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Article

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Phytochemical Profiling and Comparative Evaluation of the Wound Healing Potential of Paederia grandidieri (Drake, 1897) Leaf Extracts in Wistar Rats

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Résumé

La cicatrisation cutanée est un processus biologique complexe impliquant des mécanismes cellulaires et moléculaires étroitement coordonnés. La présente étude visait à évaluer le potentiel cicatrisant de *Paederia grandidieri* (Drake, 1897), une espèce endémique des régions arides de Madagascar, et à comparer son efficacité à celle du médicament de référence, Madecassol 1 %. Le criblage phytochimique a révélé un profil diversifié de métabolites secondaires bioactifs, notamment des polyphénols, des flavonoïdes et des polysaccharides, reconnus pour leurs propriétés antioxydantes, anti-inflammatoires et régénératrices. L'efficacité thérapeutique a été évaluée à l'aide de plaies d'excision standardisées chez des rats Wistar. L'analyse statistique n'a démontré aucune différence significative entre les pommades contenant 10 % et 20 % d'extrait de *P. grandidieri* et Madecassol 1 %, établissant ainsi une équivalence pharmacodynamique définitive. En revanche, la comparaison avec le groupe témoin négatif a révélé un effet dose-dépendant significatif, la formulation à 20 % présentant une significativité statistique plus marquée. La cinétique de cicatrisation a montré une fermeture complète en 11 à 12 jours, soit une réduction d'environ 37 % du temps de cicatrisation total par rapport aux 19 jours nécessaires chez les sujets non traités. De plus, un pic de vitesse de régénération a été observé au 6e jour, correspondant à une phase de prolifération intense. Ces résultats valident scientifiquement l'usage ethnopharmacologique de *P. grandidieri* et soulignent son potentiel en tant qu'agent naturel standardisé pour une réparation tissulaire accélérée.

Keywords:

Paederia grandidieri; cicatrisation des plaies cutanées; phytothérapie; flavonoïdes; polysaccharides; activité biologique.

Abstract

Cutaneous wound healing is a complex biological process involving tightly coordinated cellular and molecular mechanisms. The present study aimed to evaluate the wound healing potential of *Paederia grandidieri* (Drake, 1897), an endemic species from the arid regions of Madagascar, and to compare its efficacy with the reference pharmaceutical, Madecassol 1%. Phytochemical screening revealed a diverse profile of bioactive secondary metabolites, notably polyphenols, flavonoids, and polysaccharides, which are known for their antioxidant, anti-inflammatory, and regenerative properties. The therapeutic efficacy was assessed using standardized excision wounds in Wistar rats. Statistical analysis demonstrated no significant difference between ointments containing 10% and 20% *P. grandidieri* extract and Madecassol 1%, establishing definitive pharmacodynamic equivalence. In contrast, comparison with the negative control group revealed a significant dose-dependent effect, with the 20% formulation exhibiting a more robust statistical significance. Wound healing kinetics documented complete closure within 11 to 12 days, representing an approximate 37% reduction in total healing time compared to the 19 days required for untreated subjects. Furthermore, a peak in regenerative velocity was identified on the 6th day, corresponding to an intensified proliferative phase. These findings provide a robust scientific validation for the ethnopharmacological use of *P. grandidieri* and highlight its potential as a standardized natural agent for accelerated tissue repair.

Keywords:

Paederia grandidieri; cutaneous wound healing; phytotherapy; flavonoids; polysaccharides ; biological activity.

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1. Introduction

Cutaneous wound healing is a highly organized biological process based on complex interactions between skin cells, chemical mediators, and the extracellular matrix, ultimately restoring tissue integrity after injury (Gurtner *et al.*, 2008). This dynamic process is regulated by cellular and molecular signaling pathways that control immune cell activation, extracellular matrix synthesis, and cell migration required for tissue repair (Singer & Clark, 1999). Conventionally, wound healing progresses through four interdependent phases—hemostasis, inflammation, proliferation, and remodeling—requiring close coordination between resident cells, growth factors, and cytokines (Velnar *et al.*, 2009).

Conventional topical treatments aim to control inflammation, prevent infection, and promote tissue regeneration (Boateng *et al.*, 2008). However, their cost, limited accessibility, and potential adverse effects may restrict long-term use, particularly in low-resource settings, thereby increasing interest in natural therapeutic alternatives (Randrianarivony *et al.*, 2017; Nayak *et al.*, 2006). In this context, medicinal plants rich in secondary metabolites such as flavonoids, polyphenols, and tannins have demonstrated antioxidant and anti-inflammatory properties that can positively influence the different phases of wound healing (Shedoeva *et al.*, 2019).

Paederia grandidieri, an endemic plant from southern Madagascar belonging to the Rubiaceae family, is traditionally used by local populations for therapeutic purposes (Randriamampionona *et al.*, 2007). The *Paederia* genus is known for its richness in bioactive compounds, particularly flavonoids and iridoids, which are associated with various biological activities involved in tissue repair (Soni *et al.*, 2013). Nevertheless, despite its widespread traditional use, experimental data scientifically validating its wound healing activity remain limited (Beaujard *et al.*, 1990). Therefore, the present study aimed to evaluate the wound healing activity of *P. grandidieri* extract using an experimental Wistar rat model, in comparison with Madecassol **1%**, a reference treatment derived from *Centella asiatica* (Widgerow *et al.*, 2000), based on wound closure kinetics and rigorous statistical analysis (Morton & Malone, 1972).

2. Materials and Methods

2.1. Geographical distribution and botanical context

Paederia grandidieri (Rubiaceae) is an endemic species strictly confined to the arid and semi-arid biomes of southern and southwestern Madagascar. Its primary habitats include xerophilous thickets and dry deciduous forests, while it remains virtually absent from the humid eastern slopes and the central highlands (Rasoariseheno *et al.*, 2024 ; Ethnopharmacologia, 2017). The discontinuous distribution of the species, which includes isolated northern populations, indicates a high degree of edaphic and climatic specialization, governed predominantly by annual humidity gradients (Nie *et al.*, 2013). Due to these specific requirements, *P. grandidieri* serves as a reliable biological indicator of ecological transitions between subarid shrublands and western Malagasy savanna-like forests (Masters *et al.*, in press)

Figure 1 **:** Distribution map of *Paederia grandidieri*
Source : Https://geocat.iucnredlist.org

The spatial analysis presented in **Figure 1** illustrates a fragmented distribution of *Paederia grandidieri*, primarily concentrated within the arid biomes of southwestern Madagascar. This discontinuous pattern underscores a strict edaphic specialization, positioning the species as a key biological indicator of ecological transitions between xerophilous thickets and dry deciduous forests.

2.2. Experimental animals and ethical considerations

The *in vivo* phase of this investigation was conducted using clinically healthy Wistar rats, aged approximately three months, with a body mass ranging from 150 to 200 g. To ensure physiological stability and minimize stress-induced variables, the animals were acclimated within a controlled laboratory environment characterized by regulated

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temperature and humidity levels. A synchronized 12-hour light/dark cycle was maintained, and the subjects were provided with *ad libitum* access to a standardized diet and water. All experimental protocols were executed in strict compliance with international benchmarks for animal research and laboratory animal welfare, specifically adhering to the standards set by Waynforth & Flecknell (1992), the National Research Council (2011), and the Percie du Sert *et al.* (2020).

2.3. Surgical procedure and wound induction

To ensure humane handling and procedural precision, general anesthesia was induced via halothane inhalation within a semi-open circuit. The depth of the anesthetic plane was rigorously monitored and confirmed by the total loss of the righting reflex and a complete lack of nociceptive response to mechanical stimuli (Gaudy *et al.*, 1994 ; Flecknell, 2016). Once an adequate level of surgical anesthesia was reached, the dorsal region of each subject was prepared by meticulous shaving and antisepsis using 70% ethanol. Two standardized, circular, full-thickness excision wounds—each 10 mm in diameter—were surgically created using a sterile scalpel blade to expose the underlying tissue (Flecknell, 2016 ; Turner & Brabb, 2019). Following the excision, the wounds were cleansed with distilled water, and the initial bleeding time was recorded to evaluate the efficiency of the hemostatic phase (Singh *et al.*, 2020).

2.4. Experimental design and therapeutic modalities

The animal subjects were randomly allocated into four distinct experimental cohorts to evaluate the therapeutic efficacy of the botanical extract. The negative control group received topical applications of pure petroleum jelly, while the positive control group was treated with Madecassol 1%, a standard reference pharmaceutical. The two remaining test groups were treated with ointments containing 10% and 20% *Paederia grandidieri* extract, respectively. These experimental ointments were formulated by incorporating the plant extract into a petroleum jelly base until a homogeneous mixture was achieved. The resulting preparations were stored in airtight, light-resistant containers at ambient temperature to maintain phytochemical stability (Djoko *et al.*, 2019; Nayak *et al.*, 2019).

Treatments were administered topically on a daily basis without occlusive dressings until total wound closure was achieved. The progression of tissue repair was monitored via macroscopic clinical observation and precise planimetric measurements of the wound surface area using transparent tracing sheets transferred onto graph paper. This methodology represents a validated and reproducible standard for the assessment of wound contraction dynamics (Kumar *et al.*, 2018 ; Nayak *et al.*, 2019). The healing rate was subsequently derived from the successive reduction in wound dimensions, facilitating a rigorous quantitative comparison of treatment efficacy (Singh *et al.*, 2020).

2.5. Statistical analysis

Statistical processing of the data was conducted using RStudio software (version 4.4.2). Descriptive results are reported as the mean ± standard error of the mean (SEM). The distributional normality of the data was verified using the Shapiro-Wilk test. In instances where the data did not meet the assumptions of normality, intergroup variances and comparative significance were determined using Welch's Student's t-test. The threshold for statistical significance was predefined at $p < 0.05$ (Kumar *et al.*, 2007 ; Singh *et al.*, 2020).

3. Results

3.1. Phytochemical screening and biochemical rationale

The preliminary phytochemical investigation of the *Paederia grandidieri* extract yielded an extraction rate of 7%. Qualitative analysis revealed a diverse profile of bioactive secondary metabolites, notably characterized by an abundance of phenolic compounds and structural polysaccharides. As detailed in **Table 1**, the screening confirmed high concentrations (+++) of flavonoids, leucoanthocyanins, anthocyanins, steroids, polyphenols, and polysaccharides. Alkaloids were present in moderate amounts (++), while unsaturated sterols showed a lower relative presence (+). Conversely, cyanogenic glycosides, terpenes, saponins, tannins, and coumarins were not detected (–).

Table 1. Qualitative phytochemical profile of *Paederia grandidieri* extract.

Phytochemical compound	Qualitative results
Alkaloids	++
Polysaccharides	+++
Cyanogenic glycosides	–
Flavonoids	+++ (FF)
Leucoanthocyanins	+++
Anthocyanins	+++

Unsaturated sterols	+
Steroids	+++
Terpenes	–
Saponins	–
Tannins	–
Polyphenols	+++
Coumarins	–

Note : (+) : low presence; (++) : moderate presence; (+++) : abundant presence; (–) : absence

The significant wound healing activity observed in this study may be fundamentally attributed to the synergistic action of the identified metabolites, particularly the polyphenols, flavonoids, and polysaccharides. Flavonoids are well-documented for their ability to modulate the inflammatory response by scavenging reactive oxygen species at the injury site, thereby mitigating oxidative stress and establishing a microenvironment conducive to cellular regeneration (Nayak *et al.*, 2019).

Furthermore, the presence of polysaccharides is of particular interest, as these macromolecules are known to stimulate the migration and proliferation of fibroblasts, which are essential for the synthesis of Type I and III collagen and the subsequent reconstruction of the extracellular matrix (Kumar *et al.*, 2018). The high concentration of these bioactive constituents in the *P. grandidieri* extract provides a robust biochemical rationale for its traditional use and the accelerated tissue repair dynamics observed in the experimental models.

3.2. Statistical analysis of healing efficacy

Comparative analysis between the *P. grandidieri* formulations and the reference product revealed no statistically significant differences between the tested concentrations (10% and 20%) and Madecassol 1% ($p > 0.05$), thereby establishing a definitive pharmacodynamic equivalence (Singh *et al.*, 2020). Both dosages achieved a level of performance statistically equivalent to the conventional reference treatment, reinforcing their therapeutic potential.

In contrast, comparison with the negative control group demonstrated significant differences for both concentrations, with a more pronounced clinical effect observed in the 20% formulation. The *p*-value associated with the 20% dose ($p = 0.01406$) was notably lower than that of the 10% dose ($p = 0.03174$), indicating a more robust and consistent acceleration of tissue repair relative to untreated wounds. These findings suggest that the 20% formulation optimizes the wound healing process more effectively than the lower concentration (Kumar *et al.*, 2007).

3.3. Wound healing kinetics and closure dynamics

The progression of tissue repair was rigorously monitored to evaluate the efficacy of the botanical formulations. The following data delineate the reduction in wound dimensions over a nineteen-day period, highlighting the accelerated regenerative capacity induced by the phytochemical constituents of the plant extract compared to conventional and negative control groups.

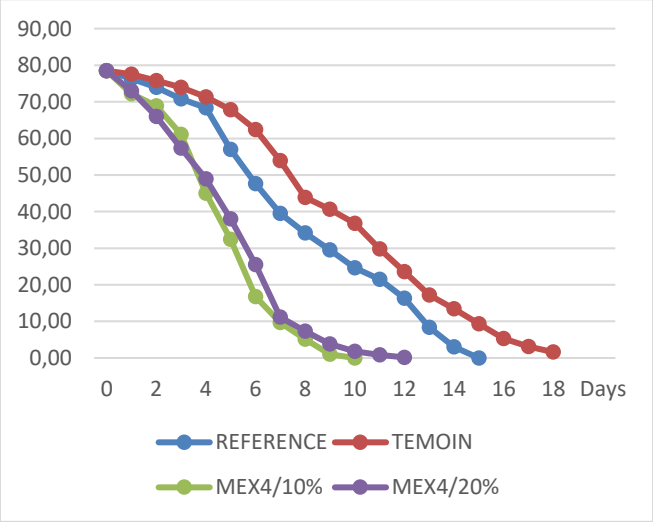

Figure 2 : Comparative evolution of wound surface area reduction for 10% and 20% *Paederia grandidieri* ointments

The longitudinal analysis in **Figure 2** demonstrates that both concentrations of *P. grandidieri* significantly outperformed the control cohorts. The 20% and 10% formulations facilitated complete epithelialization by days 12 and 11, respectively, effectively shortening the recovery period by seven days relative to the negative control and surpassing the reference drug.

The velocity of the healing process provides critical insight into the biological transition between the inflammatory and proliferative phases. By quantifying the daily rate of tissue contraction, it becomes possible to identify the specific intervals during which the extract exerts its most potent regenerative influence on the wounded dermal layers.

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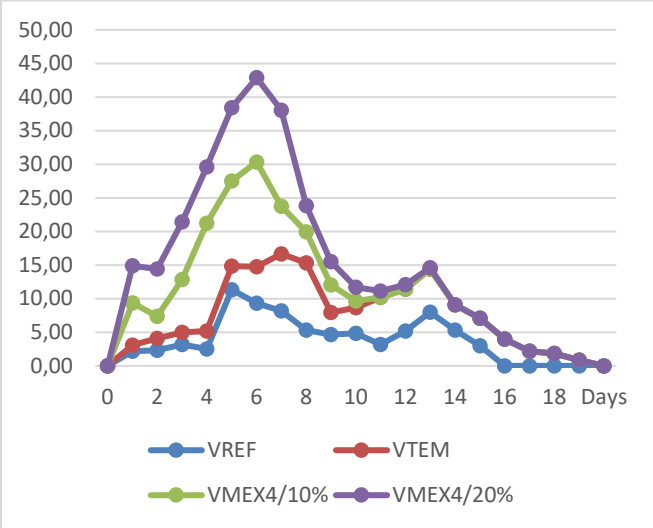

Figur 3 : Kinetic velocity curves of the cicatrization process induced by 10% and 20% *Paederia grandidieri* extracts

The kinetic profile in **Figure 3** reveals that the 20% concentration elicited an early and robust peak in biological activity, particularly during the proliferative phase on day 6. This formulation maintained a superior healing velocity from the onset, outperforming the negative control fivefold and ensuring rapid, high-quality tissue reconstruction.

3.4. Phytochemical synergy and bioactive mechanisms

The potent wound healing activity exhibited by the *Paederia grandidieri* extract is fundamentally attributable to its complex profile of bioactive secondary metabolites. Phytochemical screening identified a high prevalence of polyphenols, flavonoids, and polysaccharides, which appear to exert synergistic and pleiotropic effects across the various stages of tissue repair (Nayak *et al.*, 2019).

Specifically, flavonoids serve as critical modulators of the inflammatory response by scavenging reactive oxygen species (ROS) at the injury site. This reduction in oxidative stress mitigates secondary tissue damage and fosters a biochemical microenvironment conducive to cellular regeneration. Concurrently, the identified polysaccharides act as molecular scaffolds that stimulate fibroblast migration and proliferation. These macromolecules enhance the synthesis of Type I and III collagen, thereby facilitating the reconstruction of the extracellular matrix—a process essential for the restoration of tensile strength and skin integrity (Kumar *et al.*, 2018).

3.5. Comparative pharmacodynamic equivalence

Statistical evaluation utilizing Welch's t-test demonstrated that the therapeutic outcomes of both the 10% and 20% *P. grandidieri* formulations were not significantly different from those of Madecassol 1% ($p > 0.05$). This indicates a definitive pharmacodynamic equivalence between the botanical extract and the conventional reference pharmaceutical (Singh *et al.*, 2020). Such equivalence underscores the significant phytotherapeutic potential of *P. grandidieri* as a viable candidate for the development of standardized topical healing agents, offering an efficacious alternative to synthetic treatments (Djoko *et al.*, 2019).

3.6. Dose-dependent efficacy and healing acceleration

When compared to the negative control cohort, both experimental concentrations significantly accelerated the wound repair process, with the most robust results observed at the 20% dosage. The lower *p*-value associated with this concentration ($p = 0.01406$) suggests a favorable dose-dependent response. This is further validated by the wound closure kinetics, which documented complete cicatrization within 12 days, in stark contrast to the 19 days required for untreated subjects. This represents an approximate 37% reduction in total recovery time, highlighting the extract's ability to minimize the duration of tissue exposure and the associated risk of infection (Kumar *et al.*, 2007).

3.7. Analysis of kinetic and phase transition

The analysis of wound healing velocity curves revealed a pronounced peak in metabolic and regenerative activity on day 6 for the 20% concentration. This timing corresponds precisely with the granulation and fibroplasia phase, characterized by intense angiogenesis, heightened fibroblast density, and progressive connective tissue organization (Singh *et al.*, 2020).

Furthermore, the immediate increase in healing velocity observed from the first day of treatment suggests that the bioactive constituents of *P. grandidieri* modulate the early inflammatory phase. By facilitating a rapid transition from inflammation to the proliferative phase, the extract ensures a more efficient and functional restoration of the dermal architecture (Flecknell, 2016). This therapeutic acceleration confirms the potential of *P. grandidieri* as a viable candidate

for the development of standardized topical healing agents (Djoko *et al.*, 2019).

4. Conclusion

The present study systematically evaluated the wound healing potential of *Paederia grandidieri* (Drake, 1897) leaf extract, an endemic species inhabiting the dry and arid biomes of Madagascar. The findings provide a robust scientific validation for the traditional use of this plant in dermatological care, highlighting its efficacy as a potent natural regenerative agent. Phytochemical investigations revealed a sophisticated biochemical profile characterized by a high prevalence of polyphenols, flavonoids, and polysaccharides. These bioactive metabolites act in a synergistic and pleiotropic manner to modulate the microenvironment of the injury site, thereby optimizing the transition between the distinct phases of tissue repair.

The primary highlights of this research are demonstrated through a series of significant quantitative outcomes. Statistical analysis established a definitive pharmacodynamic equivalence between the topical formulations containing 10% and 20% of *P. grandidieri* extract and the standard reference pharmaceutical, Madecassol 1%. The absence of statistically significant differences ($p > 0.05$) between these groups confirms that the botanical extract provides a therapeutic performance comparable to conventional synthetic treatments.

Furthermore, the application of the experimental ointments facilitated complete wound closure within a period of 11 to 12 days, whereas the negative control group required 19 days for total epithelialization. This performance represents a substantial 37% reduction in the overall healing duration, which is a critical factor in minimizing tissue exposure and mitigating the risk of secondary infections. Finally, kinetic analysis indicated a rapid onset of regenerative activity immediately following the first day of treatment. The 20% formulation, in particular, elicited a pronounced metabolic peak on the 6th day, corresponding to an intensified proliferative phase involving active angiogenesis and structured collagen deposition.

P. grandidieri emerges as a highly promising candidate for the development of standardized phytotherapeutic agents. Its ability to accelerate functional dermal restoration while maintaining a level of efficacy equivalent to gold-standard treatments marks a significant advancement in the valorization of Malagasy biodiversity for global pharmaceutical and dermatological applications.

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