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Modern Wound Dressing from Shallot Skin Waste Extract: A Natural Biomaterial Approach to Alleviate Vasoconstriction in Diabetic Ulcers

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Abstract
Background: Shallot skin possesses various biological activities, including antibiotic, anti-inflammatory, and antibacterial properties, attributed to their secondary metabolites such as flavonoid (quercetin and kaempferol), saponin, and essential oil. This study aimed to determine the antibacterial activity of shallot skin made into a wound dressing patch.
Methods: This research used diabetic rats induced by alloxan. Rats with blood glucose >200 mg/dL and ulcers were divided into negative control (patch base), positive control (oxoferrin), and test groups treated with shallot peel extract at 0%, 45%, 50%, and 55%. Rats were randomly assigned after glucose screening. Data collected included swelling, gel fraction tests, and flavonoid (quercetin) identification via thin-layer chromatography. Healing was measured by wound closure percentage.
Results: Patches with higher shallot peel extract concentrations absorbed more water and maintained structure. In diabetic rats, 45%, 50%, and 55% extract patches accelerated wound closure, with 55% showing the best healing based on the comparison between the positive control and the test formulation. A slight difference was found, so it can be concluded that this formulation has potential as a treatment for diabetic ulcers.
Conclusion: Wound dressings combining calcium alginate and shallot peel extract exhibit antibacterial properties and enhance diabetic ulcer healing in rats. The combination of quercetin as an antibacterial for S. *aureus*, the leading cause of diabetic ulcers, and alginate, which can condition wounds so that they can accelerate wound healing, is a potential combination in treating cases of diabetic ulcers.

Keywords: *Diabetic Ulcer, Patch, Shallot Skin, Wound Dressing*.

Introduction

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to impaired insulin secretion, insulin action, or both[1]. In 2021, global DM cases reached 537 million, with Southeast Asia accounting for 90 million cases; Indonesia was the largest contributor in the region with 19.5 million cases, ranking fifth globally[2]. The rising number of DM cases has made complications such as diabetic ulcers a major concern, affecting about 15% of DM patients in Indonesia, with an amputation rate of 15–30% and a one-year post-amputation mortality rate of 14.8%[3,4].

Diabetic ulcers in DM patients result from pathological changes due to infection, ulceration linked to neuropathy, peripheral vascular disease, or metabolic complications in the lower extremities[5]. Poor glycemic control is a main factor in the development of foot ulcers[6]. Persistent hyperglycemia leads to vascular damage, peripheral neuropathy, and inadequate tissue blood supply[7]. Peripheral neuropathy increases the risk of foot ulcers[8–10]. Vasoconstriction and hyperglycemia also impair wound healing and increase infection risk[11]. Infection in diabetic ulcers is commonly caused by aerobic and anaerobic bacteria, such as *Escherichia* spp., *Klebsiella* spp., *Staphylococcus* spp., *Salmonella* spp., and *Shigella* spp., with *Staphylococcus aureus* being the dominant pathogen[12,13].

Shallot skin (*Allium cepa* L.) contains flavonoids, particularly quercetin, with higher concentrations in the skin than in the bulb[14]. Quercetin has vasoprotective and antibacterial effects, inhibits Inducible Nitric Oxide Synthase (iNOS), enhances Endothelial Nitric Oxide Synthase (eNOS) activity, and improves endothelial vasodilation[15]. Tests of 10% methanol extract of shallot skin produced an inhibition zone of 4.88 mm, while a 50% extract yielded 5.65 mm[16]. Shallot extract also accelerated wound healing in mice[17].

Diabetic ulcer care is costly, and most conventional wound dressings lack active ingredients, making them less effective. As a result, many people are turning to safer natural treatments. Alginate has been shown to accelerate wound closure in mice[18,19]. Researchers aim to develop and evaluate wound dressing patches that incorporate calcium alginate and shallot skin waste for the healing of diabetic ulcers, including tests for antibacterial efficacy, physicochemical properties, and formulation assessment[16,18].

Methods

Tools and Materials

The tools include measuring cups, test tubes, pipettes, inoculation needles, pipette tips, Bunsen burners, antibiotic disks, analytical scales, magnetic stirrers, rotary evaporators, and syringes. Materials used include polyvinyl alcohol (PVA), calcium alginate, distilled water, 96% ethanol, PVP K-30, PEG 400, DMD hydantoin, *S. aureus* bacteria, nutrient agar, Mueller-Hinton Agar (MHA), sodium hydroxide, tissue, gloves, oxoferrin, alloxan monohydrate, and shallot skin powder.

Simplisia Determination Procedure

Plant determination is conducted to determine the truth of the plants that will be used as test materials. Determination was carried out at the Pharmaceutical Biology Laboratory of Universitas Muhammadiyahh Purwokerto.

Extraction Process of Shallot Skin (*Allium cepa* L.)

The extraction process used the maceration method with 96% ethanol. 500 grams of shallot skin powder was used in a ratio (1:10) using 96% ethanol for 3-4 days with occasional stirring. The macerate is filtered, and the results of maceration are mixed and then evaporated using a rotary evaporator until it becomes a pellet. Then, the concentrated extract was evaporated in the oven at 40°C.

Identification of Flavonoid Compounds

Shallot skin extracts were screened for compounds using thin-layer chromatography using H_2SO_4 5% spray reagent, which produces blue, yellow, and green colors that indicate the presence of polyphenol and flavonoid compounds in the extract at 366 nm.

Wound Dressing Patch Formulation

The formulation in this study consisted of 3 formulations and 1 control, as shown in Table 1.

Table 1. Wound dressing patch formulation

Material	Function	Content			
		F0	F1	F2	F3
Shallot skin simplisia powder	Active susbtance	0	45	50	55
Calcium alginate	Active susbtance	25	25	25	25
PVA	Polymer	5	5	5	5
PVP K-30	Polymer	7	7	7	7
PEG 400	Polymer	10	10	10	10
DMD Hydantoin	Preservative	0.5	0.5	0.5	0.5
Aquadest	Solvent	Add 100			

Manufacturing Procedure

Prepare PVA and alginate as specified in the formulation. The calcium alginate concentration of 25% refers to previous research by Blessing (2021), where the best concentration in wound dressing patch formulation with calcium alginate as the base ingredient is 25%. Alginate dressings absorb wound fluid to form a gel that maintains physiological moisture and minimizes bacterial infection at the wound site[20]. Then, mix it with distilled water and stir it for 2 hours at room temperature until homogeneous. PVA and alginate solutions were mixed with shallot skin extract in a 0%, 45%, 50%, and 55% ratio. Each variation was stirred for 1 hour at 35°C. The formed hydrogel was poured into a thin mold, then heated in an oven for 1 hour so that the wound dressing patch is obtained. As for the swelling test, the hydrogel was poured into a thicker mold and into molds that are thicker and placed in the oven for 6 hours.

Antibacterial Test Procedure of Shallot Peel Waste Extract

S. aureus bacteria will be cultured first on nutrient agar (NA) media in test tubes for 24 hours. Then all the work on testing antibacterial activity is carried out in a laminar air flow. Paper disks are dipped in shallot skin extract. Petri dishes filled with NA media will be spread with *S. aureus* bacteria. Then the disc paper dipped in shallot skin extract is placed on the surface of the NA media and closed tightly. After that, incubation was carried out for 24 hours at 37 °C in an incubator, and the formation of inhibition was measured using a caliper.

Evaluation of Wound Dressing Patch Preparations

Swelling Test

The swelling test was conducted on each variation of wound dressing based on the same side size of 1 cm x 1 cm. The swelling test was conducted by immersing the sample in distilled water up to 10 ml. During the test process, the weight of the sample was measured every 10 minutes. The increase in sample weight is the amount of distilled water absorbed by the wound dressing patch[21].

$$Swelling\ ratio = \frac{Wt - Wd}{Wd} \text{ x } 100$$

Gel Fraction Test

The gel fraction test was performed by cutting a hydrogel weighing 3 grams as (W0), wrapped in gauze and soaked in 20 mL of distilled water for 24 hours, then dried back in the oven at 50ºC, for ±4 hours, and weighed as (W1). Calculation of gel fraction using the following formula[21]:

$$\%Gel\ fraction = \frac{Wd}{W0} \text{ x } 100$$

Diabetes Wound Healing Test

The test animals were first fed for 8 to 12 hours. After that, the test animals were induced using alloxan (Sigma-Aldrich 98%) at 200 mg/kg BW. On the fourth day after induction, animals were tested to determine their blood sugar levels using Accu-Chek (Instant) and declared diabetic if the blood sugar concentration was > 200 mg/dL. Animals that have diabetes are then shaved on their fur and bandaged with wound dressing patch preparations, and then made incision wounds along with their respective groups, namely the negative group given a wound dressing patch base, the positive group given oxoferin (tetrachlorodecaoxide), and the test group given the test preparation, namely the difference in the percentage of shallot simplisia powder content, namely 0%, 45%, 50% and 55%. Wound healing was evaluated for 14 days by measuring the closure of the incision wound using a caliper.

Result

Yield Results of Shallot Skin Waste Extract

The yield of 250 grams of shallot skin waste extract with 70% ethanol solvent in a ratio of 1: 10 and then dried. From an initial weight of 250 grams of fresh shallot skin waste, the dried simplicia obtained weighed 256.31 grams after processing, indicating water loss and concentration during pre-treatment. Subsequent maceration and solvent evaporation produced a crude extract weighing 20 grams. The yield percentage was calculated based on the weight of the extract relative to the weight of the dried simplicia, using the formula[22]:

$$\%Rendemen = \frac{concentrated\ extract\ (gr)}{initial\ weight\ of\ simplisia\ (gr)} \text{ x } 100\%$$

This resulted in a yield of 7.80%, which reflects the proportion of extractable compounds under the given extraction conditions.

Thin Layer Chromatography Analysis

Thin-layer chromatography is a method used for qualitative analysis, where testing is done to determine the presence of quercetin compounds. In this test, pure quercetin was used as a comparison and observed with a wavelength of 366 nm. The results obtained contained quercetin compounds because parallel spots were obtained.

Result of Antibacterial Test

Antibacterial activity test is testing method that is carried out to determine the ability of an ingredient in inhibiting bacterial growth. Tests conducted to determine the ability of a material to inhibit bacterial growth[23].

Table 2. Result of antibacterial test

Sample	Inhibition zone (mm)	Category
Formula 1	15	Intermediet
Formula 2	15.5	Intermediet
Formula 3	17	Intermediet
Control Positive	18.7	Intermediet
Control Negative	0	-

Swelling Test

The swelling and solubility properties of the physically and chemically crosslinked xerogels were investigated under different environmental conditions to examine the effect of variable temperature[21]. Table 3 shows the results of the swelling test.

Table 3. Result of swelling test

Preparation	Result (g/g)
1	36.69
2	37.59
3	38.23
4	37.60

Gel Fraction Test

The gel fraction is a useful qualitative measure of the effectiveness of network formation in hydrogels. The gel fraction indicates the number of crosslinks that occur between the polymers in the hydrogel. A higher gel fraction percentage indicates a greater degree of covalent bonding. The higher density of formed crosslinks additionally leads to a reduction in the swelling capability of the hydrogel, i.e., the ability of water to enter/exit the hydrogel structure is reduced[21]. Table 4 shows the results of the gel fraction test.

Table 4. Result of gel fraction test

Preparation	Result (%)
1	110.833
2	112.067
3	98.670
4	70.800

Diabetic Ulcer Wound Healing Test

Wound healing is a complex process, with different strategies for treating different types of wounds. Wound healing is a process of repairing skin tissue or other organs after an injury. There are three phases of wound healing: the inflammatory phase, the proliferation or fibroplasia phase, and the remodeling or maturation phase[24]. Table 5 shows the results of the diabetic ulcer wound healing test.

Table 5. Result of diabetic ulcer wound healing test

Sample	Day 14 Result (cm)	Description
1	1.6	Positive control
2	1.1	Negative control
3	0.5	Controlled
4	1.3	Test 1
5	1.5	Test 2
6	1.5	Test 3
7	1.65	Test 4

Organoleptic Test

Organoleptic testing is a product quality test using the five human senses (sight, smell, touch, hearing, and taste) to assess characteristics such as color, taste, smell, texture, and appearance. This test is important in determining product quality, especially in the food industry, as it is directly related to consumer preferences[25]. Table 6 shows the results of the organoleptic test.

Table 6. Organoleptic test

Formula	Smell	Color	Textures
F1	Stinging	Transparant Redness	Soft, flexible, homogeneous
F2	Stinging	Transparant Redness	Soft, flexible, homogeneous
F3	Stinging	Transparant Redness	Soft, flexible, homogeneous
F4	Stinging	Transparant Redness	Soft, flexible, homogeneous

Discussion

Recent innovations in wound care for diabetes include the development of smart bandages that can monitor wound conditions in real-time. These bandages are equipped with sensors to measure moisture levels, pH, and signs of infection. The information collected can provide nurses or doctors with immediate information on the progress of the wound, allowing for earlier intervention and personalization of care. This technology is expected to improve the healing process and reduce the risk of complications in diabetic patients. Diabetes is a chronic disease characterized by high blood glucose levels (hyperglycemia) due to disturbances in the body's production or use of insulin. Insulin is a hormone produced by the pancreas that regulates blood glucose levels.

Proper and advanced wound care for diabetic ulcers involves designing new wound care techniques that focus on maintaining a moist wound environment. Adequate moisture management accelerates healing, reduces wound size, and lowers infection risk. Management of diabetic wounds can be effectively done using wound dressing patches, which aim to keep the wound moist, minimize tissue fluid loss, and prevent cell death[26,27]. Maintaining wound moisture can improve healing by up to 45% and reduce the risk of infection spreading to other organs[28]. Alginate dressings have been shown to absorb exudate well, thereby preserving wound site moisture during visual observation. Wound dressing patches from shallot skin are an exciting innovation in wound care for diabetics. Shallot skin contains bioactive compounds that have the potential to help manage diabetes. Some of the compounds contained in shallot skin are quercetin, a flavonoid with antioxidant properties that can help reduce the risk of diabetic complications by protecting cells from oxidative damage, allicin, a sulfur compound that gives shallots their tangy aroma and flavor and has a potential effect in lowering blood glucose levels, saponins, a compound that can help improve insulin sensitivity and regulate blood sugar levels, and bioactive peptides that have antioxidant and anti-inflammatory activities that can support the health of cells and tissues in the body. In research conducted by Misna (2016), the average inhibition zone indicated changes in the growth of *Staphylococcus aureus* bacteria due to the active ingredients in shallot skin extract used as a sample[29]. These results demonstrate the potential of shallot skin as an antibacterial for diabetic ulcers. This will provide a scientific basis for further exploration of shallot skin patches' effectiveness, safety, and mechanism of action.

Quercetin prevents diabetic complications through its antioxidant, anti-inflammatory, and hypoglycemic activities[30]. It improves retinopathy in rats by reducing MCP-1, MMP-9, and VEGF levels, and decreases nephropathy by lowering glucose and triglyceride levels[31,32]. Quercetin also demonstrates neuroprotective effects on enteric neurons in diabetic rats, thus strengthening the foundation for the present study.

To obtain a compound, the yield must first be obtained, which will later be tested for content and effectiveness in handling cases of diabetic ulcers. In proving that the compound contains the quercetin active substance, a thin layer chromatography test was conducted. The KLT plate that has been bottled with the comparator and test solution is then observed. The observation of the KLT plate is that there are two parallel lines at the Rf value of 0.8125. This indicates that the shallot skin contains quercetin. To test the antibacterial properties of quercetin, the following tests were carried out. Table 2 It can be concluded that the higher quercetin content will affect the strength of the antibacterial properties in wound dressing patch preparations. The best antibacterial properties are in the positive control and followed by the fourth sample. Based on Table 2, it was found that the diameter of the inhibition zone formed was the irradical zone. The irradical zone represents bacterial growth that is not completely inhibited, so that in this zone, there are still some bacterial colonies that can survive or are resistant. The results of the irradical table above also obtained the largest inhibition zone at a concentration of 55%, with an inhibition rate of 17.5%. This figure is not far from the positive control, which was 18.7, so it can be concluded that shallot skin extract has potential as an antibacterial agent for treating diabetic ulcers.

The swelling ratio test on the preparation is carried out to determine the ability of the hydrogel to absorb liquid, where this ability can determine the ability of the hydrogel to absorb wound exudate. This is very important considering the diabetic ulcer wound is wet, so it must be equipped with a wound cover that is able to absorb wound exudate. These results indicate that the results of formulation 3 are best and absorb a lot of exudates. Having the highest swelling ratio value has a low gel fraction value because the higher the swelling ratio, the easier it is for the hydrogel to absorb water, and the more voids there are in the hydrogel, so that the crosslinked network formed in the hydrogel will also be smaller. The hydrogel with the designed formulation demonstrated good air retention capacity. An increase in the weight of the preparation indicates that air was successfully absorbed into the wound dressing during immersion in distilled water. This air absorption process indicates that the cross-linking process is proceeding well because the bonds are successfully formed during the manufacturing process. In wound dressing patch products, the gelation process occurs due to the reaction between the calcium alginate polymer and divalent cation ions. These divalent ions will bind to the calcium alginate, specifically to the guluronic acid structure with COO- groups. In this case, the divalent ions function as cross-linking agents that help stabilize the alginate chains, resulting in a dense gel structure[33].

Gel fraction is a fairly important parameter in the process of monomer/polymer synthesis in producing products to determine the occurrence of cross-linking or degradation. Gel fraction is used in determining the number of cross-links between polymer molecular chains in units of percent, the result can be seen in Table 4. Having the highest swelling ratio value has a low gel fraction value because the higher the swelling ratio, the easier it is for the hydrogel to absorb water, and the more cavities there are in the hydrogel, so that the crosslinked network formed in the hydrogel will also be smaller. The decrease in gel fraction value after the addition of shallot peel extract may be due to negative interactions between compounds in the extract and gelling agents such as carbomer. The metabolic secondary (tannins) compounds found in shallot peel extract can bind to the carboxylate groups in carbomer, thereby inhibiting the carbomer's ability to form a strong and stable gel network. This causes a decrease in gel viscosity and consistency, resulting in a lower gel fraction value.

Diabetic ulcer healing test, based on the data obtained from the results of the diabetic ulcer wound healing test, there are differences in each formula made due to the different active ingredient content. In Table 5, the results show that formulation 4 obtained the best results, namely 1.55 cm. This is slightly different from the positive control, namely 1.6 cm. These results are also in line with research by Tahirudin (2021), the antibacterial content in shallot skin can accelerate the healing of diabetic ulcer wounds caused by *S. aureus* bacteria[34].

Conclusions

The formulation of shallot skin extract preparations made into wound dressing preparations showed antibacterial activity against *S. aureus*. The formulation with the best results was demonstrated in formulation 4, which contained 55% extract.

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Author Contribution

Study design	:	MR
Data acquisition	:	AZD, KAA, YIS, WDT, EG
Data analysis	:	MR, AZD
Manuscript writing	:	MR, KA

Competing Interests

The authors declare that there are no conflicting interests in this particular study or subject. However, we comply with the journal's materials and data-sharing guidelines.

Abbreviation

DM	:	Diabetes mellitus
eNOS	:	Endothelial Nitric Oxide Synthase
iNOS	:	Inducible Nitric Oxide Synthase
MHA	:	Mueller-Hinton Agar
NA	:	Nutrient agar
PEG	:	Polyethylene glycol

PVA : Polyvinyl alcohol
PVP : Polyvinylpyrrolidone

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