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Ivonne Soeliono (ivonne)

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Participants

Muh. Deni Kurniawan (muhdenikurniawan)

Ivonne Soeliono (ivonne)

Messages

Note	From
Dear Editor, Thank you for your comments and suggestions. We have revised the manuscript according to the previous revision requests and uploaded the revised version for your consideration. We appreciate your time and look forward to your feedback. Kind regards, Ivonne Soeliono 423_Rev1.docx	ivonne 2026-07-09 05:57 PM
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Your manuscript will now proceed to the next stage of the editorial process. We will assign reviewers to evaluate the revised manuscript, and we will inform you once the review process has been completed.

Thank you for your cooperation and patience.

Kind regards,
Muh. Deni Kurniawan

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Notifications ×

Your submission has been sent for review

2026-07-09 06:10 PM

Dear Ivonne Soeliono,

I am pleased to inform you that an editor has reviewed your submission, Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation, and has decided to send it for peer review. An editor will identify qualified reviewers who will provide feedback on your submission.

This journal conducts double-anonymous peer review. The reviewers will not see any identifying information about you or your co-authors. Similarly, you will not know who reviewed your submission, and you will not hear from the reviewers directly. You will hear from us with feedback from the reviewers and information about the next steps.

Please note that sending the submission to peer review does not guarantee that it will be published. We will consider the reviewers' recommendations before deciding to accept the submission for publication. You may be asked to make revisions and respond to the reviewers' comments before a final decision is made.

If you have any questions, please contact me from your submission dashboard.

Muh. Deni Kurniawan

Notifications ×

Your submission has been reviewed and we encourage you to submit revisions

2026-07-15 02:06 PM

Dear Ivonne Soeliono,

Your submission Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation has been reviewed and we would like to encourage you to submit revisions that address the reviewers' comments. An editor will review these revisions and if they address the concerns adequately, your submission may be accepted for publication.

The reviewers' comments are included at the bottom of this email. Please respond to each point in the reviewers' comments and identify what changes you have made. If you find any of the reviewer's comments to be unjustified or inappropriate, please explain your perspective.

When you have completed your revisions, you can upload revised documents along with your response to the reviewers' comments at your submission dashboard. If you have been logged out, you can login again with the username ivonne.

If you have any questions, please contact me from your submission dashboard.

We look forward to receiving your revised submission.

Kind regards,

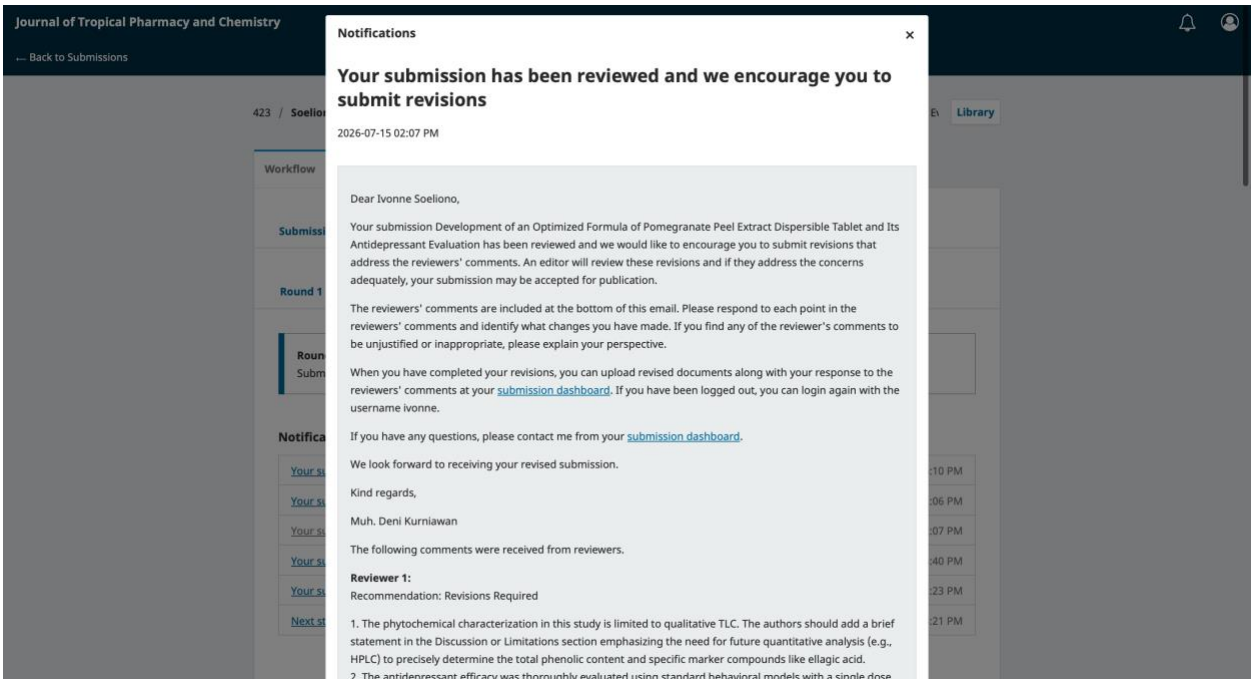
Muh. Deni Kurniawan

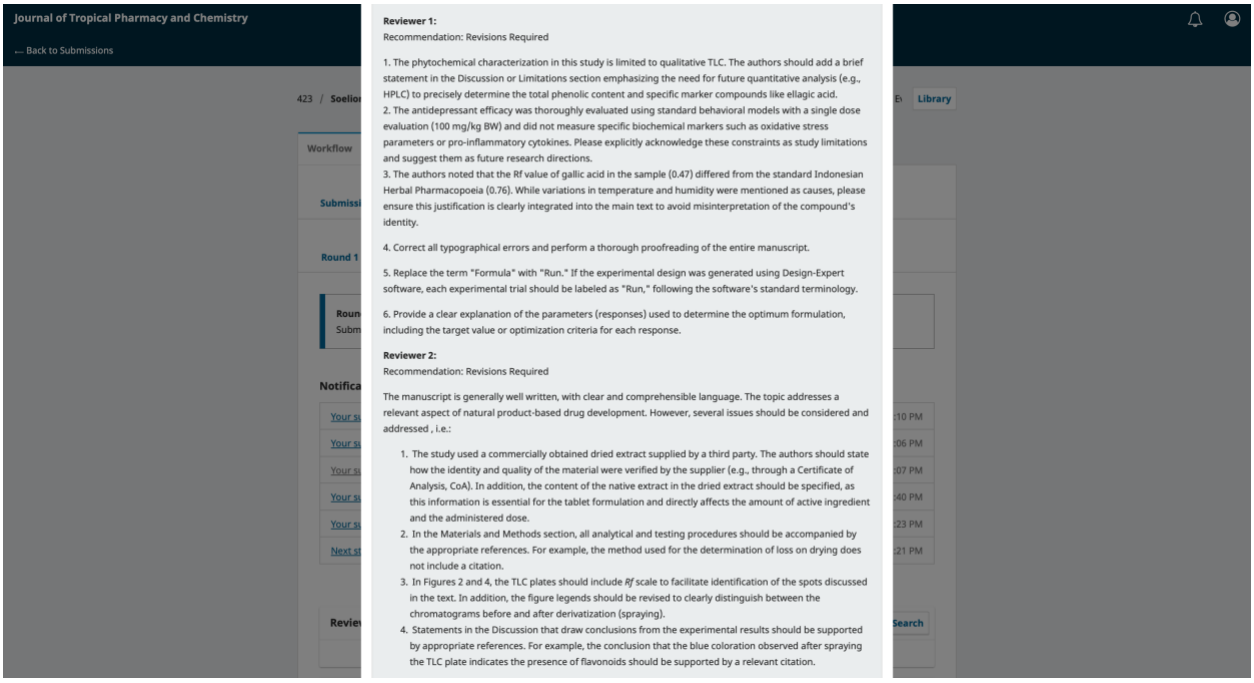
The following comments were received from reviewers.

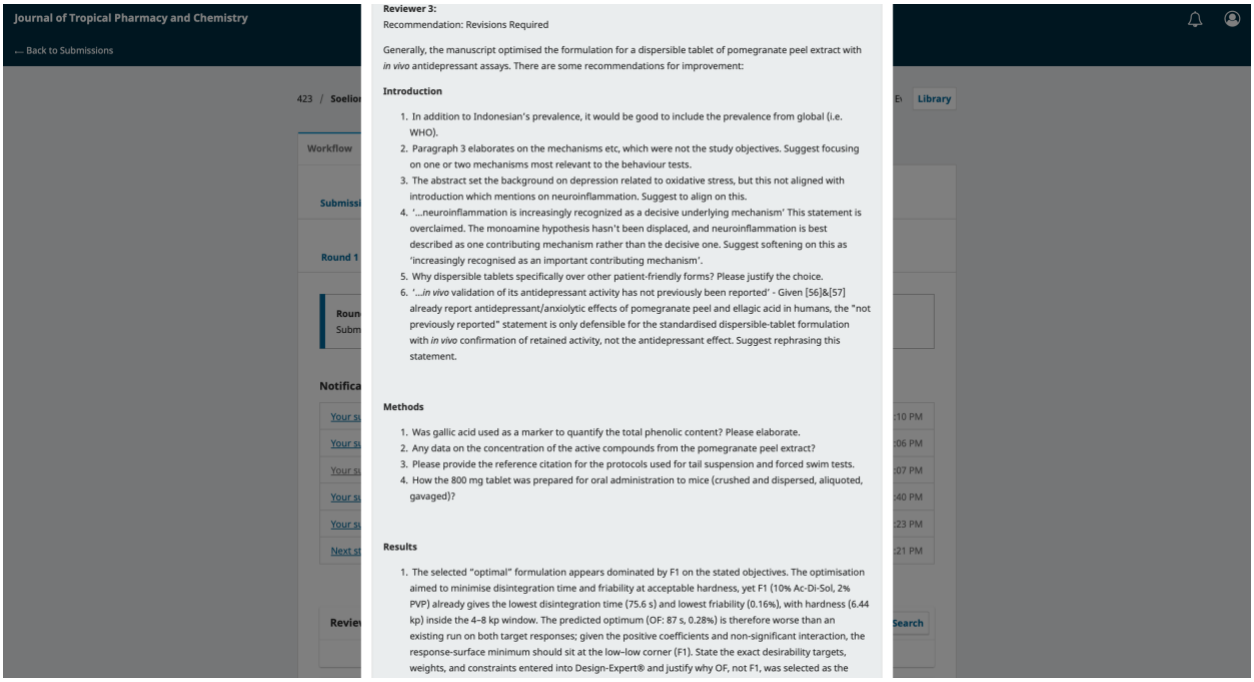
Reviewer 1:
Recommendation: Revisions Required

1. The phytochemical characterization in this study is limited to qualitative TLC. The authors should add a brief statement in the Discussion or Limitations section

Reviewer Comments/Revision Request from Reviewer






Journal of Tropical Pharmacy and Chemistry
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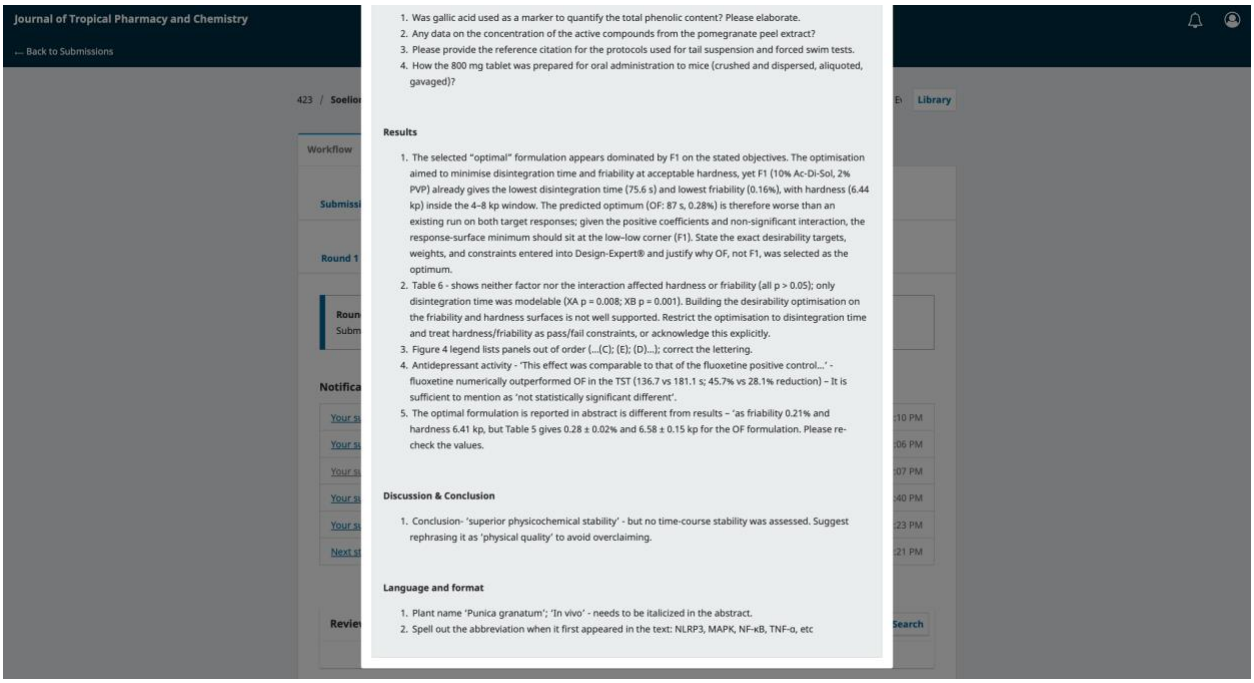
Reviewer 3:
Recommendation: Revisions Required
Generally, the manuscript optimised the formulation for a dispersible tablet of pomegranate peel extract with in vivo antidepressant assays. There are some recommendations for improvement:
Introduction
1. In addition to Indonesian's prevalence, it would be good to include the prevalence from global (i.e. WHO).
2. Paragraph 3 elaborates on the mechanisms etc, which were not the study objectives. Suggest focusing on one or two mechanisms most relevant to the behaviour tests.
3. The abstract set the background on depression related to oxidative stress, but this not aligned with introduction which mentions on neuroinflammation. Suggest to align on this.
4. '...neuroinflammation is increasingly recognized as a decisive underlying mechanism' This statement is overclaimed. The monoamine hypothesis hasn't been displaced, and neuroinflammation is best described as one contributing mechanism rather than the decisive one. Suggest softening on this as 'increasingly recognised as an important contributing mechanism'.
5. Why dispersible tablets specifically over other patient-friendly forms? Please justify the choice.
6. '...in vivo validation of its antidepressant activity has not previously been reported' - Given [56]&[57] already report antidepressant/anxiolytic effects of pomegranate peel and ellagic acid in humans, the "not previously reported" statement is only defensible for the standardised dispersible-tablet formulation with in vivo confirmation of retained activity, not the antidepressant effect. Suggest rephrasing this statement.
Methods
1. Was gallic acid used as a marker to quantify the total phenolic content? Please elaborate.
2. Any data on the concentration of the active compounds from the pomegranate peel extract?
3. Please provide the reference citation for the protocols used for tail suspension and forced swim tests.
4. How the 800 mg tablet was prepared for oral administration to mice (crushed and dispersed, aliquoted, gavaged)?
Results
1. The selected "optimal" formulation appears dominated by F1 on the stated objectives. The optimisation aimed to minimise disintegration time and friability at acceptable hardness, yet F1 (10% Ac-Di-Sol, 2% PVP) already gives the lowest disintegration time (75.6 s) and lowest friability (0.16%), with hardness (6.44 kp) inside the 4–8 kp window. The predicted optimum (OF: 87 s, 0.28%) is therefore worse than an existing run on both target responses; given the positive coefficients and non-significant interaction, the response-surface minimum should sit at the low–low corner (F1). State the exact desirability targets, weights, and constraints entered into Design-Expert® and justify why OF, not F1, was selected as the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3. Please provide the reference citation for the protocols used for tail suspension and forced swim tests.
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2. Table 6 - shows neither factor nor the interaction affected hardness or friability (all p > 0.05); only disintegration time was modelable (XA p = 0.008; XB p = 0.001). Building the desirability optimisation on the friability and hardness surfaces is not well supported. Restrict the optimisation to disintegration time and treat hardness/friability as pass/fail constraints, or acknowledge this explicitly.
3. Figure 4 legend lists panels out of order (...(C); (E); (D)...); correct the lettering.
4. Antidepressant activity - 'This effect was comparable to that of the fluoxetine positive control...' - fluoxetine numerically outperformed OF in the TST (136.7 vs 181.1 s; 45.7% vs 28.1% reduction) – It is sufficient to mention as 'not statistically significant different'.
5. The optimal formulation is reported in abstract is different from results – 'as friability 0.21% and hardness 6.41 kp, but Table 5 gives 0.28 ± 0.02% and 6.58 ± 0.15 kp for the OF formulation. Please re-check the values.
Discussion & Conclusion
1. Conclusion- 'superior physicochemical stability' - but no time-course stability was assessed. Suggest rephrasing it as 'physical quality' to avoid overclaiming.
Language and format
1. Plant name 'Punica granatum'; 'In vivo' - needs to be italicized in the abstract.
2. Spell out the abbreviation when it first appeared in the text: NLRP3, MAPK, NF-κB, TNF-α, etc

Response to Reviewers (Manuscript #423)

Reviewer 1

Reviewer Comment	Author Response	Location of Revision
1. The phytochemical characterization in this study is limited to qualitative TLC. The authors should add a brief statement in the Discussion or Limitations section emphasizing the need for future quantitative analysis (e.g., HPLC) to precisely determine the total phenolic content and specific marker compounds like ellagic acid.	We fully agree. The study limitation section has been expanded to state explicitly that the phytochemical characterization was qualitative TLC only, and that quantitative determination of the total phenolic content and of specific marker compounds such as gallic acid and ellagic acid (ideally by HPLC) was not performed and is recommended for future work to enable precise standardization of the active constituents.	Section 3.6 (Study Limitation) [highlighted in yellow]
2. The antidepressant efficacy was thoroughly evaluated using standard behavioral models with a single dose evaluation (100 mg/kgBW) and did not measure specific biochemical markers such as oxidative stress parameters or pro-inflammatory cytokines. Please explicitly acknowledge these constraints as study limitations and suggest them as future research directions.	We agree and thank the reviewer. The study limitation section now explicitly acknowledges that: 1. activity was assessed solely through behavioral outcomes without measuring oxidative-stress parameters, pro-inflammatory cytokines, or brain neurotransmitter levels, so that the antidepressant mechanism of pomegranate peel refers to a theoretical review; 2. the evaluation was limited to a single dose (100 mg/kg BW) and to acute behavioral models. We have added corresponding future directions, i.e. inclusion of biochemical biomarkers, dose-response studies, and chronic-administration studies to define the therapeutic window.	Section 3.6 (Study Limitation) [highlighted in green]
3. The authors noted that the Rf value of gallic acid in the sample (0.47) differed from the standard Indonesian Herbal Pharmacopoeia (0.76). While variations in temperature and humidity were mentioned as causes, please ensure this justification is clearly integrated into the main text to avoid misinterpretation of the compound's identity.	We agree and have harmonized the presentation of the Rf data throughout the manuscript to remove the previous internal inconsistency. Both in the initial phytochemical screening (Section 3.1) and in the identity/compatibility testing (Section 3.3), the measured Rf of the gallic-acid marker in the samples is now uniformly reported as 0.47, and the reference value of 0.76 is explicitly identified as the pharmacopoeial reference. In both sections we now state that the deviation reflects differences in analytical conditions (chamber temperature and relative humidity, degree of mobile-phase saturation, and plate type) that shift Rf without altering compound identity, and we	Section 3.1 [highlighted in yellow] Section 3.3 [highlighted in yellow]

	emphasize that identity is confirmed by the characteristic $FeCl_3$-reactive black spot and by the identical Rf profile across the extract, compression mass, and finished tablets. A supporting reference (reference 60) has been added.	
4. Correct all typographical errors and perform a thorough proofreading of the entire manuscript (include inline comment in the reviewer's attachment.)	We thank the reviewer. The entire manuscript has been carefully proofread.	Typographical errors has been corrected throughout the manuscript.
5. Replace the term "Formula" with "Run." If the experimental design was generated using Design-Expert software, each experimental trial should be labeled as "Run," following the software's standard terminology.	We sincerely thank the reviewer for highlighting the standard terminology of the Design-Expert software; however, we respectfully clarify that in our replicated 2^2 full factorial design, a "Formula" refers to one of the 4 unique treatment combinations, whereas a "Run" denotes one of the 12 individual, randomized experimental trials (3 replications per formula). Globally replacing the term "Formula" with "Run" throughout the manuscript would conflate the distinct pharmaceutical compositions with the individual statistical trials, thereby obscuring the replication strategy that is essential for estimating pure error. To fully align with the reviewer's suggestion while maintaining manuscript conciseness and scientific accuracy, we have opted not to present redundant design matrices. Instead, we have revised the methodology text to explicitly delineate that our 4 specific "Formulas" correspond directly to the 12 randomized software "Runs," ensuring the experimental design is accurately contextualized without compromising the clarity of the pharmaceutical evaluation.	Section 2.4 (Methods): design description [highlighted]
6. Provide a clear explanation of the parameters (responses) used to determine the optimum formulation, including the target value or optimization criteria for each response.	We agree and have added an explicit statement of the optimization criteria entered into Design-Expert®. In the numerical optimization (desirability) function, each of the three responses was assigned the goal "in range", i.e. a response was considered acceptable when its value fell between a defined lower and upper limit, and the software searched for the factor combination maximizing the overall (composite) desirability—the region where all three responses simultaneously satisfied their limits. The limits used were: disintegration time 1–2.5 minutes (60–150 s), friability 0.2–0.4%, and hardness 5–7 kp.	- Section 2.4 (Methods) - Section 3.2 (Results) [highlighted in yellow]

Reviewer 2

Reviewer Comment	Author Response	Location of Revision
The study used a commercially obtained dried extract supplied by a third party. The authors should state how the identity and quality of the material were verified by the supplier (e.g., through a Certificate of Analysis, CoA). In addition, the content of the native extract in the dried extract should be specified, as this information is essential for the tablet formulation and directly affects the amount of active ingredient and the administered dose.	We thank the reviewer for this important point and have revised the Materials section to document how the identity and quality of the dry extract were verified by the supplier.	Section 2.1 (Materials) [highlighted in yellow]
In the Materials and Methods section, all analytical and testing procedures should be accompanied by the appropriate references. For example, the method used for the determination of loss on drying does not include a citation.	We agree and have added the missing citations. The determination of loss on drying and total ash content is now referenced to the standardized procedures for medicinal-plant extracts in the General Standard Parameters of Medicinal Plant Extracts [37] and the Indonesian Herbal Pharmacopoeia [40]. We have also confirmed that the tablet preparation and evaluation methods, the TLC screening, and the behavioral test protocols now each carry appropriate references.	Section 2.3 Section 2.8. [highlighted in yellow]
In Figures 2 and 4, the TLC plates should include Rf scale to facilitate identification of the spots discussed in the text. In addition, the figure legends should be revised to clearly distinguish between the chromatograms before and after derivatization (spraying).	We agree. The Figure 2 and Figure 4 legend has been revised. The plate images have been annotated with the Rf scale accordingly.	Figure 2 Figure 4
Statements in the Discussion that draw conclusions from the experimental results should be supported by appropriate references. For example, the conclusion that the blue coloration observed after spraying the TLC plate indicates the	We agree and have added supporting references to the interpretive TLC statements in the Result/Discussion. Specifically, the identification of flavonoids from the characteristic blue fluorescence under UV 366 nm after $AlCl_3$ treatment is now supported by an established TLC-detection reference [59].	Section 3.1; Bibliography [highlighted in yellow]

presence of flavonoids should be supported by a relevant citation.		

Reviewer 3

Reviewer Comment	Author Response	Location of Revision
Introduction: In addition to Indonesian's prevalence, it would be good to include the prevalence from global (i.e. WHO).	We agree and have added the global prevalence. The Introduction now cites the World Health Organization estimate that approximately 280 million people (~3.8% of the population) live with depression and that it is a leading contributor to the global burden of disease, presented immediately before the Indonesian national figure.	Introduction, paragraph 1 [highlighted in yellow]
Introduction: Paragraph 3 elaborates on the mechanisms etc, which were not the study objectives. Suggest focusing on one or two mechanisms most relevant to the behaviour tests.	We agree. Introduction paragraph 3 (now describing punicalagin/ellagic acid) has been refocused on the serotonergic and adrenergic (noradrenergic) mechanisms that are most directly relevant to the tail suspension and forced swim tests used here.	Section 1 (Introduction), paragraph 3 [highlighted in yellow]
The abstract set the background on depression related to oxidative stress, but this not aligned with introduction which mentions on neuroinflammation. Suggest to align on this.	We agree and have aligned the framing. We revised the Abstract to use the identical framing, so that the Abstract and Introduction are fully consistent.	Section 1 (Introduction), paragraph; Abstract [highlighted in yellow]
'…neuroinflammation is increasingly recognized as a decisive underlying mechanism.' This statement is overclaimed. The monoamine hypothesis hasn't been displaced, and neuroinflammation is best described as one contributing mechanism rather than the decisive one. Suggest softening on this as 'increasingly recognised as an important contributing mechanism.'	We agree and have softened the statement exactly as suggested. The sentence now reads that depression is "…a complex, multifactorial disorder in which neuroinflammation is increasingly recognized as an important contributing mechanism that complements, rather than displaces, the classical monoamine hypothesis."	Section 1 (Introduction), paragraph 1 [highlighted in green]
Why dispersible tablets specifically over other patient-friendly forms? Please justify the choice.	We agree and have added an explicit justification. The Introduction now explains that the dispersible tablet was selected because it disperses rapidly into a fine, homogeneous, swallowable suspension and can accommodate the comparatively high extract load required here (500	Section 1 (Introduction), paragraph 5 [highlighted in yellow]

	mg/tablet)—a dose impractical for orodispersible or lozenge forms constrained by mouthfeel and cavity volume—while combining the manufacturing robustness, dose uniformity, and physicochemical stability of a compressed solid with the swallowing convenience of a liquid and masking the astringent taste on dispersion.	
'…in vivo validation of its antidepressant activity has not previously been reported' - Given [56]&[57] already report antidepressant/anxiolytic effects of pomegranate peel and ellagic acid in humans, the "not previously reported" statement is only defensible for the standardised dispersible-tablet formulation with *in vivo* confirmation of retained activity, not the antidepressant effect. Suggest rephrasing this statement.	We agree and have rephrased the novelty statement. The Introduction now acknowledges that the antidepressant/anxiolytic effects of pomegranate peel and ellagic acid have already been reported in preclinical models and human trials [56], [57], and restricts the novelty claim to the standardized dispersible-tablet formulation together with *in vivo* confirmation that its antidepressant activity is retained after direct compression constitutes the principal novelty.	Section 1 (Introduction), final paragraph [highlighted in blue]
Methods: Was gallic acid used as a marker to quantify the total phenolic content? Please elaborate.	We thank the reviewer and have clarified this. Gallic acid was used as a qualitative marker for the phenolic fraction of the extract, in accordance with the Indonesian Herbal Pharmacopoeia monograph for pomegranate peel; it served to confirm the identity and presence of the phenolic constituents and was not used to quantify total phenolic content. The Methods now state this explicitly, and the limitation regarding the absence of quantitative determination (e.g., by HPLC) is noted in Section 3.6.	Section 2.3 (Standardization), Section 3.6 (Study Limitation) [highlighted in yellow]
Methods: Any data on the concentration of the active compounds from the pomegranate peel extract?	We appreciate this question. Quantitative concentrations of the individual active compounds (e.g., punicalagin, ellagic acid) were not determined in this study, which employed qualitative TLC identity testing. The native-extract content of the dried extract (drug-to-extract ratio) is documented in the supplier's CoA and was used to standardize the active loading per tablet (500 mg PPE), as now stated in the Materials section. We have added the quantitative determination of these marker compounds by a validated method (e.g., HPLC) as an explicit future direction in the Study Limitation section.	Section 2.1 (Materials): native-extract content/CoA Section 3.6 (Study Limitation): recommended HPLC quantification of gallic acid and ellagic acid [highlighted in yellow]

Methods: Please provide the reference citation for the protocols used for tail suspension and forced swim tests.	We agree and have added the primary methodological citations. The tail suspension test now cites Steru et al. (1985) [41] as described by Castagné et al. (2011) [42], and the forced swim test cites Porsolt et al. (1977) [43] as described by Castagné et al. (2011) [42].	Section 2.8 [highlighted in blue]
Methods: How the 800 mg tablet was prepared for oral administration to mice (crushed and dispersed, aliquoted, gavaged)?	We agree and have added the preparation details. The Methods now describe that each 800 mg optimized dispersible tablet was dispersed in purified water to form a fine, homogeneous suspension (consistent with its intended clinical use), then reconstituted in 0.5% methylcellulose to the required concentration; the dose per animal was calculated from individual body weight to deliver PPE 100 mg/kg, and the corresponding volume of the freshly prepared suspension was administered by oral gavage.	Section 2.8 (Antidepressant Activity Testing) [highlighted in green]
Results: The selected "optimal" formulation appears dominated by F1 on the stated objectives … The predicted optimum (OF: 87 s, 0.28%) is therefore worse than an existing run on both target responses … State the exact desirability targets, weights, and constraints entered into Design-Expert® and justify why OF, not F1, was selected as the optimum.	We thank the reviewer for this rigorous analysis. We have stated the exact optimization set-up in the Methods and Results and justified why the desirability optimum, rather than F1, was selected.	- Section 2.4 (Methods) - Section 3.2 (Results) [highlighted in yellow]
Results: Table 6 shows neither factor nor the interaction affected hardness or friability (all $p > 0.05$); only disintegration time was modelable (XA $p = 0.008$; XB $p = 0.001$). Building the desirability optimisation on the friability and hardness surfaces is not well supported. Restrict the optimisation to disintegration time and treat hardness/friability as pass/fail constraints, or acknowledge this explicitly.	We thank the reviewer for this astute statistical observation and completely agree that desirability optimization should not be built on non-significant response surfaces. Because neither the individual factors nor their interactions significantly affected tablet hardness and friability ($p>0.05$), these two parameters were strictly treated as pass/fail feasibility constraints (set to "in range") rather than target responses for maximization or minimization. Consequently, the overall desirability function was exclusively governed by disintegration time, which was the only mathematically modelable response ($p<0.05$). To ensure this optimization logic is unequivocally clear and to fully align with the reviewer's recommendation, we have explicitly acknowledged this statistical reality in Section 3.2 of the	Section 3.2 (Results) [highlighted in yellow]

	revised manuscript, stating that hardness and friability served solely as feasibility constraints that any candidate optimum was required to satisfy.	
Results: Figure 4 legend lists panels out of order (…(C); (E); (D)…); correct the lettering.	We agree and have corrected the visual representation of the legend and caption for Figure 4.	Figure 4
Results (Antidepressant activity): 'This effect was comparable to that of the fluoxetine positive control…' - fluoxetine numerically outperformed OF in the TST (136.7 vs 181.1 s; 45.7% vs 28.1% reduction). It is sufficient to mention as 'not statistically significant different'.	We agree and have revised the wording accordingly.	Section 3.4 [highlighted in yellow]
Results: The optimal formulation reported in abstract is different from results – 'friability 0.21% and hardness 6.41 kp', but Table 5 gives 0.28 ± 0.02% and 6.58 ± 0.15 kp for the OF formulation. Please re-check the values.	We thank the reviewer for catching this discrepancy. There are two values of friability and hardness of the optimum formula, one is from the prediction by DesignExpert®—now mentioned as OF (predicted)—and one from the experiment —now mentioned as OF (observed) in Tablet 5. Our final report is from the observed value so that the values mentioned in the abstract were changed accordingly.	Table 5 [highlighted in yellow] Abstract
Discussion & Conclusion: 'superior physicochemical stability' - but no time-course stability was assessed. Suggest rephrasing it as 'physical quality' to avoid overclaiming.	We agree and have rephrased to avoid overclaiming.	Section 4 (Conclusion) [highlighted in yellow] Section 3.5. Discussion [highlighted in yellow]
Language and format: Plant name 'Punica granatum'; 'In vivo' - needs to be italicized in the abstract.	We agree. *Punica granatum* and *in vivo* are italicized throughout the revised main text (Introduction, Methods, and elsewhere).	Throughout the main text
Language and format: Spell out the abbreviation when it first appeared in the text: NLRP3, MAPK, NF-κB, TNF-α, etc.	We agree and have spelled out all abbreviations at first mention.	Section 1 (Introduction) [highlighted in green] Section 2.1 (Materials) [highlighted in green] Section 3.6 (Study Limitations)

		[highlighted in blue]

JOURNAL OF TROPICAL PHARMACY AND CHEMISTRY
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Volume 9.1

Original Research Article

Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation

Ivonne Soeliono[1,*], Tio Minaritatis Hutauruk[1], Martha Ervina[1], Ida Ayu Made Anom Sri Melia Laksmi[1], Nadiatul Janah[1], Sela Uswatun Nurul Chasanah[1], Eka Pramyrtha Hestianah[2], Lannie Hadisoewignyo[1]

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Abstract

Depression is a multifactorial disorder in which neuroinflammation—driven by chronic microglial and astrocyte activation—is recognized as an important mechanism that complements, rather than displaces, the classical monoamine hypothesis, dysregulating the monoaminergic systems that govern mood. Pomegranate (*Punica granatum* L.) peel polyphenols—notably punicalagin and ellagic acid—exert antidepressant-like effects principally by modulating the serotonergic and adrenergic systems and restoring stress-depleted brain monoamines, with anti-neuroinflammatory and antioxidant activity as a secondary contributor. This study developed and optimized a pomegranate peel extract dispersible tablet, validating retention of its *in vivo* antidepressant activity. Tablets were prepared by direct compression and optimized via a two-factor factorial design varying croscarmellose sodium (superdisintegrant) and polyvinylpyrrolidone K-30 (binder). The optimized tablet (equivalent to 100 mg/kg extract) was assessed in male BALB/c mice by the tail suspension and forced swim tests against unformulated extract and fluoxetine (20 mg/kg). The optimal formulation (11.68% croscarmellose sodium, 2.02% polyvinylpyrrolidone K-30) showed good physical quality (disintegration 87 s, friability 0.28%, hardness 6.58 kp). In both tests it significantly reduced immobility time ($p < 0.05$), with no significant difference from the extract or fluoxetine ($p > 0.05$). The dispersible tablet retained efficacy, supporting its potential as a preclinical nutraceutical candidate for depression.

Keywords: Dispersible Tablet; *Punica granatum*; Factorial Design; Antidepressant Activity

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1 Introduction

Mental health disorders, particularly depression, have emerged as a critical global health burden and constitute one of the leading causes of disability worldwide. Globally, the World Health Organization estimates that approximately 280 million people—around 3.8% of the population—live with depression, and the disorder is a leading contributor to the global burden of disease [1]. In Indonesia, the 2023 Indonesian Health Survey (Survei Kesehatan Indonesia) reported a national depression prevalence of 1.4%, with the highest rates observed in the 15–24-year age group [2]. In recent years, the scientific paradigm has broadened: depression is increasingly understood not merely as a consequence of monoaminergic imbalance in the brain, but as a complex, multifactorial disorder in which neuroinflammation is increasingly recognized as an important contributing mechanism that complements, rather than displaces, the classical monoamine hypothesis [3], [4], [5], [6], [7], [8]. Chronic neuroinflammation, characterized by the persistent activation of microglia and astrocytes, can disrupt neuronal homeostasis, diminish synaptic plasticity, and trigger dysregulation of the principal monoaminergic neurotransmitter systems—such as serotonin and dopamine—that govern mood regulation [9], [10], [11], [12], [13].

Pomegranate (*Punica granatum* L.) has long been utilized in traditional medicine systems. For centuries, it has featured in traditional Chinese, Ayurvedic, and Persian medicine as a remedy for conditions including atherosclerosis, diabetes, hypertension, hyperlipidemia, and certain cancers, as well as ulcers, oral-cavity disorders, and worm infestations [14], [15]. Pomegranate fruit peel, which accounts for approximately 50% of the total fruit weight, represents a particularly rich source of polyphenols [14], [16], [17]. Pomegranate peel extract (PPE) contains abundant hydrolyzable tannins—polyphenolic substances derived from gallic acid that, upon hydrolysis, split into sugars and phenolic acids such as gallic acid or ellagic acid, thereby forming gallotannins and ellagitannins, respectively [18]. The most abundant ellagitannin is punicalagin, which can be hydrolyzed into smaller phenolic compounds such as ellagic acid, its principal metabolite [14], [15].

Punicalagin and its metabolite ellagic acid produce antidepressant-like effects in preclinical models—reducing immobility and enhancing climbing behavior—principally through modulation of the serotonergic and adrenergic (noradrenergic) systems that regulate mood and motivated behavior [19], [20], [21]. Because the behavioral despair models employed in the present study (the tail suspension and forced swim tests) are especially sensitive to monoaminergic drive, this serotonergic–adrenergic mechanism is the most directly relevant to the outcomes assessed here. These monoaminergic effects are accompanied by the restoration of stress-depleted brain monoamines (dopamine and serotonin) and, as a secondary contributor, by neuroprotective and anti-neuroinflammatory activity—for example, suppression of the NLRP3 (nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3) inflammasome and of the MAPK (mitogen-activated protein kinase)/NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathways—that lowers pro-inflammatory mediators such as TNF-α (tumor necrosis factor-alpha), IL-1β, IL-6 (interleukins), COX-2 (cyclooxygenase-2), and iNOS (inducible nitric oxide synthase), together with oxidative stress [22], [16], [23].

Preclinical *in vivo* studies confirm this antidepressant potential. In olfactory-bulbectomy (OBX) model rats, oral ethanolic pomegranate peel extract at 10, 30, and 100 mg/kg significantly reversed open-field hyperactivity and improved despair-related parameters in the forced swim and sucrose-intake tests, in parallel with normalization of brain monoamine levels [24]; in mice, PPE at 100 mg/kg reduced immobility time in both the forced swim test and the tail suspension test [25].

Despite this established potential, significant translational challenges remain in applying the active extract within a clinical context. The pure viscous extract frequently exhibits unpalatable organoleptic properties and is difficult to measure accurately, thereby compromising dosing precision and limiting its therapeutic utility [26], [27]. Consequently, the formulation of the extract into a modern, patient-oriented dosage form is of paramount importance. Among the available patient-friendly dosage forms,

the dispersible tablet was selected for specific pharmaceutical reasons. Unlike conventional orodispersible or effervescent tablets, dispersible tablets disperse rapidly in a small volume of water to yield a fine, homogeneous suspension that can be swallowed easily, which is particularly advantageous for the comparatively high extract load required here (500 mg per tablet)—a dose that is impractical to accommodate in orodispersible or lozenge forms constrained by mouthfeel and cavity volume. The dispersible format further combines the manufacturing robustness, dose uniformity, and physicochemical stability of a compressed solid with the swallowing convenience of a liquid, making it well suited to geriatric and pediatric patients and to those with dysphagia, while masking the astringent taste of the extract upon dispersion [28], [29], [30].

The performance of a dispersible tablet hinges on the precise optimization of two key excipients—the binder PVP K-30 and the superdisintegrant croscarmellose sodium (Ac-Di-Sol)—which jointly govern hardness, friability, and disintegration time [31]. PVP K-30 provides strong adhesion and plastic deformation for compaction, yet its high water solubility and low viscosity keep it from delaying disintegration [32], whereas croscarmellose sodium acts through combined water wicking and swelling to generate the multidirectional internal pressure that rapidly ruptures inter-particle bonds [33]. Applying a Quality-by-Design approach with a central composite design, Shah et al. [34] confirmed both excipient concentrations as high-risk factors for friability and disintegration time, identifying an optimal profile of 20 mg/tablet croscarmellose sodium and 8 mg/tablet PVP K-30.

On this basis, the present study was conducted with two principal objectives: (1) to develop and statistically optimize a PPE dispersible tablet formulation using a factorial design in order to achieve ideal physicochemical characteristics; and (2) to perform an *in vivo* evaluation confirming that the antidepressant efficacy of the native extract is retained following formulation. The development of standardized, innovative dosage forms is an essential prerequisite for the downstreaming of natural-product–based medicines in Indonesia [35], [36]. Although the antidepressant and anxiolytic effects of pomegranate peel and of ellagic acid have already been reported in preclinical models and in human trials [56], [57], to the best of the authors' knowledge, the formulation of a standardized pomegranate peel extract dispersible tablet, together with *in vivo* confirmation that its antidepressant activity is retained after the direct-compression process, has not previously been reported. This standardized, activity-retaining dispersible-tablet formulation constitutes the principal novelty of this study.

2 Method

2.1. Materials

The materials used included pomegranate peel extract (*Punica granatum* L.), a standardized dry extract prepared by ethanol–water extraction of the pericarp and obtained from PT Phytochemindo Reksa, Bogor, West Java, Indonesia. The material was supplied with a manufacturer's Certificate of Analysis (CoA No. 20231116-3S.1-1G024DE25-001, batch 070KY), which verified its botanical identity (*Punica granatum*, pericarp) and documented its organoleptic characteristics, loss on drying, total ash, residual solvent, heavy-metal content and microbiological quality, all determined by USP 42 methods and fulfill the supplier's release specifications (overall decision: "Pass"). The material was standardized as a "DE 25" dry extract on an inert carrier of maize starch (*Amylum maydis*) and lactose. The additional excipients used in the tablet formulation comprised Avicel PH-102, PVP K-30 (polyvinylpyrrolidone K-30), Ac-Di-Sol (croscarmellose sodium), stevia, and magnesium stearate. The materials used for the determination of the gallic acid marker by Thin-Layer Chromatography (TLC) comprised a gallic acid standard solution and spot-visualization reagents, namely iron(III) chloride ($FeCl_3$), aluminium chloride ($AlCl_3$), Dragendorff's reagent, sulfuric acid (H_2SO_4), a 10% w/v potassium hydroxide (KOH) solution in methanol, and vanillin–sulfuric acid reagent. The mobile-phase solvents comprised chloroform, ethyl acetate, n-butanol, formic acid, distilled water, and ethanol.

2.2. Instruments

The instruments used included an analytical balance (Mettler Toledo ME204), Erlenmeyer flasks, funnels, parchment paper, crucibles, silica gel 60 F254 plates (20 × 20 cm), capillary tubes, a No. 30

mesh sieve, a No. 25 mesh sieve with a 710 µm pore size, filter paper, aluminium foil, plain paper, a vernier caliper, a stopwatch, and an oven. Tablet preparation and evaluation were performed using a single-punch tablet press (Erweka EP-1, Germany), a friability tester (Erweka TAR 220, Germany), a hardness tester (Erweka TBH 125, Germany), a disintegration tester (Erweka ZT3-1, Germany), a cube mixer (Erweka AR 401), a tapped-density tester (Erweka SVM-12, Germany), and a moisture analyzer. Standard laboratory glassware and other supporting apparatus were also used.

2.3. Standardization of the Dried Extract

Standardization of the dried extract encompassed both specific and non-specific parameters [37]. The specific parameters comprised identity testing and organoleptic evaluation (form, color, odor, and taste), which were performed visually. The non-specific parameters comprised the determination of loss on drying, total ash content, and phytochemical profiling by TLC. Loss on drying and total ash content were determined in accordance with the standardized procedures for medicinal-plant extracts described in the General Standard Parameters of Medicinal Plant Extracts [37]. Loss on drying was determined by heating 2 g of the extract at 105 °C for 30 minutes, followed by cooling in a desiccator for 15 minutes; the percentage mass loss was required to be below 10% w/w. Total ash content was determined by igniting 2.0 g of the extract in a furnace. For phytochemical screening, the silica gel F254 plates were eluted with a mobile phase of chloroform : ethyl acetate : n-butanol : formic acid (5:2:2:1, v/v) and sprayed with 1% $FeCl_3$, $AlCl_3$, Dragendorff's reagent, H_2SO_4, vanillin–sulfuric acid reagent, and 10% w/v KOH in methanol. Gallic acid was used as the qualitative marker compound for the phenolic constituents of the extract, in accordance with the Indonesian Herbal Pharmacopoeia monograph for pomegranate peel [40]; it served to confirm the identity and presence of the phenolic fraction and was not used to quantify total phenolic content, which was beyond the scope of this qualitative screening. The TLC sample solution was prepared by dissolving 1 g of PPE in 10 mL of 96% ethanol; 5 µL of the solution was applied to each plate before being examined under UV light at 254 nm and 366 nm.

2.4. Tablet Formulation and Optimization Using a Factorial Design

The dispersible tablets were prepared by the direct-compression method [38], [26]. A two-level, two-factor (2^2) factorial design was applied to obtain the optimum formulation [39]. The influence of Ac-Di-Sol concentration (Factor X_A: 10–15% w/w) and PVP K-30 concentration (Factor X_B: 2–4% w/w) on three principal responses—namely tablet hardness, friability, and disintegration time—was investigated. The orthogonal combination of these factor levels generated 4 unique treatment combinations, operationally defined in this study as "Formulas" (Formula 1–Formula 4). To estimate pure error and ensure statistical robustness, each formula was replicated 3 times. Consequently, this design produced a total of 12 randomized experimental trials, which strictly correspond to the 12 "Runs" analyzed within the Design-Expert® software. The complete baseline composition of each formula is presented in Table 1.

For the optimization phase, each of the three responses was assigned the goal “in range”, meaning that a response was regarded as acceptable when its value fell between a defined lower and upper limit. The limits used to delineate the optimum region were as follows: disintegration time of 60–150 s (1–2.5 minutes), friability of 0.2–0.4%, and hardness of 5–7 kp. Under these criteria, the software searched the design space for the combination of Ac-Di-Sol and PVP K-30 concentrations that maximized the overall composite desirability, i.e., the region in which all three responses simultaneously fell within their specified constraints. The predicted optimal formula was subsequently prepared, and its physical quality was evaluated experimentally to validate the model.

Table 1. Composition of the dispersible tablet formulations (mg/tablet)

Component	Function	Formula 1	Formula 2	Formula 3	Formula 4	Optimal Formulation
Pomegranate peel extract	Active ingredient	500	500	500	500	500
Ac-Di-Sol	Disintegrant	80	120	80	120	93.44

PVP K-30	Binder	16	16	32	32	16.16
Stevia	Sweetener	28	28	28	28	28
Avicel PH-102	Filler	174	134	158	118	160.40
Magnesium stearate	Lubricant	2	2	2	2	2
Total weight		800	800	800	800	800

2.5. Evaluation of the Tablet Mass and the Dispersible Tablet Preparation

The tablet mass was evaluated for its flow properties (flow rate and angle of repose) and moisture content. The compressed tablets were evaluated for weight uniformity, hardness (Erweka TBH 125), friability (Erweka TAR 220), and disintegration time (Erweka ZT3-1) in an aqueous medium at 15–25 °C. The fineness of dispersion was confirmed by verifying that the suspension obtained from the disintegrated tablet was able to pass through a 710 µm sieve.

2.6. Identity and Compatibility Testing of the Active Ingredient by Thin-Layer Chromatography (TLC)

Identity and compatibility testing of the marker compound in the extract, the tablet mass, and the dispersible tablets of pomegranate peel extract was performed using TLC, with gallic acid as the marker. This testing was intended to confirm that the direct compression process and the presence of excipients did not alter the marker spot profile; it did not constitute a quantitative stability study with respect to time or accelerated storage conditions. The procedure comprised the dissolution of the extract (±1 g), the tablet mass (3.995 g), and the tablets (5.156 g) in 10 mL volumetric flasks with ethanol to the calibration mark, after which 5 µL of each solution was applied to a silica gel F_{254} plate. Elution was carried out with a mobile phase of chloroform : ethyl acetate : n-butanol : formic acid (5:2:2:1). The plate was dried and sprayed with 1% $FeCl_3$ reagent. The spots were examined under UV light at 254 nm and 366 nm, and the Rf values were compared with that of gallic acid (Rf = 0.76) in accordance with the Indonesian Herbal Pharmacopoeia [40].

2.7. Experimental Animals and Ethical Approval

The study used male BALB/c mice (body weight 18–33 g, age 2–3 months). The animals were maintained under standard laboratory conditions (12-hour light–dark cycle, temperature 22 ± 2 °C, humidity 55 ± 10%) with *ad libitum* access to food and drinking water. All procedures were performed in accordance with the guidelines for the care and use of laboratory animals and received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Widya Mandala Surabaya Catholic University (No. 0012/WM12/KEPK/MHS/T/2025 for the tail suspension test and No. 0011/WM12/KEPK/MHS/T/2025 for the forced swim test).

2.8. Antidepressant Activity Testing

The animals were randomly allocated into six groups (n = 6 per group for each of the tail suspension test and the forced swim test): a normal control, a vehicle control (0.5% methylcellulose), a negative control (vehicle containing the tablet excipients), a positive control (fluoxetine 20 mg/kg body weight in 0.5% methylcellulose), a pomegranate peel extract group (100 mg/kg body weight in 0.5% methylcellulose), and the optimized dispersible tablet group (equivalent to PPE 100 mg/kg body weight). For oral administration of the tablet, the dispersible tablet was ground to a fine powder and transferred directly into a volumetric flask, where it was made up to the required volume with 0.5% (w/v) methylcellulose mucilage to form a fine, homogeneous suspension in accordance with its intended clinical use. The dose administered to each animal was calculated on the basis of individual body weight so as to deliver PPE 100 mg/kg, and the corresponding volume of the freshly prepared suspension was administered by oral gavage. The treatments were administered orally for 14 consecutive days, and behavioral testing was conducted one hour after the final administration on day 14. All behavioral testing was carried out during the dark phase of the light–dark cycle. Immobility duration was scored manually

as the mean of observations made by two independent, well-trained observers; when the difference between the two observers exceeded 5 seconds, the observation was repeated. The tail suspension test was performed following the method of Steru et al. [41] as described by Castagné et al. [42]: each mouse was suspended by its tail using adhesive tape approximately 1 cm from the tip, and the immobility duration was recorded over 6 minutes. The forced swim test was performed following the method of Porsolt et al. [43] as described by Castagné et al. [42]: each mouse was placed in a transparent cylinder filled with room-temperature water (24–25 °C) for 6 minutes; the first 2 minutes served as an adaptation period, while immobility time was scored during the final 4 minutes.

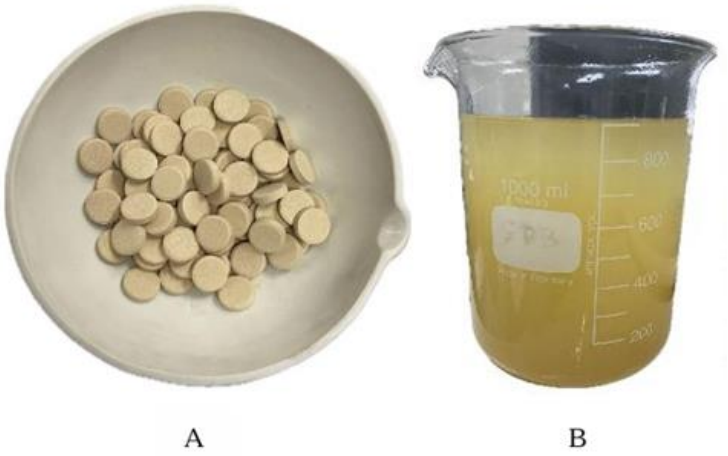
2.9. Statistical Analysis

The formulation optimization data were analyzed using Design-Expert® software. The significance of the factorial design model coefficients was tested against the pure error derived from the three replicate batches of each formulation, and the optimal formulation was selected using the numerical desirability function under the criteria defined in Section 2.4, in which disintegration time (1–2.5 minutes; 60–150 s), friability (0.2–0.4%), and hardness (5–7 kp) were each assigned the goal "in range". The behavioral data were analyzed using SPSS software (v.27). Data normality was evaluated using the Shapiro-Wilk test. One-way ANOVA followed by Tukey's HSD post hoc test was used for normally distributed data (tail suspension test), whereas the Kruskal–Wallis test followed by Dunn's post hoc test was used for non-normally distributed data (forced swim test). A p value < 0.05 was considered statistically significant.

3 Result and Discussion

3.1. Characterization of the Extract and the Tablet Mass

The pomegranate peel extract presented as a light brown powder with specific organoleptic characteristics (Figure 1). The TLC screening results (Table 2 and Figure 2) demonstrated that the phenolic class gave a positive reaction, manifested as a black spot with an Rf value of 0.47 after spraying with $FeCl_3$, confirming the presence of gallic acid as the phenolic marker. This measured Rf differed from the reference value of 0.76 specified for gallic acid in the Indonesian Herbal Pharmacopoeia [40]; such deviations are well recognized in TLC and are attributable to differences in analytical conditions, i.e. chamber temperature and relative humidity, the degree of mobile-phase saturation, and the type and activation state of the plate, which shift Rf values without altering the identity of the compound [60]. The identity of the marker was therefore confirmed by the characteristic black spot obtained with $FeCl_3$ together with a consistent Rf profile across all samples, rather than by an exact numerical match to the pharmacopoeial value. The tannin class gave a positive reaction, manifested as a dark blue spot with an Rf value of 0.47. The flavonoid class gave a positive reaction, manifested as blue fluorescence under UV light at 366 nm with Rf values of 0.41 and 0.53; the appearance of this fluorescence after treatment with $AlCl_3$ is characteristic of flavonoids and is consistent with established TLC detection criteria for this compound class [59]. The steroid class gave a positive reaction, manifested as a purple spot under UV light with an Rf value of 0.47.



A B

Figure 1. Organoleptic profile of the preparation. (A) Intact dispersible tablet; (B) tablet dispersion in water.

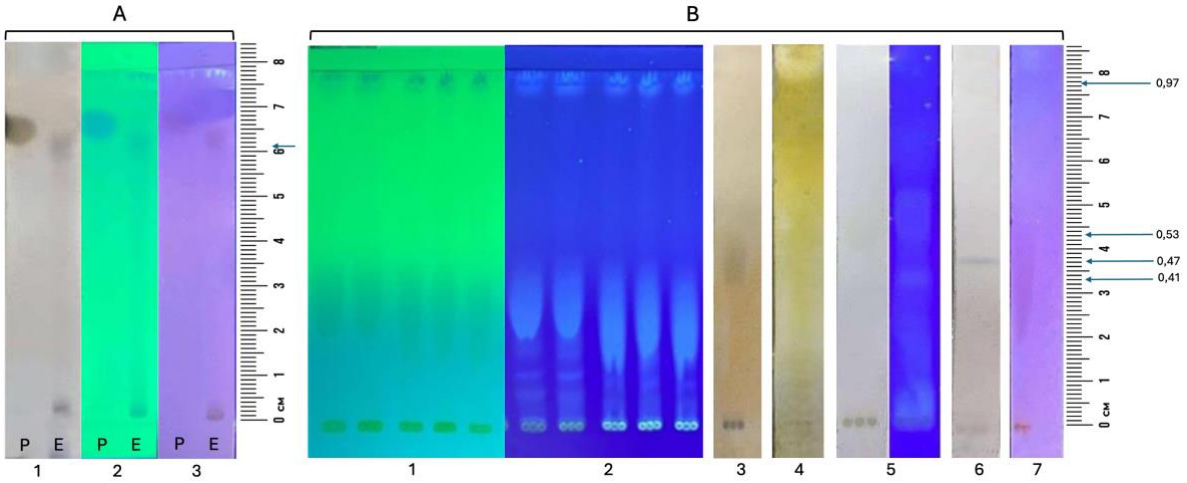


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Figure 2. TLC phytochemical screening profile of the pomegranate peel extract, with an Rf scale (0–1, from the point of application to the solvent front) shown alongside the chromatograms to facilitate localization of the spots discussed in the text. Plate A — comparison of the gallic-acid standard (P) and the extract (E) using $FeCl_3$ as the detection reagent: (A1) visual observation; (A2) under UV light at 254 nm; (A3) under UV light at 366 nm. Plate B — TLC profile of the pomegranate peel extract under different observation and detection conditions: (B1) under UV light at 254 nm (gallic acid); (B2) under UV light at 366 nm (gallic acid); (B3) $FeCl_3$; (B4) Dragendorff's reagent; (B5) $AlCl_3$; (B6) vanillin–sulfuric acid; (B7) 10% w/v KOH in methanol.

Table 2. TLC results for the constituents of the pomegranate peel extract

Compound Class	Spot-Visualization Reagent	Result	Rf
Alkaloids	Dragendorff's reagent	−	−
Flavonoids	$AlCl_3$	+	0.41 and 0.53
Tannins	$FeCl_3$	+	0.47
Phenols	$FeCl_3$	+	0.47
Saponins	H_2SO_4	−	−
Steroids/Terpenoids	Vanillin–sulfuric acid	+	0.47
Anthraquinones	10% w/v KOH in methanol	−	−

The extract satisfied all standardization requirements, including loss on drying (3.64 ± 0.20%) and total ash content (0.54 ± 0.19%). The physical properties of the compression mass for all formulas (Formula 1–Formula 4 and the optimal formulation) fell within the acceptable range for the direct compression method, exhibiting good flow properties (flow time ≤ 10 seconds, angle of repose ≤ 40°) and an appropriate moisture content (2–4%), as presented in Table 3.

Table 3. Physical characteristics of the dispersible tablet compression mass across the various formulations

Parameter	Formula 1	Formula 2	Formula 3	Formula 4	OF	Specification
Moisture content (%)	2.28 ± 0.15	2.54 ± 0.18	2.25 ± 0.11	3.13 ± 0.24	2.46 ± 0.16	2–4 [31]
Flow time (seconds)	5.64 ± 0.32	5.76 ± 0.02	5.59 ± 0.15	5.82 ± 0.07	6.53 ± 0.13	≤ 10 [31]
Angle of repose (°)	32.56 ± 1.19	33.12 ± 1.51	33.42 ± 0.36	32.11 ± 0.64	35.30 ± 1.32	≤ 40 [31]

Note: data are presented as mean ± SD (n = 3). OF: Optimal Formulation.

3.2. Formulation Optimization and Physical Quality of the Tablets

All tablet formulas (Formula 1–Formula 4 and the optimal formulation) met the requirements for weight uniformity, hardness, friability, and fineness of dispersion (Table 4). The factorial design analysis demonstrated the influence of each factor on the physical characteristics of the tablets (Table 5). Both the Ac-Di-Sol concentration (X_A) and the PVP K-30 concentration (X_B) exerted a significant effect on disintegration time ($p < 0.05$), with PVP K-30 demonstrating the more dominant effect. In contrast, neither the individual factors nor their interaction exerted a significant effect on tablet hardness or friability ($p > 0.05$). Because the factorial analysis showed that only disintegration time was significantly modelled by the two factors, disintegration time was the response that varied meaningfully across the design space and therefore effectively governed the location of the optimum region, whereas hardness and friability remained within their specified limits and served as feasibility constraints that any candidate optimum was required to satisfy.

Table 4. Physical quality evaluation results for the dispersible tablet preparations across the various formulations

Parameter	Formula 1	Formula 2	Formula 3	Formula 4	OF (Predicted)	OF (Observed)	Specification
Hardness (kp)	6.44 ± 0.07	6.34 ± 0.09	6.32 ± 0.04	6.39 ± 0.01	6.41	6.58 ± 0.15	4–8 [44]
Friability (%)	0.16 ± 0.03	0.31 ± 0.08	0.26 ± 0.09	0.24 ± 0.04	0.21	0.28 ± 0.02	≤ 1 [45]
Disintegration time (seconds)	75.6 ± 5.4	108 ± 10.2	129 ± 6.6	147 ± 3.6	1.45	87 ± 0.6	≤ 180 [46]

Note: data are presented as mean ± SD (n = 3). OF: Optimal Formulation.

Table 5. Summary of the factorial design analysis of variance for the tablet physical quality response parameters

Response	Factor	Coefficient	F Value	p Value	Remark
Hardness	X_A	−0.0085	0.10	0.7686	Not significant
	X_B	−0.0170	0.42	0.5658	Not significant
	X_AX_B	+0.0425	2.62	0.1998	Not significant
Friability	X_A	+0.0302	2.43	0.2167	Not significant
	X_B	+0.0087	0.20	0.6826	Not significant

	X_AX_B	−0.0436	5.08	0.1098	Not significant
Disintegration time	X_A	+0.2111	39.29	0.0084	Significant
	X_B	+0.3856	131.02	0.0013	Significant
	X_AX_B	−0.0600	3.17	0.1733	Not significant

The relationship between the two formulation factors and the measured responses is illustrated by the contour plots in Figure 3. Consistent with the factorial analysis (Section 3.2), only disintegration time was significantly governed by the factors; both Ac-Di-Sol and PVP K-30 entered the disintegration-time model with positive coefficients, so disintegration time was shortest in the low-Ac-Di-Sol/low-PVP corner of the design space. In agreement with this, Formula 1 (10% Ac-Di-Sol, 2% PVP K-30) gave the shortest experimental disintegration time (75.6 s) and a hardness (6.44 kp) within the specified 5–7 kp window. Its mean friability, however, was 0.16%, which fell just below the lower acceptance limit of the in-range friability goal (0.2–0.4%); Formula 1 therefore did not simultaneously satisfy all three in-range criteria defined in Section 2.4.

Applying the numerical desirability function under those criteria—all three responses assigned the goal "in range" (disintegration time 60–150 s, friability 0.2–0.4%, hardness 5–7 kp), with disintegration time being the only response significantly modelled by the factors and therefore effectively governing the location of the optimum—Design-Expert® located the optimum in the same low-PVP region but at a slightly higher Ac-Di-Sol level, namely 11.68% Ac-Di-Sol and 2.02% PVP K-30. Because friability increased modestly with Ac-Di-Sol concentration, this small upward shift raised the predicted friability from the sub-limit corner value to 0.21%, bringing it within the 0.2–0.4% window, while disintegration time (predicted 87 s) and hardness remained within their limits. The optimum thus represents the desirability-weighted solution that satisfies all three in-range goals simultaneously, rather than a single factorial corner that meets only two of the three.The corresponding optimal region was delineated on the combined overlay plot, representing the portion of the design space in which all three criteria were satisfied simultaneously: disintegration time 1–2.5 min (60–150 s), friability 0.2–0.4%, and hardness 5–7 kp. The verification batch of the optimized formulation was prepared and tested, and the measured responses agreed with the predicted values (Table 4).

The relationship between the factors and the responses was visualized through the contour plots in Figure 3. Because both significant factors carried positive coefficients for disintegration time, the model predicts the shortest disintegration time in the low-Ac-Di-Sol, low-PVP corner of the design space. Optimization was performed with the numerical desirability function in Design-Expert® under the criteria defined in Section 2.4. The two factors were constrained to their studied ranges (Ac-Di-Sol 10–15% w/w; PVP K-30 2–4% w/w), and each of the three responses was assigned the goal “in range” with limits of 60–150 s (1–2.5 min) for disintegration time, 0.2–0.4% for friability, and 5–7 kp for hardness, each weighted and given importance equally so that no single response dominated the composite desirability. An “in range” goal was chosen because each response has a functionally acceptable window rather than a monotonic “smaller- or larger-is-better” optimum. Under this configuration Design-Expert® located a single optimum at 11.68% Ac-Di-Sol and 2.02% PVP K-30, whose predicted responses (disintegration time 87 s, friability 0.21%, hardness 6.41 kp) all fell within the specified limits, giving an overall desirability of 1. Although Formula 1 (10% Ac-Di-Sol, 2% PVP K-30) shows a numerically shorter disintegration time (75.6 s) and a lower friability (0.16%), under the “in range” criteria actually used this does not make it the better solution. For disintegration time, both 75.6 s and 87 s lie within the 60–150 s window and thus carry the same maximal desirability, because the objective was acceptability within a window and not minimization. For friability, Formula 1's 0.16% lies below the 0.2% lower acceptance limit, placing it outside the optimum region with zero desirability for that response. Therefore, Formula 1 does not satisfy all three constraints simultaneously and cannot be returned as a valid desirability optimum, whereas the predicted optimum satisfies all three. The characterization of the optimum as worse on both target responses follows from a smaller-is-better interpretation that was not the optimization goal defined a priori. For these reasons the desirability-based optimum, rather than Formula

1, was carried forward and verified experimentally. This optimum region was marked on the combined overlay plot, representing the portion of the design space in which all three responses simultaneously met their specified limits. The verification batch of the optimal formulation yielded results consistent with the predicted values and met all quality specifications (Table 4).

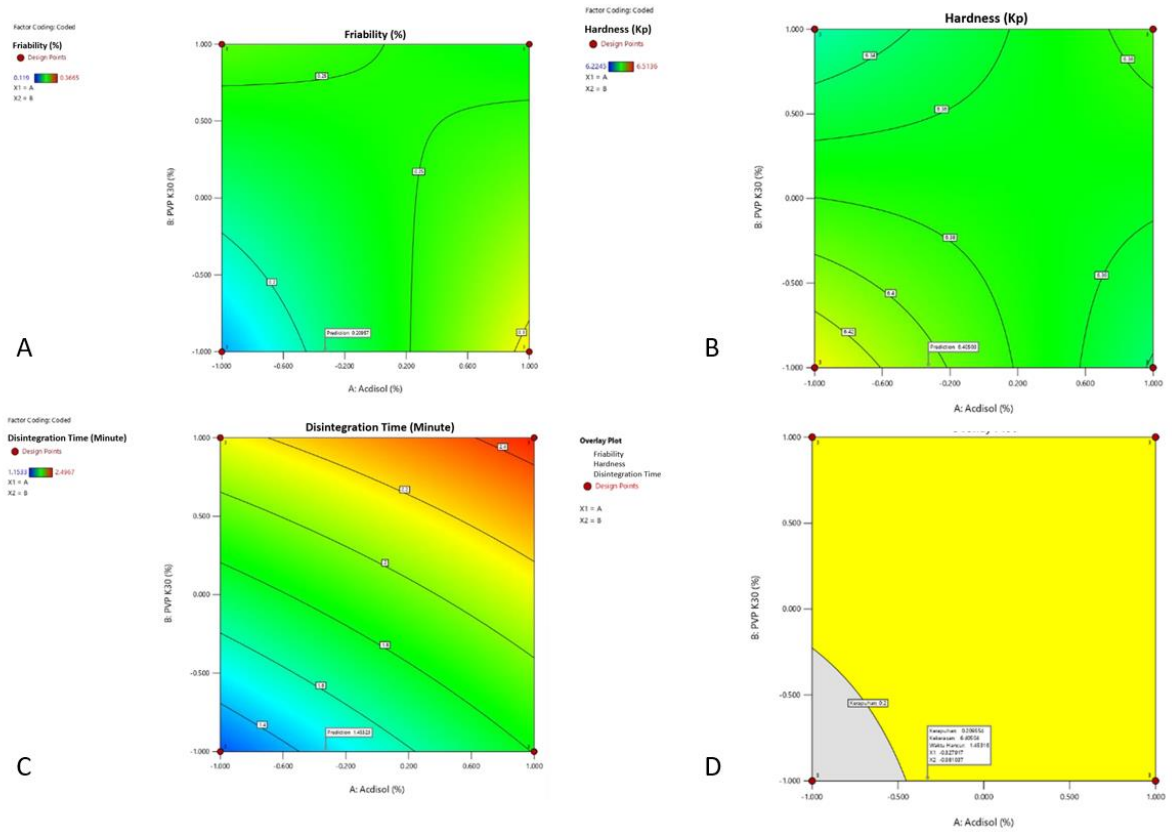


Figure 3. Contour plots of the factorial design analysis depicting the influence of Ac-Di-Sol concentration (%) and PVP K-30 concentration (%) on (A) friability, (B) hardness, and (C) disintegration time. (D) The combined overlay plot displays the optimal formulation region (yellow) satisfying all quality criteria, together with the marking of the selected optimal point.

3.3. TLC-Based Identity and Compatibility Testing of the Active Ingredient

The pomegranate peel extract contained total phenols, which gave a positive reaction, manifested as a black spot when sprayed with $FeCl_3$ reagent. The Rf value of gallic acid in the PPE sample and in samples M1, F1, M2, F2, M3, F3, M4, and F4 was 0.47 (black spot). As noted in Section 3.1, this value did not correspond exactly to the reference Rf of 0.76 specified in the Indonesian Herbal Pharmacopoeia [40]; the deviation reflects differences in analytical conditions like chamber temperature and relative humidity, the degree of mobile-phase saturation, and the type of plate. They are known to shift Rf values without changing the identity of the compound [60], and it should therefore not be interpreted as a difference in the identity of the marker. Crucially, the identical Rf value and spot appearance obtained across the extract, the compression mass, and the finished tablets—on visual observation and under UV light at 254 nm and 366 nm—confirm that the marker compound remained consistently identifiable and compatible with the excipients and the direct-compression process. It must be emphasized that this testing was qualitative in nature and did not encompass a quantitative assessment of stability over time (Figure 4).

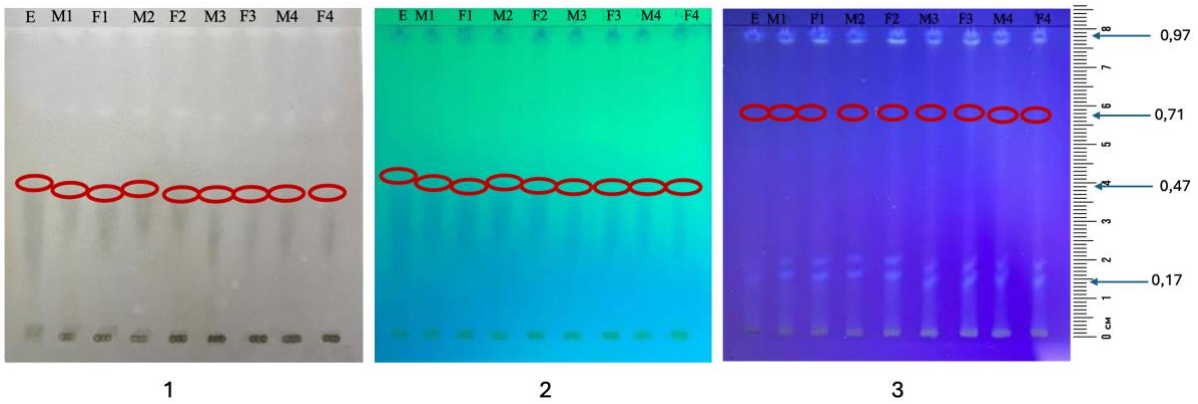
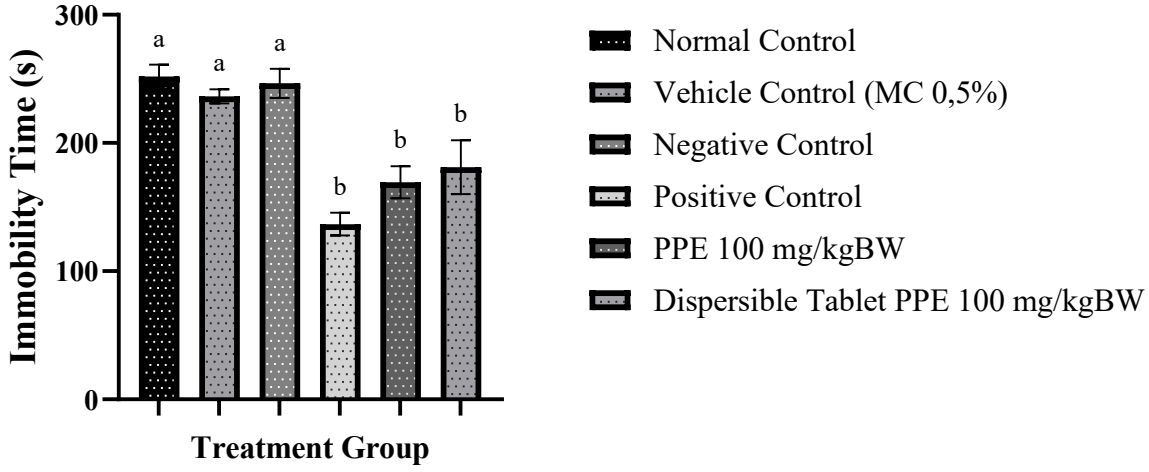


Figure 4. TLC profiles for the stability evaluation of the extract, the tablet compression mass, and the finished tablets, visualized under three detection modes: (1) visible light; (2) UV light at 254 nm; and (3) UV light at 366 nm. Lanes: (E) extract; (M1) compression mass of Formula 1; (F1) tablet of Formula 1; (M2) compression mass of Formula 2; (F2) tablet of Formula 2; (M3) compression mass of Formula 3; (F3) tablet of Formula 3; (M4) compression mass of Formula 4; and (F4) tablet of Formula 4.

3.4. Antidepressant Activity

The behavioral test results demonstrated a significant antidepressant effect for both the pomegranate peel extract and the optimized dispersible tablet. In the Tail Suspension Test, the pomegranate peel extract group (169.38 ± 12.47 seconds) and the optimal formulation group (181.14 ± 21.00 seconds) exhibited a significant reduction in immobility time compared with the normal control (251.84 ± 9.33 seconds), the vehicle control (236.44 ± 5.55 seconds), and the negative control (246.59 ± 11.40 seconds), with $p < 0.01$ for both treatments. Although the fluoxetine positive control produced a numerically greater reduction in immobility time (136.70 ± 8.95 seconds), the difference between the optimal formulation and fluoxetine did not reach statistical significance ($p > 0.05$) (Figure 5A). A similar pattern was observed in the Forced Swim Test. The pomegranate peel extract group (94.00 ± 11.11 seconds) and the optimal formulation group (93.96 ± 20.53 seconds) significantly reduced immobility time compared with the normal control (193.90 ± 7.39 seconds; $p < 0.001$ for both), the vehicle control (173.00 ± 5.94 seconds; $p < 0.01$ for both), and the negative control (151.70 ± 19.57 seconds; $p < 0.05$ for both). The immobility time in the optimal formulation group did not differ significantly from that of fluoxetine (81.11 ± 7.85 seconds; $p > 0.05$) (Figure 5B).

A



B

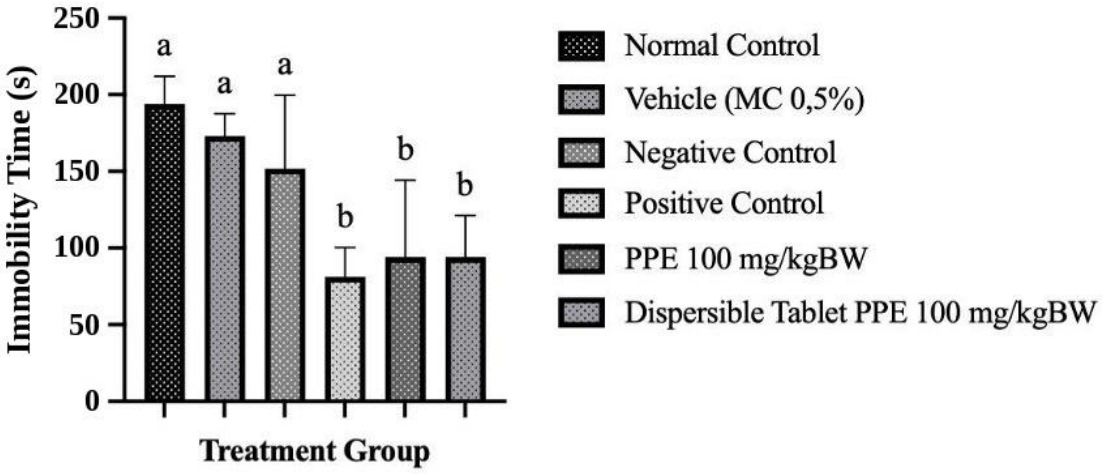


Figure 5. Effect of the pomegranate peel extract and the optimized dispersible tablet formulation on immobility time in mice. (A) Tail Suspension Test. (B) Forced Swim Test. Data are presented as mean ± SEM (n = 6/group). Groups labeled with different letters differ significantly ($p < 0.05$).

3.5. Discussion

The present study successfully demonstrated the translation of a pharmacologically active herbal extract into a rationally designed, patient-oriented dosage form. The principal achievement is the development of an optimized pomegranate peel extract dispersible tablet with favourable physical quality, together with *in vivo* validation confirming that the formulation process preserved the antidepressant activity of the extract.

The use of a 2^2 factorial design proved to be an efficient and systematic approach for optimizing the tablet formulation. The analysis demonstrated that, although hardness and friability remained stable across the range of concentrations tested, disintegration time was strongly influenced by changes in the concentration of both the superdisintegrant (Ac-Di-Sol) and the binder (PVP K-30). An increase in binder concentration prolonged disintegration time, and within the range studied the superdisintegrant acted in the same direction, as detailed below. The final optimal formulation, containing 11.68% Ac-Di-Sol and 2.02% PVP K-30, achieved an ideal balance—namely a rapid disintegration time (< 90 seconds) without compromising the mechanical strength of the tablet. This approach ensured that the preparation met the quality criteria for dispersible tablets and has the potential to deliver good clinical performance.

The factorial analysis showed that disintegration time was significantly influenced by both the superdisintegrant (Ac-Di-Sol) and the binder (PVP K-30), each carrying a positive coefficient (X_A = +0.21 min, $p = 0.008$; X_B = +0.39 min, $p = 0.001$), whereas their interaction was not significant ($X_A \cdot X_B$ = −0.06 min, $p = 0.173$). Both factors therefore tended to prolong disintegration across the concentration range studied. PVP K-30 exerted the dominant effect, consistent with its role as a binder that strengthens interparticle bonds and thereby impedes water penetration into the tablet core. The positive coefficient for Ac-Di-Sol may appear counter-intuitive, since croscarmellose sodium is a superdisintegrant expected to accelerate disintegration; however, at the relatively high levels employed here (10–15% w/w, well above the concentration typically used in direct compression), excess croscarmellose sodium can swell into a viscous, coherent hydrated layer that retards further water wicking into the core and consequently prolongs disintegration [47]. The optimal formulation (11.68% Ac-Di-Sol, 2.02% PVP K-30) balanced these opposing influences, achieving a rapid disintegration time (< 90 s) without compromising mechanical strength.

The pharmacological evaluation confirmed that the antidepressant efficacy was retained. In the tail suspension test and the forced swim test—two widely accepted screening models for antidepressant activity—the optimized tablet significantly reduced the despair-like behavior represented by immobility time in mice. Quantitatively, the optimal formulation reduced immobility duration by 28.1% in the tail

suspension test and 51.5% in the forced swim test relative to the normal control; these magnitudes were similar to those of the pure extract (32.7% and 51.5%). Although fluoxetine produced numerically larger reductions (45.7% and 58.2%), the differences between the optimal formulation and fluoxetine did not reach statistical significance in either model, indicating that the formulation retained a pharmacologically meaningful antidepressant-like effect.

The more pronounced effect observed in the forced swim test suggests a difference in the sensitivity of the two models to the intervention. It should be emphasized that the tablet formulation demonstrated efficacy equivalent to, rather than superior to, that of the pure extract. Accordingly, the principal contribution of the formulation process lies in the retention of efficacy together with improvements in dosing accuracy and ease of administration, rather than in enhanced bioavailability, which was not measured in this study. This distinction is pertinent because ellagic acid is characterized by inherently low oral bioavailability, attributable to its poor aqueous solubility [48], [49]. This finding of retained efficacy nevertheless remains crucial, as it demonstrates that the excipients and the direct-compression process did not interact negatively with, or degrade, the bioactive compounds of the extract.

Although this study did not directly measure biochemical markers, the observed antidepressant activity is consistent with the neuropharmacological properties of the principal secondary metabolites of pomegranate peel extract reported in the literature, particularly ellagic acid and other polyphenols. The pathophysiology of depression is closely associated with neuroinflammation: chronic activation of glial cells triggers the release of pro-inflammatory cytokines that cause neuronal damage and neurotransmitter imbalance [4], [8]. Polyphenols are potent modulators of these pathways.

Various studies have shown that ellagic acid produces antidepressant-like effects through modulation of the serotonergic and adrenergic systems as well as suppression of the neuroinflammatory response [20], [21], [50], [19]. Consistent with this, punicalagin has been reported to restore hippocampal dopamine and serotonin levels in a chronic unpredictable mild stress model [22]. This is consistent with broader evidence that a polyphenol-rich diet is associated with improved mental health and sleep quality [51]. The utility of herbal therapy in managing mood disorders is also supported by a recent review [52]. In addition, understanding of the gut–brain axis has reinforced the notion that dietary components can influence mental health through modulation of the gut microbiota—a pathway of particular relevance given that pomegranate ellagitannins and ellagic acid are metabolized by the colonic microbiota into urolithins [53], [54]—although this specific mechanism was not explored in the present study [55].

Clinical-trial results from previous research further corroborate the findings of this study. Pomegranate peel supplementation has been reported to ameliorate symptoms of depression, anxiety, and stress in patients with non-alcoholic fatty liver disease [56], and ellagic acid exerted positive effects on depressive and anxiety symptoms in a blinded clinical trial [57]. Furthermore, various parts of the pomegranate fruit have been shown to exhibit potent antioxidant activity [58]. These findings support the rationale for the antidepressant mechanism of pomegranate peel and underscore the potential of *Punica granatum* as a source for nutraceutical development.

3.6. Study Limitation

This study has several limitations that warrant attention when interpreting the results. First, antidepressant activity was assessed solely through behavioral outcomes (the Tail Suspension Test and the Forced Swim Test), without measurement of specific biochemical correlates such as oxidative stress parameters (e.g., malondialdehyde, superoxide dismutase, catalase), pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), or brain neurotransmitter levels. The attribution of the observed activity to the antioxidant and anti-neuroinflammatory mechanisms discussed is therefore inferential, based on the literature, and has not been directly demonstrated; future studies should incorporate these biochemical markers to substantiate the underlying mechanism. Second, the phytochemical characterization was qualitative (TLC) only; quantitative determination of the total phenolic content and of specific marker compounds such as gallic acid and ellagic acid (ideally by a validated quantitative method such as high-performance liquid chromatography) was not performed and is recommended for future work to enable

precise standardization of the active constituents. Third, the evaluation was limited to a single dose equivalent to 100 mg/kg body weight and to acute behavioral models; dose-response and chronic-administration studies are needed to characterize the therapeutic window. In view of these limitations, recommended further research includes the HPLC (high performance liquid chromatography)-based quantitative determination of marker compounds, measurement of oxidative-stress and pro-inflammatory-cytokine biomarkers, dose-response studies, dissolution and pharmacokinetic profiling, and long-term (time-course) stability evaluation. Ultimately, the success of the pomegranate peel extract in retaining its efficacy in dispersible tablet form opens opportunities for the development of more accessible herbal preparations, particularly for geriatric and pediatric patients or those experiencing difficulty swallowing.

4. Conclusion

1. The pomegranate peel extract dispersible tablet was successfully formulated and optimized using a 2^2 factorial design, yielding an optimal formulation (11.68% Ac-Di-Sol and 2.02% PVP K-30) with good physical quality and a rapid disintegration time (87 seconds).
2. The *in vivo* test results confirmed that the optimized tablet formulation was able to retain the antidepressant activity of its parent extract, yielding results equivalent to those of the pure extract and fluoxetine in both the Tail Suspension Test and the Forced Swim Test. These results support the potential of the pomegranate peel extract dispersible tablet as a promising, patient-friendly nutraceutical candidate for the management of depressive disorders.

5. Declarations

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5.2 Author contributions

Ivonne Soeliono: Conceptualization, Methodology, Investigation, Validation, Supervision, Writing - original draft, Writing - review & editing, Project administration. Tio Minaritatis Hutauruk: Investigation, Formal analysis, Writing - original draft, Visualization. Martha Ervina: Validation, Supervision. Ida Ayu Made Anom Sri Melia Laksmi: Investigation, Formal analysis, Writing - original draft, Visualization. Nadiatul Janah: Investigation, Formal analysis, Writing - original draft, Visualization. Sela Uswatun Nurul Chasanah: Investigation, Formal analysis, Writing - original draft, Visualization. Eka Pramyrtha Hestianah: Validation, Supervision. Lannie Hadisoewignyo: Conceptualization, Methodology, Resources, Validation, Supervision. All authors have read and agreed to the published version of the manuscript.

5.3 Ethics

Ethical approval for this study was granted by the Health Research Ethics Committee of the Faculty of Medicine, Widya Mandala Surabaya Catholic University, under approval No. 0012/WM12/KEPK/MHS/T/2025 (tail suspension test) and No. 0011/WM12/KEPK/MHS/T/2025 (forced swim test).

5.4 Conflict of Interest

The authors declare no conflict of interest.

5.5 Funding Statement

This research received no external funding.

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Original Research Article

Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation

Abstract

Depression, a leading cause of global disability (1.4% prevalence in Indonesia), is linked to oxidative stress from reactive oxygen species (ROS) accumulation disrupting neurotransmission. Pomegranate (Punica granatum L.) peel polyphenols exhibit antioxidant activity, potentially lowering ROS and conferring antidepressant effects. This study developed and optimized a pomegranate peel extract dispersible tablet and validated retention of in vivo antidepressant activity. Tablets were produced by direct compression and optimized via two-factor factorial design, varying croscarmellose sodium (superdisintegrant) and polyvinylpyrrolidone K-30 (binder) concentrations. Antidepressant activity of the optimized tablet (equivalent to 100 mg/kg extract) was assessed in male BALB/c mice using the tail suspension and forced swim tests, with unformulated extract and fluoxetine (20 mg/kg) as comparators. The optimal formulation contained 11.68% croscarmellose sodium and 2.02% polyvinylpyrrolidone K-30, exhibiting excellent physicochemical properties: rapid disintegration (87 s), low friability (0.21%), and adequate hardness (6.41 kp). In both tests, the optimized tablet significantly reduced immobility time ($p < 0.05$), comparable to unformulated extract and fluoxetine. An effective pomegranate peel extract dispersible tablet was developed without compromising pharmacological efficacy, supporting its potential as a preclinical nutraceutical candidate for managing depressive symptoms.

Keywords: Dispersible Tablet; *Punica granatum*; Factorial Design; Antidepressant Activity

1 Introduction

Mental health disorders, particularly depression, have emerged as a critical global health burden and constitute one of the leading causes of disability worldwide [1]. In Indonesia, the 2023 Indonesian Health Survey (*Survei Kesehatan Indonesia*) reported a national depression prevalence of 1.4%, with the highest rates observed in the 15–24-year age group [2]. In recent years, the scientific paradigm has shifted: depression is no longer regarded merely as a consequence of biochemical imbalance in the brain, but rather as a complex, multifaceted pathological disorder in which neuroinflammation is increasingly recognized as a decisive underlying mechanism [3], [4], [5], [6], [7], [8]. Chronic neuroinflammation, characterized by the persistent activation of microglia and astrocytes, can disrupt neuronal homeostasis, diminish synaptic plasticity, and trigger dysregulation of the principal monoaminergic neurotransmitter systems—such as serotonin and dopamine—that govern mood regulation [9], [10], [11], [12], [13].

Pomegranate (*Punica granatum* L.) has long been utilized in traditional medicine systems. For centuries, it has featured in traditional Chinese, Ayurvedic, and Persian medicine as a remedy for conditions including atherosclerosis, diabetes, hypertension, hyperlipidemia, and certain cancers, as well as ulcers, oral-cavity disorders, and worm infestations [14], [15]. Pomegranate fruit peel, which accounts for approximately 50% of the total fruit weight, represents a particularly rich source of polyphenols [14], [16], [17]. Pomegranate peel extract (PPE) contains abundant hydrolyzable tannins—polyphenolic substances derived from gallic acid that, upon hydrolysis, split into sugars and phenolic acids such as gallic acid or ellagic acid, thereby forming gallotannins and ellagitannins, respectively [18]. The most abundant ellagitannin is punicalagin, which can be hydrolyzed into smaller phenolic compounds such as ellagic acid, its principal metabolite [14], [15].

Punicalagin and its metabolite ellagic acid produce antidepressant-like effects in preclinical models—reducing immobility and enhancing climbing behavior—largely through modulation of the serotonergic and adrenergic systems [19], [20], [21]. These effects are underpinned by the restoration of stress-depleted brain monoamines (dopamine and serotonin) and by broad neuroprotective, anti-neuroinflammatory action that suppresses the NLRP3 inflammasome and the MAPK/NF-κB pathways, thereby lowering pro-inflammatory markers (TNF-α, IL-1β, IL-6, COX-2, iNOS) and oxidative stress [22], [16], [23].

Preclinical *in vivo* studies confirm this antidepressant potential. In olfactory-bulbectomy (OBX) model rats, oral ethanolic pomegranate peel extract at 10, 30, and 100 mg/kg significantly reversed open-field hyperactivity and improved despair-related parameters in the forced swim and sucrose-intake tests, in parallel with normalization of brain monoamine levels [24]; in mice, PPE at 100 mg/kg reduced immobility time in both the forced swim test and the tail suspension test [25].

Despite this established potential, significant translational challenges remain in applying the active extract within a clinical context. The pure viscous extract frequently exhibits unpalatable organoleptic properties and is difficult to measure accurately, thereby compromising dosing precision and limiting its therapeutic utility [26], [27]. Consequently, the formulation of the extract into a modern, patient-oriented dosage form is of paramount importance. Dispersible tablets offer a superior solution, as they disintegrate and disperse rapidly in water, improving palatability, facilitating the administration of large doses, and potentially enhancing bioavailability [28], [29], [30].

The performance of a dispersible tablet hinges on the precise optimization of two key excipients—the binder PVP K-30 and the superdisintegrant croscarmellose sodium (Ac-Di-Sol)—which jointly govern hardness, friability, and disintegration time [31]. PVP K-30 provides strong adhesion and plastic deformation for compaction, yet its high water solubility and low viscosity keep it from delaying disintegration [32], whereas croscarmellose sodium acts through combined water wicking and swelling to generate the multidirectional internal pressure that rapidly ruptures inter-particle bonds [33]. Applying a Quality-by-Design approach with a central composite design, Shah et al. [34] confirmed both excipient

concentrations as high-risk factors for friability and disintegration time, identifying an optimal profile of 20 mg/tablet croscarmellose sodium and 8 mg/tablet PVP K-30.

On this basis, the present study was conducted with two principal objectives: (1) to develop and statistically optimize a PPE dispersible tablet formulation using a factorial design in order to achieve ideal physicochemical characteristics; and (2) to perform an *in vivo* evaluation confirming that the antidepressant efficacy of the native extract is retained following formulation. The development of standardized, innovative dosage forms is an essential prerequisite for the downstreaming of natural-product–based medicines in Indonesia [35], [36]. To the best of the authors' knowledge, the development of a standardized dispersible tablet from pomegranate peel extract accompanied by *in vivo* validation of its antidepressant activity has not previously been reported, thereby constituting the principal novelty of this study.

2 Method

2.1. Materials

Pomegranate peel extract (*Punica granatum* L.) was supplied by PT Phytochemindo Reksa (Bogor, West Java) and had been prepared by extraction with 50% ethanol–water. Tableting employed Avicel PH-102, PVP K-30, Ac-Di-Sol, stevia, and magnesium stearate as excipients. For determination of the gallic acid marker by thin-layer chromatography (TLC), a gallic acid reference solution was used together with the following detection reagents: iron(III) chloride ($FeCl_3$), aluminium chloride ($AlCl_3$), Dragendorff's reagent, sulfuric acid (H_2SO_4), methanolic potassium hydroxide (KOH, 10% w/v), and vanillin–sulfuric acid. Chloroform, ethyl acetate, n-butanol, formic acid, distilled water, and ethanol served as the mobile-phase solvents.

2.2. Instruments

General apparatus comprised an analytical balance (Mettler Toledo ME204), an oven, a vernier caliper, a stopwatch, crucibles, silica gel 60 F254 plates (20 × 20 cm), capillary tubes, and sieves of mesh No. 30 and mesh No. 25 (710 µm), along with Erlenmeyer flasks, funnels, filter paper, parchment paper, aluminium foil, and plain paper. Tablet manufacture and testing relied on Erweka instruments: an EP-1 single-punch press, a TAR 220 friability tester, a TBH 125 hardness tester, a ZT3-1 disintegration tester, an AR 401 cube mixer, and an SVM-12 tapped-density tester (all Erweka, Germany), together with a moisture analyzer. Routine laboratory glassware was also employed.

2.3. Standardization of the Dried Extract

Standardization addressed both specific and non-specific parameters [37]. As specific parameters, identity and organoleptic attributes — form, color, odor, and taste — were judged visually. The non-specific set comprised loss on drying, total ash, and TLC phytochemical profiling. Loss on drying was recorded after a 2 g portion had been held at 105 °C for 30 min and cooled in a desiccator for 15 min; mass loss was required to stay under 10% w/w. For total ash, 2.0 g of extract underwent furnace incineration. Phytochemical screening used silica gel F254 plates run in a 5:2:2:1 (v/v) mixture of chloroform, ethyl acetate, n-butanol, and formic acid, followed by detection with 1% $FeCl_3$, $AlCl_3$, Dragendorff's reagent, H_2SO_4, vanillin–sulfuric acid, and methanolic KOH (10% w/v). Each plate was spotted with 5 µL of a test solution (1 g PPE dissolved in 10 mL of 96% ethanol) and then viewed under UV at 254 and 366 nm.

2.4. Tablet Formulation and Optimization Using a Factorial Design

Direct compression was used to prepare the dispersible tablets [38], [26]. A two-level, two-factor (2^2) factorial design served to locate the optimum formula [39], examining how Ac-Di-Sol level (Factor XA: 10–15% w/w) and PVP K-30 level (Factor XB: 2–4% w/w) affected three key responses — tablet hardness, friability, and disintegration time (Table 1). Four experimental runs (F1–F4) resulted, each prepared as three batches; Table 2 lists the full composition. Using the desirability approach in Design-Expert®, the optimum was identified by minimizing disintegration time and friability while holding hardness within an acceptable window.

Table 1. Factorial Design for Formulation Optimization

Formulation	Factor XA: Ac-Di-Sol (%)	Factor XB: PVP K-30 (%)	Factor Level (XA, XB)
F1	10	2	(−1, −1)
F2	15	2	(+1, −1)
F3	10	4	(−1, +1)
F4	15	4	(+1, +1)

Table 2. Composition of the dispersible tablet formulations (mg/tablet)

Component	Function	F1	F2	F3	F4	Optimal Formulation
Pomegranate peel extract	Active ingredient	500	500	500	500	500
Ac-Di-Sol	Disintegrant	80	120	80	120	93.44
PVP K-30	Binder	16	16	32	32	16.16
Stevia	Sweetener	28	28	28	28	28
Avicel PH-102	Filler	174	134	158	118	160.40
Magnesium stearate	Lubricant	2	2	2	2	2
Total weight		800	800	800	800	800

2.5. Evaluation of the Tablet Mass and the Dispersible Tablet Preparation

Flowability (flow rate and angle of repose) and moisture content were determined on the tablet mass. For the compressed tablets, weight uniformity, hardness (Erweka TBH 125), friability (Erweka TAR 220), and disintegration time (Erweka ZT3-1) were measured, the last in water held at 15–25 °C. Adequate fineness of dispersion was confirmed when the suspension from a disintegrated tablet passed completely through a 710 µm sieve.

2.6. Identity and Compatibility Testing of the Active Ingredient by Thin-Layer Chromatography (TLC)

Using gallic acid as the marker, TLC was applied to verify the marker compound in the extract, the tablet mass, and the finished dispersible tablets. The intent was to check that neither the excipients nor the direct-compression step altered the marker's spot profile; it was not a quantitative, time- or accelerated-storage stability study. Samples — extract (±1 g), tablet mass (3.995 g), and tablets (5.156 g) — were each made up to 10 mL with ethanol in volumetric flasks, and 5 µL of every solution was spotted onto a silica gel F_{254} plate. Plates were developed in chloroform–ethyl acetate–n-butanol–formic acid (5:2:2:1), dried, and sprayed with 1% $FeCl_3$. Spots were read under UV at 254 and 366 nm, and their Rf values checked against gallic acid (Rf = 0.76) per the Indonesian Herbal Pharmacopoeia [40].

2.7. Experimental Animals and Ethical Approval

Male BALB/c mice (18–33 g; 2–3 months old) were housed under controlled conditions — a 12 h light–dark cycle, 22 ± 2 °C, and 55 ± 10% relative humidity — with food and water available ad libitum. All procedures followed accepted laboratory-animal care and use guidelines and were approved by the Health Research Ethics Committee, Faculty of Medicine, Widya Mandala Surabaya Catholic University (No. 0012/WM12/KEPK/MHS/T/2025, tail suspension test; No. 0011/WM12/KEPK/MHS/T/2025, forced swim test).

2.8. Antidepressant Activity Testing

Mice were assigned at random to six groups (n = 6 per group in each of the tail suspension and forced swim tests): normal control; vehicle control (0.5% methylcellulose); negative control (vehicle carrying the tablet excipients); positive control (fluoxetine, 20 mg/kg body weight in 0.5% methylcellulose); a PPE group (100 mg/kg body weight in 0.5% methylcellulose); and the optimized-tablet group (dose equivalent to 100 mg/kg PPE). Dosing was oral and continued for 14 consecutive

days, with behavioral assessment performed on day 14, one hour after the final dose, during the dark phase of the light–dark cycle. Two independent, trained observers scored immobility and their mean was taken; any pair of readings differing by more than 5 s was re-scored. For the tail suspension test [41], [42], each animal was taped by the tail and observed for 6 min. For the forced swim test [43], [42], each animal was lowered into a clear cylinder of water at 24–25 °C for 6 min, the first 2 min allowed for acclimatization and immobility recorded over the final 4 min.

2.9. Statistical Analysis

Design-Expert® handled the formulation-optimization dataset; factorial-model coefficients were tested against the pure error derived from the three replicate batches per formulation, and the optimum was chosen for minimal disintegration time and friability at an acceptable hardness. Behavioral data were processed in SPSS v.27. After checking normality with the Shapiro–Wilk test, normally distributed results (tail suspension test) were compared by one-way ANOVA with Tukey's HSD, whereas non-normal results (forced swim test) were analyzed by the Kruskal–Wallis test with Dunn's post hoc comparison. Significance was set at $p < 0.05$.

3 Result and Discussion

3.1. Characterization of the Extract and the Tablet Mass

The pomegranate peel extract presented as a light brown powder with specific organoleptic characteristics (Figure 1). The TLC screening results (Table 3 and Figure 2) demonstrated that the phenolic class gave a positive reaction, manifested as a black spot with an Rf value of 0.76, which met the Indonesian Herbal Pharmacopoeia [40] requirement for gallic acid content. The tannin class gave a positive reaction, manifested as a dark blue spot with an Rf value of 0.47. The flavonoid class gave a positive reaction, manifested as blue fluorescence under UV light at 366 nm with Rf values of 0.41 and 0.53. The steroid class gave a positive reaction, manifested as a purple spot under UV light with an Rf value of 0.47.

Figure 1. Organoleptic profile of the preparation. (A) Intact dispersible tablet; (B) tablet dispersion in water.

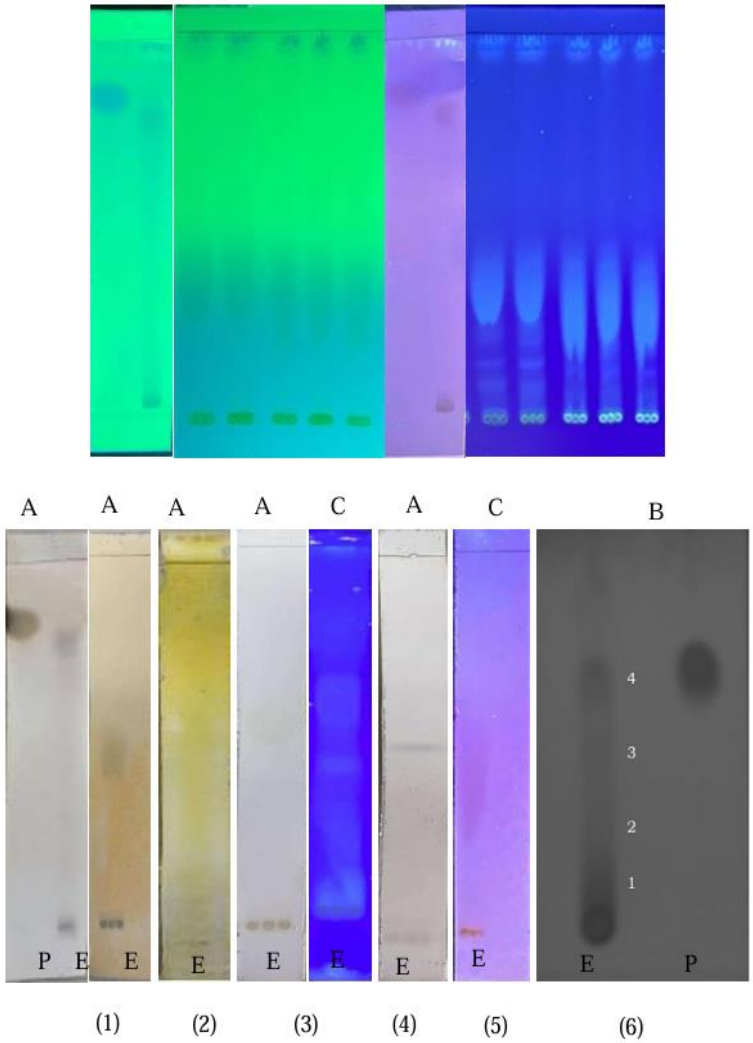

Figure 2. TLC phytochemical screening profile of the pomegranate peel extract. (P) gallic acid standard; (E) pomegranate peel extract; (A) visual observation; (B) UV light at 254 nm; (C) UV light at 366 nm. Spot-visualization reagents: (1) $FeCl_3$; (2) Dragendorff's reagent; (3) $AlCl_3$; (4) vanillin–sulfuric acid; (5) 10% w/v KOH in methanol. Chromatogram (6) shows the comparison between the pomegranate peel extract and gallic acid in accordance with the Indonesian Herbal Pharmacopoeia [40].

Table 3. TLC results for the constituents of the pomegranate peel extract

Compound Class	Spot-Visualization Reagent	Result	Rf
Alkaloids	Dragendorff's reagent	−	−
Flavonoids	$AlCl_3$	+	0.41 and 0.53
Tannins	$FeCl_3$	+	0.47
Phenols	$FeCl_3$	+	0.76
Saponins	H_2SO_4	−	−
Steroids/Terpenoids	Vanillin–sulfuric acid	+	0.47
Anthraquinones	10% w/v KOH in methanol	−	−

The extract satisfied all standardization requirements, including loss on drying (3.64 ± 0.20%) and total ash content (0.54 ± 0.19%). The physical properties of the compression mass for all formulations (F1–F4 and the optimal formulation) fell within the acceptable range for the direct compression method, exhibiting good flow properties (flow time ≤ 10 seconds, angle of repose ≤ 40°) and an appropriate moisture content (2–4%), as presented in Table 4.

Table 4. Physical characteristics of the dispersible tablet compression mass across the various formulations

Parameter	F1	F2	F3	F4	OF	Specification
Moisture content (%)	2.28 ± 0.15	2.54 ± 0.18	2.25 ± 0.11	3.13 ± 0.24	2.46 ± 0.16	2–4 [31]
Flow time (seconds)	5.64 ± 0.32	5.76 ± 0.02	5.59 ± 0.15	5.82 ± 0.07	6.53 ± 0.13	≤ 10 [31]
Angle of repose (°)	32.56 ± 1.19	33.12 ± 1.51	33.42 ± 0.36	32.11 ± 0.64	35.30 ± 1.32	≤ 40 [31]

Note: data are presented as mean ± SD (n = 3). F1–F4: Formulations 1 to 4; OF: Optimal Formulation.

3.2. Formulation Optimization and Physical Quality of the Tablets

All tablet formulations (F1–F4 and the optimal formulation) met the requirements for weight uniformity, hardness, friability, and fineness of dispersion (Table 5). The factorial design analysis demonstrated the influence of each factor on the physical characteristics of the tablets (Table 6). Both the Ac-Di-Sol concentration (XA) and the PVP K-30 concentration (XB) exerted a significant effect on disintegration time ($p < 0.05$), with PVP K-30 demonstrating the more dominant effect. Conversely, neither the individual factors nor their interaction exerted a significant effect on tablet hardness or friability ($p > 0.05$).

Table 5. Physical quality evaluation results for the dispersible tablet preparations across the various formulations

Parameter	F1	F2	F3	F4	OF	Specification
Hardness (kp)	6.44 ± 0.07	6.34 ± 0.09	6.32 ± 0.04	6.39 ± 0.01	6.58 ± 0.15	4–8 [44]
Friability (%)	0.16 ± 0.03	0.31 ± 0.08	0.26 ± 0.09	0.24 ± 0.04	0.28 ± 0.02	≤ 1 [45]
Disintegration time (seconds)	75.6 ± 5.4	108 ± 10.2	129 ± 6.6	147 ± 3.6	87 ± 0.6	≤ 180 [46]

Note: data are presented as mean ± SD (n = 3). F1–F4: Formulations 1 to 4; OF: Optimal Formulation.

Table 6. Summary of the factorial design analysis of variance for the tablet physical quality response parameters

Response	Factor	Coefficient	F Value	p Value	Remark
Hardness	XA	−0.0085	0.10	0.7686	Not significant
	XB	−0.0170	0.42	0.5658	Not significant
	XAXB	+0.0425	2.62	0.1998	Not significant
Friability	XA	+0.0302	2.43	0.2167	Not significant
	XB	+0.0087	0.20	0.6826	Not significant
	XAXB	−0.0436	5.08	0.1098	Not significant
Disintegration time	XA	+0.2111	39.29	0.0084	Significant
	XB	+0.3856	131.02	0.0013	Significant
	XAXB	−0.0600	3.17	0.1733	Not significant

The relationship between the factors and the responses was visualized through the contour plots in Figure 3. Based on this analysis, the Design-Expert® software predicted an optimal formulation with an Ac-Di-Sol concentration of 11.68% and a PVP K-30 concentration of 2.02%. This optimal region was marked on the combined overlay plot, representing the design space in which all quality criteria (friability

≤ 1%, hardness 4–8 kp, disintegration time < 3 minutes) were satisfied. The verification batch of the optimal formulation, prepared and tested, yielded results consistent with the predicted values (Table 5).

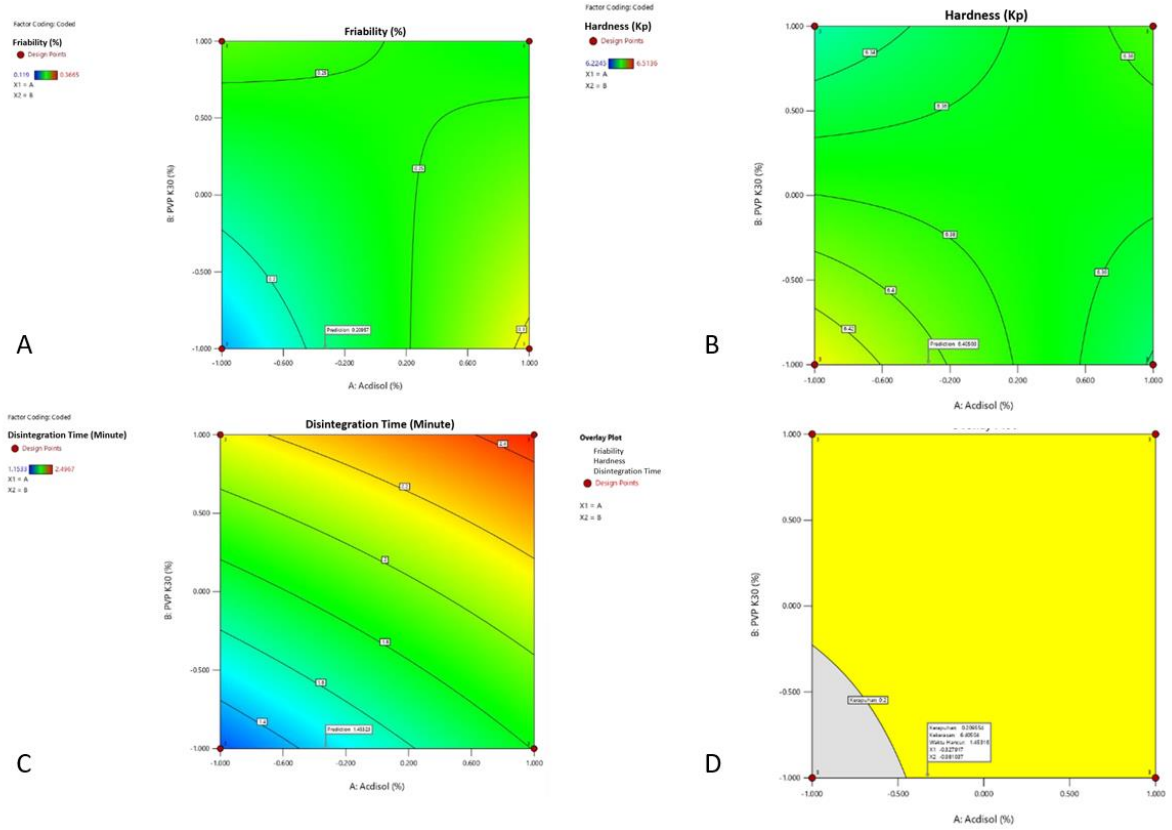

Figure 3. Contour plots of the factorial design analysis depicting the influence of Ac-Di-Sol concentration (%) and PVP K-30 concentration (%) on (A) friability, (B) hardness, and (C) disintegration time. (D) The combined overlay plot displays the optimal formulation region (yellow) satisfying all quality criteria, together with the marking of the selected optimal point.

3.3. TLC-Based Identity and Compatibility Testing of the Active Ingredient

The pomegranate peel extract contained total phenols, which gave a positive reaction, manifested as a black spot when sprayed with $FeCl_3$ reagent. The Rf value of gallic acid in the PPE sample, M1, F1, M2, F2, M3, F3, M4, and F4 was 0.47 (black spot). The obtained Rf value did not correspond exactly to the standard of the Indonesian Herbal Pharmacopoeia [40], owing to variation in the analytical conditions—such as differences in temperature, humidity, the degree of mobile-phase saturation, and the type of plate—which can influence the shift in Rf value. On visual observation as well as under UV light at 254 nm and 366 nm, the extract, compression mass, and tablet samples exhibited identical Rf values. This indicates that the marker compound remained consistently identifiable and compatible with the excipients and the direct compression process; it must be emphasized that this testing was qualitative in nature and did not yet encompass a quantitative assessment of stability over time (Figure 4).

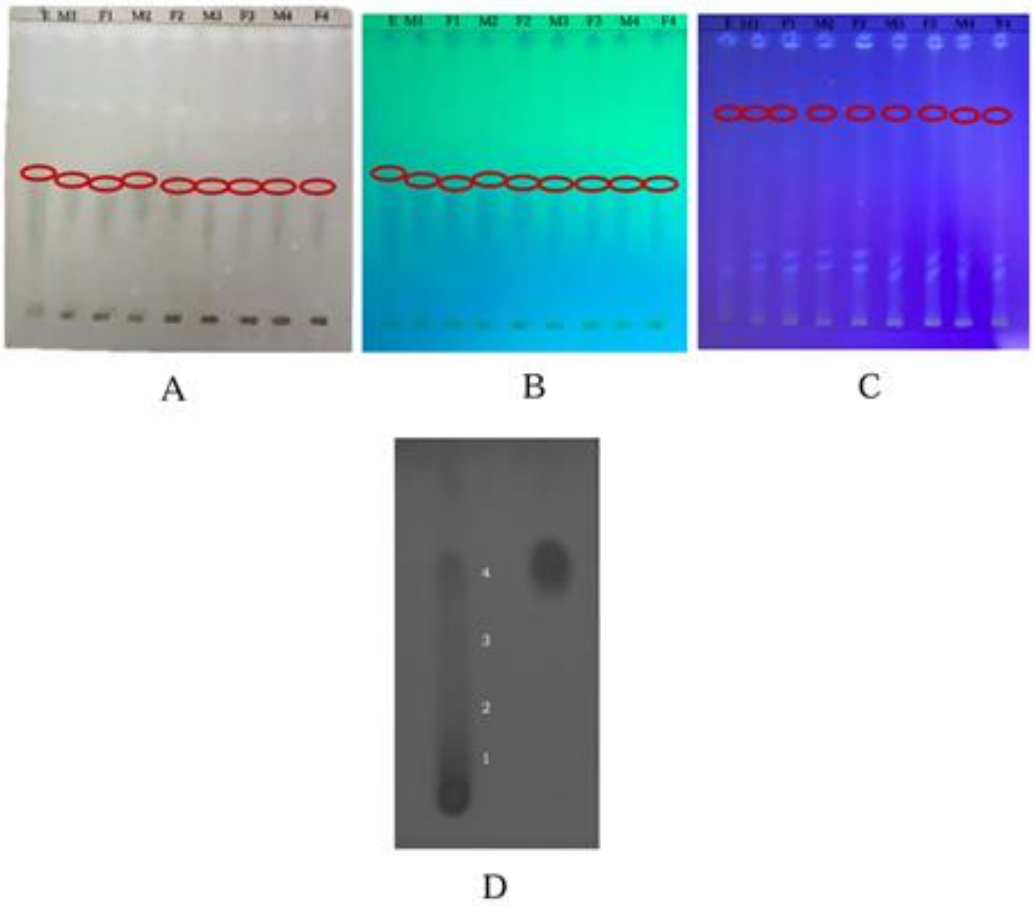

Figure 4. TLC results for the identity and compatibility testing of the extract, the compression mass, and the tablet preparations: (A) spot appearance with $FeCl_3$ reagent; (B) UV light at 254 nm; (C) UV light at 366 nm; (E) pomegranate peel extract; (D) chromatogram of the pomegranate peel extract and gallic acid in accordance with the Indonesian Herbal Pharmacopoeia [40]; (M1-M4) compression mass of dispersible tablet formulations 1-4; (F1-F4) dispersible tablet formulations 1-4.

3.4. Antidepressant Activity

The behavioral test results demonstrated a significant antidepressant effect for both the pomegranate peel extract and the optimized dispersible tablet. In the Tail Suspension Test, the pomegranate peel extract group (169.38 ± 12.47 seconds) and the optimal formulation group (181.14 ± 21.00 seconds) exhibited a significant reduction in immobility time compared with the normal control (251.84 ± 9.33 seconds), the vehicle control (236.44 ± 5.55 seconds), and the negative control (246.59 ± 11.40 seconds), with $p < 0.01$ for both treatments. This effect was comparable to that of the fluoxetine positive control (136.70 ± 8.95 seconds) and was not statistically significantly different ($p > 0.05$) (Figure 5A). A similar pattern was observed in the Forced Swim Test. The pomegranate peel extract group (94.00 ± 11.11 seconds) and the optimal formulation group (93.96 ± 20.53 seconds) significantly reduced immobility time compared with the normal control (193.90 ± 7.39 seconds; $p < 0.001$ for both), the vehicle control (173.00 ± 5.94 seconds; $p < 0.01$ for both), and the negative control (151.70 ± 19.57 seconds; $p < 0.05$ for both). This effect did not differ significantly from that of fluoxetine (81.11 ± 7.85 seconds; $p > 0.05$) (Figure 5B).

A

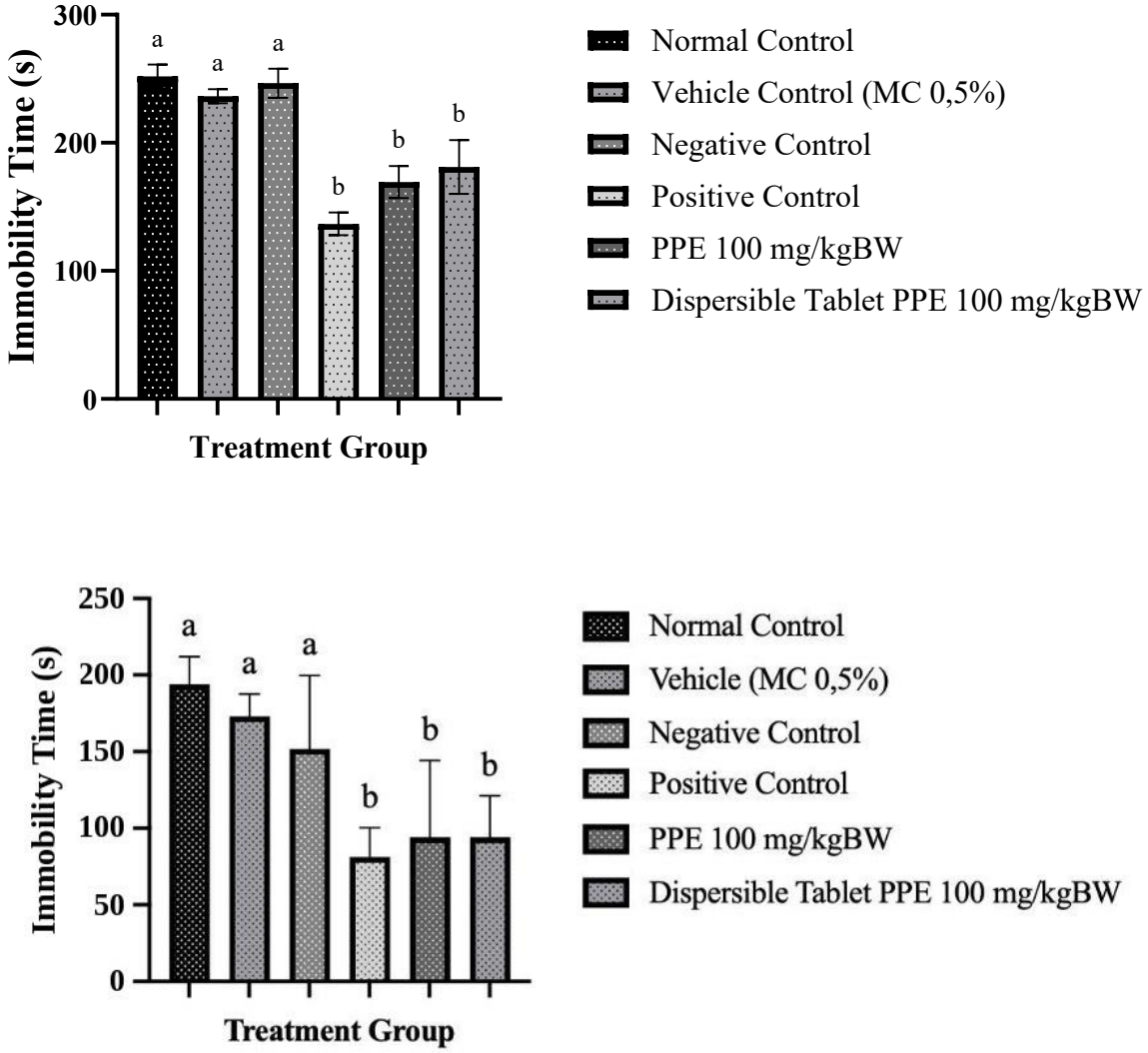

Figure 5. Effect of the pomegranate peel extract and the optimized dispersible tablet formulation on immobility time in mice. (A) Tail Suspension Test. (B) Forced Swim Test. Data are presented as mean ± SEM (n = 6/group). Groups labeled with different letters differ significantly ($p < 0.05$).

3.5. Discussion

The present study successfully demonstrated the translation of a pharmacologically active herbal extract into a rationally designed, patient-oriented dosage form. The principal achievement is the development of an optimized pomegranate peel extract dispersible tablet with superior physicochemical properties, together with *in vivo* validation confirming that the formulation process preserved the antidepressant activity of the extract.

The use of a 2^2 factorial design proved to be an efficient and systematic approach for optimizing the tablet formulation. The analysis demonstrated that, although hardness and friability remained stable across the range of concentrations tested, disintegration time was strongly influenced by changes in the concentration of both the superdisintegrant (Ac-Di-Sol) and the binder (PVP K-30). An increase in binder concentration prolonged disintegration time, and within the range studied the superdisintegrant acted in the same direction, as detailed below. The final optimal formulation, containing 11.68% Ac-Di-Sol and 2.02% PVP K-30, achieved an ideal balance—namely a rapid disintegration time (< 90 seconds) without compromising the mechanical strength of the tablet. This approach ensured that the preparation met the quality criteria for dispersible tablets and has the potential to deliver good clinical performance.

The factorial analysis showed that disintegration time was significantly influenced by both the superdisintegrant (Ac-Di-Sol) and the binder (PVP K-30), each carrying a positive coefficient (X_A = +0.21 min, $p = 0.008$; X_B = +0.39 min, $p = 0.001$), whereas their interaction was not significant ($X_A \cdot X_B$ = −0.06 min, $p = 0.173$). Both factors therefore tended to prolong disintegration across the concentration range studied. PVP K-30 exerted the dominant effect, consistent with its role as a binder that strengthens interparticle bonds and thereby impedes water penetration into the tablet core. The positive coefficient for Ac-Di-Sol may appear counter-intuitive, since croscarmellose sodium is a superdisintegrant expected to accelerate disintegration; however, at the relatively high levels employed here (10–15% w/w, well above the concentration typically used in direct compression), excess croscarmellose sodium can swell into a viscous, coherent hydrated layer that retards further water wicking into the core and consequently prolongs disintegration [47]. The optimal formulation (11.68% Ac-Di-Sol, 2.02% PVP K-30) balanced these opposing influences, achieving a rapid disintegration time (< 90 s) without compromising mechanical strength.

The pharmacological evaluation confirmed that the antidepressant efficacy was retained. In the tail suspension test and the forced swim test—two widely accepted screening models for antidepressant activity—the optimized tablet significantly reduced the despair-like behavior represented by immobility time in mice. Quantitatively, the optimal formulation reduced immobility duration by 28.1% in the tail suspension test and 51.5% in the forced swim test relative to the normal control; these magnitudes were comparable to those of the pure extract (32.7% and 51.5%) and approached those of the fluoxetine positive control (45.7% and 58.2%).

The more pronounced effect observed in the forced swim test suggests a difference in the sensitivity of the two models to the intervention. It should be emphasized that the tablet formulation demonstrated efficacy equivalent to, rather than superior to, that of the pure extract. Accordingly, the principal contribution of the formulation process lies in the retention of efficacy together with improvements in dosing accuracy and ease of administration, rather than in enhanced bioavailability, which was not measured in this study. This distinction is pertinent because ellagic acid is characterized by inherently low oral bioavailability, attributable to its poor aqueous solubility [48], [49]. This finding of retained efficacy nevertheless remains crucial, as it demonstrates that the excipients and the direct-compression process did not interact negatively with, or degrade, the bioactive compounds of the extract.

Although this study did not directly measure biochemical markers, the observed antidepressant activity is consistent with the neuropharmacological properties of the principal secondary metabolites of pomegranate peel extract reported in the literature, particularly ellagic acid and other polyphenols. The pathophysiology of depression is closely associated with neuroinflammation: chronic activation of glial cells triggers the release of pro-inflammatory cytokines that cause neuronal damage and neurotransmitter imbalance [4], [8]. Polyphenols are potent modulators of these pathways.

Various studies have shown that ellagic acid produces antidepressant-like effects through modulation of the serotonergic and adrenergic systems as well as suppression of the neuroinflammatory response [20], [21], [50], [19]. Consistent with this, punicalagin has been reported to restore hippocampal dopamine and serotonin levels in a chronic unpredictable mild stress model [22]. This is consistent with broader evidence that a polyphenol-rich diet is associated with improved mental health and sleep quality [51]. The utility of herbal therapy in managing mood disorders is also supported by a recent review [52]. In addition, understanding of the gut–brain axis has reinforced the notion that dietary components can influence mental health through modulation of the gut microbiota—a pathway of particular relevance given that pomegranate ellagitannins and ellagic acid are metabolized by the colonic microbiota into urolithins [53], [54]—although this specific mechanism was not explored in the present study [55].

Clinical-trial results from previous research further corroborate the findings of this study. Pomegranate peel supplementation has been reported to ameliorate symptoms of depression, anxiety, and stress in patients with non-alcoholic fatty liver disease [56], and ellagic acid exerted positive effects on depressive and anxiety symptoms in a blinded clinical trial [57]. Furthermore, various parts of the pomegranate fruit have been shown to exhibit potent antioxidant activity [58]. These findings support the

rationale for the antidepressant mechanism of pomegranate peel and underscore the potential of *Punica granatum* as a source for nutraceutical development.

3.6. Study Limitation

This study has several limitations that warrant attention when interpreting the test results. First, antidepressant activity was assessed solely through behavioral outcomes (the Tail Suspension Test and the Forced Swim Test), without measurement of oxidative stress markers, proinflammatory cytokines, or neurotransmitter levels. The association of the activity with the antioxidant and anti-neuroinflammatory mechanisms discussed is therefore inferential, based on the literature, and has not been directly demonstrated. Second, the phytochemical characterization was qualitative (TLC), whereas quantitative determination of total phenolic content and of specific marker compounds (e.g., ellagic acid) has not yet been performed. Third, the evaluation was limited to a single dose equivalent to 100 mg/kg body weight and to acute behavioral models. In view of these limitations, recommended further research includes the quantitative determination of marker compounds, dose-response studies, dissolution and pharmacokinetic profile evaluation, and long-term stability studies. Ultimately, the success of the pomegranate peel extract in retaining its efficacy in dispersible tablet form opens opportunities for the development of more accessible herbal preparations, particularly for geriatric and pediatric patients or those experiencing difficulty swallowing.

4. Conclusion

1. The pomegranate peel extract dispersible tablet was successfully formulated and optimized using a 2^2 factorial design, yielding an optimal formulation (11.68% Ac-Di-Sol and 2.02% PVP K-30) with superior physicochemical stability and a rapid disintegration time (87 seconds).
2. The *in vivo* test results confirmed that the optimized tablet formulation was able to retain the antidepressant activity of its parent extract, yielding results equivalent to those of the pure extract and fluoxetine in both the Tail Suspension Test and the Forced Swim Test. These results support the potential of the pomegranate peel extract dispersible tablet as a promising, patient-friendly nutraceutical candidate for the management of depressive disorders.

5. Declarations

5.1 Acknowledgements (Optional)

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5.2 Author contributions

Ivonne Soeliono: Conceptualization, Methodology, Investigation, Validation, Supervision, Writing - original draft, Writing - review & editing, Project administration. Tio Minaritatis Hutauruk: Investigation, Formal analysis, Writing - original draft, Visualization. Martha Ervina: Validation, Supervision. Ida Ayu Made Anom Sri Melia Laksmi: Investigation, Formal analysis, Writing - original draft, Visualization. Nadiatul Janah: Investigation, Formal analysis, Writing - original draft, Visualization. Sela Uswatun Nurul Chasanah: Investigation, Formal analysis, Writing - original draft, Visualization. Eka Pramyrtha Hestianah: Validation, Supervision. Lannie Hadisoewignyo: Conceptualization, Methodology, Resources, Validation, Supervision. All authors have read and agreed to the published version of the manuscript.

5.3 Ethics

Ethical approval for this study was granted by the Health Research Ethics Committee of the Faculty of Medicine, Widya Mandala Surabaya Catholic University, under approval No. 0012/WM12/KEPK/MHS/T/2025 (tail suspension test) and No. 0011/WM12/KEPK/MHS/T/2025 (forced swim test).

5.4 Conflict of Interest

The authors declare no conflict of interest.

5.5 Funding Statement

This research received no external funding.

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Dear Ivonne Soeliono,

Your revised submission, Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation, has been sent for a new round of peer review. You will hear from us with feedback from the reviewers and information about the next steps.

If you have any questions, please contact me from your submission dashboard.

Kind regards,

Muh. Deni Kurniawan

Notifications ×

Your submission has been accepted to Journal of Tropical Pharmacy and Chemistry

2026-07-31 02:23 PM

Dear Ivonne Soeliono,

I am pleased to inform you that we have decided to accept your submission without further revision. After careful review, we found your submission, Development of an Optimized Formula of Pomegranate Peel Extract Dispersible Tablet and Its Antidepressant Evaluation, to meet or exceed our expectations. We are excited to publish your piece in Journal of Tropical Pharmacy and Chemistry and we thank you for choosing our journal as a venue for your work.

Your submission is now forthcoming in a future issue of Journal of Tropical Pharmacy and Chemistry and you are welcome to include it in your list of publications. We recognize the hard work that goes into every successful submission and we want to

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