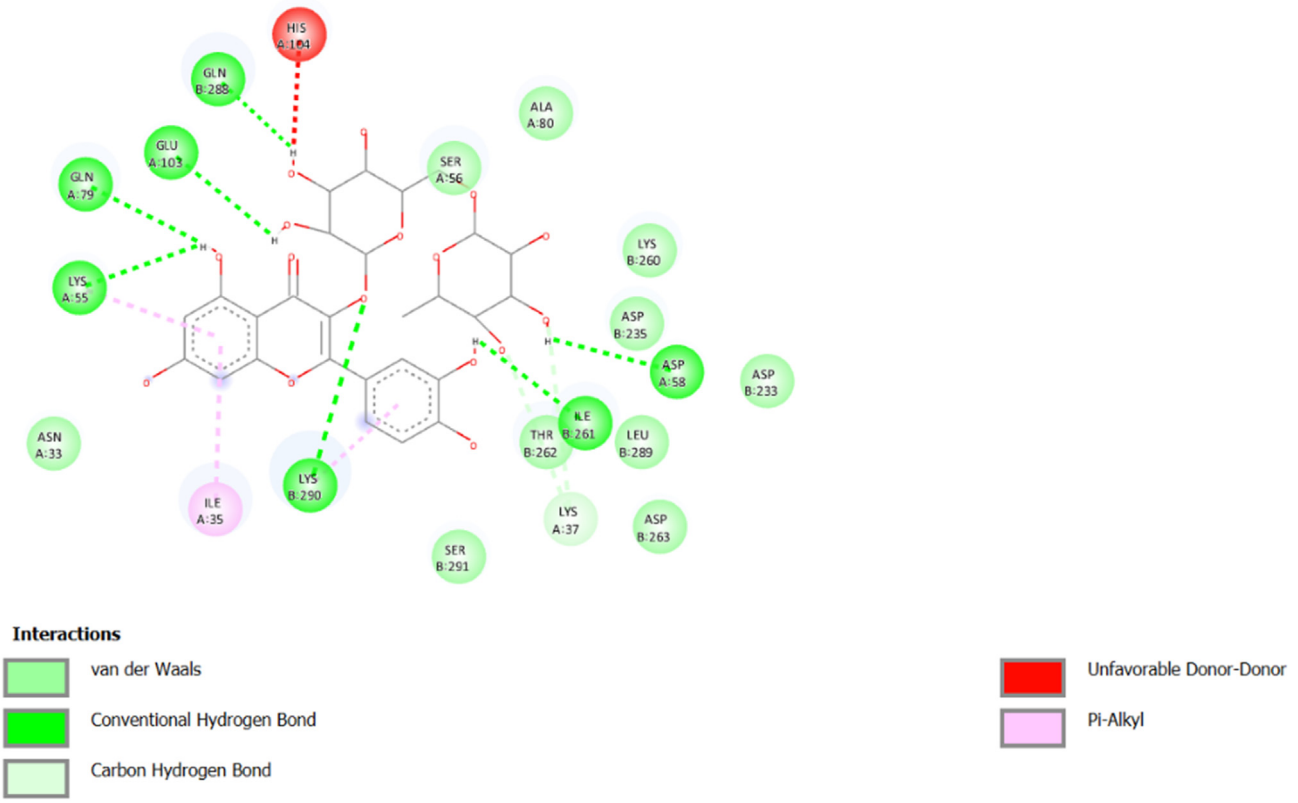

Figure 8: Interaction map of the binding pocket of TLR2 with rutin.

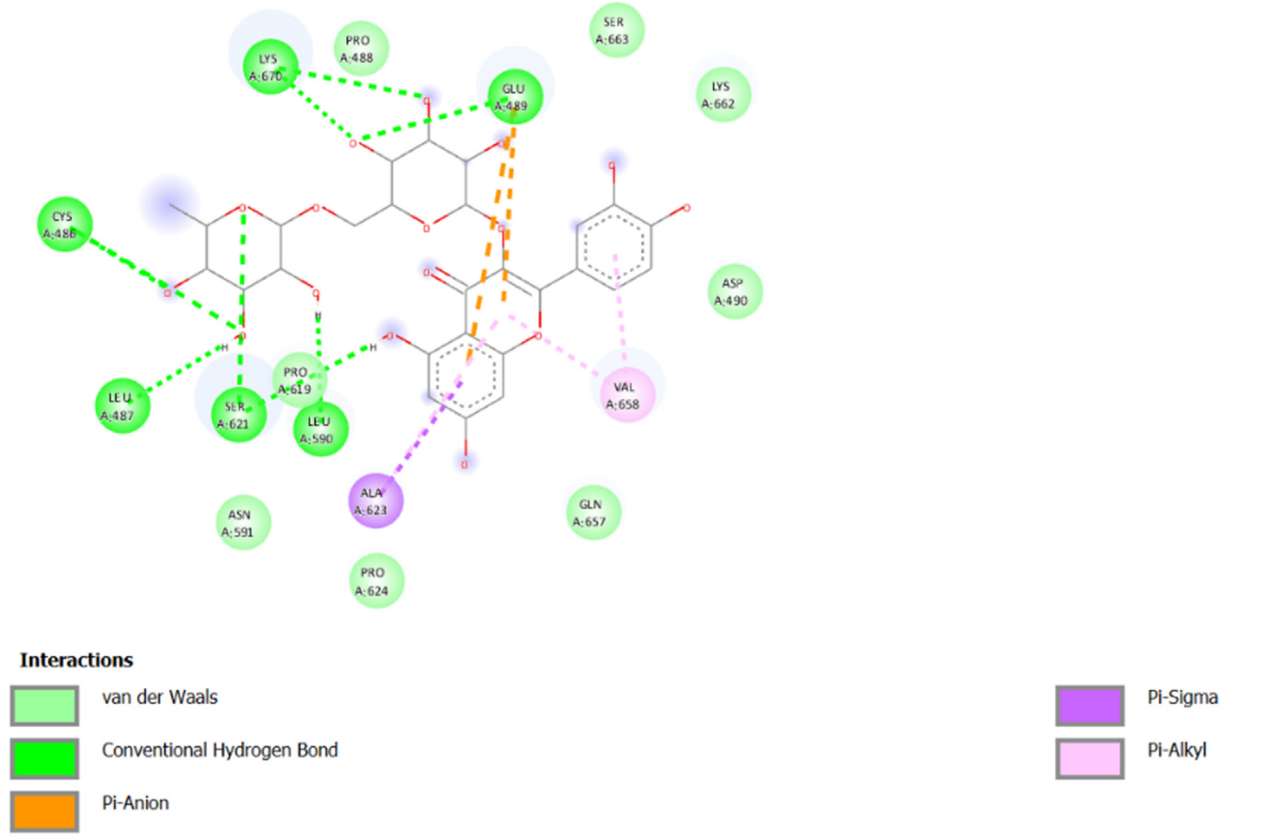

Figure 9: Interaction map of the binding pocket of NF-κβ inducing kinase with rutin.

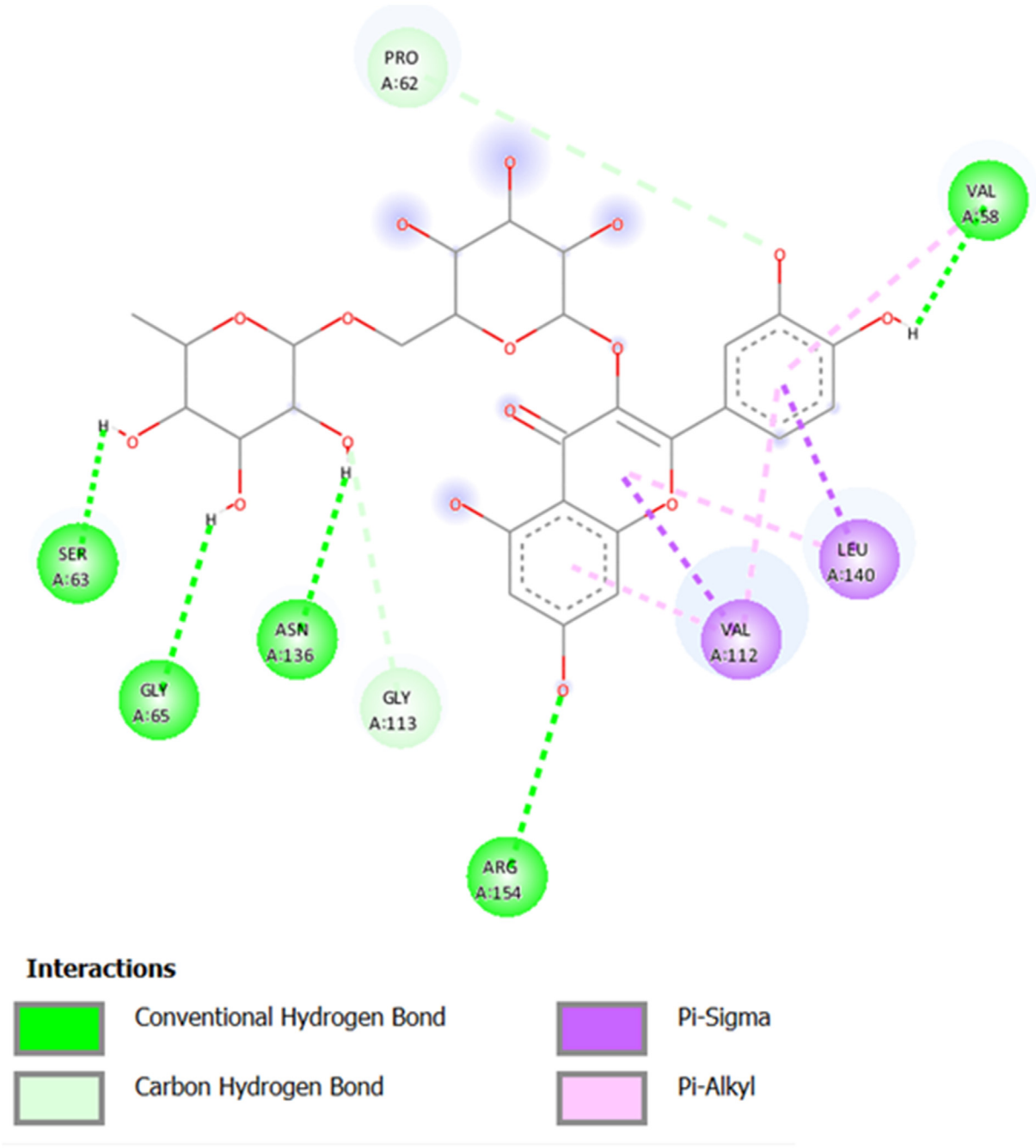

Figure 10: Interaction map of the binding pocket of NF-κβ p50 homodimer with rutin.

Discussion

Our study demonstrated that MBPE exhibited anti-inflammatory and antibacterial properties in an AV rat model. Its anti-inflammatory activity was characterized by a decrease in proinflammatory cytokines and inhibition of the formation of tissue pathology. Its antibacterial activity was demonstrated by a decrease in the number of bacteria present in AV lesions. Molecular docking revealed that rutin had the highest affinity among the MBPE phytochemicals assessed.

The dimer structure used in the TLR2 docking tests was confirmed to be the active form of the receptor. According the theory meant, the ligand/agonist interact with the heterodimer in a non-competitive manner.[36] In this study, the crystal structure of the TLR1-TLR2 heterodimer produced by lipopeptide binding was chosen as the ID:2Z80 protein. According to phytochemical docking tests, rutin interacted very easily with the heterodimer. Mapping of the interactions indicated the presence of van der Waals interactions, conventional hydrogen bonding, carbon-hydrogen bonding, and hydrophobic interactions between rutin and TLR2. A previous study has revealed that TLR ligand binding occurs at amino acids 266–355 and 318–398 for the dimerization process on amino acids.[37] Consequently, the rutin and TLR2

interaction map contained several ligand binding and dimerization linkage. The interaction between rutin and TLR2 is expected to suppress downstream TLR-2 signaling generated by *P. acnes*.

Among the analyzed phytochemicals, rutin interacted with NF-κB inducing kinase (NIK) most easily in the docking, which is the signal for the synthesis of IFN-γ. The N-terminal TRAF3-binding domain (residues 30−120), negative regulatory domain (residues 121−318), core serine/threonine kinase domain (residues 390−660), and non-catalytic C-terminal region domain required for signaling comprise the 947 amino acids of NIK. Furthermore, these interactions formed through van der Waals interactions, conventional hydrogen bonds, and hydrophobic contacts, thus suggesting that rutin binds the core serine/threonine kinase domain as well as the non-catalytic C-terminal region domain necessary for signaling. Consequently, rutin docking in the core serine/threonine kinase domain and non-catalytic C-terminal domain may explain at least some of the MBPE-induced decrease in IFN-γ production.

The nuclear transcription factor NF-κβ is a key player in the activation and regulation of innate and adaptive immune responses. The NF-κβ signaling pathway receives signal inputs from various TLR receptors and dissociates from the NF-κβ/IκB complex via IκB protein degradation mediated by the IκB kinase (IKK) complex. Subsequently, the transcription factor is translocated to the nucleus. The IKK complex phosphorylates IκB during this step, thus targeting IκB for proteosome destruction. The IKK complex is composed of two catalytically active kinases: IKKα and IKKβ. NF-κB is a homodimer that has two domains in each tertiary unit. The joining of these two domains in the two tertiary units forms the active site of DNA binding together.[38] In this investigation, we discovered that rutin interacts with the NF-κβ p50 homodimer more easily than the other phytochemicals. This interaction occurs via conventional hydrogen bonds, hydrogen carbon bonds, and hydrophobic interactions. Thus, rutin appears to inhibit the development of the active site binding DNA, as well as the activation of NF-κB signaling. We observed nodule growth and accumulation of inflammatory cells in the dermis and epidermis tissue, in agreement with the hypothesis that TLR2 activation in monocytes results in the production of proinflammatory cytokines such as IL-6, IL-1, IL-12, and IL-8. IL-8 attracts neutrophils to the region of active lesions, where lysosomal enzymes are released, thus causing epithelial follicular rupture and inflammation.[39,40] After 14 days of observation, we discovered that administering MBPE doses of 0.30% and 0.60% had effects and activity comparable to those of clindamycin in suppressing nodule formation. Notably, the nodule size decreased more rapidly when the MBPE dose was increased. The loss of inflammatory cells from the dermis to the subcutis and epidermis was responsible for the histological elimination of these nodules. However, bacterial colonies were observed after treatment with MBPE doses of 0.30% and 0.60%. These findings suggest that MBPE has anti-inflammatory properties. MBPE's antibacterial activity at doses of 0.30% and 0.60% was not similar to that of clindamycin.

P. acnes triggers an inflammatory response in AV. The inflammatory response in human monocytes infected with *P. acnes* involved TLR2 activation, thereby triggering the release of inflammatory mediators, including IL-6, IL1β, IL-8, and TNF-α, through the NF-κβ signaling pathway.[27] Inflammatory mediators affect hyperkeratinization, in which the first step is the development of microcomedones. Abnormal production of various lipids results from the release of IL-1 from epithelial cells. Consequently, IL-1 acts on keratinocytes, thereby triggering a cascade of events during acne initiation and development. In addition, IL-1α induces the production of other inflammatory markers, particularly TNF-α from keratinocytes.[41] This cytokine then activates keratinocytes.[42] Various studies have indicated that TNF-α is elevated in AV.[43,44] In this study, the levels of IL-1α and TNF-α were significantly decreased by all three doses of MBPE, although the effectiveness of these treatments was not comparable to that of clindamycin. These findings indicated that MBPE has anti-inflammatory properties and inhibits the development of AV. According to the histopathological results, we suspect that a relationship between decreased IL-1 and TNF-α levels and decreased monocyte activity has a role in the resolution of inflammation. The relationship between the decrease in monocytes due to the resolution of tissue inflammation and the decrease in IL-1 and TNF-α was observed in all administered MBPE doses.

P. acnes infection induces an immunological response by releasing IL-8. IL-8 in turn stimulates neutrophil migration, thus leading to the formation of acne and pus lesions. Consequently, neutrophils generate free radicals that kill the bacteria. An inflammatory reaction is triggered by the excessive generation of free radicals.[45] *P. acnes* infection was found to markedly increase IL-8 production. The three doses of MBPE, but not clindamycin, decreased IL-8 levels. Therefore, MBPE has anti-inflammatory properties, because it inhibited the IL-8 production caused by *P. acnes* infection. On the basis of the histopathological results, we suspect that a relationship between decreased IL-8 levels and suppression of neutrophil migration might be involved in resolving inflammation. This relationship was observed for all MBPE doses.

The TLR-2 pathway stimulates the release of pro-inflammatory cytokines, such as IFN-γ, TNF-α, and IL-8, by mononuclear cells when the innate immune system is activated. The lipoteichoic acid component of the *P. acnes* cell wall has a major role in TNF-α stimulation. Through the TLR-2 pathway, *P. acnes* also stimulates keratinocytes to release pro-inflammatory cytokines, such as TNF-α, IL-1α, IL-1β, and IL-8.[46] Substantially greater levels of IFN-γ and IL-8 in peripheral blood mononuclear cells have been observed in patients with acne than healthy controls.[47] Herein, the three doses of MBPE effectively decreased the elevated IFN-γ, TNF-α, and IL-8, but not to the levels observed in the clindamycin group. This finding demonstrated that MBPE decreases the synthesis of IFN-γ, TNF-α, and IL-8.

The phytochemical components of MBPE, including trigonelline, vanillin, ferulic acid, isovanillic acid, rutin, and salsolinol, play roles in its anti-inflammatory activity against AV. To our knowledge, no previous studies have demonstrated the roles of these phytochemical substances in the pathogenesis of AV. Trigonelline (N-methylpyridinium-3-carboxylate) is a phytochemical heterocyclic alkaloid[48] with established anti-inflammatory activity. Trigonelline has been found to inhibit NF-κB and Toll-like receptor 4 (TLR4)

expression in mice after lipopolysaccharide exposure.[49] Vanillin is an aromatic aldehyde polyphenol.[50] Chemically, the primary functional groups in this phenolic aldehyde are R1 (aldehyde), R2 hydroxyl, and R3 (ether). The core vanillyl group (hydroxy-3-methoxybenzyl) is formed by R2 and R3.[51] *Musa cavendishii* has been found to contain vanillin.[52] Several investigations in inflammatory models have shown that vanillin inhibits generation of the proinflammatory cytokine TNF-α and blocks NF-κβ activation.[53–55] In this study, we showed that vanillin suppresses proinflammatory cytokines in AV. According to the *in silico* studies, the mechanism for lowering proinflammatory cytokines involves regulation of the NF-κβ pathway. *M. cavendishii* contains ferulic acid.[52] Ferulic acid is antibacterial, owing to irreversible changes in membrane components caused by changes in hydrophobicity, decreased surface negative charges, and local rupture or creation of holes in the bacterial cell membrane.[56] According to a recent study, ferulic acid does not have antimicrobial activity against *P. acnes*.[2] Our study revealed that ferulic acid works only as an anti-inflammatory agent, but not as an antibacterial agent, against *P. acnes*. Rutin is a flavonoid that has been found to be present in bananas[52,57,58] and to inhibit the migration of inflammatory cells. This effect is dependent on the inhibition of NF-κβ p65 phosphorylation.[59] Furthermore, rutin from bananas has been found to inhibit IFN-γ synthesis.[60] In this study, we demonstrated that MBPE limits IFN-γ production in AV by blocking NF-κB phosphorylation. *In silico* results showed that rutin, compared with the other investigated compounds, interacts most easily with TLR2. Salsolinol has an asymmetric core at C-1 and exists as R and S enantiomers. Our discovery of salsolinol in bananas is consistent with the results of previous studies.[61,62] Salsolinol has been demonstrated to decrease TNF-α production.[63] Herein, we observed that salsolinol inhibited TNF-α production in the AV model.

Conclusions

In conclusion, rutin had the highest TLR2 affinity among the analyzed phytochemicals in MBPE, and was found to interact with TLR2 and the NF-κβ pathway. MBPE was found to have anti-inflammatory activity against AV by suppressing nodule formation, inhibiting tissue inflammation, and decreasing proinflammatory cytokine production.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

All experimental animals were kept in facilities according to protocols approved by the research ethics committee of the Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia (approval number: 764/UN4.6.4.5.31/PP36/2A21; date: December 21, 2021).

Authors' contributions

DS: Conceptualization; project administration; methodology; resources, data curation, investigation, formal analysis, software, writing—original draft. SW, AB, KD, MH: Conceptualization; project administration; methodology; resources; writing—review and editing. PR, BB, SW, FH, YR: Conceptualization; methodology; formal analysis, writing—review and editing. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. **Lancet 2012**; 380(9859): 2163–2196.
2. Kim S, Oh S, Noh HB, Ji S, Lee SH, Koo JM, et al. In vitro antioxidant and anti-propionibacterium acnes activities of cold water, hot water, and methanol extracts, and their respective ethyl acetate fractions, from *Sanguisorba officinalis L. Roots*. **Molecules 2018**; 23: 3001.
3. Han G, Armstrong A, Desai S, Guenin E. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in an Asian population. **J Drugs Dermatol 2019**; 18(9): 910–916.
4. Harper JC. Acne vulgaris: what's new in our 40th year. **J Am Acad Dermatol 2020**; 82(2): 526–527.
5. Zheng N, Zhou M, He Y, Xu H, Chen X, Duan Z, et al. Low curcumin concentrations combined with blue light inhibits cutibacterium acnes biofilm-induced inflammatory response through suppressing MAPK and NF-κβ in keratinocytes. **Photodiagnosis Photodyn Ther 2022**; 40:103204.
6. Wang VY, Hata TR, Tong YL, Kao MS, Zouboulis CC, Gallo RL, et al. The anti-inflammatory activities of propionibacterium acnes CAMP factor-targeted acne. **J Invest Dermatol 2018**; 138: 2355–2364.
7. Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. **J Am Acad Dermatol 2016**; 74: 945–973 e933.
8. Van Den Bergh B, Michiels JE, Wenseleers T, Windels EM, Boer PV, Kestemont D, et al. Frequency of antibiotic application drives rapid evolutionary adaptation of Escherichia coli persistence. **Nat Microbiol 2016**; 1(5):16020.
9. Hamdy AA, Kassem HA, Awad GEA, El-Kady SM, Benito MT, Doyagüez EG, et al. In-vitro evaluation of certain Egyptian traditional medicinal plants against *Propionibacterium acnes*. **South Afr J Bot 2017**; 109: 90–95.
10. Masoud F, Badali P, Isa MA, Alamdari HA, Asnaashari S, Shokri J, et al. The novel topical herbal gel might be an alternative treatment in patients with acne vulgaris: a randomized, double-blind controlled study. **Phytomedicine 2022**; 2:100232.
11. Segura-Badilla O, Kammar-García A, Mosso-Vazquez J, Sanchez RA, Ochoa-Velasco C, Hernandez-Carranza P, et al. Potential use of banana peel (*Musa cavendish*) as ingredient for pasta and bakery products. **Heliyon 2022**; 8:e11044.

12. Zaini HM, Roslan J, Saalah S, Munsu E, Sulaiman NS, Pindi W. Banana peels as a bioactive ingredient and its potential application in the food industry. **J Funct Foods 2022**; 92:105054.
13. Pereira A, Maraschin M. (Banana (Musa spp) from peel to pulp: ethnopharmacology, source of bioactive compounds and its relevance for human health. **J Ethnopharmacol 2015**; 160: 149–163.
14. Kraithong S, Issara U. A strategic review on plant by-product from banana harvesting: a potentially bio-based ingredient for approaching novel food and agro-industry sustainability. **J Saudi Soc Agr Sci 2021**; 20: 530–543.
15. Aboul-Enein A, Salama Z, Gaafar A, Aly HF, Abou-Elella F, Ahmed H. Identification of phenolic compounds from banana peel (*Musa paradaisica* L.) as antioxidant and antimicrobial agents. **J Chem Pharmaceut Res 2016**; 8(4): 46–55.
16. Barnossi AE, Moussaid F, Housseini AI. Tangerine, banana and pomegranate peels valorisation for sustainable environment: a review. **Biotechnol Rep 2021**; 29:e00574.
17. Ademakinwa AN, Agunbiade MO. Banana peel wastes as a source of tyrosinase useful in the production of l-DOPA. **Sustain Chem Pharm 2022**; 30:100853.
18. Singh R, Saati AA, Faidah H, Bantun F, Jalal NA, Haque S. Prospects of microbial cellulase production using banana peels wastes for antimicrobial applications. **Int J Food Microbiol 2023**; 38(2):110069.
19. Mosa ZM, Khalil AF. The effect of banana peels supplemented diet on acute liver failure rats. **Ann Agric Sci (Cairo) 2015**; 60(2): 373–379.
20. Bagabaldo PAA, Atienza LM, Castillo-Israel KAT, Estacio MAC, Gaban PJV, Maniwang JRC, et al. 'Saba' banana (Musa acuminata x balbisiana BBB Group) peel pectin supplementation improves biomarkers of obesity and associated blood lipid disorders in obese hypercholesterolemic mice. **Curr Res Food Sci 2022**; 5: 251–260.
21. Saleem M, Saeed MT. Potential application of waste fruit peels (orange, yellow lemon and banana) as wide range natural antimicrobial agent. **J King Saud Univ Sci 2020**; 32: 805–810.
22. Eddie-Amadi BF, Ezejiofor AN, Orish CN, Rovira J, Allison TA, Orisakwe EO. Banana peel ameliorated hepatorenal damage and exerted anti-inflammatory and anti-apoptotic effects in metal mixture mediated hepatic nephropathy by activation of Nrf2/Hmox-1 and inhibition of Nfkb pathway. **Food Chem Toxicol 2022**; 170:113471.
23. Abdel-Rahman GN, Fouzy ASM, Amer MM, Saleh EM, Hamed IA, Sabry BA. Control of carbendazim toxicity using banana peel powder in rats. **Biotechnol Rep 2022**; 36:e00773.
24. Islam MR, Kamal MM, Kabir MR, Md Hasan M, Haque AR, Hasan SMK. Phenolic compounds and antioxidants activity of banana peel extracts: testing and optimization of enzyme-assisted conditions. **Measurement: Food 2023**; 10:100085.
25. Kamelia E, Islam AA, Hatta M, Miko H, Pattelongi I, Karo MBR. Evaluation of the activity of F2-isoprostane in alzheimer's disease rats given banana extract. **PJMHS 2020**; 14(2): 1459–1464.
26. Rosmarlina R, Hatta M, Djaharuddin I, Patellongi I, Susanto AD, Islam AA, et al. The changes of HIF-1α and ICAM-1 expression after Miana (*Coleus scutellariodes* [L} treatment in Balb/C mice with *Mycobacterium tuberculosis* infection. **Biomed & Pharmacol J 2022**; 15(1): 73–81. March.
27. Han R, Blencke HM, Cheng H, Li C. The antimicrobial effect of CEN1HC-Br against *Propionibacterium acnes* and its therapeutic and anti-inflammatory effects on acne vulgaris. **Peptides 2018**; 99: 36–43.
28. Savitri D, Djawad K, Hatta M, Wahyuni S, Bukhari A. Active compounds in kepok banana peel as anti-inflammatory in acne vulgaris: review Article. **Ann Med Surg 2022**; 84:104868.
29. Savitri D, Wahyuni S, Bukhari A, Djawad K, Hatta M. Molecular docking of compounds from banana peels extract on the NF-κβ pathway in acne vulgaris. **Nat Volatiles Essent Oil 2021**; 8(5): 2240–2248.
30. O'Boyle N, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: an open chemical toolbox. **J Cheminf 2011**; 3: 33.
31. Arnold K, Bordoli L, Kopp J, Schwede T. The SWISS-MODEL workspace: a web-based environment for protein structure homology modelling. **Bioinformatics 2006**; 22(2): 195–201.
32. Kiefer F, Arnold K, Kunzli M, Bordoli L, Schwede T. The SWISS-MODEL repository and associated resources. **Nucleic Acids Res 2009**; 37(Database issue): 387–392.
33. Macindoe G, Mavridis L, Venkatraman V, Devignes MD, Ritchie DW. HexServer: an FFT-based protein docking server powered by graphics processors. **Nucleic Acids Res 2010**; 38: 445–449. Web server issue).
34. Laskowski RA, Swindells MB. LigPlot+: multiple ligand-protein interaction diagrams for drug discovery. **J Chem Inf Model 2011**; 51(10): 2778–2786.
35. Wolber G, Langer T. LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. **J Chem Inf Model 2005**; 45(1): 160–169.
36. Murgueitio MS, Ebner S, Hörtnagl P, Rakers C, Bruckner R, Henneke P, et al. Enhanced immunostimulatory activity of in silico discovered agonists of Toll like receptor 2 (TLR2). **BBA – General Subjects 2017**; 1861: 2680–2689.
37. Jin MS, Kim SE, Heo JY, Lee ME, Kim HM, Paik SG. Crystal structure of the TLR1-TLR2 Heterodimer induced by binding of a tri-acylated lipopeptide. **Cells 2007**; 130: 1071–1082.
38. Maiti S, Banerjee A, Kanwar M. Effects of theaflavin-gallate in-silico binding with different proteins of SARS-CoV-2 and host inflammation and vasoregulations referring an experimental rat-lung injury. **Phytomed Plus 2022**; 2:100237.
39. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, et al. New developments in our understanding of acne pathogenesis and treatment. **Exp Dermatol 2009**; 18: 821–832.
40. Hwang H, Hyun S, KimY Yu J. Reduction of helical content by insertion of a disulfide bond leads to an antimicrobial peptide with decreased hemolytic activity. **ChemMedChem 2013**; 8: 59–62.
41. Younis S, Javed Q. The interleukin-6 and interleukin-1A gene promoter polymorphism is associated with the pathogenesis of acne vulgaris. **Arch Dermatol Res 2015**; 307(4): 365–370.
42. Paithankar DY, Sakamoto FH, Farinelli WA, Kositratna G, Blomgren RD, Meyer TJ, et al. Acne treatment based on selective photothermolysis of sebaceous follicles with topically delivered light-absorbing gold microparticles. **J Invest Dermatol 2015**; 135(7): 1727–1734.
43. Akoglu G, Tan C, Ayvaz DC, Tezcan I. Tumor necrosis factor α-308 G/A and interleukin 1 b-511 C/T gene polymorphisms in patients with scarring acne. **J Cosmet Dermatol 2019**; 18(1): 395–400.
44. Younis S, Shamin S, Nisar K, Deeba F, Mehmood S, Mumtaz S, et al. Association of TNF-α polymorphisms (857, 863 and 1031), TNF-α serum level and lipid profile with acne vulgaris. **Saudi J Biol Sci 2021**; 28: 6615–6620.
45. Jesumani V, Du H, Aslam M, Pei P, Huang N. Potential use of seaweed bioactive compounds in skincare—a Review. **Mar Drugs 2019**; 17: 688.
46. Popovic S, Urbam E, Lukic M, Conlo M. Peptides with antimicrobial and anti-inflammatory activities that have therapeutic potential for treatment of acne vulgaris. **Peptides 2012**; 34(2): 275–282.
47. Sugisaki H, Yamana K, Kakeda M, Kitagawa H, Tanaka K, Watanabe K, et al. Increased interferon-γ, interleukin-12p40 and IL-8 production in *Propionibacterium acnes*-treated peripheral blood mononuclear cells from patient with acne vulgaris: host response but not bacterial species is the determinant factor of the disease. **J Dermatol Sci 2009**; 55(1): 47–52.

48. dos Santos EM, de Macedo LM, Tundisi LL, Ataide JA, Camargo GA, Alves RC, et al. Coffee by-products in topical formulations: a review. **Trends Food Sci Technol 2021**; 111: 280−291.
49. Khalili M, Alavi M, Esmaeil-Jamaat E, Baluchnejadmojarad T, Roghani M. Trigonelline mitigates lipopolysaccharide-induced learning and memory impairment in the rat due to its antioxidative and anti-inflammatory effect. **Int Immunopharm 2018**; 61(Aug): 355−362.
50. Tripathi AS, Awasthi S, Maurya RK, Yasir M, Mohapatra L, Srivastav V. Protective effect of vanillin on the management of cecal ligation and puncture induced sepsis rat model. **Microb Pathog 2022**; 165(April):105493.
51. Olatunde A, Mohammed A, Ibrahim MA, Tajuddeen N, Shuaibu MN. Vanillin: a food additive with multiple biological activities. **Eur J Med Chem Rep 2022**; 5:100055.
52. Geduk AS, Zengin F. LC−MS/MS characterization, antidiabetic, antioxidative, and antibacterial effects of different solvent extracts of Anamur banana (*Musa Cavendishii*). **Food Sci Biotehcnol 2021**; 30(9): 1183−1193.
53. Makni M, Chtorou Y, Fetoui H, Garoui EM, Bondawaran T, Zeghal N. Evaluation of the antioxidant, anti-inflammatory and hepatoprotective properties of vanillin in carbon tetrachloride-treated rats. **Eur J Pharmacol 2011**; 668(1−2): 133−139.
54. Wang P, Li C, Liao G, Huang Y, Lv L, Liu X, et al. Vanillin attenuates proinflammatory factors in a tMCAO mouse model via inhibition of TLR4/NF-kB signaling pathway. **Neuroscience 2022**; 491(May): 65−74.
55. Guo W, Liu B, Hu G, Kan X, Li Y, Gong Q. Vanillin protects the blood−milk barrier and inhibits the inflammatory response in LPS-induced mastitis in mice. **Toxicol Appl Pharmacol 2019**; 365(Feb): 9−18.
56. Borges A, Ferreira C, Saavedra MJ, Simões M. Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. **Microb Drug Resist 2013**; 19: 256−265.
57. Kumari S, Katare PB, Elancheran R, Nizami HL, Paramesha B, Arava S, et al. Musa balbisiana fruit rich in polyphenols attenuates isoproterenol-induced cardiac hypertrophy in rats via inhibition of inflammation and oxidative stress. **Oxid Med Cell Longev 2020**:7147498.
58. Wongwaiwech D, Kamchonemenukool S, Ho CT, Li S, Thongsook T, Majai N, et al. Nutraceutical difference between two popular Thai namwa cultivars used for sun dried banana products. **Molecules 2022**; 27(17): 5675.
59. Liu LL, Zhang Y, Zhang XF, Li FH. Influence of rutin on the effects of neonatal cigarette smoke exposure-induced exacerbated MMP-9 expression, Th17 cytokines and NF-κβ/iNOS-mediated inflammatory responses in asthmatic mice model. **Korean J Physiol Pharmacol 2018**; 22(5): 481−491. 2018.
60. Gadelha FAAF, Cavalcanti RFP, Vieira GC, Ferreira LKDP, de Sousa GR, Filho JMB, et al. Immunomodulatory properties of Musa paradisiaca L. Inflorescence in combined allergic rhinitis and asthma syndrome (CARAS) model towards NFκB pathway inhibition. **J Funct Foods 2021**; 83:104540.
61. DeCuypere M, Lu Y, Miller DD, LeDoux MS. Regional distribution of tetrahydroisoquinoline derivatives in rodent, human, and Parkinson's disease brain. **J Neurochem 2008**; 107: 1398−1413.
62. Deng Y, Maruyama W, Kawai M, Dostert P, Yamamura H, Takahashi T, et al. Assay for the (R)- and (S)-enantiomers of salsolinols in biological samples and foods with ion-pair high-performance liquid chromatography using beta-cyclodextrin as a chiral mobile phase additive. **J Chromatogr B Biomed Sci Appl 1997**; 689: 313−320.
63. Kurnik-Łucka M, Latacz G, Martyniak A, Bugajski A, Kieć-Kononowicz K, Gil K. Salsolinol—neurotoxic or neuroprotective? **Neurotox Res 2020**; 37: 286−297.

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