

# Review: Modification of Nanocellulose as Conjugate of infection-causing Antibacterial Hydrogel

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## ABSTRACT

Infection is the process of entering and reproducing microorganisms such as bacteria, viruses, fungi, and parasites that cause tissue injury. Some of the common types of bacteria that play a role in wound infection are *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermis* and *Pseudomonas aeruginosa*. The antibacterial able to inhibit bacterial growth by inhibiting cell wall biosynthesis, increasing the permeability of the bacterial cytoplasmic membrane, and interfering with the normal bacterial protein synthesis. Our specific aim of this review article is to conduct a study of nanocellulose as an antibacterial hydrogel conjugate. The method used is to summarize information from various recent journals related to nanocellulose, nanocellulose modification, nanocellulose-based hydrogels, and their application as antibacterial. Some journals from primary sources such as the PMC system (PubMed Central), National Library of Medicine (NIH), Science Direct, Elsevier, Nature, ACS Chemical Society, and several other sources. Nanocellulose consists of  $\beta$ -1, 4-glucose and there are three hydroxyls active at the C<sub>2</sub>, C<sub>3</sub>, and C<sub>6</sub> positions of the pyranose attachment. Nanocellulose can respond by the reaction of oxidation, esterification, or etherification, by adding a new functional group. Nanocellulose can become nanocellulose nanocrystals (CNC), cellulose nanofibers (NFC), and nanocellulose bacteria (BNC). Nanocellulose formulated in the form of hydrogels and combined with antibiotics will increase the effectiveness in reducing the risk of infection that is resistant to antibiotics.

## Introduction

Infection is a process of entry and reproduction of microorganisms such as bacteria, fungi, viruses, and even parasites that cause tissue injury [1]. The mortality rate for children under five years in Indonesia caused by infectious diseases reaches 1-20% every year [2]. Bacterial infections can attack various organ and respiratory systems. Some of the bacteria that commonly caused human infections are *Streptococcus pneumoniae*, Group A *Streptococci*, and *Haemophilus influenzae* type B [3]. Skin infections (7-10%) are caused by *Staphylococcus aureus* [4], gastrointestinal infections (5%) are frequently caused by *Shigella*, *Escherichia coli*, *Campylobacter* [5]. Urinary tract infections (0.7–0.9%) are often caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* [6].

When the body is injured, microorganisms will enter into the body, marked by damage to the tissue around the lesion and causing

abscesses in the form of pus, infection, necrosis of the wound tissue, then resulting in the clotting of fibrin around the lesion and lymph vessels, and forming a wall that limits the necrosis process. . Several types of bacteria that generally play a role in wound infection are *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Pseudomonas aeruginosa* [6–8].

*Staphylococcus aureus* is the bacteria that most often cause infections in humans, classified as gram-positive bacteria, often in the body of healthy people on the skin and mucosa, 20-75% are found in the upper respiratory tract, face, hands, hair, and genitals [9]. *Staphylococcus aureus* and *staphylococcus epidermis* generally cause various infections such as acne, ulcers, impetigo, and wound infections characterized by abscesses with pus [9,10]. *Methicillin-Resistant Staphylococcus aureus* (MRSA) is a type of pathogenic bacteria that often attacks

postoperative patients with a high risk of causing death [11]. MRSA is a type of pathogenic *Staphylococcus aureus* that causes infection and has developed resistance to various antibiotics [12].

Due to the high case number of infections caused by bacteria hence, antibacterial (antibiotics) are needed to treat the infection. The discovering of antibiotics has continued to develop since the discovery of penicillin in 1928 [8]. The efforts to developments to find antibacterial compounds continue to develop along with the evolution experienced by bacteria so that they are resistant to several antibiotic compounds [13]. Commonly the are used synthetic antibacterial compounds are salicylates (SAL), chlorhexidine (CHX), isothiazolinone (ITZ), Octenidine (OCT), Quaternary Ammonium (QA) and thiosemicarbazone (TSC) [14].

The research regarding efficient and safe antibacterial compounds and formulations is developing an alternative to the risk of antibiotic resistance and regulate the toxicity of antibacterial drugs [15]. There are growing challenges due to antibiotic resistance researchers have studied various innovative antibacterial ingredients, including using several metal ion complexes and natural compound extracts as antibacterial agents [16]. However, these compounds kill not only pathogenic microbes but also normal cells in the human body. Somehow, that the application of the use of these materials is limited [17].

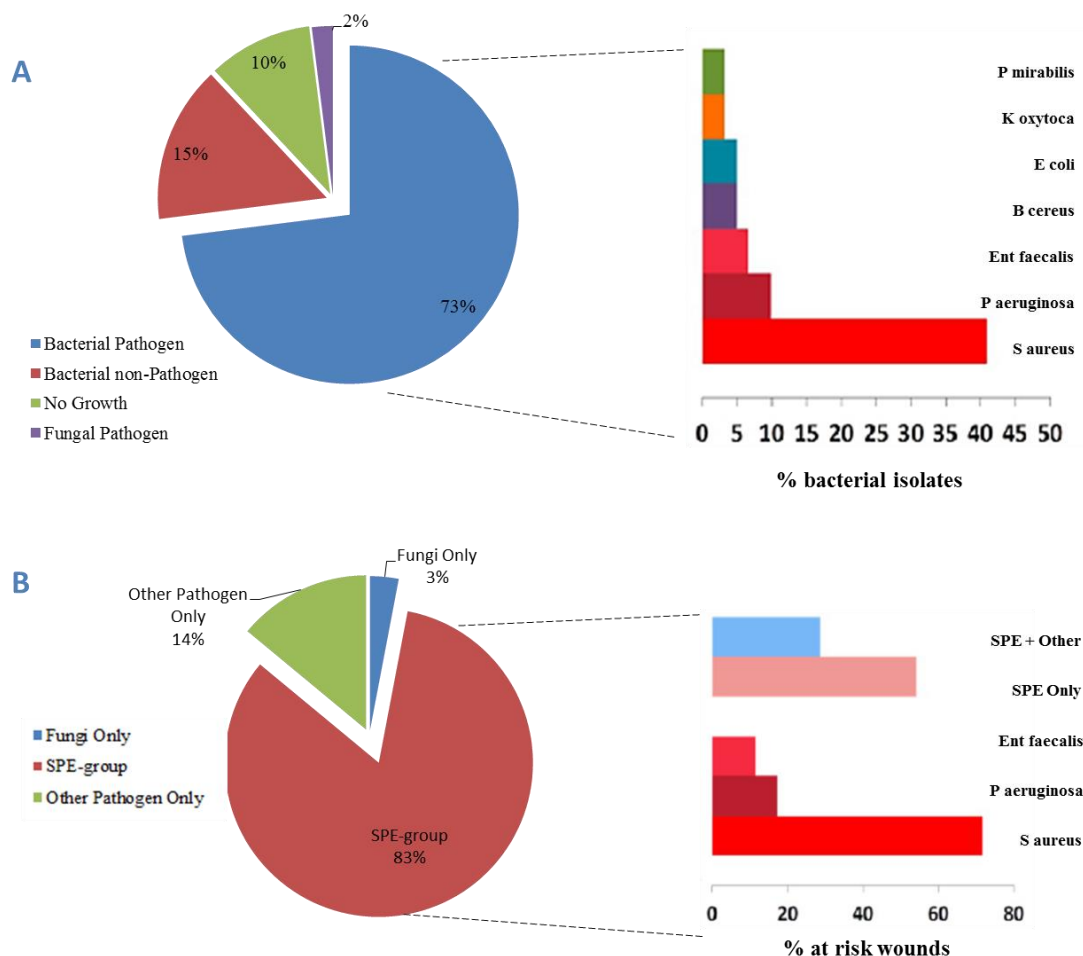
The hydrogel is an antibacterial formulation that develops using materials from natural or synthetic polymers [17,18]. The hydrogel was developed as an antibacterial transport medium used in infectious wounds with the characteristics of being transparent, soft, flexible, and non-irritating [19]. The hydrogel can be developed from polymer chitosan, cellulose, and some plant extracts [19,20]. Based on the hydrogel matrix classification and antibacterial agents, hydrogels are divided into three types: (1) Hydrogels containing metal /inorganic nanoparticles (2) Hydrogels with an

antibacterial substances (3) Hydrogels with inherent antibacterial abilities. Based on the description above, in this review article, we will explain some of the latest references on how to synthesize hydrogels, the characteristics of hydrogel preparations, the hydrogel antibacterial mechanism, and cellulose modification based hydrogels as an innovative antibacterial compound.

### Infection-Causing Bacteria

Infection-causing bacteria have a profound effect on public health [1–3]. The bacterial is easier infection than viruses because bacteria are fast-growing and resistant to an antimicrobial. Thus, it requires continuous development and searches to produce new antimicrobial products [4–7,9].

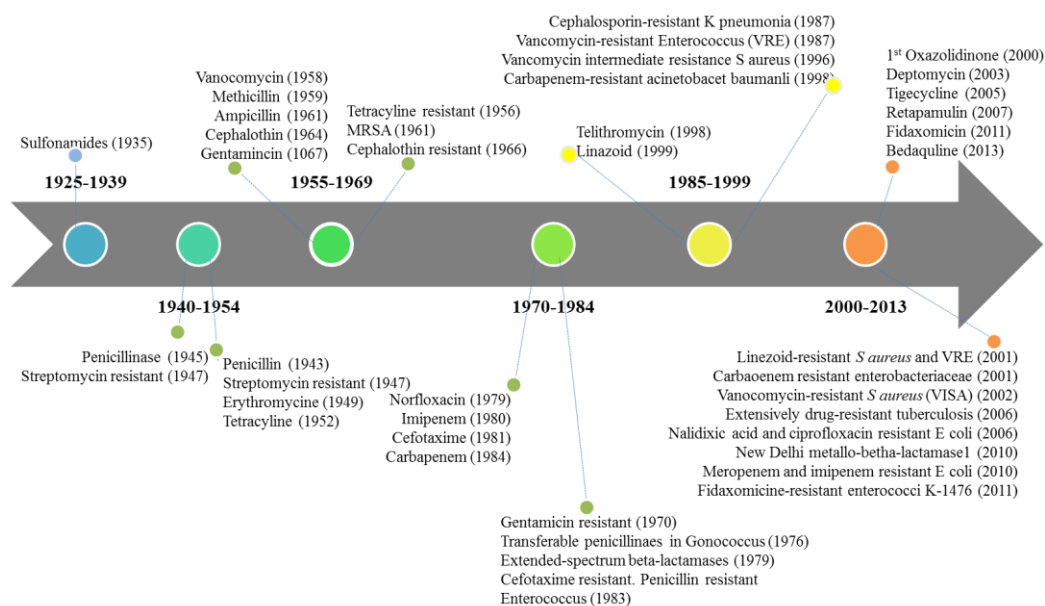
Bacteria have an outer layer in the form of a cell wall composed of peptidoglycan. Antibacterial can interfere with the formation of the cell wall by blocking the work of enzymes, the cell wall is not formed or damaged and causes bacterial cells to lysis and die, due to the cell wall functions as a regulator of the exchange of substances from outside and into cells, and gives cell shape [21]. *S. Aureus*, *p. aeruginosa*, and *E. paecalis* are common bacteria, complicating wounds, and from independent studies of clinical records relating to wounds, it was found that the survey wounds were colonized by pathogenic bacteria (Figure 1A). *S. aureus* is the most common bacteria found in wounds, slowing the wound healing process by -75%, making it very risky to infect wounds. Also, *P. aeruginosa* and *E. coli* with a percentage of -17% and -11% infected wounds (Table 1). *Staphylococcus aureus* usually carried by people on their skin or mucous membranes then causes skin and soft tissue infections, but also spreads easily throughout the body via the bloodstream and can cause infection of the lungs, stomach, heart valves, and almost anywhere else. The disease can be caused by damage to body cells by organisms or the body's immune response to infection [6].



**Figure 1.** Data on the proportion of wounds colonized by pathogenic microbes and cases due to specific pathogens. (A) The proportion of burns colonized by pathogenic bacteria or fungi at risk of causing infection. (B) The proportion of wounds at risk of being colonized by the dominant SPE class pathogens, consisting of *S. aureus*, *P. aeruginosa*, and *E. faecalis* [4].

**Table 1.** List of bacteria studied in the development of wound biofilm models

Species	Microbial Strains	Virulence Activity	References
<i>E. coli</i>	<i>DH5α</i>	Control	[12,22]
<i>S. aureus</i>	<i>MSSA475, RN4282, USA300, Agr+, Agr</i>	Pathogenic (except Agr-)	[12,23,24]
<i>P. aeruginosa</i>	<i>PAO1</i>	Pathogenic.	[12,22,24]
<i>E. faecalis</i>	<i>E43, E57, E68</i>	Pathogenic.	[5,6]
<i>N. meningitidis</i>	-	Infecious	[25,26]



**Figure 2.** The history timeline of the antibacterial development and the microorganism acquisition of resistance [27]

Bacteria can infect humans through certain organs. *Neisseria meningitidis* commonly infect the meninges by covering of the central nervous system, causing meningitis, and can also infect the lungs, causing pneumonia. Moreover, bacterial infection causes systemic inflammatory response syndrome (SIRS), is an inflammatory response to infection, by the release of large amounts of cytokines, cytokine storms, and there are signs of infection and early signs of hemodynamic instability (Daron and Gorbach, 2008).

### Antibacterial Compound

The evolution of bacteria leads to efforts to develop technology and knowledge to find antibacterial compounds that can work optimally [28]. Generally the antibacterial mechanism work by damaging cell walls, changing membrane permeability, interfering of protein and nucleic acid synthesis, and inhibiting enzyme action [25,26,28]. The discovery of antibiotics has continued to develop since 1928, the discovered penicillin and has been widely used as an antibacteria [8]. The efforts to discover an antibacterial compound continue to develop along with the bacteria, resistant to several antibiotic compounds [13]. In inhibition of bacterial cell protein synthesis, generally antibacterial, will cause misread the code in mRNA by tRNA

(translation and transcription barrier of genetic material) such as aminoglycosides, also inhibit following the same inhibition pathway. Generally, antibacterial compounds will bind to one of the components that play a role in the synthesis stage [29]. The clinical use of synthetic antibacterials has disadvantages such as high toxicity, high cost, and their use often leads to the emergence of resistance. *Staphylococcus epidermidis* bacteria have been resistant to penicillin and methicillin antibiotics [30]. Recently, efforts and development for alternative antibacterials, by utilizing natural ingredients (secondary metabolites) as traditional medicines (ethnobotany) instead of synthetic antibiotics [31].

The antibacterial mechanism is influenced by the content of secondary metabolite compounds as active compounds. Tannin compounds, as antibacterial can able to inhibit bacterial cell synthesis by topoisomerase inhibition [32]. Moreover, tannins has cell wall polypeptides target, and the formation of the cell walls does not complete, then causes bacterial cells to become lysed due to osmotic or physical pressure so that the bacterial cells will die [33]. The mechanism of antibacterial activity of flavonoids by inhibiting nucleic acid synthesis, cell membrane permeability function, and energy metabolism inhibition [34].

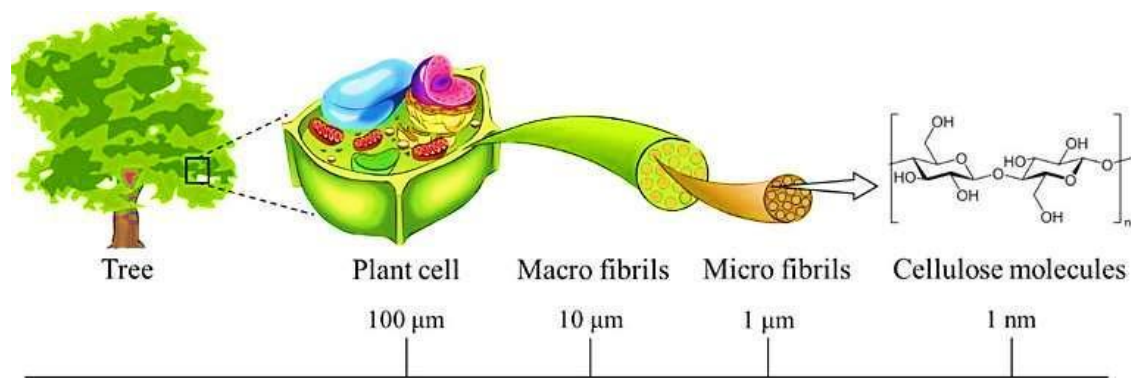
Flavonoids inhibit nucleic acid synthesis, which is A and B rings play an important role in the hydrogen bonding process by inhibiting the formation of DNA and RNA. Flavonoids also cause to damage the permeability of bacterial cell walls, microsomes, and liposomes [34]. Flavonoids can form a complex compound from extracellular and dissolved proteins counterparts, the cell membrane will be damaged, and intracellular compounds will come out [34,35]. Meanwhile, its can inhibiting energy metabolism, bacteria unable to use oxygen uptake, then preventing the energy formation in the cytoplasmic membrane, inhibiting the bacteria motility, which plays a role in antimicrobial activity and extracellular proteins [36]. Alkaloid compounds have an inhibitory mechanism by damaging the peptidoglycan constituent components in bacterial cells that the cell wall layer is not fully formed and causes cell death [34,37].

Saponin antibacterial activity can reduce the cell walls' surface tension and increase surface permeability, cell leakage, and intracellular compounds being released [35]. The terpenoid mechanism is through the process of breaking down the membrane by lipophilic components so that it damages the bacterial cell membrane [21,38]. The antibacterial mechanism of phenol compounds in killing microorganisms is by denaturing cell proteins, the hydrogen bonds formed between phenols and proteins causing the protein structure to be damaged and affecting the permeability of the cell wall and cytoplasmic membrane, which is disturbed which can cause unbalanced macromolecules and cell ions, and finally the cells become lysis.

A semicrystalline polysaccharide of nanocellulose-based antibacterial cellulose exists in nature in the fibers form, ranging from

0.5 to 0.8 mm [39]. Cellulose composes  $\beta$ -D-glucopyranose, which is connected by 1-4- $\beta$ -glycosidic bonds. The *compound* chains come together and form basic fibrils consisting of crystalline and amorphous domains. The structure of cellulose allows it to break down into nanocellulose, which are produced using mechanical-based methods, by bacteria into crystal nanocellulose (CNC), bacterial nanocellulose (BNC), and cellulose nanofibers (CNF) [40]. Previous studies have found that nanocellulose utilizing has several advantages for cellular culture, medicinal excipients, drug candidate administration; cellulose immobilization, and either enzymes and proteins recognition. Moreover, it also the macroscopic biomaterial level (Blood vessels, soft tissue substitutes, skin, bone tissue repair agents, and antimicrobial agents).

The functional modification of nanocellulose has high potential biomedical applications of nanocellulose modified [13,41]. Furthermore, nanocellulose is used as drug delivery by adding to the content of antibiotic compounds. These antibiotic compounds are used to strengthen the antimicrobial activity of cellulosic materials such as polymyxin B, ampicillin, tetracycline-HCl, gentamycin, ceftriaxone, and chloramphenicol. Nanocellulose formulated in the form of a hydrogel and combined with antibiotics will increase the effectiveness in reducing the risk of infection that is resistant to antibiotics. In addition to nanocellulose, several polymer compounds that are widely used are chitosan, an antimicrobial polymer that shows good antibacterial activity in either *Bacillus cereus* and *Salmonella typhimurium*. The presence of chitosan biofilm of the nano-fiber chitosan (NFC) showed an antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*.



**Figure 3.** Cellulose found in plants or trees has a hierarchical structure from the meter to the nanometer scale [26].

The development of nanocellulose-based antimicrobials has attracted a lot of attention because of their unique characteristics and potential for widespread use. The nanocellulose was used for wound healing, drug delivery, and other advanced materials. Nanocellulose-based antimicrobial agents are an abundantly source, biodegradable, and much more easily be prepared. The method in modifying nanocellulose as an antibacterial material is carried out [1,6,9] by modifying the surface of the nanocellulose. Nanocellulose consists of β-1,4-glucose with three hydroxyls active group at the C<sub>2</sub>, C<sub>3</sub>, and C<sub>6</sub> positions of the co-pyranose glu-ring. Nanocellulose can modify through oxidation, esterification, or etherification reaction, which will introduce new functional groups. Functional groups contain antimicrobial properties include the quaternary aldehyde and ammonium groups, that shows good antibacterial activity and biocompatibility. Besides, in combination with nanomaterials, inorganic nanoparticles are also widely used based on nanocellulose as an antimicrobial material, such as precious metal nanoparticles and metal oxide nanoparticles. The minimal inhibitory concentration (MIC) of

nanocellulose-based materials containing inorganic nanoparticles is much lower than that of single metal or metal oxide nanoparticles, which are beneficial to humans, environment, and health [24–26].

#### Modification of Nanocellulose

There are various bio-nano composites, which are produced based on CNC as nanofillers and natural polymer matrices, protein, gluten, chitosan, gelatin, cyclodextrins, maltodextrins, starch, alginate, natural rubber, xanthine, and cellulose derivatives CMC (carboxymethyl cellulose), hydroxypropyl cellulose, regenerated cellulose, and cellulose diacetate). Modifications have been to optimize nanocellulose, such as surface modification. The modifications of nanocellulose can be carried out by oxidation of hydroxyl using TEMPO-oxidation or ammonium persulfate [41]. Modification of nanocellulose to 2,3-dialdehyde NFC (DANFC) using periodate sodium and DANFC has antibacterial activity against both of multidrug-resistant (MDR) of *S. aureus* and *S. aureus* increases in proportion to the increase in aldehyde content [26].

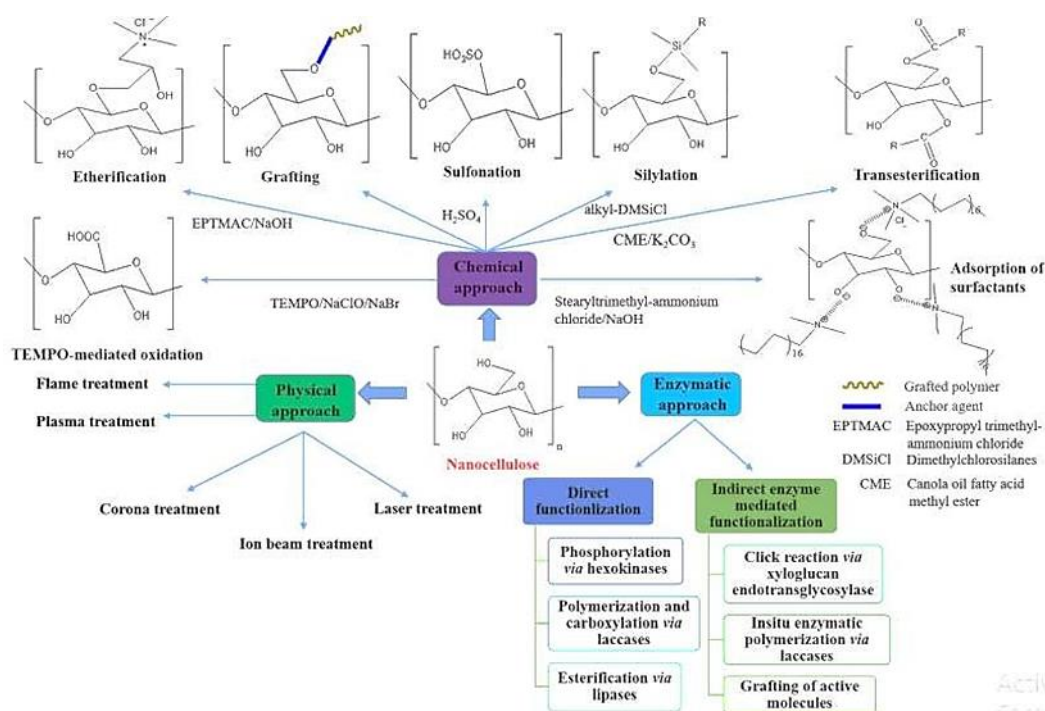


Figure 4. Schematic representation of the nanocellulose surface modification route [26].

Recently, nanocellulose-based antibacterial has been developed by grafting quaternary ammonium compounds. Which are the most widely used antimicrobial agents due to their antibacterial properties, such as low toxicity, and environmental compatibility. The cationic phosphorous on the NCC surface was modified via the Cu(I)-catalyzed Huisgen-Meldal-Sharpley reaction, capable to inactivated *S. aureus*, and *Mycobacterium smegmatis*, although with little activity against *E. coli*.

### Hydrogel as an Antimicrobial Agent

The hydrogel is a polymer with 3-dimensional network can absorb and bind water molecules with very high ability in a relatively short time and can maintain a swelling state at a certain pressure [24,42], due to the hydrogel has hydrophilic groups, able to absorb fluids and retain a number of fluids, and release them under certain conditions. Moreover, the hydrogel absorb a large amounts of water molecules and has a good biocompatibility, so the hydrogel can be used as a wound covering, release system medicine, cosmetics, medicinal shell, and agriculture. Instead of natural hydrogels, it also can produced by synthetic polymers, polyvinyl pyrrolidone, from polyacrylic acid, as well as natural polymers such as chitosan, cellulose,

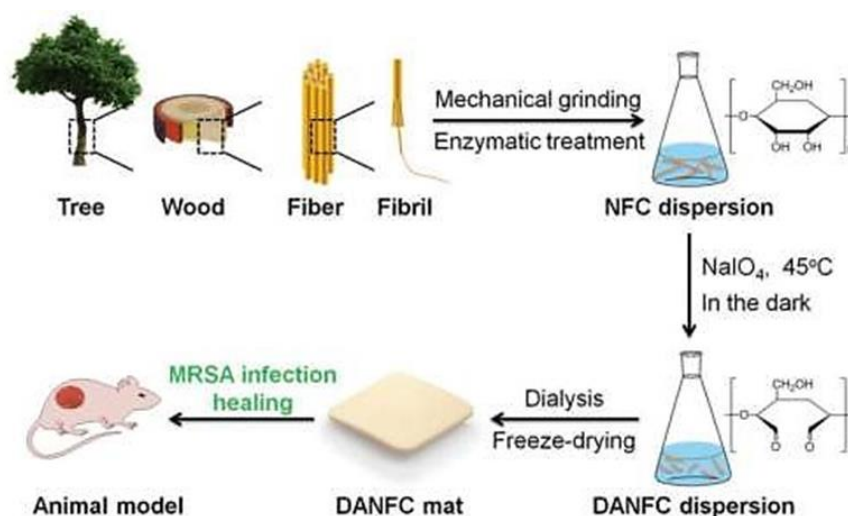
carrageenan, and alginate [19]. The hydrogel then applied as a drug delivery, the hydrogel network can control the release system for small molecule encapsulates so that it can be used as an antimicrobial agent, antibiotics, metal compounds, and other organic compounds [43]. The hydrogel that has been developed is a hydrogel with a polymer base, without the addition of drugs, the hydrogel is developed with the addition of banana sap to accelerate the wound healing process. The PEO-PEGDMA hydrogel film with the addition of banana sap was proven to be able to increase the acceleration of the speed of wound healing with the optimal percentage of wound healing occurring at a 15% concentration of PEO-PEGDMA-Banana Gum which can be inserted into the hydrogel tissue which acts as a matrix [20,44].

The hydrogel can be used as a wound cover made from PVA chitosan and starch, with the addition of smoke. Coconut shell liquid and vitamin K [19] which can heal irritated wounds in test animals can heal on day 10. Somehow, it also can incorporate Ag NPs into hydrogel matrix by semi-interpenetrating polymer fingers [16]. Ag-hydrogel nanocomposite has been used as wound healing, wound dressings, for biomedical applications, and water purification. Chitin-Chitosan have antibacterial

activity and metal-binding shifts. The hydrogels can be made by utilizing antibacterial compounds from natural ingredients as active compounds, such as banana sap, seaweed, and betel leaf. The content of banana sap which functions as an antibiotic, pain reliever, and can stimulate skin cell growth, is used as a basic ingredient in the manufacture of hydrogels as antibacterial agents. The application of hydrogel can inhibit wound infection so that it can be categorized as antibacterial [45]. The content of secondary metabolites of Tapak Kuda leaves such as flavonoids, steroids, alkaloids, saponins, terpenoids, tannins, and anthraquinones have been formulated antibacterial gel [46]. *Tagetas erecta* leaves contain flavonoid and phenolic as bioactive compounds, that have antibacterial activity [13,19,21,24–26,28–33,35–41,43–47]. In addition, it is also known that the Ceremai plant (*Phyllanthus acidus* (L.) is useful as an antibacterial which plays a role in preventing

infection [46]. Moreover, plant seeds contain phytochemical compounds, flavonoids as antibacterial, the ethyl acetate extract of Ceremai leaves has an effective antibacterial activity using a concentration of 8% [23].

Hydrogel production produced by the process of Freezing Thawing, and gamma-ray irradiation [13,25]. The hydrogel is formed by macromolecular cross-linking to produce specific 3-dimensional structures with precise chemical and mechanical properties. Previous studies reported that hydrogels obtain by cross-linking of Pegagan leaves extract with N,N-methylene bis-acrylamide [38]. In addition, hydrogels can also take advantage of rice straw which contains sufficient cellulose for the manufacture of hydrogels. Hydrogels are synthesized using tea plants, by utilizing cellulose content which is carried out using the cross-linking method with a mixture of aluminum sulfate [21,37,38].



**Figure 5.** Schematic of the DANFC experimental process and the effect of wound cover on the Mouse Model [48]

The hydrogel synthesis method is the hydrothermal method, using Na-CMC Self-Cross-linking reaction on an unstable active hydroxyl group on NaCMC, the addition of chitosan can reduce the occurrence of Self-Crosslinking so that it can strengthen the hydrogel [49]. The manufacture of hydrogel based on natural polymers, pectin, and gelatin. These two materials, combined using the cross-linking by adding citric acid as a cross-linking agent and affects the hydrogel properties of the hydrogel material. The hydrogel made in the

form of a film will produce the highest thickness, Swelling Ratio, and degree of substitution at a concentration of 10% citric acid. While the highest gel fraction was produced by hydrogel with 20% of citric acid.

### Hydrogel characterization

Characterization of the physical and chemical properties of the hydrogel was carried out to determine the raw material standards to suit the needs [25]. Viscosity characterization to determine the level of solution viscosity, gel strength, water content, ash content to



determine mineral content and determine the ash content that is insoluble in acid, measure the gel fraction, swelling ratio, water vapor transmission speed, and mechanical properties, determine the chemical structure and the morphology can use FTIR and SEM, to prove the acceleration of wound healing speed was analyzed using in vivo test [1,5,7]. SEM test to analyze the surface, shape, texture, and size of the membrane from the hydrogel as a cover for burns, the presence of a pore on the hydrogel shows that the membrane covering the hydrogel wound contains the active compound [19].

The swelling ratio is the main parameter of the hydrogel to determine hydrogel weight in the water-absorbing state [20]. Preparation of hydrogels with a combination of Galactomannan polymer from guar gum and PVA. PVA has a structure that can interact with hydrogen bonds, so that it can bind insoluble compounds and make them easily soluble and hydroscopic so that they can absorb water, form a good gel, and have high adhesion [50]. For example, the Hydrogel formula for Wound Dressings Using a Combination of Galactomannan and PVP Polymers [42].

The results of the physical characteristics of the preparations were the diameter, thickness, and folding power of the preparations. Based on table 4, the hydrogel thickness test shows that formula three is following the specifications, 0.4-0.7 mm, but formulas 1, 2, 4, and 5 have very low thickness [42].

#### **Hydrogel contains Antibiotics**

The hydrogel is able to selectively kill bacteria, so it can be used as an effective anti-infection in the right dose [44]. The addition of other compounds to the hydrogel matrix aims to build hydrogel composites that can act as antimicrobials, for example, the addition of trisodium phosphate, acidified sodium chloride which is incorporated into starch as an antimicrobial [51].



**Figure 6.** Hydrogel formula for galactomannan polymer wound dressings [42]

Furthermore, several modifications were made to increase the hydrogel antibacterial activity by adding antibiotic or metal compounds. AgNP-modified Nanocomposite of Hydrogel has good antibacterial activity against both gram positive and negative bacteria. The modification uses the biopolymer sodium alginate as the main component [52]. In addition to modifications using metal elements, several modifications have also been made to the surface of the nanocellulose. Cellulose nanocrystals (CNCs) of surface modified bears with various functional groups such as  $\text{SO}_4$ , esters after sulfuric acid isolation, OH after enzymatic or hydrochloric acid treatment, and COOH after oxidative isolation in the presence of 2,2,6,6-tetramethyl- piperidinyl-1 -oxyl (TEMPO) radicals [53].

Hydrogel as an antimicrobial can quickly prevent infection, make wounds heal faster [54], smooth, easy to use, able to keep skin moist, have an attractive appearance, do not irritate the skin, and last longer in wound tissue [55]. In addition, the hydrogel functions to keep the wound environment moist softens, and destroys the necrotic tissue without damaging healthy tissue, which is then absorbed into the gel structure and removed with the dressing (natural autolytic debridement) [56].

The use of hydrogel as an antibacterial material needs to be continuously developed so that the remaining matrix that remains after the drug is released can be removed [43]. Chitosan-based hydrogel with honey and gelatin has weaknesses in water absorption and modulus young so that it is not good for dressing wounds for a long time, high chitosan viscosity and poor honey dilution can cause losses in the compatibility of hydrogel components [57,58].

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## Conclusion

Our finding in this article review that infection can occur, one of which is caused by the presence of bacteria and viruses. The discovery and development of antibacterial compounds have been carried out with various innovations such as being developed in the form of a hydrogel. Nanocellulose is one of the ingredients that can be used as an antibacterial hydrogel either directly with nanocellulose or modified with other materials. Nanocellulose can be modified into nanocrystal nanocellulose (CNC), cellulose nanofibers (NFC), and bacterial nanocellulose (BNC). Nanocellulose is formulated in the form of a hydrogel and combined with antibiotics will increase its effectiveness in reducing the risk of infection that is resistant to antibiotics.

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