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Optimization of Gel Formulation and Antibacterial Activity against *Cutibacterium acnes* from Combined Extracts of *Caesalpinia sappan* and *Carthamus tinctorius* Using Simplex Lattice Design

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ABSTRACT

Acne vulgaris is a common dermatological disorder associated with the imbalance of skin microbiota, particularly *Cutibacterium acnes*, which has encouraged the exploration of safe and plant-based topical formulations. This study was conducted to develop and optimize a herbal gel containing combined extracts of *Caesalpinia sappan* and *Carthamus tinctorius*. Formulation optimization was performed using a statistical mixture approach to determine an appropriate proportion of Carbopol 940 and triethanolamine in the gel system. The prepared formulations were assessed for physical characteristics, stability under temperature variation, sensory acceptance, and antibacterial activity. The optimized gel demonstrated acceptable viscosity, spreadability, and pH values suitable for topical application. Stability testing indicated that the formulation maintained its physicochemical properties without noticeable changes. Sensory evaluation showed good acceptance in terms of odor, texture, and non-irritating effect. The antibacterial assay confirmed that the optimized gel was able to inhibit the growth of *C. acnes*. Overall, the combined extracts of *C. sappan* and *C. tinctorius* produced a stable herbal gel with favorable antibacterial performance, supporting its potential use as a natural topical preparation for acne management.

INTRODUCTION

Acne vulgaris is a common dermatological disorder that predominantly affects areas with high sebaceous activity, such as the face and back, where *Cutibacterium acnes* is the most abundant bacterium. Although *C. acnes* is widely recognized for its role in acne pathogenesis, it also contributes to normal skin homeostasis through lipid metabolism, microbial competition, and protection against oxidative stress (Rozas et al., 2021). Under specific conditions, however, excessive proliferation of this bacterium may disrupt this balance and initiate inflammatory processes that lead to acne lesions.

The long-term use of conventional acne treatments, particularly topical antibiotics, has increasingly raised concerns regarding antimicrobial resistance. A recent multinational study demonstrated that resistance of *C. acnes* to clindamycin increased from 25.5% during 1983–2014 to 35.4% in 2015–2023, while resistance to macrolide antibiotics such as erythromycin and azithromycin also showed a marked upward trend (Beig et al., 2024). In contrast, resistance to levofloxacin and tetracyclines remains relatively low. These findings emphasize the need to explore alternative acne therapies that are effective, safe, and do not rely on conventional antibiotics, particularly those derived from natural sources.

In this context, medicinal plants traditionally used in Indonesia offer promising potential. *Caesalpinia sappan* (sappan wood) is rich in bioactive compounds, including brazilin, brazilein, sappan chalcone, and protosappanin A, which are known to possess antioxidant, anti-inflammatory, and antimicrobial properties (Vij et al., 2023). Previous studies have shown that brazilin extracted from *C. sappan* can suppress inflammatory mediators such as nitric oxide (NO), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), while also exhibiting strong antibacterial activity against pathogenic microorganisms, supporting its potential application as a topical anti-acne agent (Pattananandecha et al., 2022). Additionally, *Carthamus tinctorius* (kasumba turatea) has been reported to contain polysaccharides with antioxidant, anti-inflammatory, and antibacterial activities, suggesting its suitability for use in topical antibacterial gel formulations targeting *C. acnes* (Hansur et al., 2024).

Several studies have evaluated the antibacterial activity of *C. sappan* and *C. tinctorius* individually. Extracts of *C. sappan* have demonstrated strong inhibitory effects against *Cutibacterium acnes*, with reported inhibition zones of approximately 19–20 mm, as well as measurable minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values for brazilin, indicating substantial antibacterial potency. Meanwhile, *C. tinctorius* extracts have been shown to inhibit the growth of various pathogenic bacteria, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, largely attributed to their high phenolic and flavonoid content. However, direct evidence of their antibacterial activity against *C. acnes* remains limited. Taken together, these findings suggest that although each plant exhibits notable antimicrobial properties—particularly *C. sappan* against *C. acnes*—the potential benefits of combining both extracts have not yet been systematically investigated. This provides a rationale for comparing the antibacterial performance of the combined extracts with previously reported activities of the individual extracts in support of a dual-extract gel formulation.

Despite the growing body of literature describing the pharmacological activities of *C. sappan* and *C. tinctorius*, research focusing on their combined use in topical dosage forms is still scarce. Gel formulations are particularly advantageous for acne-prone skin due to their cooling sensation, non-greasy texture, and ease of application. Nevertheless, the development of a stable and effective herbal gel requires careful optimization of excipient composition. Carbopol 940 and triethanolamine (TEA) are commonly employed in gel formulations, and variations in their proportions can markedly influence viscosity, pH, and overall physical stability of the final product.

Accordingly, a clear research gap can be identified. Although the antibacterial activities of *C. sappan* and *C. tinctorius* have been individually reported, no previous study has developed and optimized a combined herbal gel formulation targeting *C. acnes* using a statistical design of experiments approach. The novelty of this study lies in the integration of both plant extracts into a single topical gel and the application of the Simplex Lattice Design (SLD) method to optimize excipient composition, with the aim of improving physical stability while maintaining antibacterial efficacy.

Therefore, this study aims to (i) optimize a herbal gel formulation containing combined extracts of *C. sappan* and *C. tinctorius* using the SLD approach, (ii) evaluate the physical characteristics and stability of the formulated gel, and (iii) assess its antibacterial activity against *C. acnes*. The results are expected to provide a scientific basis for the development of stable, effective, and natural product-based topical preparations for acne management.

METHODS

Research Design

This study was conducted as an experimental laboratory-based investigation aimed at optimizing a herbal gel formulation containing combined extracts of *Caesalpinia sappan* and *Carthamus tinctorius*. A Simplex Lattice Design approach was applied using Design Expert® version 13 to evaluate the effect of formulation variables on gel performance. The concentrations of Carbopol 940 and triethanolamine served as independent variables, while physical characteristics, stability, sensory acceptance, and antibacterial activity against *Cutibacterium acnes* were treated as response variables.

Materials And Equipment

The plant materials used in this study consisted of *C. sappan* heartwood obtained from traditional markets in Makassar and *C. tinctorius* flowers collected from Enrekang, South Sulawesi. The chemicals employed included Carbopol 940, triethanolamine, propylene glycol, DMDM hydantoin, citrus oil, distilled water, and ethanol. *C. acnes* ATCC 11827 was used as the test microorganism. Clindamycin gel was applied as a positive control, while a plain gel base served as a negative control. The main instruments used comprised a rotary evaporator, Brookfield viscometer, ultraviolet–visible spectrophotometer, digital pH meter, incubator, and autoclave.

Sample Preparation And Extraction

Dried plant materials were powdered and extracted separately using ethanol through maceration at room temperature. The extraction process was carried out over several days with periodic agitation. The resulting filtrates were concentrated under reduced pressure using a rotary evaporator and subsequently stored under refrigerated conditions. The extracts were evaluated for yield and basic quality parameters prior to formulation.

Gel Formulation And Optimization

Gel formulations were prepared according to the experimental design matrix generated by the Simplex Lattice Design. Carbopol 940 was dispersed in distilled water and allowed to hydrate, followed by the incorporation of plant extracts and other excipients. Triethanolamine was added gradually to neutralize the system and obtain the desired gel consistency. Optimization was performed by analyzing the desirability function, with priority given to formulations exhibiting balanced physical properties and stability.

Evaluation of Gel Properties

Organoleptic Properties and Homogeneity

The prepared gels were visually examined for color, odor, and uniformity to ensure acceptable appearance and homogeneity.

pH and Viscosity

The pH of each formulation was measured using a calibrated digital pH meter, while viscosity was determined using a Brookfield viscometer under controlled conditions.

Spreadability

Spreadability was evaluated by measuring the diameter of gel dispersion between glass plates under a standardized load after a fixed period.

Stability Testing

Stability was assessed using repeated freeze–thaw cycles. Each cycle consisted of alternating storage at low and elevated temperatures. Changes in physical appearance, pH, viscosity, and spreadability were monitored after each cycle.

Hedonic Evaluation

Sensory acceptance of the optimized gel was assessed by volunteer panelists with no history of skin sensitivity. Parameters evaluated included odor, texture, color, and irritation response using a structured preference scale.

Antibacterial Activity Test

Antibacterial activity was evaluated using the agar diffusion method. Test samples were applied to sterile paper discs and placed on agar media inoculated with *C. acnes*. Following incubation under anaerobic conditions, inhibition zones were measured to assess antibacterial effectiveness.

Data Analysis

Experimental data were analyzed using Design Expert® software to determine optimal formulation conditions. Statistical evaluation was conducted using appropriate analysis of variance techniques, and results were expressed as mean values with standard deviations.

Ethical Consideration

All experimental procedures were conducted in accordance with laboratory biosafety guidelines. Ethical approval for the involvement of microbial isolates and human panelists was obtained from the institutional ethics committee.

RESULTS AND DISCUSSION

The extraction yields of *Caesalpinia sappan* and *Carthamus tinctorius* were 5.00% and 5.02%, respectively, and both extracts complied with the physicochemical quality standards of the Indonesian Herbal Pharmacopoeia (**Table 1**). Although the yields were below the ideal threshold (>10%), this outcome is consistent with previous reports indicating that extraction efficiency is strongly influenced by raw material characteristics and solvent polarity (Daud & Suryanti, 2017; Febriyenti et al., 2018; Vij et al., 2023). These results confirm that the extracts were suitable for formulation despite moderate yield values.

Table 1. Standardization and Yield of Extracts

Parameter	C. sappan	C. tinctorius	Reference Standard (FHI)
Moisture content (%)	9.2	9.5	≤ 10%
Total ash (%)	1.3	4.2	≤ 1.4 (sappan), ≤ 4.4 (kasumba)
Acid-insoluble ash (%)	0.5	1.6	≤ 0.6 (sappan), ≤ 1.7 (kasumba)
Extractive (ethanol) (%)	5	4	≥ 4%
Extractive (water) (%)	3	3	≥ 3%
Yield (%)	5	5.02	> 10% (ideal)

Source: *Data of this study; (Daud & Suryanti, 2017); (Febriyenti et al., 2018); (Vij et al., 2023)*

Table 2. IC50 Values of Extracts and Combination

Sample	IC50 (μg/mL)	Category
C. sappan extract	48.74	Very strong (<50)
C. tinctorius extract	45.95	Very strong (<50)
Combination extract	43.18	Very strong (<50)
Quercetin (control)	49.92	Very strong (<50)

Source: *Data of this study; classification based on Yusuf et al., (2022)*

Antioxidant evaluation using the DPPH assay demonstrated strong radical scavenging activity for both single extracts and their combination (**Table 2**, **Figure 1**).

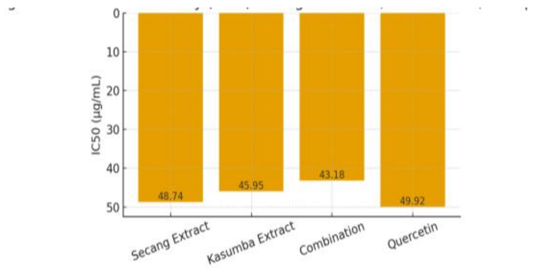

Figure 1. Antioxidant activity (IC50) of single extracts, combination, and quercetin

Notably, the combined extract showed the lowest IC_{50} value, indicating superior antioxidant capacity compared with individual extracts. This enhancement is consistent with the presence of multiple bioactive constituents in *C. sappan*, such as brazilin, brazilein, and sappan chalcone, which are known for their antioxidant and anti-inflammatory properties (Syamsunarno et al., 2021; Vij et al., 2023), as well as hydroxysafflor yellow A (HSYA) in *C. tinctorius*, a compound with strong antioxidant and cytoprotective effects (Bai et al., 2025; Hansur et al., 2024). The observed improvement supports previous evidence that phytochemical combinations may exert complementary antioxidant mechanisms, which are relevant to oxidative stress–related conditions such as acne vulgaris.

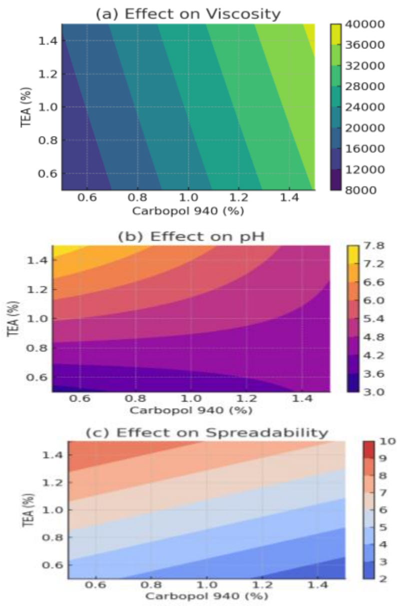

Figure 2. Contour plots of SLD optimization ((a) Effect of Carbopol 940 and TEA on viscosity, (b) Effect on pH, (c) Effect on spreadability)

Optimization of the gel formulation using the Simplex Lattice Design revealed clear effects of Carbopol 940 and triethanolamine (TEA) on viscosity, pH, and spreadability (**Table 3**, **Figure 2**). Carbopol 940 predominantly governed viscosity, consistent with its established role as a rheology-modifying polymer (Safitri et al., 2021), whereas TEA exerted a stronger influence on pH due to its neutralizing function in Carbopol-based systems (Kaya et al., 2024; Yusuf et al., 2022).

Table 3. Results of Gel Characterization

Run	Viscosity (cps)	pH	Spreadability (cm)
1	15,067	5	5.2
2	15,400	4.75	5.7
3	16,333	4.55	5.7
4	16,400	4.31	5.4
5	14,800	6.45	6.4
6	14,733	7.25	6.9
7	16,733	4.32	5.3
8	14,133	7.7	5.6

Source: Data of this study; interpretation based on Nafisa et al. (2021); Garg et al. (2002).

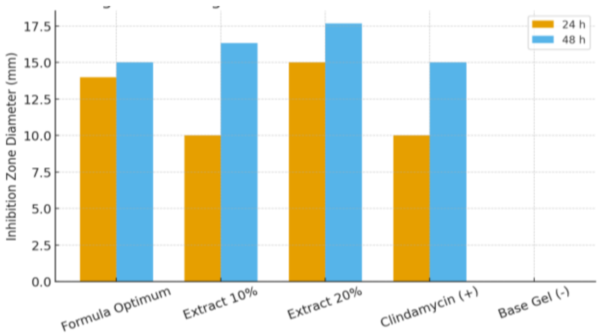

Figure 3. Histogram of inhibition zones at 24 h and 48 h

The negative interaction term observed in the pH model reflects the neutralization balance between these components, in line with TEA-induced ionization of Carbopol carboxyl groups (Shmakov et al., 2023). Spreadability showed an inverse relationship with viscosity, increasing at higher TEA levels, a trend widely reported in gel formulation studies (Garg et al., 2002; Nafisa et al., 2021). Based on the desirability function, the optimal formulation was identified at 1.5% Carbopol 940 and 0.5% TEA, yielding a desirability value of 0.931.

Table 4. Polynomial Regression Equations Derived from the Simplex Lattice Design Models

Response	Model type	Polynomial equation (mixture terms)
Viscosity (cps)	Cubic (mixture)	$Y_1 = 19837.22059 \cdot A + 3831.27941 \cdot B + 647.05882 \cdot A \cdot B$
pH	Quadratic (mixture)	$Y_2 = 2.65881 \cdot A + 5.88992 \cdot B - 3.49961 \cdot A \cdot B$
Spreadability (cm)	Quadratic (mixture)	$Y_3 = 3.10278 \cdot A + 4.68056 \cdot B - 2.13333 \cdot A \cdot B$

Source: Design-Expert® SLD output (experimental data of this study).

Table 5 ANOVA Summary and Model Adequacy Parameters for SLD Responses

Response	Model type	Model df	Adj. R^2	Model F-value	Model p-value	Lack-of-fit p	Adequate precision
Viscosity (cps)	Cubic (mixture)	3	0.8728	14.27	0.0097	0.4511	8.7426
pH	Quadratic (mixture)	2	0.9632	52.63	< 0.0001	0.2332	19.9469
Spreadability (cm)	Quadratic (mixture)	2	0.8584	11.39	0.0033	0.2239	9.5551

Source: Design-Expert® SLD output (experimental data of this study).

Table 6. Average Physical Stability Parameters During Cycling Test (Mean ± SD)

Cycle	pH (mean ± SD)	Viscosity (cps ± SD)	Spreadability (cm ± SD)
1	5.11 ± 0.12	16,364 ± 45.6	5.57 ± 0.06
3	4.90 ± 0.10	16,296 ± 5.8	5.67 ± 0.15
6	4.57 ± 0.03	15,844 ± 50.4	5.63 ± 0.15

Source: Data of this study; cycling test protocol adapted from Ramadhani et al., (2017); Lestari et al., (2020).

Table 7. Hedonic Test Results (Panelist Preferences)

Attribute	Strongly Dislike (%)	Neutral (%)	Like (%)	Strongly Like (%)
Odor	0	10	30	40
Color	10	20	40	10
Texture	0	20	50	20
Non-irritating	0	10	30	50

Source: Data of this study (primary data, hedonic evaluation).

Table 8. Antibacterial Activity (Inhibition Zone, mm)

Treatment	24 h (mean ± SD)	48 h (mean ± SD)	Category
Formula optimum gel	14 ± 1.0	15.0 ± 0.0	Strong
Combination 10%	10 ± 0.0	16.3 ± 2.3	Moderate–Strong
Combination 20%	15 ± 0.0	17.7 ± 2.5	Strong
Clindamycin (+)	10 ± 0.0	15.0 ± 0.0	Strong
Base gel (-)	0	0	None

Source: Data of this study; classification of antibacterial strength adapted from Lukmayani et al. (2022); Cahyani et al.

a b c d e

Figure 4. Representative inhibition zone images for each treatment against *Cutibacterium acnes* ((a)Optimized gel, (b)10% extract, (b) 20% extract, (d) Clindamyci, (e) Base gel)

Model adequacy was confirmed by ANOVA results (**Table 5**), which showed high adjusted R^2 values (0.8584–0.9632), significant model p-values, non-significant lack-of-fit, and adequate precision values exceeding the recommended threshold. These parameters indicate that the SLD models reliably predicted formulation behavior, supporting their application for gel optimization (Deka, 2022; Litovin & Noveski, 2022; Nahdhia et al., 2025; Pratiwi et al., 2024).

Physical stability testing demonstrated that the optimized gel maintained consistent pH, viscosity, and spreadability throughout six freeze–thaw cycles (**Table 6**). Statistical analysis showed no significant differences among cycles ($p > 0.05$), and no visual instability was observed, including phase separation or color change. These findings are consistent with earlier reports that Carbopol–TEA systems exhibit good resilience under thermal stress (Lestari et al., 2020; Ramadhani et al., 2017). Hedonic evaluation further indicated acceptable sensory characteristics, particularly for odor, texture, and non-irritating properties, while slightly lower color preference was attributed to natural pigments from the plant extracts.

Antibacterial testing against *Cutibacterium acnes* demonstrated that the optimized gel and extract-containing formulations produced clear inhibition zones compared with the base gel (**Table 8**, **Figure 3**, **Figure 4**). The 20% extract formulation showed the strongest activity, reflecting a concentration-dependent antibacterial effect, whereas the optimized gel containing 10% extract maintained strong inhibition while achieving balanced physical properties. Statistical analysis confirmed significant differences among treatments ($p < 0.05$). These results are consistent with previous reports on the antibacterial relevance of plant-derived compounds in addressing antibiotic resistance (Beig et al., 2024) and the pathogenic role of *C. acnes* involving biofilm formation and immune modulation (Cavallo et al., 2022; Mayslich et al., 2021). The enhanced activity of the combined extracts aligns with earlier findings on synergistic antibacterial effects of phytochemical combinations (Singh et al., 2023; Yan et al., 2021). Moreover, the antioxidant and anti-inflammatory properties of *C. sappan* and *C. tinctorius* may concurrently mitigate oxidative stress and inflammation associated with acne pathogenesis (Almasaudi, 2021; Bai et al., 2025; Carballido et al., 2024; Olmos & González-Benito, 2021).

Overall, these findings support the successful integration of dual herbal extracts into a statistically optimized gel matrix, addressing formulation stability and antibacterial efficacy simultaneously. While challenges such as raw material variability and limited in vitro scope remain (Litovin & Noveski, 2022), the application of SLD provides a robust framework for rational herbal gel development and supports future refinement using advanced delivery systems (Dixit, 2021; Hayat et al., 2023; Sindhu et al., 2022; Wekalao et al., 2025).

CONCLUSIONS

This study demonstrates that the combination of *Caesalpinia sappan* and *Carthamus tinctorius* extracts can be successfully formulated into a stable and effective herbal gel using a Simplex Lattice Design approach. The optimized formulation exhibited acceptable physicochemical properties, maintained stability under freeze–thaw conditions, and showed strong antioxidant and antibacterial activity against *Cutibacterium acnes*. These findings support the study hypothesis that a statistically optimized dual-extract herbal gel can achieve both formulation stability and biological efficacy. Overall, the results confirm the feasibility of integrating combined plant extracts with systematic formulation optimization for the development of natural anti-acne topical preparations.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally to the study conception, research design, experimental work, data analysis, and manuscript preparation.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

ETHICAL CONSIDERATION

Ethical issues including plagiarism, data fabrication, falsification, and double publication have been completely observed by the authors.

BIBLIOGRAPHY

A.K. Garg, J. Kim, T.G. Owens, A.P. Ranwala, Y.D. Choi, L.V. Kochian, & R.J. Wu, Trehalose accumulation in rice plants confers high tolerance levels to different abiotic stresses, *Proc. Natl. Acad. Sci. U.S.A*. 99 (25) 15898-15903, https://doi.org/10.1073/pnas.252637799 (2002).

Almasaudi, S. (2021). The antibacterial activities of honey. *Saudi Journal of Biological Sciences*, *28*(4), 2188–2196. https://doi.org/10.1016/j.sjbs.2020.10.017

Bai, H., Yang, J., & Wang, R. (2025). Carthamus tinctorius L.: A comprehensive review of its ethnomedicine, phytochemistry, pharmacology, and clinical applications. *Frontiers in Pharmacology*, *16*, 1609299. https://doi.org/10.3389/fphar.2025.1609299

Beig, M., Shirazi, O., Ebrahimi, E., Banadkouki, A. Z., Golab, N., & Sholeh, M. (2024). Prevalence of antibiotic-resistant Cutibacterium acnes isolates: A systematic review and meta-analysis. *Journal of Global Antimicrobial Resistance*, *39*, 82–91. https://doi.org/10.1016/j.jgar.2024.07.005

Carballido, F., Philippe, A., Maitre, M., Lauze, C., Chanssard, N., Garidou, L., Duplan, H., & Tan, J. (2024). A dermocosmetic product containing the sap of oat plantlets and Garcinia mangostana extract improves the clinical signs of acne. *Journal of the European Academy of Dermatology and*

Venereology. https://doi.org/10.1111/jdv.19876

Cavallo, I., Sivori, F., Truglio, M., De Maio, F., Lucantoni, F., Cardinali, G., & al., et. (2022). Skin dysbiosis and Cutibacterium acnes biofilm in inflammatory acne lesions of adolescents. *Scientific Reports*, *12*, 21104. https://doi.org/10.1038/s41598-022-25614-7

Daud, N. S., & Suryanti, E. (2017). Patchouli Oil Anti-Acne Emulgel Formulation. *Jurnal Mandala Pharmacon Indonesia*, *3*(2), 90–95. https://doi.org/10.35311/jmpi.v3i02.3

Deka, T. (2022). Box-Behnken Design Approach to Develop Nano-Vesicular Herbal Gel. *International Journal of Applied Pharmaceutics*, *14*(6), 19. https://doi.org/10.22159/IJAP.2022V14I6.45867

Dixit, G. (2021). Formulation and evaluation of herbal gel for management of mouth ulcers. *Indian Journal of Pharmacy and Pharmacology*, *8*(3), 139–143. https://doi.org/10.18231/J.IJPP.2021.039

Hansur, L., Aras, D. U., & Dwijayanti, E. (2024). Potential of Hydroxysafflor yellow A as Anti-Inflammatory. *Pharmacon: Jurnal Farmasi Indonesia*, *21*(2). https://doi.org/10.23917/pharmacon.v21i2.4908

Hayat, M., Nawaz, A., Chinnam, S., Muzammal, M., Latif, M. S., Yasin, M., Ashique, S., Zengin, G., & Farid, A. (2023). Formulation development and optimization of herbo synthetic gel. *Process Biochemistry*, *130*, 116–126. https://doi.org/10.1016/j.procbio.2023.04.010

Kaya, Y., Kobya, V., Mardani, A., & Assaad, J. J. (2024). Effect of modified Triethanolamine on grinding efficiency. *Talanta Open*, *9*, 100293. https://doi.org/10.1016/j.talo.2024.100293

Lestari, F. A., Hajrin, W., & Hanifa, N. I. (2020). Optimization of Katuk Leaf Extract Cream Formula. *Jurnal Kefarmasian Indonesia*, *10*(2), 110–119. https://doi.org/10.22435/jki.v10i2.2496

Litovin, H., & Noveski, R. (2022). Challenges and best practices in phytopharmaceutical production. *Macedonian Pharmaceutical Bulletin*, *68*(Suppl 2), 117–118. https://doi.org/10.33320/maced.pharm.bull.2022.68.04.052

Mayslich, C., Grange, P. A., & Dupin, N. (2021). Cutibacterium acnes as an Opportunistic Pathogen: An Update of Its Virulence-Associated Factors. *Microorganisms*, *9*(2), 303. https://doi.org/10.3390/microorganisms9020303

Nahdhia, N., Hendradi, E., & Rijal, M. A. S. (2025). Design and optimization of nanoemulsion system by simplex lattice design method to improve solubility of topical diclofenac sodium. *Research Journal of Pharmacy and Technology*, *18*(5), 2237–2243. https://doi.org/10.52711/0974-360X.2025.00320

Nafisa, A., Wattoo, F. H., Qayyum, M., & Gulfraz, M. (2021). The association between chronic stress, hair cortisol, and angiographically documented coronary atherosclerosis, a case-control study. *Stress*, *24*(6), 1008–1015. https://doi.org/10.1080/10253890.2021.1985994

Olmos, D., & González-Benito, J. (2021). Polymeric Materials with Antibacterial Activity: A Review. *Polymers*, *13*(4), 613. https://doi.org/10.3390/polym13040613

Pattananandecha, T., Apichai, S., Julsrigival, J., Ogata, F., Kawasaki, N., & Saenjum, C. (2022). Antibacterial Activity against Foodborne Pathogens and Inhibitory Effect on Anti-Inflammatory Mediators' Production of Brazilin-Enriched Extract from Caesalpinia sappan Linn. *Plants*, *11*(13), 1698. https://doi.org/10.3390/plants11131698

Pratiwi, G., Ramadhiani, A. R., Shiyan, S., & Chabib, L. (2024). Combination Simplex Lattice Design Modelling with Chemometrics Analysis for Optimization Formula Self-Nano Emulsion Loaded Quercetin. *Biomedicines Research International*, *14*(1), 14. https://doi.org/10.33263/BRIAC141.014

Ramadhani, R. A., Riyadi, D. H. S., Triwibowo, B., & Kusumaningtyas, R. D. (2017). Review of the

Utilization of Design Expert to Optimize the Composition of Vegetable Oil Blends as Raw Material for Biodiesel Synthesis. *Jurnal Teknik Kimia Dan Lingkungan*, *1*(1), 11. https://doi.org/10.33795/jtkl.v1i1.5

Rozas, M., de Ruijter, A. H., Fabrega, M. J., Zorgani, A., Guell, M., Paetzold, B., & Brillet, F. (2021). From Dysbiosis to Healthy Skin: Major Contributions of Cutibacterium acnes to Skin Homeostasis. *Microorganisms*, *9*(3), 628. https://doi.org/10.3390/microorganisms9030628

Shmakov, S. L., Babicheva, T. S., Kurochkina, V. A., Lugovitskaya, T. N., & Shipovskaya, A. B. (2023). Structural and Morphological Features of Anisotropic Chitosan Hydrogels Obtained by Ion-Induced Neutralization in a Triethanolamine Medium. *Gels*, *9*(11), 876. https://doi.org/10.3390/gels9110876

Sindhu, R. K., Gupta, R., Wadhera, G., & Kumar, P. (2022). Modern Herbal Nanogels: Formulation, Delivery Methods, and Applications. *Gels*, *8*(2), 97. https://doi.org/10.3390/gels8020097

Singh, V. K., Sahoo, D., Agrahari, K., Khan, A., Mukhopadhyay, P., Chanda, D., & Yadav, N. P. (2023). Anti-inflammatory, anti-proliferative and anti-psoriatic potential of apigenin in RAW 264.7 cells, HaCaT cells and psoriasis like dermatitis in BALB/c mice. *Life Sciences*, *328*, 121909. https://doi.org/10.1016/j.lfs.2023.121909

Syamsunarno, M. R. A. A., Safitri, R., & Kamisah, Y. (2021). Protective Effects of Caesalpinia sappan Linn. And Its Bioactive Compounds on Cardiovascular Organs. *Frontiers in Pharmacology*, *12*, 725745. https://doi.org/10.3389/fphar.2021.725745

Vij, T., Prashant Anil, P., Shams, R., Dash, K. K., Kalsi, R., Pandey, V. K., Harsányi, E., Kovács, B., & Shaikh, A. M. (2023). A Comprehensive Review on Bioactive Compounds Found in Caesalpinia sappan. *Molecules*, *28*(17), 6247. https://doi.org/10.3390/molecules28176247

Wekalao, J., Premalatha, S., Prabakaran, P., & Rathish, C. R. (2025). Graphene-integrated Multiresonator Architecture with Machine Learning Enhancement for Enhanced Isoquercitrin Detection System in Phytopharmaceutical Formulations. *Plasmonics*.

Yan, Y., Li, X., Zhang, C., Lv, L., Gao, B., & Li, M. (2021). Research Progress on Antibacterial Activities and Mechanisms of Natural Alkaloids: A Review. *Antibiotics*, *10*(3), 318. https://doi.org/10.3390/antibiotics10030318

Yusuf, A. L., Nugraha, D., Wahlanto, P., Indriastuti, M., Ismail, R., & Himah, F. A. (2022). Formulation and Evaluation of Bitter Melon Fruit Extract Gel Preparation (Momordica Charantia L.) with Variations in Carbopol 940 Concentration. *Pharmacy Genius*, *1*(1). https://doi.org/10.56359/pharmgen.v1i01.149