REVEAL THE POTENCY OF WATER HYACINTH AND RED GINGER EXTRACT AS HYDROGEL WOUND DRESSING FOR MRSA DIABETIC WOUND: A SHORT REVIEW

Maulidan Firdaus, Muhammad Iqbal Daniswara, Khoirul Jamaluddin, Novi Andriani
Sebelas Maret University – Surakarta (Indonesia)

Abstract. Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria that colonize diabetic foot ulcers can cause dangerous infections and even amputations. To improve the healing process, hydrogel wound dressing loaded with antibacterial agents can be selected as viable alternatives to reduce MRSA colonization and infection. This review highlights the potential use of water hyacinth cellulose (*Eichornia crassipes*) as a base for hydrogel plaster and red ginger rhizome (*Zingiber officinale* var. Rubrum) as an antibacterial agent. Comprehensive studies show that water hyacinth weed that contains high cellulose has the potency to be converted into hydrogels. In addition, further studies show that the active compounds of red ginger rhizome extract such as 6-gingerol, gingerenone-A, and 6-shogaol are proven to inhibit MRSA which could be incorporated into hydrogels. These findings prove that the hydrogel derived from water hyacinth cellulose and the active compounds of red ginger extract is very promising for the future as a new alternative to diabetic wound dressing.

Keywords: diabetic wound; hydrogel plaster; MRSA; red ginger; water hyacinth

Introduction

The number of people with diabetes mellitus (DM) in 2019 is around 463 million, especially in developing countries and this is estimated to increase to 578 million (10.2%) in 2030 (Saeedi et al., 2019). Untreated DM wounds result in complications such as diabetic foot ulcers, slow wound healing, and infection due to MRSA. MRSA is a pathogenic bacteria that is resistant to antibiotics. Moist skin surface is the most common habitat of MRSA (Stacey et al. 2019). Modern wound dressing methods such as hydrogels, hydrocolloids, foams, films, and alginates have a soft texture to wounds. Based on the research of Dumville et al. (2011), hydrogel wound dressing showed more effective healing than conventional wound dressings. Hydrogel, three-dimensional hydrophilic polymer networks, is a material that has capability to absorb enormous volumes of biological fluids. It was reported that

cellulose can be modified into sodium carboxymethylcellulose (Na-CMC) which can be used as a hydrogel base (Setiawan et al., 2018).

One of the abundant sources of natural fibre cellulose is water hyacinth. Waterhyacinth, which has been considered as a weed, has a large abundance with growth reaching 125 tons in an area of 1 hectare for only 6 months (Istirokhatun et al., 2015). Its high cellulose content (60%) compared to hemicellulose (8%) and lignin (17%) makes water hyacinth a good material for making hydrogels (Setyaningsih et al., 2019). DM wound healing using hydrogel provides in vivo recovery results in the form of an anti-inflammatory function of the hydrogel and increases the rate of wound recovery (Luo et al. 2010). However, ordinary hydrogels only assist in wound dressing without preventing the growth of microorganisms, so it is thought necessary to add antibacterial agents.

Antibacterial tests of several plant extracts against MRSA have been carried out, including moringa leaf extract (Abdalla et al., 2016). The long growing period of moringa (12 – 18 months) reduces its potential as an MRSA inhibitor. Testing of pineapple fruit extracts (Lubaina et al., 2019) and honey (Mama et al., 2019) showed antibacterial activity against MRSA. However, both are also consumed, causing competition as food or medicine. One of the potential candidates as an antibacterial agent is red ginger. Prasad and Tyagi (2015) studied that red ginger rhizome contains 6-gingerol which has antioxidant, antibacterial, anti-inflammatory activity, and contains secondary metabolites such as flavonoids, phenols, terpenoids, and essential oils. The test results showed that red ginger extract was proven to kill MRSA bacteria (Widiastuti & Pramestuti, 2018).

Several recent comprehensive reviews of DM wound dressings have been reported, among them Simões et al. (2018) on antimicrobial agents in wound dressings, Rajendaran et al. (2018) regarding wound dressing nanoparticles, Shah et al. (2019) reviewing the potency of biomaterials and polymers for drug delivery arrangements, especially for the diabetic wounds treatment. However, currently there is no single effective wound dressing to treat various difficult conditions in chronic DM wounds (Rajendaran et al., 2018). Literature studies showed that no one has reported a comprehensive and systematic review of the potential of water hyacinth cellulose and the antimicrobial agent of red ginger as a wound plaster. This review aims to show the potential of water hyacinth cellulose as a hydrogel base and red ginger rhizome as an antimicrobial agent for a new alternative to DM wound healing plaster. The porosity of the hydrogel makes it possible to load the drug into the gel matrix (Shetye et al., 2015). The hydrogel from water hyacinth is combined with red ginger extract which is able to kill MRSA thereby preventing infection in the wound healing process.

Results and Discussion

Hydrogel from Water Hyacinth Cellulose

Water hyacinth contains of lignocellulose which consists of cellulose, hemicellulose, and lignin (Figure 1). Cellulose, a rigid and strong linear polymer, is the highest compound in water hyacinth (around ~ 66.87%). Nanocellulose has a low density (1.6 g / cm^3) with high tensile strength and elastic modulus (130-150 GPa). Cellulose isolation is classified as simple which generally consists of 3 stages, namely pre-hydrolysis, delignification, and bleaching. Pre-hydrolysis accelerates the separation of hemicellulose through immersion, delignification using strong alkaline aims to dissolve lignin from fibres, while bleaching using chlorination and oxidation reactions aims to obtain white cellulose results (Indriyati et al., 2016).

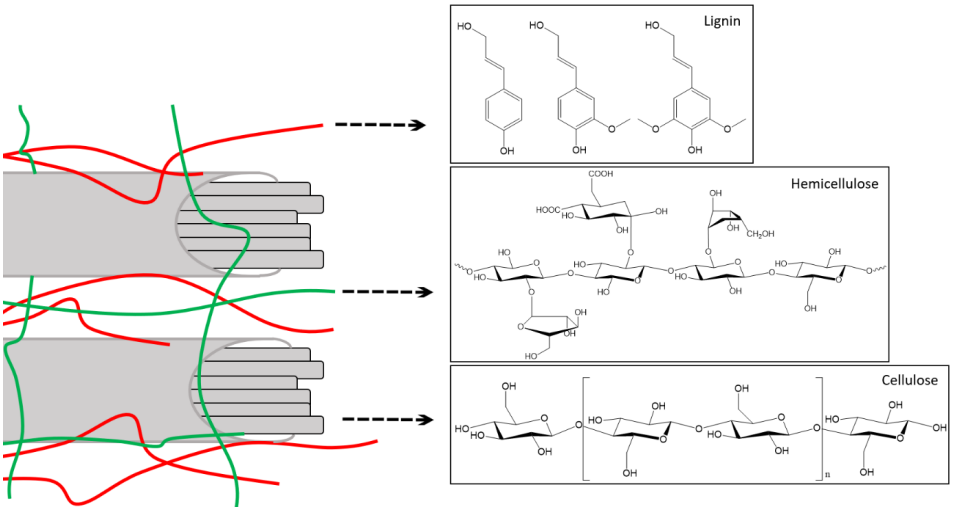

Figure 1. Ilustration of lignocellulose structure containing cellulose, lignin, and hemicellulose. Adapted from Alonso et al. (2012)

Derivatization of cellulose can be carried out by chemical modification to sodium carboxymethylcellulose (Na-CMC). Initially Na-CMC was synthesized from wood cellulose, but along with development it used plant waste such as water hyacinth which also has the potential to be used as raw material (Saputra et al., 2015). The synthesis of Na-CMC can be carried out through alkalization, carboxymethylation, neutralization, washing, and drying processes (Nisa & Widya, 2014). Na-CMC dissolves in water and is able to form hydrogel structures that absorb water or biological fluids in large quantities due to the chemical or physical cross-linking between the polymer and the crosslinking agent.

Di-functional molecules are used as crosslinkers in cellulose or its derivatives to form covalent bonds in hydrophilic three-dimensional networks (Masruchin et al., 2015). Some cross-linking agents for hydrogel synthesis and swelling ratio are shown at the Table 1.

Table 1. Cross-linking agent at the Na-CMC hydrogel and swelling ratio

No	Cross-linking agent	Swelling ratio	Reference
1	Citric acid	1419% (8:2 isobutyl:isopropyl alcohol)	Saputra et al. (2015)
2	Polyethylene-glycol, Citric acid	>5000% (CMC DS: 0,77; 10% citric acid)	Capanema et al. (2018)
3	Epichlorohydrin	725 g water/g gel	Alam et al. (2019)
4	Xylane, ethylene glycol, diglycidyl ether	625% (xylene/CMC: 25/75 mol %)	Kundu et al. (2019)
5	Divinyl sulfone	~42 g water/g gel (NaCMC/HEC: 5/1)	Astrini et al. (2012)
6	Starch, Aluminium sulphate octadecahydrate	58 g water/g gel (2% of $Al_2(SO_4)_3.18H_2O$)	Braihi et al. (2014)
7	Aluminium sulphate	712% (CMC: 4.5 wt%)	Liu et al. (2018)
8	N,N'-methylene-bis-acrylamide (MBA)	~55 g water/g gel (MBA: 1 $w/w_{polymer}$%)	Fekete et al. (2016)
9	Calcium chloride	45.29 g water/g gel (CMC: 7 w/v%)	Nan et al. (2019)
10	Diglycidyl ether, polyaniline	104 g water/g gel (CMC: 5 w/w%)	Li et al. (2017)

In Table 1, although divinilsulfone and epichlorohydrin (ECH) can be used as cross-linking agents, they are both toxic and must be completely removed before using the hydrogel. Citric acid can be chosen as an alternative cross-linking agent due to its non-toxic nature, and this compound can be obtained from abundant pineapple peel waste (Amenaghawon, 2017). The carboxylate group will be attached to the cellulose chain (Figure 2). Hydrogels from natural materials such as cellulose are hydrophilic and have advantages in terms of biocompatibility, biodegradability, environmentally friendly, inexpensive, and renewable. In addition, it has good permeability, as well as low friction and toxicity, making it like real living tissue. Drug delivery in hydrogels takes place optimally if it sticks to the skin for a certain time (Kindangen, 2018). Setiawan et al. (2018) stated that Na-CMC has high adhesion as a hydrogel, is able to soften the surface and bind more so that it has the potential to be inserted with antibacterial agents.

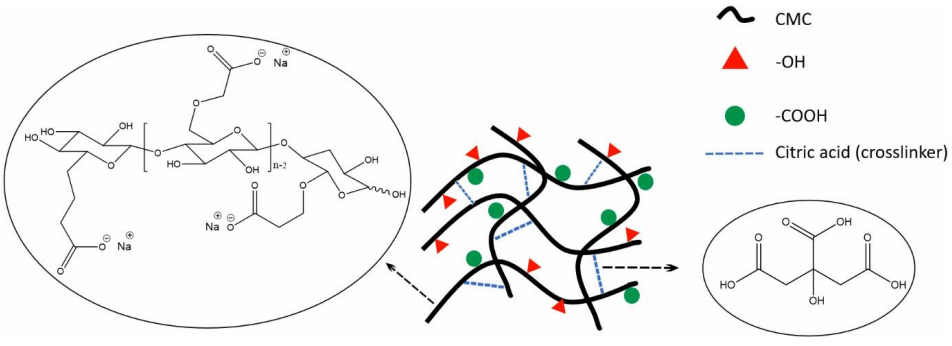

Figure 2. Illustration of cross-linking on Na-CMC using citric acid cross-linking agent. Adapted from Capanema et al. (2018)

B. MRSA on DM wound

Wound healing in healthy individuals only takes 2-3 weeks, whereas chronic wounds will take more than 6 – 8 weeks due to pathological damage to the surrounding tissue (Tatiana et al. 2012). DM wound will stop in the inflammatory phase without progressing to the next phase such as proliferation and maturation which inhibits the production of numerous cells, cytokines, proteins, and growing factors that are important for the proliferation and relocation of fibroblasts and keratinocytes. The imbalance between pro- and anti-inflammation that constantly disturbs the wound environment thus hinders the normal wound healing process (Rajendran et al., 2018).

There are several factors delaying the healing of diabetic wounds such as vasculopathy, neuropathy, and infection (Figure 3). Type 1 of diabetic is identical with macrovascular disorders in which the distal arteries are not capable to properly allocate oxygen and nutrients to the wound location (Ferrier et al., 1967). In addition, thickening of the basement membrane affects the movement of leukocytes, reduces the rate of hyperemia, and disrupts the balance of autoregulatory capacity (Pereira et al., 2015). Neurological disorders are caused by weakened sensory, motor, and autonomic fibers so that they cannot detect stimuli i.e. pressure, heat, and injury (Boulton et al., 2004). Diabetic wounds and infected ulcers can hinder wound healing, hospitalization, and amputation. Persistent hypoxia at the injury location can induce reperfusion of wound by generating oxygen radicals (Patel et al., 2005).

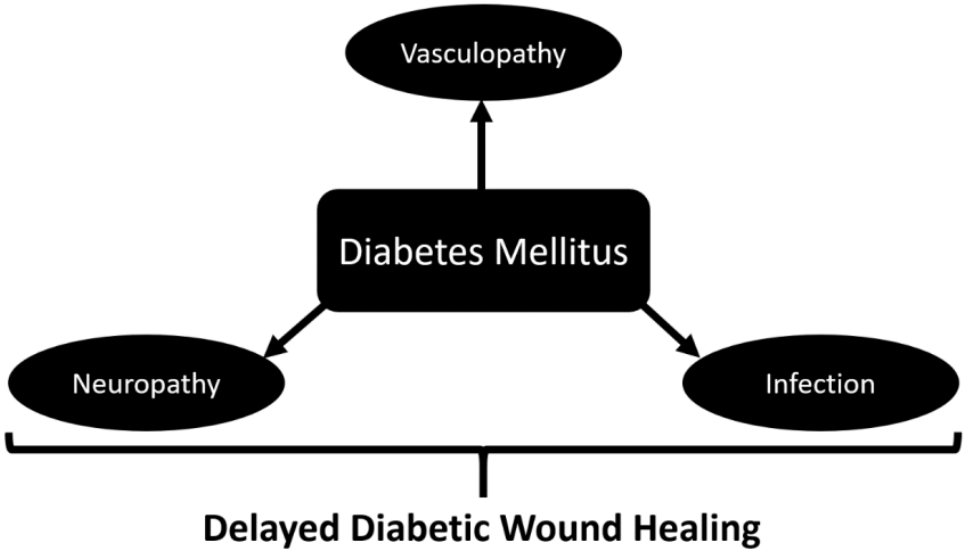

Figure 3. Delayed factor for diabetic wound healing

The presence of *Staphylococcus aureus* has the potential to infect DM wounds up to five times. *S. aureus* has been identified to be resistant to antibiotics from the time penicillin was discovered and continues to develop against other antibiotics. *S. aureus* began to become resistant to methicillin and became known as MRSA (Green et al., 2012). These bacteria tend to be found on the surface of human skin which can enter through wounds, causing a complex response by mobilizing immune cells to the infection site (Shamsuddin & Basri, 2018). Ulcer formation becomes an acute inflammatory response to bacteria as a mechanism to collect and kill pathogens. Ulcer contains inflammatory products consisting of PMN (polymorphonuclear), tissue fragments, fibrin, and live bacteria. In general, PMN plays a role in the formation of ulcers. However, genetic disorders can cause the inability of PMNs and phagocytes to produce peroxides, worsening MRSA infection. These infections form ulcers and turn into granulomas that block organ function and must be removed surgically (Kobayashi et al., 2015).

One of those who have a big chance of being infected with MRSA is DM sufferers. The results of the analysis by Lin et al. (2018) showed the presence of *S. aerus* bacteria in 49 patients (43.8%) and MRSA in 27 patients (24.1%) from 112 samples of diabetic foot ulcer patients. In 2018, Lutpiatina and Eriana also conducted a similar research in Indonesia. Of the 30 samples of diabetic foot ulcer patients, 14 patients had *S. aureus* and 8 of them contained MRSA.

C. Bioactive compounds on Red Ginger Extracts

Chemical analysis of *Z. officinale var. rubrum* shows more than 400 different compounds with the main components of the rhizome, namely carbohydrate (50 – 70%), lipid (3 – 8%), various terpenes i.e. β-bisabolene, zingiberene, β-sesquiphellandrene, α-farnesene, and α-curcumene, and several phenolic compounds such as gingerol, paradol, and shogaol. Gingerol and Shogaol were found in greater amounts in two other types of ginger with an average level of gingerol (23 – 25%) and shogaol (18 – 25%) (Prasad & Tyagi 2015). Compound 6-gingerol can be degraded to 6-shogaol and its derivates i.e. zingerone, gingerdion, and gingerdiol (Ali et al. 2008). A number of the active compounds from the red ginger extract that inhibit MRSA are presented in Table 2. The test for the antibacterial activity of the red ginger extract against MRSA showed that the zone of bacterial growth was inhibited in the disc diffusion method and disc paper (Widiastuti & Pramestuti, 2018).

Table 2. Active compounds in red ginger rhizome that inhibit the growth of MRSA

No.	Isolation Method	Dominant compounds content	Reference
1	Pentane-Hydrodistilllation	Monoterpenoid, campene, geranyl acetate, geranial, neral, geraniol, dan 1,8-sineole	Sivasothy et al. (2011)
2	Aquadest-Pressurized hot water extraction	6-gingerol, 6-shogaol, 10-gingerol	Sarip et al. (2014)
3	Ethanol-Maceration	6-gingerol, 8-gingerol, 10-gingerol, dan 6-shogaol	Prasad dan Tyagi, (2015)
4	Ethanol-Reflux	6-gingerol, 8-gingerol, 6-shogaol, 8-shogaol	Ghasemzadeh et al. (2016)
5	Supercritical fluid extraction	6-gingerol, 6-shogaol	Ko et al. (2019)

D. The potency of red ginger extract on hydrogel wound dressing against MRSA

DM wounds under certain conditions can be certainly contaminated by various pathogens, endogenous microbes that live in mucous membranes, or by microflora present in contiguous skin. Gram positive bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, and gram negative bacteria, such as S. aureus, are the main pathogens in charge of for skin contagion and successive infection (Simões et al., 2018). Currently, a functional hydrogel wound plaster with an antibacterial agent is a solution that is considered to be effective. Table 3 summarizes several studies in involving antibiotics for hydrogel wound

plaster to increase their bactericidal activity. The antibiotics streptomycin, doxycycline tetracycline HCl, and vancomycin have been shown to be effective in inhibiting the growth of *S. aureus*. Although some antibiotics are successful at treating skin contagions, their repeated use might promote resistances for bacteria. Numerous studies report that the inappropriate usage of antibiotics causes the enlargement of new bacterial resistance, thus leading to worldwide spread. More than 70% of those bacteria in charge of wound infection show antibiotic resistance at least for one particular type. MRSA and vancomycin resistant enterococci are two multiresistant microbial incorporated in skin contagions (Simões et al., 2018).

Table 3. Hydrogel plaster loaded with antibiotics

No	Matrix	Antibiotic Agent	Bacteria	Reference
1	PVA/Alginate	Ampicillin	*E. coli*	Kamoun et al. (2015)
2	PVA/cellulose	Streptomycin	*S. aureus, E. coli*	Simões et al. (2018)
3	Fibroin/gelatin	Doxycycline tetracycline HCl	*S. aureus, E. coli*	Chen et al. (2017)
4	Alginate/CMC	Vancomycin	*S. aureus, E. coli*	Lan et al. (2014)
5	mPEG-PLGA	Teicoplanin	*S. aureus*	Peng et al. (2010)
6	mPEG-PLCPHA	Cefazolin	*E. coli*	Lai et al. (2014)
7	O-CMCS	Lincomycin	*S. aureus, E. coli*	He et al. (2016)
8	Calcium-alginate-gelatin with CS/poly-γ-glutamic acid	Amoxicillin	H. pylori	Chang et al. (2010)
9	Chitosan/Gelatin/β-glycerolphosphate	MTZ vancomycin hydrochloride	*C.sporogenes*	Pakzad and Ganji (2016)
10	PNDJ	Gentamicin	*S. aureus*	Overstreet et al. (2015)

Representation of antibacterial wound dressing which aimed to act as a physical blockade for protecting the wound from bacterial attack, supporting fibroblasts movement and differentiation, is schematically depicted in Figure 4. The open wound is susceptible to microbial infection, which trigger a prolonged inflammatory phase and an enlarged appearance of metalloproteinases that are encompassed in the degradation of extra cellular matrix constituents and also inhibit new granulation tissue formation. When the antibacterial wound dressings are applied to shield

the wound bed, it takes action as a physical blockade avoiding pathogens entering into the wound or killing the bacteria. Moreover, the antibacterial wound dressing improves the healing progression by immune system stimulation and relocation of keratinocyte/fibroblast.

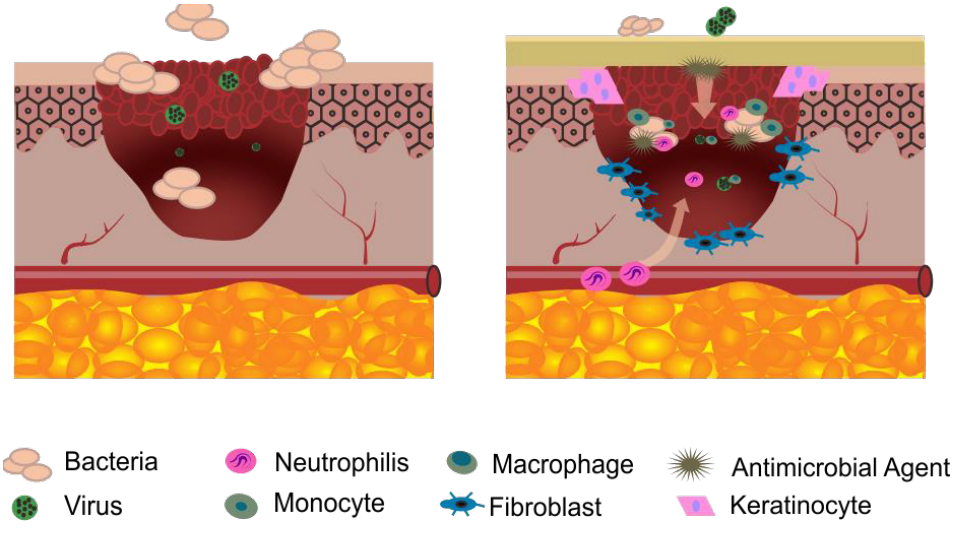

Figure 4. Illustration of the healing mechanism in an open (left) and antimicrobial wound dressing covered (right) wound. Adapted from Simões et al. (2018)

MRSA resistance to all antibacterial classes is increasing so that new effective variants are needed. Simulations conducted by Rampogu et al. (2018) showed 6-gingerol, gingerenone-A and 6-shogaol (Figure 5) on red ginger caused an inhibitory effect against *S. aureus* by preventing the activity of 6-hydroxymethyl-7,8-dihydropterin pyrophosphokinase (SaHPPK) on these pathogens. SaHPPK is an enzyme that catalyzes the transmission of the pyrophosphoril group from ATP to 6-hydroxymethyl-7,8-dihydropterin (HMDP) and has been selected as a drug target because it is not present in humans. The SaHPPK enzyme is an ideal target for drug design because it is only found in MRSA pathogens although it is also found in other bacteria (Dennis et al. 2016). This inhibition is due to the interaction in the form of hydrogen bonds that are formed between the ginger extract molecules and the active SaHPPK group. Gingerenone-A forms four hydrogen bonds with Val46, Gln51, Asn56, and Arg121. Gingerol forms two hydrogen bonds with Val46 and Gln51, while Shogaol forms 2 hydrogen bonds with Val46 and Tyr48. The SaHPPK enzyme is an ideal target for drug design because it is only found in MRSA pathogens although it is also found in other bacteria (Rampogu et al., 2018)

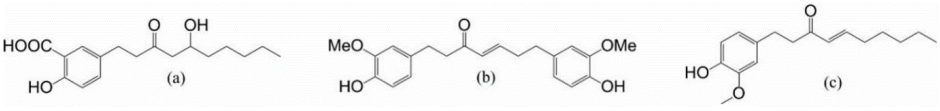

Figure 5. Structure of (a) 6-gingerol, (b) Gingerenone-A, dan (c) 6-shogaol

Phenolic compounds can interact with proteins to form protein-phenolic complexes at low levels even though the bonds between the two are weak and can be broken down. The results of this study showed that the active compounds of JM, namely 6-gingerol, gingerenone-A and 6-shogaol, which can inhibit MRSA growth when put on a hydrogel plaster have the potential to be used as a wound healer with MRSA infected DM wounds. The literature search shows that no one has reported the functionalization of the active compound in red ginger into a hydrogel wound plaster.

E. Recommendation and Future Prospect

Currently, most people have had a skin wound. These wounds can certainly be infected with various pathogens in the nearby environment. A wound dressing that acts as an antibacterial agent is needed to overcome this health problem. After a comprehensive literature study was carried out, the insertion of the active compound of red ginger into the Na-CMC hydrogel provided potential as a new alternative in the form of MRSA-infected DM wound healing plaster instead of conventional wound plaster. Further studies need to be done to determine the mechanism of the role of the hydrogel in synergy with red ginger extract in healing DM wounds. To be safe for use on skin surfaces, the correct method of isolating red ginger extract needs to be determined. Optimization in determining the best composition between Na-CMC hydrogel and red ginger extract against DM wounds also needs to be done.

Conclusion

There is potential from the extract of red ginger rhizome which can inhibit the growth of MRSA bacteria and water hyacinth as a source of cellulose for the synthesis of hydrogels which can accommodate active compounds as a neutralizer of bacterial diabetes mellitus wounds. The use of water hyacinth cellulose and red ginger rhizome extract can be combined to create new alternatives in healing DM wounds.

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✉ **Dr. Maulidan Firdaus (corresponding author)**
Muhammad Iqbal Daniswara
Khoirul Jamaluddin
Department of Chemistry
Faculty of Mathematics and Natural Sciences
Sebelas Maret University
36A, Jl. Ir. Sutami
57126 Surakarta, Indonesia
E-mail: maulidan.firdaus@staff.uns.ac.id

✉ **Novi Andriani**
Pharmacy Study Program, Vocational School
Sebelas Maret University
57126 Surakarta, Indonesia