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*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]**

[1]Fakultas Farmasi, Universitas Katolik Widya Mandala Surabaya, Jalan Raya Kalisari Selatan No. 1, Pakuwon City, Surabaya, Indonesia, 60112
[2] Fakultas Kedokteran Hewan, Universitas Airlangga, Kampus C, Mulyorejo, Surabaya, Indonesia, 60115
*Correspondence email : ivonne-s@ukwms.ac.id

## 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

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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

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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.

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**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

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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.

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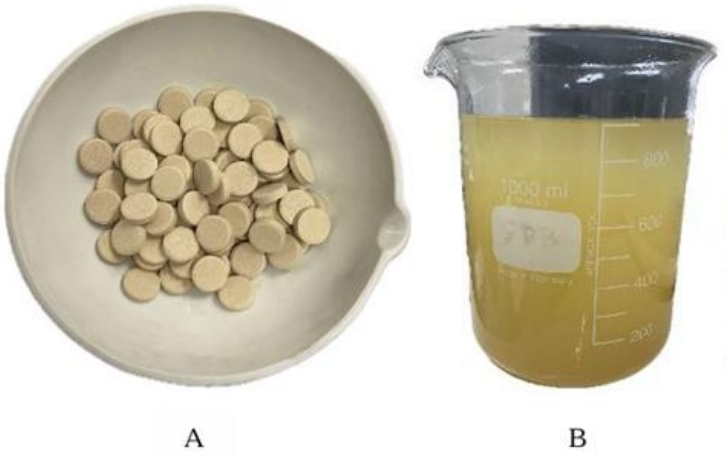


Figure 1. Organoleptic profile of the preparation. (A) Intact dispersible tablet; (B) tablet dispersion in water.

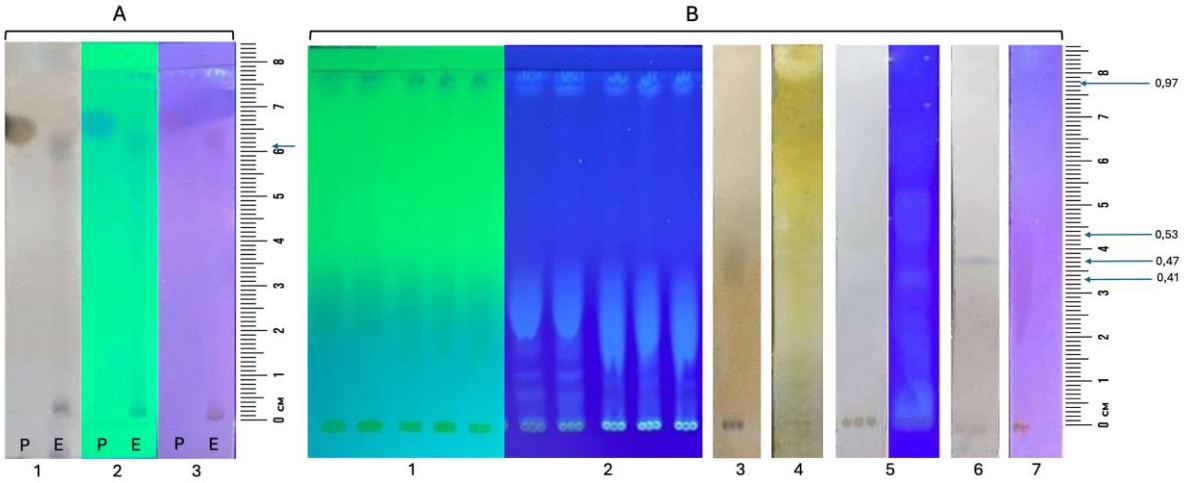


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Figure 2. TLC phytochemical screening profile of the pomegranate peel extract, with an Rf scale (0–1, from the point of application to the solvent front) shown alongside the chromatograms to facilitate localization of the spots discussed in the text. 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 | − | − |

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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.

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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.

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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).

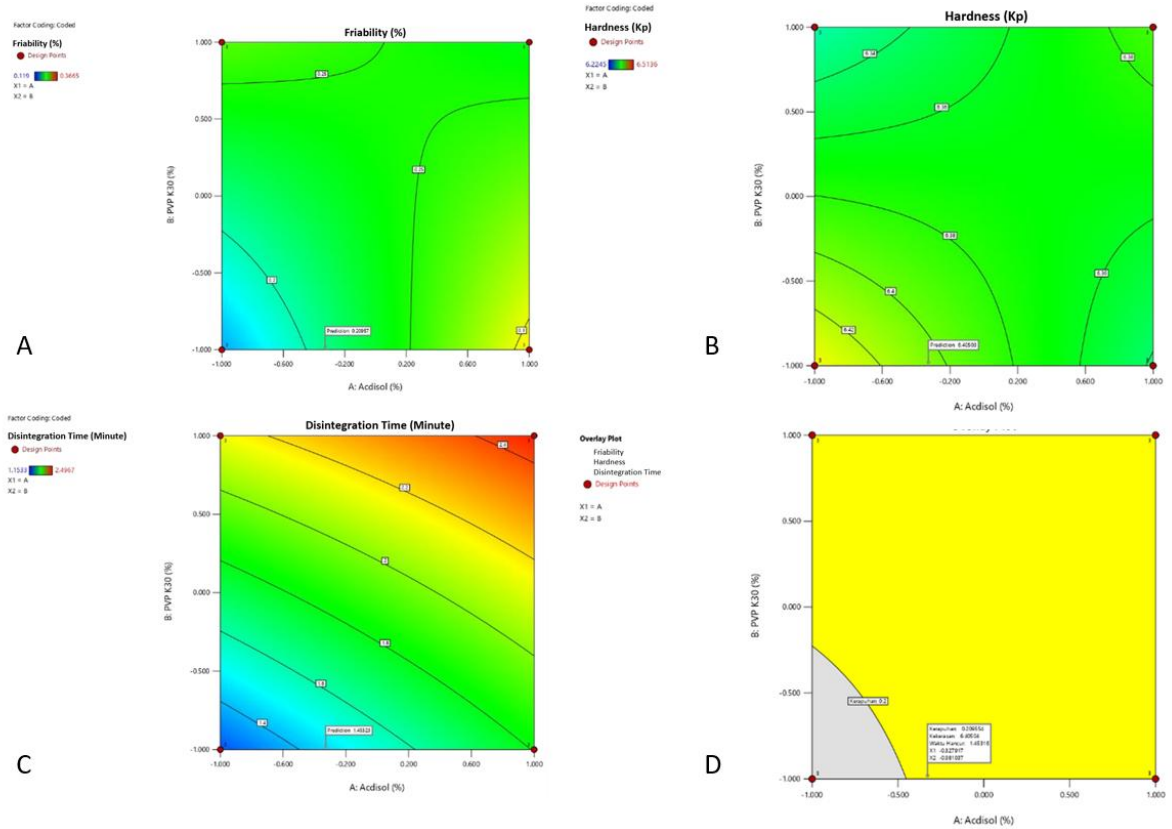


Figure 3. Contour plots of the factorial design analysis depicting the influence of Ac-Di-Sol concentration (%) and PVP K-30 concentration (%) on (A) friability, (B) hardness, and (C) disintegration time. (D) The combined overlay plot displays the optimal formulation region (yellow) satisfying all quality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

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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).

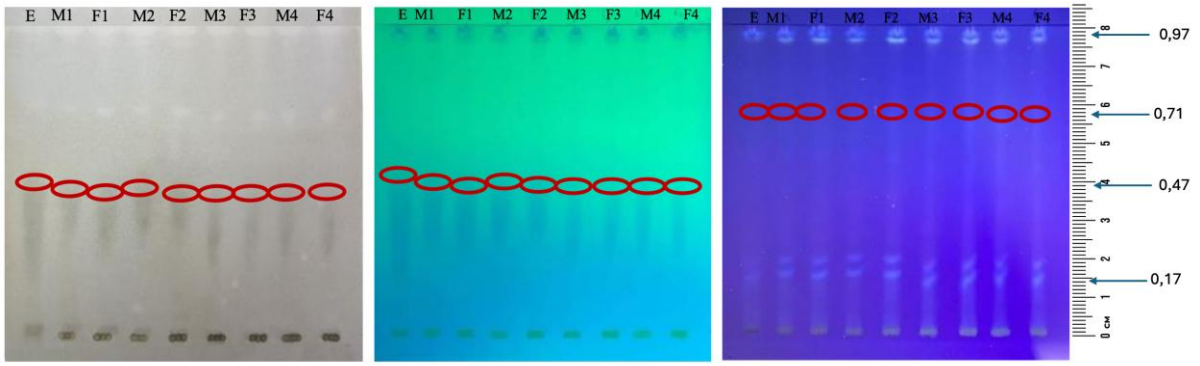


Figure 4. TLC profiles for the stability evaluation of the extract, the tablet compression mass, and the finished tablets, visualized under three detection modes: (1) visible light; (2) UV light at 254 nm; and (3) UV light at 366 nm. Lanes: (E) extract; (M1) compression mass of Formula 1; (F1) tablet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

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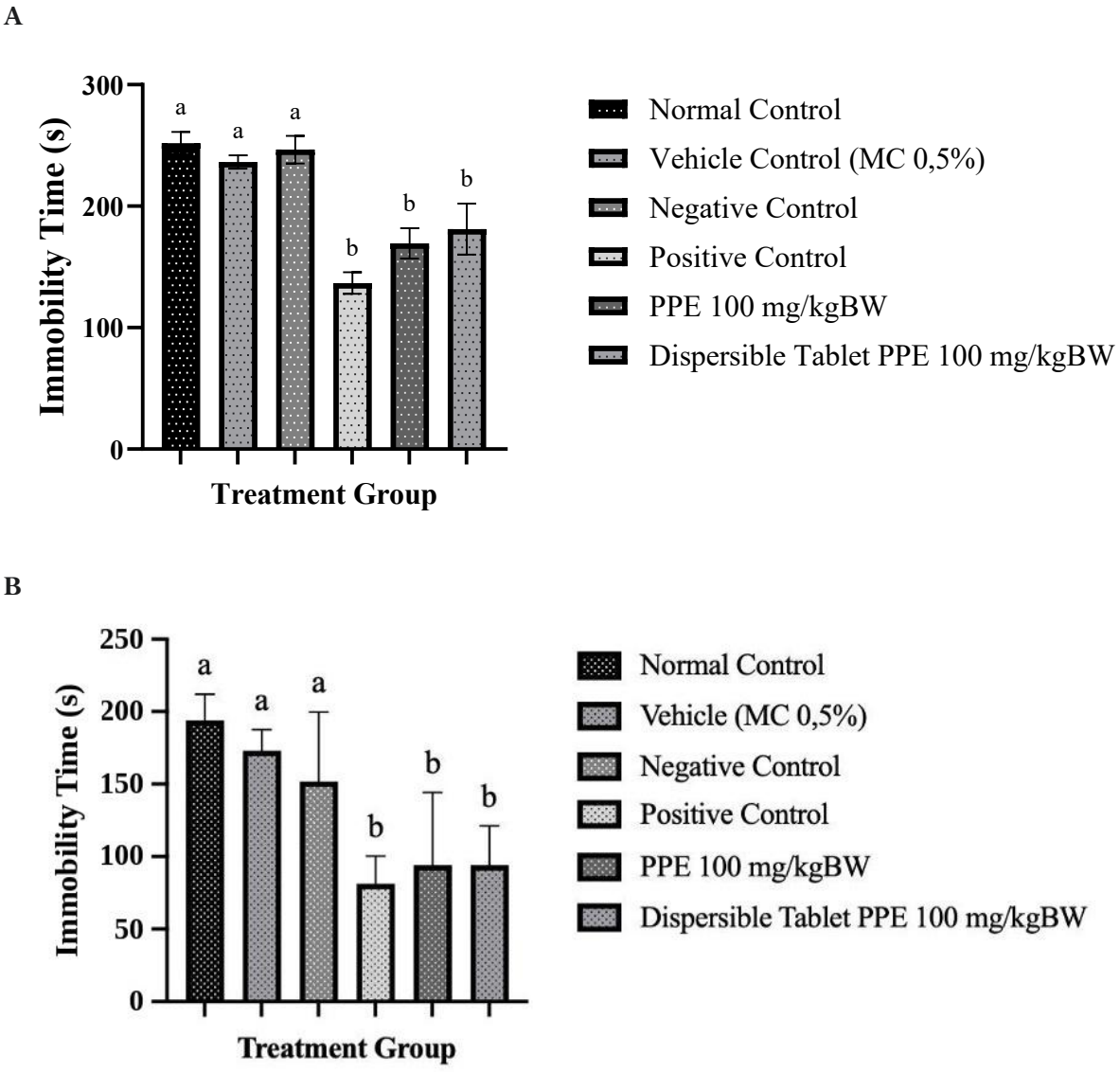


Figure 5. Effect of the pomegranate peel extract and the optimized dispersible tablet formulation on immobility time in mice. (A) Tail Suspension Test. (B) Forced Swim Test. Data are presented as mean ± SEM (n = 6/group). Groups labeled with different letters differ significantly ($p < 0.05$).

### 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

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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].

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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

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). 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

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