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Formulation and In Vitro Evaluation of Fig Leaf (*Ficus carica* L.) Ethyl Acetate Extract Transdermal Patch as a Candidate for Wound Healing Application

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ABSTRACT

Wound healing can be enhanced through both non-pharmacological and pharmacological approaches. Non-pharmacological methods include proper wound cleaning and dressing, while pharmacological strategies utilize antiseptics and synthetic antibiotics to prevent infection. Recently, natural compounds such as Ficus carica L. leaves, rich in flavonoids, have gained attention for their wound-healing potential. Flavonoids play a crucial role in accelerating wound contraction, enhancing collagen deposition, and promoting granulation tissue formation. This study aimed to formulate and evaluate a wound-healing patch incorporating the ethyl acetate extract of Ficus carica L. leaves, obtained via multistep maceration. The total flavonoid content (TFC) of the extract was 89.299 ± 0.14 mgQE/g. The patch was developed using the solvent casting method with HPMC K100M as the polymer matrix and propylene glycol as a plasticizer. The optimized formulation, containing 5.6% ethyl acetate extract (equivalent to 50 mg quercetin), met key evaluation criteria, exhibiting a uniform structure without wrinkling, a thickness of 1.0 ± 0.2 mm, a pH of 5, and a folding endurance of >200 cycles. In vitro permeation studies demonstrated effective active compound penetration, with a cumulative quercetin permeation of 21.76% within 180 minutes. The flux profile revealed an initial burst release followed by a transition toward controlled diffusion behavior, which is characteristic of HPMC-based monolithic matrices.

Keywords: Ficus carica; Wound healing; Quercetin content; Patch formulation; HPMC; Franz diffusion

INTRODUCTION

Wound healing is a complex biological process that involves cellular components, signaling molecules, mechanical factors, and structural scaffolding. These elements must work together to restore tissue integrity and prevent infections [1]. The skin, as the body's largest organ, acts as a protective barrier against external threats while also regulating temperature and immune responses. Structurally, the skin consists of three layers: the epidermis, dermis, and subcutaneous adipose tissue, each playing a role in wound healing [2,3]. When an injury occurs, the body activates a series of biological mechanisms to repair the damaged tissue. The wound healing process consists of several phases: hemostasis, inflammation, proliferation, epithelialization, and remodeling. Hemostasis occurs first, stopping bleeding through vasoconstriction, platelet aggregation, and fibrin clot formation [4]. The inflammatory phase follows, where neutrophils and macrophages work to clear pathogens and cellular debris. In the proliferation phase, fibroblasts, keratinocytes, and endothelial cells stimulate tissue regeneration and angiogenesis. The final remodeling phase strengthens newly formed tissue, ensuring the wound regains its structural and functional integrity [5].

Proper wound care is crucial to accelerate healing and prevent complications such as infections or chronic wounds. Treatment can be divided into non-pharmacological methods, including wound cleaning and dressing, and pharmacological approaches, such as using antiseptics and synthetic antibiotics [6]. While synthetic drugs are widely used, they may cause side effects like antibiotic resistance, skin irritation, and delayed healing. Therefore, researchers have explored natural bioactive compounds as alternative wound therapies [7]. Flavonoids, saponins, and tannins are natural compounds known for their antioxidant, anti-inflammatory, and tissue-regenerating properties. Flavonoids help accelerate wound contraction, collagen synthesis, and granulation tissue formation [8]. Saponins enhance fibroblast activation and extracellular matrix production, which are crucial for wound closure. Tannins provide astringent properties, reducing bleeding and preventing microbial infections. The combination of these bioactive compounds presents a promising alternative to conventional wound treatments [9,10]. Natural-based therapies may offer safer, more effective, and eco-friendly wound management solutions.

Fig leaves (*Ficus carica* L.) have been widely recognized for their medicinal properties, particularly in wound healing applications. The leaves contain high concentrations of flavonoids, saponins, tannins, and phenolic compounds that contribute to tissue regeneration and immune modulation [11,12]. One of the key flavonoids found in fig leaves, quercetin, plays an important role in reducing oxidative stress, enhancing epithelialization, and stimulating fibroblast activity. Several studies have demonstrated that fig leaf extract can increase macrophage

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proliferation, which enhances immune response and tissue recovery. The application of fig leaf extract in wound care has shown positive effects, including accelerated wound contraction, improved collagen deposition, and faster epithelialization [13]. Previous studies have incorporated fig leaf extract into ointment formulations, which significantly enhanced wound healing compared to untreated wounds. The mechanisms involved include antioxidant activity, inflammatory modulation, and extracellular matrix stabilization [14]. Due to these properties, fig leaf extract is a potential candidate for modern wound-care formulations. Developing innovative wound-healing therapies from natural ingredients can provide effective and sustainable solutions for various types of wounds.

This study focuses on extracting *Ficus carica* L. leaves using the maceration method with ethyl acetate as the solvent. Ethyl acetate was selected due to its moderate polarity and its reported effectiveness in extracting flavonoid compound from *Ficus carica* L. leaves, as reported by Li et al., who demonstrated that the ethyl acetate extract exhibited the highest flavonoid content (83.92 ± 0.01 mg/g) [15]. The extracted compounds are then formulated into a patch-based wound dressing using HPMC. The patch system is known to provide controlled drug release, maintain drug contact with the skin for a longer period of time, and is non-invasive. In addition, the use of hydrophilic polymers in the patch system can help maintain the moisture of the wound environment, allow permeability to water and oxygen, and protect the wound from bacterial contamination, thus supporting the wound healing process (Saghazadeh, won fen wong 17 dan 41)

Although Ficus carica L. leaf extract has been extensively studied for its wound healing activity, research on the formulation of this extract into a transdermal patch system and the evaluation of its physicochemical characteristics and permeation profile remains limited. Therefore, this study aimed to: (1) formulate a wound healing patch containing ethyl acetate extract of Ficus carica L. leaves, (2) evaluate the physicochemical properties of the patch, and (3) assess the permeation profile of quercetin using a Franz diffusion cell assay. This research is expected to contribute to the development of more practical, effective, and environmentally friendly natural-based wound healing therapies. The bioactive patch formulation based on Ficus carica L. leaf extract has the potential to be an alternative drug delivery system to increase the effectiveness of wound healing therapies while supporting the development of biocompatible and sustainable wound care products. The results of this study are expected to contribute to the development of more practical, effective, and environmentally friendly natural-based wound healing therapies. The bioactive patch formulation based on Ficus carica L. leaf extract has the potential to be an alternative drug delivery system to increase the effectiveness of wound healing therapies while supporting the development of biocompatible and sustainable wound care products [16,17].

MATERIALS AND METHODS

Fig Leaves Collection

The plant used in this study was fig (*Ficus carica* L.), which was obtained from the Ciwidey Fig Plantation, Bandung, West Java, Indonesia. The selection of this plant was based on its known phytochemical content, particularly flavonoids, which have been widely studied for their pharmacological potential. To ensure the accuracy of plant identification, the sample was authenticated at the Herbarium Bandungense, School of Life Sciences and Technology, Bandung Institute of Technology, Indonesia. The authentication process involved morphological examination and comparison with existing herbarium specimens to confirm the species identity. The verification was documented under certificate number 851/IT1.C11.2/TA.00/2022, ensuring that the plant used in this study was correctly identified.

Extraction of Fig Leaves

A total of 1.2 kg of dried fig leaves was extracted using a multistep maceration method with three different solvents: n-hexane, ethyl acetate, and 70% ethanol, at a 1:3 solvent-to-sample ratio. Before the extraction process, all equipment and materials were prepared and cleaned to prevent contamination. The dried leaves were then placed into a clean macerator, where they were soaked in each solvent sequentially for 48 hours with occasional stirring to enhance compound dissolution. After maceration, the mixture was filtered to separate the liquid extract from the solid residue, ensuring the complete recovery of soluble compounds. The resulting macerate was concentrated using a rotary vacuum evaporator at controlled temperatures of 37°C for n-hexane, 40°C for ethyl acetate, and 70°C for ethanol, followed by further evaporation in a water bath to remove residual solvents, producing a thick extract. Only the ethyl acetate extract was selected for further analysis in this study due to its high flavonoid content, as suggested by previous research [18].

Determination of Total Flavonoid Content

The total flavonoid content (TFC) of the fig leaf extract was determined using the differential spectrophotometry method, which relies on the formation of a complex between flavonoids and aluminum chloride ($AlCl_3$). To establish a standard curve, quercetin was used as the reference compound at concentrations of 4, 7, 10, 13, and 16 µg/mL, dissolved in ethanol. The results were expressed as milligrams of quercetin equivalents per gram of extract (mgQE/gE), providing a quantitative measure of flavonoid content. For sample

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preparation, 25 mg of the ethyl acetate extract was dissolved in a volumetric flask and diluted to a final volume of 25 mL with ethanol to ensure uniform distribution. Subsequently, 1 mL of the test solution was pipetted and further diluted with absolute ethanol to reach a total volume of 10 mL before adding 1 mL of 2% $AlCl_3$ and 1 mL of 120 mM potassium acetate. The prepared solution was then incubated at room temperature for 30 minutes to allow optimal complex formation between flavonoids and $AlCl_3$, which enhances absorbance at a specific wavelength. This incubation period is crucial to ensure complete reaction and stability of the complex, preventing variability in absorbance readings. Following incubation, the absorbance of the resulting solution was measured using a UV-Vis spectrophotometer at 432.5 nm, which corresponds to the maximum absorption wavelength of quercetin. The recorded absorbance values were then used to determine the flavonoid content of the extract based on the standard calibration curve [19].

Optimization of Patch Base

The optimization of the patch base was conducted prior to incorporating the ethyl acetate extract of fig leaves. This process aimed to determine the most suitable patch base formula by evaluating key parameters, including mechanical strength, folding endurance, and pH stability. The optimization was achieved by varying the concentration of propylene glycol, which functions as a plasticizer to improve the flexibility and mechanical properties of the patch. A higher concentration of propylene glycol is expected to enhance the patch's elasticity, while an optimal balance must be maintained to prevent excessive softness or fragility. The final optimized patch base formula is presented in **Table 1**, illustrating three different formulations (F1, F2, and F3) with varying propylene glycol concentrations to identify the best composition.

Table 1. Optimized patch base formula.

Ingredients	F1 (%)	F2 (%)	F3 (%)
HPMC K100M	8.0	8.0	8.0
Propylene glycol	3.0	6.0	9.0
Ethanol 96%	40.0	40.0	40.0
Distilled water	ad 100.0	ad 100.0	ad 100.0

Formulation of Ethyl Acetate Fig Leaf Extract Patch

The optimized patch base formula was then utilized for the formulation of a transdermal patch containing the ethyl acetate extract of fig leaves. The amount of extract incorporated into the patch was determined based on its total flavonoid content, expressed as quercetin equivalents. The ethyl acetate extract of fig leaves was used at a concentration of 5.6%, calculated from the flavonoid content analysis. Quercetin, the dominant flavonoid in fig leaves, is well known for its wound-healing properties, making it a promising active compound for patch formulations targeting skin regeneration. Analytical testing confirmed that the quercetin content in the fig leaf ethyl acetate extract was 89.266 ± 0.14 mgQE/g extract. At the selected concentration of 5.6%, this translates to 50 mg of quercetin per 10 grams of the patch formulation, ensuring effective therapeutic delivery. Previous research suggests that quercetin-3-rhamnopyranosyl-(1-6) glucopyranoside (QRPG), a quercetin derivative, demonstrates significant wound-healing activity at a concentration of 0.5%, promoting wound contraction up to 98.2%. Furthermore, epithelialization was observed within 18 days, indicating accelerated tissue regeneration. These findings support the incorporation of quercetin-rich fig leaf extract in transdermal patch formulations as a potential wound-healing agent [20].

Table 2. The formula of the fig leaf extract patch (F2A).

Ingredients	%	Amount in 10 g
Ethyl acetate extract of fig leaf	5.6	0.56 g
HPMC K 100 M	8.0	0.8 g
Propylene glycol	6.0	0.6 g
Ethanol	40.0	4.0 g
Aquadest ad	100.0	10.0 g

The patch preparation process involved several key steps to ensure uniformity and stability. Initially, HPMC K100M was dissolved in aquadest under continuous stirring at 300 rpm using a magnetic stirrer, forming Mixture 1. In a separate container, the ethyl acetate fig leaf extract was dissolved in ethanol to create Mixture 2. Both mixtures were then combined and stirred until a homogeneous blend was achieved. Propylene glycol, the plasticizer, was added to the combined solution and stirred again to ensure uniform dispersion of all components.. The resulting formulation was left to stand for 24 hours under airtight conditions, covered with plastic wrap to prevent solvent evaporation. After the incubation period, the mixture was poured into a 10 × 10 cm mould and

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dried in an oven at 50°C for 18 hours to form the final patch film. Once completely dried, the patch film was carefully peeled from the mould and cut into 4 × 4 cm pieces. Each patch was then coated with a Tegaderm backing layer, which provides support and enhances adherence to the skin. The final composition of the fig leaf extract patch (F2A) is presented in **Table 2**. This optimized patch formulation is designed to ensure controlled release of flavonoids, particularly quercetin, while maintaining desirable mechanical properties for transdermal applications. The incorporation of HPMC K100M provides a stable matrix for drug dispersion, while propylene glycol enhances flexibility. The ethanol content facilitates the solubility of active compounds, while aquadest ensures adequate hydration during the preparation process.

Evaluation of Patch Base and Ethyl Acetate Fig Leaf Extract Patch Formulation

Organoleptic Test

The organoleptic evaluation of the patch was conducted by assessing its physical characteristics, including shape, color, and odor. The patch should exhibit a uniform shape, free from deformities such as shrinkage or uneven textures. Color consistency is essential to ensure proper formulation stability, and any discoloration may indicate potential degradation of the active compounds. The odor should be mild and characteristic of the formulation ingredients, without any signs of rancidity or undesirable smells that might indicate contamination. The patch should maintain these characteristics throughout the storage period to ensure product acceptability and stability [21].

Elongation Break and Tensile Strength

The elongation break and tensile strength of the patch were analyzed using an Autograph machine to determine the mechanical properties of the formulation. The test began with mounting the patch sample onto the machine grips, ensuring a secure hold. The machine applied a controlled tensile force while continuously recording real-time elongation and the applied force until the patch ruptured. The elongation break was calculated as the percentage increase in the patch's length relative to its original size, indicating its flexibility. Meanwhile, tensile strength was determined as the maximum force the patch could withstand before breaking, reflecting its structural integrity. These parameters are crucial to ensuring that the patch is both flexible for skin application and strong enough to resist tearing under normal usage conditions [22].

Folding Endurance Test

The folding endurance test was conducted to evaluate the patch's resistance to repeated flexing. This test involved manually folding and unfolding the patch until it broke to determine its durability. A patch formulation with high folding endurance indicates good mechanical properties, preventing breakage during handling or application. For transdermal patches, a folding endurance of more than 200 folds is considered acceptable, ensuring long-term usability and resistance to mechanical stress [23].

Thickness Test

The thickness of the patch was measured to ensure uniformity across different samples. The measurement was performed using a digital caliper at three different points on each patch, and the average thickness was calculated. A well-formulated patch should have a thickness not exceeding 1 mm, as excessive thickness may hinder flexibility and affect drug release. Maintaining consistent thickness ensures reproducibility in drug content and mechanical properties, which are essential for effective transdermal delivery [23].

pH Test

The pH test was conducted to determine whether the patch formulation was compatible with skin pH levels. The patch was dissolved in 5 mL of distilled water and left to stand for two hours to allow for equilibrium. The pH was then measured using a universal pH indicator to ensure that the formulation remained within the typical pH range for topical applications (4–8). A pH within this range is essential to prevent skin irritation while maintaining optimal drug stability and efficacy [23].

Total Flavonoid Content in Film

The total flavonoid content (TFC) in the patch formulation was quantified to assess the retention of active compounds in the film matrix. A 10 × 10 cm patch weighing 1.5 grams was dissolved in 100 mL of distilled water in a volumetric flask to extract the flavonoids. Subsequently, 1 mL of the test solution was pipetted and diluted to 50 mL with water in another volumetric flask. To facilitate flavonoid complex formation, 1 mL of the test solution was combined with 1 mL of 2% $AlCl_3$ and 1 mL of 120 mM potassium acetate, followed by incubation at room temperature for 30 minutes. The resulting solution's absorbance was measured using a UV-Vis spectrophotometer at 432.5 nm, the maximum wavelength for quercetin, to determine the flavonoid content in the patch. This analysis ensures that the active flavonoid concentration remains within the desired therapeutic range [24].

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In Vitro Drug Diffusion Studies

The in vitro drug diffusion study was conducted to evaluate the release rate and permeability of the active flavonoid compound, quercetin, from the patch formulation. This study aimed to assess the patch's effectiveness in delivering the active compound transdermally by simulating physiological conditions and measuring the extent of drug permeation. Before conducting the diffusion test, the maximum absorption wavelength of quercetin (376.5 nm) in phosphate buffer solution (pH 7.4) was determined. A calibration curve was prepared using a series of standard quercetin solutions in the same buffer to ensure accurate quantification, allowing precise measurement of the flavonoid content released from the patch over time. The diffusion test was performed using a Franz diffusion cell system equipped with an HT Tuffryn synthetic membrane commonly used for preliminary diffusion screening studies. The diffusion area of the membrane was 4.9 cm^2, and the receptor compartment was filled with 15 mL phosphate buffer solution (pH 7.4) to maintain sink conditions, ensuring continuous drug diffusion. The ethyl acetate extract patch was placed in the donor compartment, ensuring direct contact with the membrane. To simulate physiological conditions, the entire system was maintained at 32°C (equivalent to skin surface temperature) with continuous stirring at 300 rpm. During the experiment, samples (2 mL) were withdrawn from the receptor compartment at specified intervals (15, 30, 45, 60, 90, 120, 150, and 180 minutes). Each withdrawn sample was immediately replaced with an equal volume of fresh phosphate buffer solution (pH 7.4) to maintain constant diffusion conditions. The collected samples were treated with 1 mL of 2% $AlCl_3$ and 1 mL of 120 mM potassium acetate, vortexed to ensure homogenization, and incubated at room temperature for 30 minutes before analysis. The absorbance of each sample was measured using a UV-Vis spectrophotometer at 376.5 nm, and the concentration of the active compound was determined using the quercetin calibration curve as a reference. The diffusion flux (rate of drug release per unit area per time) and the percentage of the diffused active compound were calculated to evaluate the effectiveness of drug release from the patch formulation. This in vitro drug diffusion study provides critical insights into the permeability and release kinetics of the flavonoid compound, helping to determine whether the patch formulation is suitable for effective transdermal drug delivery. The data obtained can be used to optimize patch composition and enhance formulation performance, ultimately improving its therapeutic potential for wound healing and other applications [25,26].

RESULTS

Total Flavonoid Content Analysis

The standard used to determine the total flavonoid content is quercetin, a flavonoid from the flavonol group that is widely found in various plants. Quercetin was chosen as the standard due to its ability to represent the flavonoid content in fig leaves. This compound possesses a chemical structure containing a chromophore group, making it identifiable using a UV-Vis spectrophotometer [27]. Prior to analysis, the maximum absorption wavelength of quercetin was determined, yielding a result of 432.5 nm. The extraction process using ethyl acetate produced a yield of 12.9% (w/w) from fig leaves. Subsequently, a quercetin calibration curve was constructed to obtain a linear regression equation (y=0,0402+0,0418x) with an R-squared value of 0.9922, which was then used to calculate the total flavonoid content in the extract, expressed as quercetin equivalent (mgEQ/g). The results indicated that the ethyl acetate extract of fig leaves contained 89.266 ± 0.14 mgQE/g of flavonoids.

Evaluation of Patch Base

The patch base used in this study comprises HPMC K100M, propylene glycol, 96% ethanol, and distilled water. In the base optimization process, the concentration of propylene glycol varied due to its dual role as a plasticizer and a penetration enhancer. As a plasticizer, propylene glycol enhances polymer flexibility by weakening intermolecular bonds within the polymer chains, resulting in a more flexible and less brittle patch [28]. Additionally, as a penetration enhancer, propylene glycol increases the mobility and disorder of the stratum corneum (SC) lipids, disrupts lipid-lipid interactions, and extracts cholesterol from the SC. These effects facilitate drug partitioning into the SC and enhance skin permeability. The concentration of propylene glycol in the formulation significantly influences the mechanical properties of the patch, which are crucial for maintaining a balance between flexibility, strength, and drug release efficiency [29,30]. The optimization results are summarized in **Table 3**, and **Figure 1** illustrates the optimized patch base.

Table 3. Evaluation results of patch base optimization.

Parameters	F1	F2	F3
Tensile strength (MPa)	14.39 ± 0.76	13.73 ± 1.99	2.16 ± 0.41
Elongation break (%)	21.00 ± 4.36	92.33 ± 14.57	111.60 ± 14.17
Folding endurance (times)	> 200	> 200	> 200
pH	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0

Data are presented as mean ± standard deviation (SD) (n=3)

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The selection of the optimal formulation was based on the patch's physical evaluation criteria, including tensile strength, elongation at break, folding endurance, and pH. The test results showed that all formulations (F1, F2, and F3) exhibited comparable folding endurance and pH values within acceptable ranges. All patches demonstrated folding endurance greater than 200 cycles, indicating good resistance to mechanical stress [31]. In addition, the pH of each formulation was consistent at 5.0 ± 0.0. Physiologically, healthy human skin maintains a slightly acidic pH, ranging from approximately 4.5 to 5.3 on the skin surface, which gradually increases to around 6.8 in the lower stratum corneum. In contrast, most open wounds exhibit a more alkaline microenvironment, with reported pH values ranging from 7.42 to 8.9 [32]. This alkaline condition may be influenced by bacterial activity, including ammonia production from urea degradation by the enzyme urease, which can increase wound pH [33]. The formulated patch in this study exhibited a pH of 5.0, which lies within the slightly acidic range and is generally well tolerated for topical skin application without causing irritation. A mildly acidic pH has been reported to support wound healing by inhibiting bacterial growth and biofilm formation, improving tissue oxygenation, and promoting re-epithelialization. In addition, an acidic environment can support fibroblast activity, including migration, proliferation, and collagen synthesis, which collectively contribute to the wound-healing process [34]. Previous studies have also demonstrated that in vivo wound acidification with acidic buffers at pH 4 accelerates wound healing compared to pH 6, further highlighting the role of pH in wound management [35]

Regarding mechanical properties, tensile strength which reflects the patch's resistance to tension showed that formulations F1 and F2 exhibited higher tensile strength, whereas F3 demonstrated lower tensile strength, indicating a more fragile structure and a higher risk of tearing. The reduced tensile strength observed in F3 may be attributed to the higher propylene glycol concentration, as increasing plasticizer content is known to decrease tensile strength while increasing elongation at break [36]. Excessive plasticizer weakens polymer–polymer interactions by reducing hydrogen bonding within polymer chains, thereby decreasing molecular attraction forces. Therefore, F3 was eliminated at this stage of selection. Subsequently, F1 and F2 were compared based on elongation at break, with F2 exhibiting the highest elongation, indicating superior flexibility and mechanical resilience. Based on these considerations, F2 was identified as the optimal patch base, as it demonstrated a balanced combination of adequate tensile strength and high elongation at break, making it more flexible and less prone to tearing. Consequently, F2 was selected as the most suitable formulation to be used as the base for the ethyl acetate extract of fig leaf patch in the subsequent stage of the study.

Figure 1. Visual examination of the optimized patch base.

The visual examination of the optimized patch base formulations (F1, F2, and F3). All formulations appear transparent and flexible, with slight differences in texture and surface smoothness. F1 exhibits a relatively rigid structure with minimal surface irregularities, whereas F2 appears more uniform and flexible, aligning with its optimal balance of tensile strength and elongation break. F3, however, demonstrates a softer and more elastic texture but appears to have reduced mechanical strength, making it more susceptible to tearing. These visual characteristics correspond with the mechanical evaluation results, further supporting the selection of F2 as the optimal patch base formulation.

Evaluation of Ethyl Acetate Extract of Fig Leaf Patch

The fig leaf extract patch was formulated using the optimized base, identified as F2. This base was selected due to its balanced mechanical properties, ensuring both flexibility and adequate tensile strength. The formulation process involved incorporating ethyl acetate fig leaf extract into the polymer matrix, which was then cast and dried to achieve a uniform film. The selection of the ethyl acetate extract was based on its high flavonoid

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content, which is known for its antioxidant and anti-inflammatory properties. The incorporation of the extract into the transdermal patch system aims to enhance the controlled release of active compounds through the skin barrier [37,38]. **Table 4** presents the evaluation results of the patch formulation, highlighting its physical and mechanical characteristics, such as thickness, flexibility, and pH stability. A well-optimized formulation is crucial for ensuring effective adhesion and drug release properties when applied to the skin.

Table 4. Evaluation results of ethyl acetate extract of fig leaf patch (F2A).

Parameters	Results
Organoleptic	Dark green to blackish Characteristic fig leaf scent Thin Does not shrink/wrinkle
Thickness (mm)	1.0 ± 0.2
Folding endurance (times)	> 200
pH	5.0 ± 0.0

Meanwhile, **Figure 2** provides a visual representation of the final patch, demonstrating its appearance and suitability for transdermal application. The patch formulation exhibits a dark green to blackish color, indicating the presence of polyphenolic compounds such as flavonoids and tannins. These compounds contribute to its antioxidant activity, which plays a role in skin protection and healing. The thin structure of the patch ensures comfort during application, while the absence of shrinkage and wrinkling reflects its formulation stability. The patch was cut into a 4x4 cm square and applied onto a Tegaderm backing layer, which provides additional support and enhances adhesion to the skin. The flexibility of the patch, as confirmed by its high folding endurance, ensures that it remains intact even with repeated movement. The thickness measurement of 1.0 ± 0.2 mm indicates that the patch is sufficiently durable without being overly rigid. Additionally, the pH of the patch formulation is within the physiological range, making it safe for topical application without causing irritation [39]. These characteristics collectively indicate that the patch is well-suited for transdermal drug delivery applications.

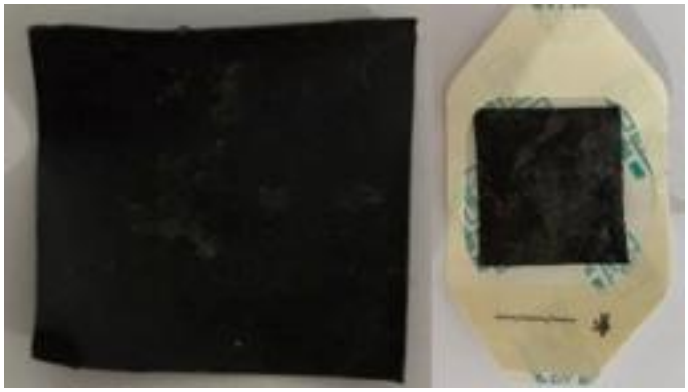

Figure 2. Final patch formulation cut into 4x4 cm and applied to a Tegaderm backing layer.

The final patch formulation incorporating ethyl acetate fig leaf extract, prepared using the optimized F2 base. The patch appears dark green to blackish in color, with a characteristic fig leaf scent, a thin structure, and no visible shrinkage or wrinkling. It was cut into a 4x4 cm square and applied onto a Tegaderm backing layer, ensuring adhesion and ease of application. The uniformity and flexibility of the patch suggest its suitability for transdermal drug delivery. The Tegaderm backing layer enhances the stability of the patch, preventing it from detaching prematurely while also protecting the active ingredients from external environmental factors [40]. The color uniformity of the patch further indicates a well-dispersed extract within the polymer matrix, preventing phase separation that could affect the release profile of the active compound. The mechanical properties of the patch, specifically tensile strength (13.73 ± 1.99 MPa) and elongation at break (92.33 ± 14.57%), were evaluated exclusively on the base formulation (F2). This approach is justified since F2A differs solely by incorporation of 5.6% extract, while the concentrations of HPMC K 100M and propylene glycol remained constant. However, folding endurance was re-evaluated for the final formulation (F2A), confirming its capacity to withstand physical stress without breaking or tearing (>200 times). This optimal combination of HPMC and propylene glycol contributed to a smooth texture and reliable structural integrity, which are critical for ensuring controlled and prolonged drug release to achieve sustained therapeutic effects [41].

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In Vitro Diffusion Study

This study utilized a Franz diffusion cell, which separates the donor and receptor compartments with a semi-permeable membrane. The donor compartment contained the patch formulation, while the receptor compartment was filled with a suitable receptor fluid to mimic physiological conditions. The active compound penetrating the receptor fluid was quantified using a spectrophotometer at predetermined time intervals. The membrane used in this study, HT Tuffryn, is a polysulfone-based microfiltration membrane designed to mimic human skin permeability [42]. This membrane was selected due to its consistent pore size and hydrophilic properties, ensuring controlled diffusion of active compounds. The diffusion study aimed to evaluate two key parameters: the cumulative amount of quercetin that penetrated the membrane over time and the flux or penetration rate at each time point. By analyzing these parameters, the study provides insights into the release kinetics and efficiency of quercetin delivery through the transdermal system [43]. The in vitro diffusion test results are presented in **Table 5**, detailing the release profile over time and helping to determine the suitability of the patch formulation for sustained drug delivery.

Table 5. In vitro diffusion test results of patch containing ethyl acetate fig leaf extract.

Time (min)	Cumulative Quercetin Penetration (%)	Flux (µg/cm².h)
15	2.79	130.04
30	4.37	101.71
45	5.9	91.6
60	8.01	83.27
90	10.33	80.2
120	15.44	89.89
150	19.61	91.32
180	21.76	84.41

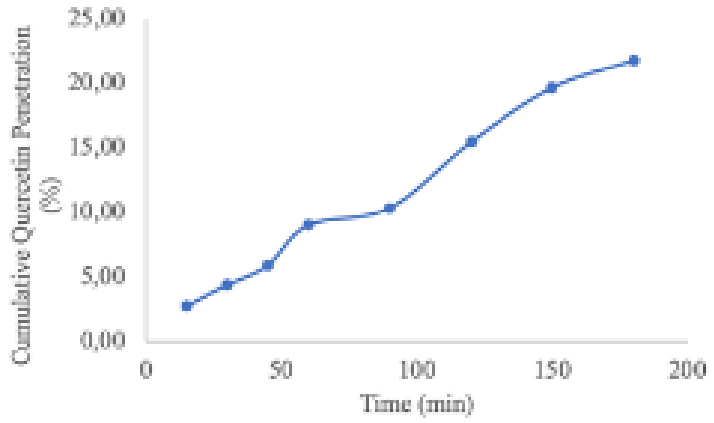

Figure 3. Cumulative quercetin penetration (%) over time from patch containing ethyl acetate fig leaf extract.

The cumulative quercetin continuously increased over time, reaching 21.76% within 180 minutes (**Figure 3**). This gradual increase indicates sustained penetration; however, the overall penetration rate over the studied period falls in the moderate category. The observed penetration profile is influenced by multiple physicochemical and formulation-related factors, including molecular size, partition coefficient, and matrix composition. Quercetin, with a molecular weight of 302.23 Da and a partition coefficient of 1.48, exhibits balanced lipophilic and hydrophilic properties, facilitating its diffusion through the membrane. However, intermolecular interactions within the extract may affect penetration efficiency by altering the solubility and diffusion rate of quercetin [44]. In addition to quercetin's intrinsic properties, formulation excipients play a critical role in governing its release behavior. The presence of HPMC, a matrix-forming polymer, and propylene glycol can enhance HPMC's elasticity. Propylene glycol can enhance elongation at break and permeability, but may reduce tensile strength. This modifies the patch's microenvironment, thereby influencing drug mobility and release kinetics [45].

Based on the data presented in Table 5, the in vitro skin permeation flux of quercetin followed a highly dynamic, non monotonic curve throughout 180 minute study. The initial phase of penetration, a relatively high

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flux of 130.04 mcg/cm².h was observed, indicating an initial burst release, which refers to the rapid diffusion of active compounds from the patch surface upon hydration. This phenomenon is commonly observed in monolithic matrix-based delivery systems when the active ingredient is not fully entrapped within the polymer network [46]. The flux did not exhibit a steady state condition; instead, a non-monotonic flux pattern was clearly observed, particularly between 90 and 150 minutes. This behavior was presumably influenced by the hydration and swelling processes of the HPMC K100M matrix during diffusion. Upon contact with the diffusion medium, HPMC formed a gel layer that altered the diffusion resistance over time, resulting in temporary fluctuations in quercetin release.

Specifically, between 90 and 150 minutes, continuous hydration likely induced polymer chain relaxation and localized structural rearrangements within the gel network. This structural shift, potentially coupled with the delayed penetration-enhancing effect of propylene glycol, temporarily lowered diffusion resistance and triggered a secondary influx of the drug. In addition, the gradual absorption of the medium by the patch matrix may have affected the quercetin release rate, causing the resulting flux values to be not entirely constant throughout the diffusion process. The flux did not establish a steady-state condition; instead, a distinct non-monotonic flux pattern was clearly observed, particularly between 90 and 150 minutes. This behavior was presumably influenced by the hydration and swelling kinetics of the HPMC K100M matrix during the diffusion process. Immediate contact with the diffusion medium triggers water imbibition, which subsequently induces polymer chain relaxation and gradual gel layer formation. The initial decline in flux occurs as the gel layer thickens, thereby increasing the diffusion path length. However, further hydration causes the polymer matrix to reach a critical relaxation threshold, transiently lowering diffusion resistance and accelerating quercetin release. Additionally, the presence of propylene glycol enhances drug solubility within the localized gel phase. This intertwined condition triggers a secondary influx or an temporary surge in drug release before the flux eventually declines due to drug depletion in the donor compartment or alterations in matrix porosity. Ultimately, this moving boundary phenomenon, coupled with the strict dependence of the diffusion coefficient on local moisture content, prevents the flux from reaching a constant steady-state plateau, resulting in the observed non-monotonic profile [47–50]. These factors highlight the importance of formulation optimization to balance drug retention within the matrix and its controlled penetration into the receptor compartment. Meanwhile, to assess penetration behavior more comprehensively, testing over a longer duration is required to evaluate increases in cumulative penetration and the possibility of reaching a plateau condition.

DISCUSSIONS

In the extraction process of fig leaves (*Ficus carica* L.), ethyl acetate ($CH_3COOC_2H_5$) was used as the extraction solvent and selected based on its classification as a green solvent. Compared to petroleum-based solvents, ethyl acetate is widely used in extraction processes due to its relatively low toxicity, pleasant odor, high biodegradability, and favorable solubility for semi-polar compounds, particularly flavonoids such as quercetin, the primary bioactive compounds targeted in this study. From an environmental sustainability perspective, more than 90% of ethyl acetate can be biodegraded within 28 days. Additionally, its short atmospheric half-life (approximately 1.3 days) allows rapid degradation in the air, thereby reducing its long-term environmental persistence. Ethyl acetate also exhibits low aquatic toxicity, with LC_{50} values for fish species ranging from 1000 to 2000 mg/L. Furthermore, its relatively low carbon footprint (approximately 3.5 gCO_2-eq/kg) and moderate contribution to the formation of volatile organic compounds (VOCs), support its sustainability as an environmentally acceptable extraction solvent [51,52].

The ethyl acetate extract obtained from fig leaves was subsequently evaluated for its total flavonoid content and used to optimize a transdermal patch formulation to enable effective delivery of the bioactive compound. The ethyl acetate extract contained 89.266 ± 0.14 mgEQ/g of flavonoids, demonstrating the effectiveness of ethyl acetate as a solvent due to its moderate polarity. This solvent choice aligns with previous research showing that hydroalcoholic solvents enhance flavonoid extraction with higher antioxidant properties than aqueous extracts [53]. The optimized patch formulation was influenced by propylene glycol concentration, acting as both a plasticizer and penetration enhancer. Increasing its concentration reduced tensile strength while improving elongation break, creating a flexible and durable patch. These findings are supported by previous studies, which highlight how penetration enhancers like propylene glycol improve transdermal permeability and mechanical stability [54]. The optimized patch base ensured proper extract dispersion, preventing phase separation that could alter drug release. The high folding endurance observed further supports the mechanical stability of the patch formulation. Ensuring adequate tensile strength is essential to maintain patch integrity during application and use.

The formulated transdermal patch exhibited favorable physicochemical characteristics, including a dark green to blackish color, a smooth texture, high flexibility, and resistance to shrinkage or wrinkling. These attributes indicate successful incorporation of the extract into the polymer matrix. In addition, the present formulation showed the ability to release quercetin through the HPMC based matrix system, indicating that the polymer matrix was capable of facilitating flavonoid diffusion from the patch. The in vitro diffusion study

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demonstrated a gradual increase in quercetin penetration, with a cumulative release of 21.76% within 180 minutes. This result indicates that the formulated patch was capable of releasing quercetin from the HPMC matrix in a controlled manner. Although the present study did not evaluate the therapeutic concentration of quercetin at the wound site in vivo, the obtained diffusion profile suggests the potential of the formulation to provide flavonoid delivery for wound healing application. The 180-minute diffusion study duration does not fully reflect the sustained release profile or the long-term behavior of the monolithic matrix patch intended for wound management. Therefore, this diffusion study was designed as a preliminary investigation to evaluate the initial diffusion profile and the ability of the active compound to be released from the polymer matrix.

The release profile exhibited an initial burst effect, followed by a stable diffusion phase, which is characteristic of HPMC based monolithic matrix systems. Similar results have been reported in transdermal patches loaded with olive leaf extract, in which the polyphenol content contributed to sustained drug release and antioxidant benefits [55]. Non-linear flux pattern observed suggests that polymer hydration dynamics and intermolecular interactions play a crucial role in regulating drug diffusion [56]. To comprehensively characterize the long-term release profile, further studies with extended diffusion duration are required. Another limitation of the present study is absence of stability evaluation of the developed patch formulation. Therefore, future studies should investigate the physical and chemical stability of the patch under different storage conditons to ensure product quality and performance throughout its shelf life.

Overall, the study demonstrated the feasibility of the formulated transdermal patch in delivering flavonoid-rich extracts from fig leaves. The combination of ethyl acetate extraction and an optimized polymeric base resulted in a stable, flexible, and efficient drug delivery system. These findings are consistent with research highlighting the advantages of herbal-based wound healing formulations, such as mangosteen peel extract and bacterial cellulose-based patches [57]. The ability of this patch to control release kinetics and ensure skin compatibility suggests its potential for further development as a transdermal delivery system. Future studies should focus on further optimization by modifying polymer concentrations, incorporating additional penetration enhancers, or conducting in vivo assessments to evaluate therapeutic efficacy. Additionally, exploring alternative biopolymeric materials may enhance the patch's performance and broaden its application in transdermal drug delivery. Investigating different flavonoid-rich plant extracts may further improve the patch’s bioactivity. Expanding research into clinical trials will provide more comprehensive data on its potential therapeutic benefits.

CONCLUSIONS

The optimized transdermal patch formulation containing ethyl acetate fig leaf extract was successfully developed using 8% HPMC K100M as the polymer and 6% propylene glycol as the plasticizer. The evaluation results confirmed that the patch met the required criteria, including a smooth and wrinkle-free surface, a thickness of 1 mm ± 0.2 mm, a pH of 5 ± 0, and a folding endurance exceeding 200 cycles. The in vitro diffusion study demonstrated a cumulative quercetin release of 21.76% within 180 minutes, influenced by molecular size, carrier properties, and formulation composition. The flux profile exhibited an initial burst release followed by a more stable diffusion phase, indicating the characteristic diffusion behavior of an HPMC based monolithic matrix system during 180 minutes observation period. Nevertheless, the cumulative penetration achieved is still considered moderate, so further testing with a longer duration and in vivo evaluation is needed to assess the performance and therapeutic relevance of the developed transdermal patch. Future studies should focus on extended in vitro diffusion studies using a skin model, assessment of the stability of the developed patch, and in vivo evalaution of wound healing efficacy.

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