Materials Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *Mater. Adv.*, 2022, 3, 7463

Cellulose composites containing active constituents of coffee and tea: a prospective novel wound dressing

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Received 5th June 2022,
Accepted 6th August 2022

DOI: 10.1039/d2ma00642a

rsc.li/materials-advances

Cellulose-based wound dressings are increasingly in demand due to their biocompatibility and extracellular matrix (ECM) mimicking properties. Although they contain no active constituents, pure cellulose-based scaffolds have promoted tissue regeneration. On the other hand, the absence of active ingredients opens the opportunity for the wound to become infected through microbial contamination and reactive oxygen, which will prolong the wound healing time. Microbial resistance to antibiotics has also become a problem that needs to be solved by replacing them using bioactive constituents of coffee and tea, which will be incorporated in a cellulose-based biopolymer matrix. Here, we discuss the potential development of a prospective wound dressing using cellulose composites with active ingredients found in coffee and tea. The mechanisms of coffee and tea wound healing properties are discussed, including their *in vitro* and *in vivo* characterization.

1. Introduction

The wound healing mechanism is a complex series of events involving various cellular and biochemical processes to reconstruct and regenerate damaged tissue.[1] The wound healing process involves three distinct phases: inflammation, proliferation, and maturation.[2] Wound dressings are essential to cover and protect open wounds; an ideal wound dressing should be non-toxic, inexpensive and sterile, not release non-biodegradable particles, and be flexible and easy to use. It also maintains

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moisture in the wound, and is rarely changed, produces minimal pain during replacement, maintains wound at optimal temperature and pH, provides an antimicrobial barrier and activity, absorbs excess exudate, inactivates proteolytic enzymes in chronic wound fluid, provides hemostatic activity and effective wound debriding activity, and is permeable to oxygen, CO_2, and water vapor.[3,4] Wound dressings are generally widely available in the form of traditional cotton gauze. However, cotton gauze has no active healing ability.[5] Synthetic polymers have been extensively modified as biomedical materials such as in drug delivery systems (DDSs), tissue engineering, wound dressings, and other medical applications. However, these polymers are controversial in their biocompatibility and bioaccumulation and are limited in their efficiency and versatility.[6] Textile wound dressings also impact wound maceration and often cause severe pain upon removal. This limitation can be overcome by utilizing natural polymer-based wound dressings, such as cellulose hydrogel scaffolds to maintain environmental humidity and drug delivery.[7]

The availability of abundant natural biopolymers leads to the optimization of cellulose hydrogels' application in DDSs and tissue engineering.[8] Several other natural polymers have also shown biocompatibility in tissue engineering and DDS applications, for example, chitosan,[9] hyaluronic acid,[10] collagen,[11] alginates,[12] and biopolymers. In modern wound care, wound dressings are expected to be able to maintain wound moisture while being able to absorb excess exudate. Even though they have shown their biocompatibility, these natural biopolymers have limitations in absorbing wound fluid (*e.g.*, chitosan, alginates, and collagen) and are relatively

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expensive (collagen).[13] Compared to these biopolymers, the use of cellulose in wound dressing applications is superior in terms of:

a. Low cost due to abundant availability which depends also on process technology and modifications

b. Having a nanostructure, especially bacterial cellulose (BC)

c. High hydrophilicity, especially after being modified, so it has a high exudate absorption capacity

d. Tending to be easy to modify

Of the many types of cellulose available, BC has been widely studied in medical biomaterial applications, is biocompatible with living tissue, and could support tissue growth due to its nanopore structure, good mechanical properties, and features that mimic the skin extracellular matrix (ECM). The 3D structural property of BC is supported by its superior physicochemistry, as its nano-size allows it to store the drug before it is released at the target site. In addition, the nanometer pore size and high hydrophilicity allow the added benefit of absorbing excess wound exudate.[14]

Biofilms and antibiotic resistance are often the main problems in choosing drugs to heal chronically infected wounds. In the long-term, topical antibiotics alter the microbiological environment attached to the skin and alter the bacteriology of the anterior nares and oropharynx, resulting in the emergence of resistant pathogens.[15] Bacteria can wrap themselves in a matrix of hydrated polysaccharides and proteins and form a slimy layer called a biofilm.[16] Biofilm formation increases bacterial tolerance to antibiotics and chemical disinfectants and protects bacteria against phagocytosis and other components of the body's defense system, resulting in chronic infection.[17] Bacteria in chronic wounds that form biofilms will be protected from host defenses and develop resistance to antibiotic treatment.[18] Of course, chronic infection by bacteria is very detrimental to wound healing. Therefore, the topical route offers several advantages in avoiding systemic toxicity and side effects, decreased induction of bacterial resistance, and high concentrations of antibacterial agents at the site of infection.[15]

Cellulose on its own does not contain active constituents that would act as antimicrobials or antioxidants. Antimicrobial activity, growth factor delivery, exogenous cell therapy, and biocompatible and biodegradable matrix construction play a role in designing high-tech dressings.[19] Hence, adding active pharmaceutical ingredients (APIs) or drugs to the scaffold matrix based on cellulose is an attractive way to augment their activity. Some stimulant plants, such as coffee and tea, contain naturally active ingredients for wound healing and are available in abundance in natural ingredients or herbal products sold commercially. They provide a stimulant effect when consumed, but these plants can also be helpful as cheap topical drugs to accelerate wound healing.

Active constituents such as alkaloids, flavonoids, phenolics, essential oils, saponins, and other bioactive phytochemicals are the key to the potential of stimulant plants to repair damaged skin tissue. The active phytochemicals of plant stimulants are very complex, making it difficult to determine the specific constituents that contribute to wound healing. However, some specific constituents were found to contribute to the acceleration of wound healing activity, such as chlorogenic acid in coffee and green tea polyphenols. On the other hand, caffeine has shown contradictory characteristics, namely accelerating and inhibiting wound healing simultaneously.[20] Furthermore, caffeine may contribute to antioxidant, anti-inflammatory, and antibacterial mechanisms, but caffeine can also inhibit cell proliferation.[20–22] The natural active constituents of stimulant plant-based drugs are an attractive alternative to reduce the excessive use of antibiotics.

The combination of cellulose-based wound dressings as a natural, sustainable biopolymer and medicinal medium with natural active ingredients from stimulant plants as a source of antimicrobials and antioxidants could enhance wound healing. This article reviews the potential combination of cellulose biopolymers and plant stimulants as natural, bioactive wound dressings.

2. Cellulose wound dressing

The unique structural, hydrophilic, and physicochemical properties make cellulose an exciting option as a potential wound dressing. Cellulose can be found in the lignocellulosic biomass of plants and hemicellulose, lignin, and other components; and is also produced by bacteria, algae, and marine animals. Surface modification of nanocellulose can improve dispersion ability in solvents of different polarities, making it useful in DDS, tissue engineering, protein immobilization, and inorganic reaction templates.[23] In addition, based on the fiber size, nanometer-structured biopolymers can significantly improve wound healing compared to conventional fibrous dressings.[24]

BC is superior to vegetable cellulose due to its high porosity, purity, permeability to gases and liquids, water absorption, mechanical resistance, and biocompatibility. It allows modification to obtain local drug delivery features and an antibacterial response.[25–27] Furthermore, BC hydrogels have improved the nonhealing lower extremities, including diabetic ulcers, by accelerating epithelialization in human studies.[28,29] In addition, chemically functionalized cellulose, like carboxymethyl cellulose (CMC)-based wound dressings, is also an attractive source for the development of wound dressings because of its biocompatibility, biodegradability, resemblance to extracellular tissue, low cost, and non-toxicity.[30]

Cellulose-based wound dressings have been widely developed by forming composite dressings with other polymers. For example, Harkins *et al.*[31] developed a composite wound dressing of cellulose and chitosan that exhibited biocompatible, non-toxic, and biodegradable properties. It effectively inhibited the growth of vancomycin-resistant *E. faecalis* (ATCC 51299) and *E. coli* (ATCC 8739). BC soaked in chitosan, followed by a freeze-drying process, showed no cytotoxicity, inhibited *S. aureus* and *E. coli*, and accelerated epithelialization and regeneration of wound tissue in a rat model.[32] The hydrogel composite of carboxymethyl chitosan and dialdehyde-modified

nanocellulose crystals is also biocompatible and supports the growth of partial-thickness burn cells.[33]

BC and montmorillonite nanocomposites, which have antimicrobial activity against *S. aureus* and *E. coli*, have been developed and applied as a dressing to accelerate tissue regeneration for wound healing.[34] Adding zein, a maize protein, to the nanocellulose acetate fiber membrane increased the hydrophilicity and bioactivity and created a moist wound environment.[35] Cellulose/gelatin composite sponges were influential in wound healing and exhibited micro-and macro-porous architectures.[5] Cellulose–collagen composites were found to support the healing of moderate depth donor site wounds with little or no postoperative pain.[36] Nanoelectrospores of poly-(ε-caprolactone), cellulose acetate, dextran, and tetracycline hydrochloride were developed for wound dressing applications.[37] The incorporation of dextran and the antibiotic enhanced the adhesion and cell proliferation of the nanocomposite fibers and antimicrobial activity. Using crosslinking and freeze-drying methods, Yin *et al.*[38] combined gelatin, hyaluronic acid, and cellulose nanocrystals to produce a hydrogel wound dressing. Nanocellulose significantly improved the hydrogel properties and played a vital role in displaying the appropriate rheological and swelling responses. NIH-3T3 cells were able to adhere, proliferate, and grow in these hydrogel composites. These studies show that cellulose composites increase the multifunctionality of the developed biomaterial and increase their potential use as bioactive wound dressings.

Commercialized, modern wound dressings are made of biopolymers containing active compounds.[24] Several methods can incorporate drug models (such as natural active constituents, antibiotics, and metal dioxides) into cellulose polymers, such as crosslinking, suspension and solution mixing, synthesis, impregnation, immersion, UV irradiation, and immobilization (Table 1). Nanocellulose fibers containing chemicals, biochemically APIs, or even stem cells can be used as a delivery vehicle for wound dressings.[39] For example, silver nanoparticles added in the adsorbed cellulose and chitosan composites were biocompatible with NIH3T3 fibroblastic cells and displayed antibacterial efficacy against Gram-positive and Gram-negative bacteria.[40] Table 1 summarizes some biocompatibility studies incorporating cellulose and its derivatives with active ingredients (model drugs) for wound dressing applications.

3. Cellulose as a medium for drug delivery systems (DDSs))

In general, wound dressings consist of a matrix/medium and a drug model, in which the delivery efficiency affecting the drug efficacy is discussed in DDS. The DDS must be considered in designing and developing cellulose-based wound dressings to prevent infection or increase the drug efficacy. A DDS determines the active compound's concentration in the blood with minimum fluctuations and predictability. The DDS is also helpful in protecting bioactive compounds with very short half-lives, eliminating their side effects due to drug wastage and the need for frequent dosing, thereby optimizing their therapeutic effect by solving drug stability problems.[53] Hydrogels, as a DDS, have been shown to demonstrate good biocompatibility, a flexible network structure to control drug diffusion, an adaptable affinity for drugs, an ability to encapsulate water-soluble compounds, and sustained local bioactive release.[53,54] The hydrogel formation mechanism as a drug delivery medium can be carried out through:[55] (1) physical crosslinking, achieved by using various environmental triggers (ionic strength, temperature, and pH) and various physicochemical interactions (charge condensation, hydrophobic interactions, stereocomplexation, hydrogen bonding, or supramolecular chemistry), and (2) covalent crosslinking *via* small-molecule or polymer–polymer crosslinking initiated *via* redox polymerization, esterification with an anhydride, and imine linkage formation.

Cellulose might be an excellent DDS due to its biodegradability, biocompatibility, abundance, and unique encapsulation properties. Hydrogels, based on cellulose, can be easily prepared through physical interactions (van der Waals, hydrogen bonds, mechanical chain entanglement, electronic associations, or hydrophobic) or chemical crosslinking (using crosslinker agents).[56] Cellulose and its derivatives can change the solubility or gelling of drugs to control the drug release profile sustainably.[57] Because of its high surface area and polymerization, nanocellulose provides high loading and binding capacities for APIs, allowing drug-release control.[58] Cellulose nanofiber-based media enable controlled drug release by dispersing the drug in the fiber, changing processing conditions, and exploiting the unique chemical properties of cellulose nanofibers.[59] As a medium for controlling drug release, nanocellulose forms a dense fiber network around the incorporated drug entity.[60] Electrospun cellulose nanofibers have been studied as a DDS due to their antioxidant, anti-inflammatory, antimicrobial, anti-cancer, vitamin, and amino acid characteristics. However, these fibers are not fully biodegradable in the human body because of the absence of cellulase enzymes.[61] The routes that could be used to control the rate of drug release include:[55]

(1) Drug–hydrogel interactions (Fig. 1)

a. Physical interactions: through charge interactions between ionic polymers and charged drugs.

b. Covalent bonding: drugs are covalently conjugated to the hydrogel matrix, the release of which is controlled by the chemical or enzymatic cleavage rate of the polymer–drug bond.

(2) Gel Tissue Engineering (Fig. 2)

a. Interpenetrating Polymer Networks (IPNs): the second hydrogel network is polymerized in the pre-polymer hydrogel by immersing the pre-polymerized hydrogel into the monomer solution and polymerization initiator.

b. Surface Diffusion Control: this reduces the permeability "film" layer on the hydrogel surface, often with a thermosensitive switch for on–off drug release.

c. Composite Hydrogels: drug encapsulated microparticles are added to the hydrogel network.

The difference in the drug solubility impacts the ease of dispersion in the cellulose matrix. BC is one type of cellulose utilized for topical drug delivery.[62] The surface of the BC matrix

Table 1 Study of cellulose as a wound dressing

Type of cellulose	Active compound	Cell culture model	Microbial target	Methods	Results	Ref.
Hydroxyethylcellulose	Tungsten oxide	Human dermal fibroblast cell	*Salmonella* sp., *P. aeruginosa*	Crosslink with citric acid	The hydrogel membrane was anti-inflammatory and antibacterial, and tungsten was safe against normal human cells (white blood cells and dermal fibroblasts).	41
Cellulose	Diclofenac	—	—	Mixing trimethylsilyl cellulose (DSSi:2.5) solutions with diclofenac dissolved in tetrahydrofuran	The kinetics of drug release from cellulose films had potential as a model platform for viscose-based wound dressings.	42
BC	Nanosilver	Rat fibroblasts	*S. aureus*	Self-assembly of silver nanoparticles on the BC surface	BC-containing silver nanoparticles reduce inflammation, inhibit bacterial growth and low cytotoxicity, and accelerate the healing of blisters.	43
BC	Nanosilver	Epidermal cells	*E. coli*, *S. aureus*, *P. aeruginosa*	Synthesize and impregnate silver nanoparticles onto the BC	The composite had significant antibacterial properties and allowed epidermal cell attachment and growth without cytotoxicity, reduced inflammation, and accelerated wound healing.	44
BC	Nanosilver	—	*E. coli*, *S. aureus*	Immersion of BC in silver nitrate solution and reducing it using sodium borohydride	The membrane had a potent effect against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria	45
Cellulose	Lysostaphin	Keratinocytes	*S. aureus*	Immobilization of lysostaphin enzymes and cellulose-chitosan and polymethylmethacrylate cellulose	Bandage preparations showed activity against *S. aureus* based on *in vitro* skin models, low keratinocyte toxicity, and good biocompatibility in wound healing applications.	46
BC	Vaccarin	Testing in a rat model	—	Immersion of BC in vaccarin solution	BC and bacterial-vaccarin cellulose membranes were non-cytotoxic and suitable for cell growth. Wounds treated with BC and vaccarin resulted in faster epithelialization and regeneration than those treated with BC.	47
BC	Silver nanoparticles	—	*E. coli*	Silver nanoparticle synthesis in BC by UV irradiation.	Composites killed bacteria and supported wound healing.	48
BC	Chitosan, copper sulfate	Living cell L929 mouse fibroblasts, human dermal fibroblasts	*E. coli*, MRSA	—	After undergoing antimicrobial and live-cell tests, BC/sodium alginate/chitosan/copper sulfa composites were promised to be applied as wound dressings.	49
BC	Silver sulfadiazine	Epidermal cell	*P. aeruginosa*, *E. coli*, *S. aureus*	Immersing BC into silver sulfadiazine suspension using ultrasonication	The BC and silver sulfadiazine membrane composites showed potential as antimicrobial and biocompatible wound dressings.	50
BC	Amoxicillin	Red blood cells	Fungus, Gram-positive and -negative bacteria	Amoxicillin and BC grafting	Sponges were non-toxic *in vitro* and *in vivo*, showed antimicrobial activity, and accelerated wound healing *in vivo*.	51
BC	Ampicillin	—	*E. coli*, *C. albicans*, *S. aureus*	Synthesized using glutaraldehyde	The BC and gelatin composite sponge showed excellent antibacterial activity and potential as a wound dressing.	52

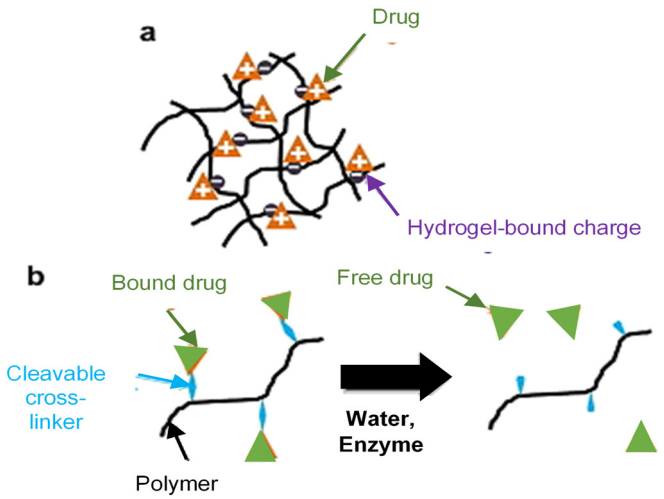

Fig. 1 Drug–hydrogel interaction strategy, (a) physical, for example, the opposite charge interaction between cellulose and drugs, and (b) chemistry, for example, crosslinking agents facilitate drug interactions with cellulose.[55] Adopted with permission from ref. 55.

can be modified before drug loading to inhibit drug release. Modification before and after the drug loading changes the physicochemical properties of the BC matrix. It is influenced by the chemical structure, loaded drug concentration, and surface modifier concentration. This surface modification has been studied in drug models in the form of famotidine which is poorly soluble in water, and tizanidine which is very soluble in water.[63] The studies showed that most of the drug was released in 0.5–3 h from famotidine loaded matrices and 0.25–0.5 h from tizanidine loaded matrices, depending on the chemical structure, loaded concentration drug, the surface modifier concentration, and pre- and post-drug loading modifications. Glutaraldehyde as a binding agent for the BC hydrogel formation and gelatin are also considered good candidates for DDSs.[64]

Cellulose esters also play an essential role in modern drug delivery technology due to their very low toxicity, having endogenous dietary components as a byproduct of their decomposition process, stability, film strength, high water permeability, compatibility with various active ingredients, high T_g, and the ability to form micro-and nanoparticles.[65] For example, ultrasound-assisted preparation of hydroxypropylmethylcellulose-based nanocomposites through the blending of cellulose nanofibrils has been explored to generate biopolymers for a transdermal DDS.[66] Meanwhile, sodium CMC wafers containing neomycin trisulfate showed advantageous wound dressing characteristics (flexibility, sponge-like properties, uniform wafer texture, and high drug content uniformity) and Gram-positive and Gram-negative bacterial inhibition.[67] Other studies on cellulose as a drug delivery vehicle are summarized in Table 2.

Based on studies in Tables 1 and 2, cellulose can be inserted or bound with various drug models such as active ingredients in oils and extracts, metal oxides, and commercially available antibiotics. When using metal oxides as model drugs, paying

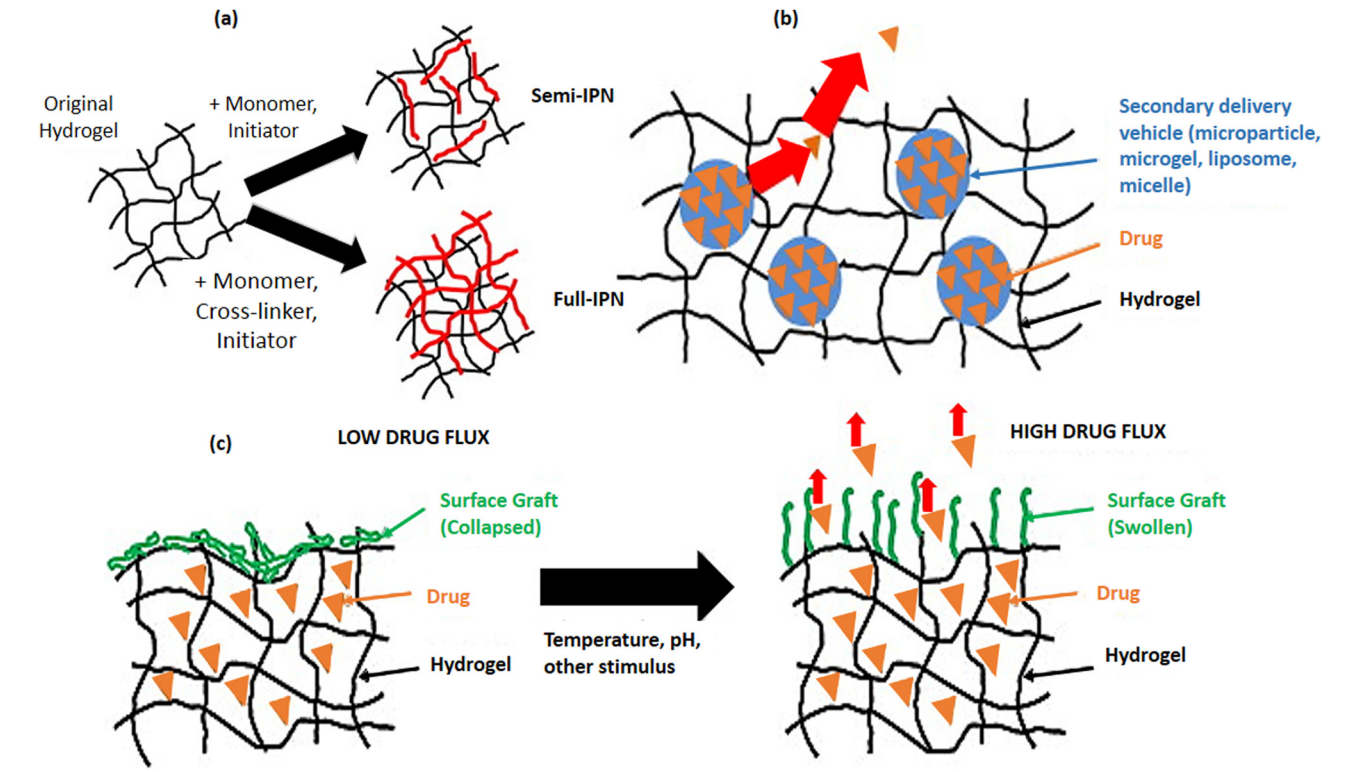

Fig. 2 Engineering gel network *via* (a) semi and full interpenetration (IPN), (b) composite hydrogels containing a drug, and (c) surface diffusion control.[55] Adopted with permission from ref. 55.

Table 2 Cellulose application as a medium of DDSs

Type of cellulose	Drug model	Characteristics of drug delivery vehicles	Ref.
Cellulose nanofiber	Bendamustine hydrochloride	The porous and woven matrix had good mechanical properties with the release of approximately 69.205% ± 2.5% drug (for 24 hours, pH = 1.2) and ~78% ± 2.28% drug (pH = 7.4) with floating behavior for ~7.5 hours. Cellulose nanofiber gels are helpful for a gastroretentive DDS.	68
Hydroxyethyl cellulose	Isoliquiritigenin	The hydrogel synthesized by crosslinking hyaluronic acid and hydroxyethylcellulose can be a transdermal delivery system whose properties are influenced by the swelling medium and crosslink density.	69
Cellulose	Galangin	The crosslinked cyclosophorose/cellulose hydrogel inhibited the *S. aureus* growth, which was maintained for up to 72 hours, making it potentially efficient antibacterial dressing material for a long time without frequent replacement.	70
Ethylcellulose microspheres	Ceftazidime	The hydroxyapatite/polyurethane composite containing microspheres (ceftazidime encapsulated in ethylcellulose) reduced initial blast release with the sustained release for up to 60 days. This composite proved to be an effective DDS with good cytocompatibility and antibacterial properties.	71
Cellulose acetate nanofiber	Tetracycline hydrochloride	Tetracycline hydrochloride bonded in spun cellulose acetate nanofiber composites showed effectiveness in reducing *E. coli* up to 77–88% (after 10 minutes to 1 hour) and *S. aureus* around 83–85% (after 10 minutes to 1 hour).	72
CMC	Doxorubicin	The combination of graphene quantum dots in the CMC hydrogel and doxorubicin increased *in vitro* swelling, degradation, pH-sensitive drug delivery properties, and water vapor permeability, although with little toxicity to blood cancer cells (K562).	73
Mucoadhesive hydrophobic cationic amino cellulose	Camptothecin	Cellulose derivatives can reduce the rate of release of camptothecin, making it promising for DDS applications that are difficult to dissolve in water.	74
Ethylcellulose hydroxypropyl methylcellulose	Hydrochlorothiazide	Hydrochlorothiazide release from patches formulated with ethylcellulose and hydroxypropyl methylcellulose (1 : 1 and 2 : 1 in ratio) occurs *via* diffusion. Therefore, the process can be an effective alternative delivery approach for hydrochlorothiazide.	75
Cellulose nanocrystals	Curcumin	Incorporating curcumin into nanocellulose in surfactant media provides a promising approach for delivering to the stomach and upper intestinal tract.	76

attention to their effects they accumulate in tissues is essential. Future studies expect to focus on dispersing and binding the drug in the cellulose matrix so that the release time is slow and follows the rate of tissue regeneration needed. The future challenge is to produce drug release kinetics using compatible raw materials that offer cheap and reliable process technology.

4. Wound healing activity of coffee and tea

Bioresource-based wound healing is a growing field in modern biomedical science.[77] Natural active ingredients derived from plants can modulate wound healing by promoting angiogenesis, stimulating collagen production, antimicrobial and antioxidant activity, and other mechanisms.[78] Plant-based medicine for wound healing is cheap, affordable, and safe because hypersensitivity reactions are rare.[79] Efficient downstream processing of APIs is highly dependent on their particulate properties, such as size and shape distribution.[80] In promoting wound healing mechanisms, the potency of natural active ingredients is assessed through microbial, animal, and human studies.

4.1 Coffee

Coffee has long been known as a traditional wound healing treatment modality. Coffee is the most efficient and inexpensive medicine for treating acutely infected wounds.[81] Winata *et al.*[82] showed that wound treatment with coffee grounds and hydrocolloid wound dressings was better for lowering MMP-1 levels and accelerating epithelialization than saline gauze dressings. Saline-gauze could not reduce MMP-1 levels, which resulted in delayed epithelialization.

Yuwono *et al.*[81] studied the effect of coffee on healing acute and chronic wounds in 130 patients. All wounds were treated using topical coffee grounds as wound dressings which were changed every four weeks until they healed. In this study, coffee grounds were used as a new paradigm in wound management due to their antimicrobial and antioxidant activity, pleasing odor, increased wound dressing longevity, absorption capacity to maintain a moist wound environment, autolytic debridement capacity, cost-effectiveness, and minimal adverse reactions.

The coffee's pharmacological properties are due to its high polyphenol content, such as chlorogenic and caffeic acid, diterpenes (kahweol and cafestol), melanoidin, and trigonelline. The constituents contribute to anti-inflammatory, antioxidant, anti-angiogenic, anti-cancer, chemoprotective, and hepatoprotective effects.[83] In addition, the chlorogenic acid

hydrogel significantly reduced the wound area in the inflammatory phase, related to its anti-inflammatory and antioxidant action.[84] The content of coffee oil has been studied to provide skin wound healing effects. Lania *et al.*[85] showed that coffee oil from green coffee and roasted coffee produced systemic effects observed in serum cytokine levels and second harmonics generation (SHG) analysis through rat tests. However, more work is still needed to identify the most active molecule and the mechanism of action of coffee oil.

On the other hand, coffee has an anti-angiogenesis effect due to cafestol and kahweol. Therefore, anti-angiogenic compounds in coffee are promising for treating cancer.[86] Cafestol and kahweol are diterpenes commonly found in unfiltered coffee. Cafestol provides benefits through various biological activities, including antitumorigenic, antioxidant, and anti-inflammatory effects. Cafestol inhibits human umbilical vascular endothelial cell angiogenesis by influencing proliferation, migration, and tube formation.[86] Kahweol is an anti-angiogenic and anti-inflammatory compound tested in angiogenesis *in vivo* and *ex vivo*, and has potential for use in antitumor therapy.[87]

Caffeine is an alkaloid found in coffee that serves as an antioxidant and anti-inflammatory agent in wound healing mechanisms.[88] Ojeh *et al.*[20] showed that coffee can also act as an antagonist and negates the adenosine receptors' effect that promotes wound healing. Furthermore, the study confirmed that caffeine could limit keratinocyte cell proliferation depending on the dose. Moreover, differentiation and cell adhesion remained unaffected in single layer cultures treated with different caffeine doses. Caffeine has also been shown to inhibit epithelialization in human *ex vivo* studies.[20]

Several studies in animal models showed the biocompatibility of the active ingredients of coffee in providing wound-healing effects. Humaryanto and Ave[89] studied green coffee bean extracts extracted with 70% ethanol for wound healing in rats. The percentage of total wound closure on day 16 in the rat group smeared with the coffee extract was 83% higher than that in the control group (only 66%). Setyawan *et al.*[90] assessed the healing of *S. aureus* infected wounds using macroscopic indicators (dry wounds, non-hyperemic wound edges, and average leukocyte count) in male Wistar rats. There was a significant difference in healing infected wounds using coffee grounds compared to honey. The healing time of infected wounds using coffee grounds is faster than using honey (3.4 weeks). Coffee plus honey was the most effective treatment modality for persistent post-infectious cough (PPC).[91,92] Another study showed that wound healing using coffee grounds or honey was not significantly different.[93] Although it shows a positive performance, future research is vital to determine the effective coffee powder dose and honey in providing a wound-healing effect.

Histopathological studies on thirty-six New Zealand white rabbits supported the wound healing activity of green coffee bean extracts. Shahriari *et al.*[94] studied the green coffee bean extract in a full-thickness wound model. Coffee (10%) increased the wound closure rate, exhibited a shorter epithelialization period, increased hydroxyproline content, and suppressed lipid peroxidation compared with eucerin treatment. The therapeutic effect of 10% green coffee beans was significantly superior to phenytoin in increasing the speed of wound closure, decreasing the epithelialization period, increasing the hydroxyproline content, and suppressing lipid peroxidation.

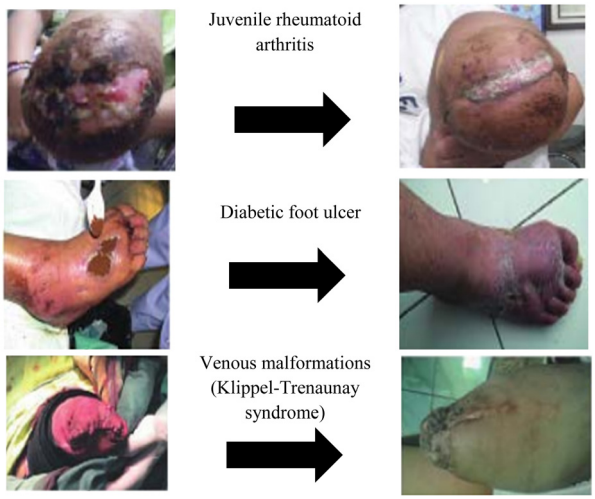

Fig. 3 Wound healing by coffee through human study.[81] Adopted with permission from ref. 81.

The effectiveness of coffee in healing acute and chronic wounds has been proven by Yuwono *et al.*[81] (Fig. 3). They investigated wound healing properties using topical coffee grounds (n = 82) and compared this to those obtained using saline (n = 78 with gauze dipped in 0.9% NaCl) in diabetic patients. A total of 130 wound patients suffering from type-2 diabetes mellitus (90 cases), autoimmune disorder (1 case juvenile rheumatoid arthritis), burns (6 cases), post amputation wounds in Buerger's disease (15 cases), cellulitis (6 cases), venous malformations (10 cases), and deep femoral soft tissue injuries (2 cases) were studied. They have identified that the healing of diabetic wounds by coffee grounds depends on the size and depth of the wound. Wound drying occurs at week 8, and skin epithelial closure occurs at week 12–16, depending on the size of the wound. In juvenile rheumatoid arthritis patients, soft tissue and skin covered the wound with a typical scar by the eighth week. In the case of venous malformations (Klippel–Trenaunay syndrome), ground coffee could stop bleeding from the subcutaneous layer at week 8, which was difficult to stop with tight sutures only.[82]

4.1.1. Deodorization. The aspect that distinguishes coffee from other wound remedies is the coffee aroma. Coffee contains distinctive aromatic compounds. Therefore, the use of coffee as a wound medicine can disguise the smell of wounds or other unpleasant drugs and increase enthusiasm for the wound healing process.[95]

4.1.2. Acidity aspects. During the wound healing process, the increase in proteases and the release of oxygen will affect the pH level on the wound surface to become acidic. This condition will reduce the toxicity of bacteria as ammonia

products increase collagen breakdown in wounds, trigger angiogenesis, and increase macrophage, fibroblast, and enzyme activity. If the pH of the wound exudate is around 7.3, the growth of bacteria in the wound can result in inflammation or infection.[96]

A low pH environment can suppress bacterial growth, control infection, release oxygen, alter protease activity, reduce the bacterial end product toxicity, and promote epithelialization and angiogenesis. Acids for topical application, including citric acid, acetic acid, ascorbic acid, boric acid, and alginic acid, have been reported to control infection and promote wound healing.[97] The level of acidity also plays an essential role in optimizing the inflammatory phase in preventing the timing of these phases, which can be caused by microbial contamination.[96]

Coffee has a pH ranging from 4.5–5.0, almost the same as the skin's natural pH (4.5–5.5), and reported to be the optimum pH to accelerate wound healing.[81,98] In this case, coffee can maintain the pH of the wound to be slightly acidic, reducing the effect of increasing ammonia (alkaline) as a microbial product. Although a wound pH of 4–6 creates an unfavorable environment for bacterial growth, this will reduce the chances of inflammatory complications. Arimbi and Yuwono[96] have reported the clinical effect of coffee acidity on wound healing mechanisms.

Besides that, the pH profiles of healthy skin and acute and chronic wounds differ significantly. Chronic wounds have an alkaline pH, whereas healthy skin has a slightly acidic pH.[99,100] It has also been reported that open wounds typically have a neutral to alkaline pH in the pH range of 6.5 to 8.5, while chronic wounds have a pH range of 7.2 to 8.9.[101] It has been shown that wounds with a more alkaline pH have a lower healing rate than wounds with a pH close to 7. Although pH affects protease production and bacterial proliferation in wounds, there is little evidence to suggest an effect on ECM synthesis and degradation.[99] The reduction of wound pH during the healing stage could help to identify wounds that do not heal early and advise on the most appropriate treatment.[99] On the other hand, alkaline pH is not always detrimental; for example, it has been reported to play an essential role in restoring skin grafts that require an alkaline environment.[98]

4.1.3. Antioxidant activity. ROS radical formation plays a vital role in delayed wound healing. Coffee contains many polyphenol constituents as antioxidants in controlling ROS radicals. Oxidative stress occurs following the pro-oxidant/antioxidant balance decrease in chronic wounds, causing a delay in healing. A good balance between the endogenous antioxidant defense system and oxidative stress is beneficial for wound healing under redox control.[102] Caffeinated coffee and decaffeinated coffee act as antioxidant and anti-inflammatory agents, which can be beneficial during the therapeutic processes or be used as preventive agents in pathological situations. The therapeutic potential of coffee is derived from its bioactive compounds, especially chlorogenic acid, caffeine, caffeic acid, cafestol, and kahweol. Together, the compounds have been shown to reduce inflammation, accelerate wound healing, and modulate inflammatory and neuropathic pain in animal models.[103]

The function of topical antioxidants in coffee grounds is critical in diabetic or autoimmune ulcers (*e.g.*, juvenile rheumatoid arthritis).[81] Pergolizzi *et al.*[104] evaluated the topical anti-inflammatory activity of an ointment prepared using methanol extracts of green robusta coffee beans *via* histology of carrageenan-induced leg edema. The methanol extract from coffee was proven to scavenge the increase in free radicals by the DPPH test, thereby contributing to anti-inflammatory activity. The antioxidant and radical scavenging activities of coffee ground biomass and chlorogenic acid can accelerate wound healing by controlling overexposure to wound oxidative bed stress.[84] In addition, the systemic antioxidant activity of chlorogenic acid in the wound healing process was also studied by Bagdas *et al.*[102] This study confirmed that chlorogenic acid improved wound healing, increased hydroxyproline content, reduced glutathione, decreased nitric oxide/malondialdehyde levels, and did not affect the superoxide dismutase/catalase levels of the wound bed. Chlorogenic acid also reduced the level of lipid peroxidation. Therefore, chlorogenic acid, one of the most extensive constituents of coffee, is a good candidate for diabetic wound management both for topical application and dietary intake.

4.1.4. Antimicrobial activity. Daglia *et al.*[105] confirmed that coffee contains antimicrobial activity due to the formation of other compounds produced during roasting, involving the Maillard reaction, caramelization of carbohydrates, and product decomposition due to heat. For example, robusta coffee grounds inhibited methicillin-resistant *S. aureus* (MRSA)[81] due to phenolic acidity and hyperosmolarity when mixed with wound fluid. Plain caffeine, trigonelline, chlorogenic acid, caffeic acid, and protocatechuic acid at 2.0 mg mL^{-1} exerted a similar effect against *S. mutans*.[106]

Caffeine or caffeic acid provides an antibacterial effect against *S. aureus*.[107–109] Caffeic acid anilides with an electron donor group at the p position of the benzene ring have better bacterial inhibitory activity against *B. subtilis*.[110] Caffeine also inhibits the bacterium *E. coli* O157:H7.[111] Caffeine–isophthalic acid, theophylline–trimesic acid, and caffeine–trimesic acid cocrystals were reported to inhibit pathogenic bacteria, namely *K. pneumonia*, *A. baumannii*, *P. aeruginosa*, and *E. coli*.[112] Caffeic acid, gallic acid, and pyrogallol also show potential as antimicrobial agents, although they have no direct antibacterial and antifungal action.[113] Protocatechuic acid, chlorogenic acid, and caffeine showed powerful effects on *E. cloacae* and *S. marcescens*. Trigonelline, caffeine, and protocatechuic acid were natural antimicrobial agents against *S. enterica*.[114] The alkaloid compounds yohimbine and vincamine (indole-type), scopolamine and atropine (tropane-type), colchicine (tropolone-type), allantoin (imidazolidine-type), trigonelline (pyridine-type) as well as synephrine, octopamine, and capsaicin (exocyclic amine-type); the flavonoid derivatives genistein, quercetin, apigenin, silymarin, naringin, and silibinin; and phenolic acids, namely gallic acid, chlorogenic acid, caffeic acid, and quinic acid, have been reported to have strong antibacterial effects against *E. coli*, *P. mirabilis*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, *E. faecalis*, *S. aureus*, and *B. subtilis*.[115]

In addition, the coffee extract is known to inhibit the growth of *C. albicans*,[116,117] possibly due to the effect of caffeine.[118] Caffeine prevents biofilm formation in a concentration-dependent manner.[119] Chlorogenic acid exhibits antifungal activity in an energy-independent manner, without hemolytic effects on human erythrocytes or disrupting the cell membrane structure.[120] Ma[121] synthesized chlorogenic acid derivatives with a combination of protected chlorogenic acid or *p*-octyloxyaniline and selected amino acids. Most of the compounds showed significant potency against *C. neoformans* and *Candida* species. The 4,5-dihydroxyl group in the quinic acid group is required for activity, and introducing a free amino group increases activity against *A. fumigatus*. da Silva[122] tested the antifungal activity of chlorogenic acid against fluconazole-resistant strains of *Candida* spp. Chlorogenic acid can decrease cell viability, increase mitochondrial depolarization potential and reactive oxygen species production, DNA fragmentation, and phosphatidylserine externalization, which indicate apoptotic processes. In addition, chlorogenic acid showed a significant interaction with the ALS3 active site residue of *C. albicans*, which is vital in the process of adhesion and resistance to fluconazole. In addition, it was also reported that the lower concentration of coffee ground extracts (0.5 mg mL^{-1}) showed stronger inhibition against *C. krusei* and *C. parapsilosis*.[123]

4.2. Tea

A green tea extract (GTE), *Camellia sinensis*, contains antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, and antimutagenic properties, reducing adhesion formation, and improving wound healing.[124–130] Based on the *in vitro* study on LPS-stimulated human oral gingival epithelial keratinocytes, GTE produces an anti-inflammatory response activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway increasing levels of the antioxidant protein heme oxygenase-1 (HO-1).[131] In addition, GTE exhibited anti-diabetic activity and was also crucial in promoting diabetic wound healing by stimulating angiogenesis.[132]

Tea polyphenols can support the mechanism of wound healing. Green tea contains catechins, polyphenolic or flavonoid compounds, polysaccharide conjugates, amino acids, caffeine, and vitamins.[133] Catechins are the primary green tea polyphenolic compounds, including epigallocatechin, epigallocatechin-3-gallate, epicatechin-3-gallate, epicatechin, gallocatechin, and gallocatechin gallate. Theaflavins and thearubigins are commonly found in black tea.[134] A green tea polyphenol complex accelerates advanced tissue granulation, epithelialization formation, and activation of transglutaminase expression epidermal morphogenesis to repair skin injuries.[128]

Epigallocatechin-3-gallate is the most common green tea catechin. Collagen sponges containing epigallocatechin-3-gallate at low concentrations improved diabetic rats' wound healing by accelerating angiogenesis and re-epithelialization and increased cellular reorganization of granulation tissue by triggering cellular reorganization by triggering myofibroblast activity.[135] Epigallocatechin-3-gallate acted as an anti-inflammatory agent and antioxidant to improve wound healing and reduce scar tissue formation. Epigallocatechin-3-gallate affects transforming growth factor -β1 in the collagen gel contraction inhabited by fibroblast cells through myofibroblast differentiation and expression of connective tissue growth factor genes; and reduces the expression of collagen type I gene regulation.[136] In addition, epigallocatechin-3-gallate regulates cytokine secretion and skin cell activation during wound healing.[137] Epigallocatechin-3-gallate also induces differential effects between normal and tumor cells, making it helpful in treating wounds or certain skin conditions characterized by altered metabolism or cellular activity.[138] On the other hand, catechins have clinically mild side effects on laparotomy wound healing in mice.[139]

Several composite products from tea constituents have been investigated for wound healing. Shahrahmani *et al.*[140] developed an ointment based on GTE. An electrospinning technique by Sadri *et al.*[141] produced an environmentally friendly composite GTE wound dressing made from chitosan and polyethylene oxide. When tested in a mouse model, a composite based on polyethylene oxide, green tea, and chitosan showed the best healing effect compared to other wound dressings. In this composite, GTE helped reduce inflammation, keep the wound surface moist, and increase the rate of wound healing. Qin *et al.*[130] combined green tea polyphenols and chitosan to heal male Sherman rat wounds by accelerating epithelialization. The combination of epigallocatechin gallate with gold nanoparticles and lipoic acid was shown to significantly accelerate wound healing in rat skin through its anti-inflammatory and antioxidant effects.[142] Chen *et al.*[143] conducted studies using green tea polyphenols encapsulated in hydrogels made from polyvinyl alcohol and alginate. The hydrogel enhanced diabetic wound healing in a mouse model by regulating the PI3K/AKT signalling pathway. Kim *et al.*[137] showed that adding one wt% epigallocatechin-3-gallate in an electrospun dressing consisting of poly(lactic-*co*-glycolic acid) could promote wound healing full-thickness accelerating cell infiltration, re-epithelialization, and angiogenesis. Several studies utilizing tea in wound healing mechanisms are summarized in Table 3.

4.2.1. Antioxidant activity. Tea contains high antioxidants due to various polyphenols that can modulate oxidative stress *in vivo*, especially epigallocatechin-3-gallate, epicatechin-3-gallate, theaflavins, and thearubigins.[149–151] Tea polyphenols can scavenge ROS and nitrogen species and chelate redox-active transition metal ions indirectly through:[149] (a) inhibition of nuclear factor-κB, redox-sensitive transcription factors, and activator protein-1, (b) inhibition of pro-oxidant enzymes such as inducible nitric oxide synthase, lipoxygenase, cyclooxygenase, and xanthine oxidase, and (c) induction of phase II and antioxidant enzymes such as glutathione S-transferases and superoxide dismutase. Chinese green tea has been shown to have antioxidant activity against H_2O_2, and O^{2-}.[152] Black tea, green tea, brown rice green tea, Malva tea, and herbal tea showed relatively high antioxidant activity in scavenging the ABTS cation radical and DPPH free radical.[153]

The total antioxidant capacity of tea is not related to the specific type of polyphenol but rather to the combined activity of various antioxidants. Green tea has higher antioxidants than

Table 3 Wound healing activity by utilizing the active constituents of tea

Preparation	Test model	Results	Ref.
The mixture of Vaseline and GTE	36 male Wistar rats	The duration of healing in the GTE group was significantly reduced ($P = 0.05$) in the first two weeks than the Vaseline, so GTE helped in the wound healing process.	127
Tea plant methanol extract	NIH3T3 fibroblast cells	Extract exhibits important apoptotic properties and wound healing potential.	129
Green tea drink	Male Wistar rats	Drinking green tea can accelerate epithelial reform on the third day after surgery.	133
Green tea ointment	99 primiparous women	Green tea showed better wound healing properties and effectively relieved episiotomy pain through the Redness, Edema, Ecchymosis, Discharge, Approximation (REEDA) test.	142
GTE and hyaluronic acid	Rats	GTE microneedles and hyaluronic acid were not cytotoxic to human embryonic kidney cells (293T), mouse muscle cells (C2C12), and Chinese hamster ovary cells (CHO-K1). The material reduces the growth of bacteria at the site of the infected wound on the skin and enhances the wound healing process.	144
GTE	34 male Wistar rats	GTE significantly reduces the healing time of surgical wounds and burns.	145
Tea extract	Sprague Dawley rat male	Wounds treated with extracts contained less inflammatory cells and more collagen and angiogenesis, so they healed faster, with a smaller scar width than controls.	146
Green tea ethanolic extract	36 male Wistar rats	GTE can help in the wound healing process, especially for burns	147
Green tea	Rats	Green tea significantly reduces the size of the burn, making it practical for the healing process of second-degree burns.	148

black tea.[154] When consuming green tea as a capsule supplement, the absorption and plasma antioxidant activity of flavanols are increased compared to just drinking black or green tea.[155] Consuming 300 to 450 mL green tea can significantly increase the total antioxidant capacity of plasma, depending on the dose.[156] In animal model studies of skin, colon, lung, liver, and pancreatic cancers, tea polyphenols inhibited the carcinogen-induced increase in the oxidized DNA base, 8-hydroxy-2′-deoxyguanosine. Green and black teas in animal models of atherosclerosis improved lipoprotein resistance to oxidation *ex vivo*.[149] Having demonstrated beneficial effects under those pathological conditions suggests that high antioxidant content in tea could also be very beneficial for healing chronic wounds.

4.2.2. Antimicrobial activity. Theaflavin is one of the constituents that play a role in the antimicrobial mechanism of tea.[157] Theaflavins can suppress the activity of 1-deoxy-D-xylulose 5-phosphate reductoisomerase, which contributes to the terpenoid MEP biosynthetic pathway and is a validated antimicrobial target.[157] Park *et al.*[144] reported that GTE and hyaluronic acid showed a ~95% reduction in Gram-negative (*S. typhimurium*, *E. coli*, and *P. putida*) and Gram-positive (*B. subtilis* and *S. aureus*) bacteria. Tea polyphenols also inhibited the growth of violin production in *C. violaceum* 12472 (nearly 98% at 3125 mg mL^{-1}) and *P. aeruginosa* by reducing total proteolytic activity and swarming motility, elastase, and biofilm formation, depending on concentration. The authors explained that they could develop new non-antibiotic quorum sensing inhibitors from tea polyphenols, which would act as antivirulence compounds to control bacterial infections without killing the bacteria.[158] The Nigerian black tea inhibits *E. coli* (sensitive between 6%, 8% and 10% aqueous extract and 2% to 10% methanol extract), *S. aureus* (sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract sensitive between 4% to 10% aqueous extract and 2% to 10% methanol extract), *P. aeruginosa* (sensitive to 2% to 10% aqueous extracts and between 6%, 8% and 10% methanol extracts), and *B. subtilis* (sensitive to 4%, 6% and 8% aqueous extracts and 4% to 10% methanol extracts but sensitive to 10% aqueous extracts).[159]

Epigallocatechin-3-gallate has been reported to inhibit *S. maltophilia*, MRSA, and multidrug-resistant *P. aeruginosa*.[160,161] Green tea leaf decoction inhibited *S. aureus* (inhibition zone of 19 mm) and *V. parahaemolyticus* (inhibition zone of 17.5 mm). GTE in methanol showed the same inhibition zone against *Pseudomonas* spp. (clear zone of 18 mm).[162] The combination of silver nanoparticles with tea extracts was also reported to inhibit *S. aureus* (ATCC 29213), *P. aeruginosa* (ATCC 27853), *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 700603), and *S. enterica* (ATCC 14028).[163] The tea constituents' antimicrobial properties are summarized in Table 4.

5. Future directions and prospects

5.1. Coffee and tea constituents for wound healing

Coffee and tea contain many natural active ingredients that help the wound healing process and are inexpensive and easy

Table 4 Antimicrobial properties of compounds contained in tea

Constituents	Effect of antimicrobials	Ref.
Epicatechin-(4β → 8)-epicatechin-(4β → 8, 2β → O → 7)-catechin	These compounds have strong properties against *P. intermedia* and *P. gingivalis*	164
Catechin, chlorogenic acid, dan phloridzin	All phenolics inhibited *E. coli* O157:H7, *L. innocua*, and *P. chrysogenum* at 25 mM.	165
(−)-epicatechin gallate (ECg)	Relatively low concentrations of (−)-epicatechin gallate sensitized clinical isolates of MRSA to oxacillin levels. (−)-Epicatechin gallate intercalates into a phospholipid bilayer affecting virulence and antibiotic resistance by interfering with the function of critical processes associated with the bacterial cytoplasmic membrane.	166
Catechin	Catechin has antibacterial activity against *S. aureus*.	167
Catechin-lysozyme	Depending on the concentration, the film has inhibitory activity against *E. coli* and *S. aureus*	168
Epigallocatechin gallate	Epigallocatechin gallate inhibits the growth and biofilm formation of *S. mutans* and does not interact with streptococcal lipoteichoic acid.	169
(−)-Epigallocatechin-3-gallate, (−)-epicatechin-3-gallate, (−)-gallocatechin-3-gallate, (−)-catechin-3-gallate, theaflavin-3′-gallate, theaflavin-3, 3′-digallate, and theaflavin-3-gallate	These compounds have antimicrobial activity at the nanomolar level in *B. Cereus* and are mostly more active than tetracycline or vancomycin.	170
Epigallocatechin-3-*O*-gallate, epigallocatechin, castalagin, punicalagin, tannic acid, prodelphinidin, procyanidins, geraniin, black tea theaflavin, and green tea polyphenols treated with loquat polyphenol oxidase	The mean minimum inhibitory concentrations of all polyphenols against *S. aureus* (192 ± 91 g mL) and the genus *Vibrio* (162 ± 165 g mL^{-1}) were much lower than those against genus *Salmonella* (795 ± 590 g mL^{-1}) and *E. coli* (1519 ± 949 g mL^{-1}).	171
Black tea processing waste containing catechins and theaflavins	The extracts showed antimicrobial activity against *S. flexneri* (1.33–3.89 mm), *S. aureus* (1.26–3.65 mm), and *B. cereus* (1.87–3, 90 mm)	172
Epigallocatechin gallate	Epigallocatechin gallate enhances the curcumin's antibacterial activity against multidrug-resistant *A. baumannii*.	173
Pu-erh tea constituents	The tea constituents significantly inhibited the growth of *S. typhimurium* (0.18 mg mL^{-1}), *L. monocytogenes* (0.07 mg mL^{-1}), *S. faecalis* (0.50 mg mL^{-1}), *B. anthracis* (0.48 mg mL^{-1}), and *E. coli* (0.42 mg mL^{-1})	174
Green and black tea extract	Tea extract is an antimicrobial agent for *S. aureus* ATCC 25923 and *E. coli* ATCC 25922, which are resistant to antibiotics. Also, it can use the combination of GTE with penicillin to manage resistant pathogenic bacteria.	175

to find. There are still many other active constituents that have not been identified; it is exciting and challenging at the same time because raw coffee extracts can have wound healing activity, but pure compounds such as caffeine harm the healing process.[20] This effect can be minimized by reducing the amount of caffeine content of coffee through the coffee decaffeination process, which is the choice of the decaffeination method. It need to be considered to keep the other active constituents. Likewise, other minor compounds are reported to be anti-angiogenic, such as cafestol and kahweol.[86,87] In order to avoid the effect of this minor constituent, it is imperative to study the dose and whether the effect at that dose is significant when combined with other active constituents such as chlorogenic acid. A combination of various constituents is required for adequate healing activity, and it remains to be studied to find the ideal combination.

Generally, complex active compounds in coffee and tea can be polar and non-polar. The selection of the correct type of solvent and extraction method will impact the effectiveness of the wound healing mechanism. For example, when selecting a target compound, chlorogenic acid, the researcher must identify the solubility properties and characteristics of the compound. If the chlorogenic acid is polar, it can be extracted using a solvent of suitable polarities, such as methanol. Both polar and non-polar fractions need to be investigated *in vivo* and *in vitro*. It should be noted that some solvents may be toxic to skin cells, so the extraction process must ensure that the final isolate is solvent-free. Knowledge of the characteristics of the extracted active ingredients will also determine the appropriate extraction method. Some compounds may be sensitive to high temperatures. Therefore, controlling the temperature during the extraction process is very important to avoid damage to the active compounds.

There are exciting things about the active compounds that have been reported to have performance as antibiofilms.[63,144] Although it is not known precisely how the antibiofilm mechanism is, it is crucial to explore the contribution and dosage of these compounds in inhibiting the formation of various types of biofilms formed by resistant microbes. In the future, this knowledge will be advantageous in reducing the use of antibiotics that cause microbial resistance.

5.2. Wound dressing novel synthesis

A number of methods have been used to synthesize wound dressing hydrogels based on cellulose biopolymers.[55,176] When synthesizing new wound dressings, it is also necessary to pay attention to how they interact with the supporting components (*e.g.* addition of polymers, drugs, and other composite materials) and their changes. For example, collagen has been tested to accelerate wound healing, but this protein is expensive, and has no antimicrobial properties, and limited exudate absorption. It is also possible to consider synergistic composites with other types of support materials to produce an ideal novel by considering these weaknesses. Chitosan has also demonstrated its biocompatibility in tissue engineering. However, its insolubility in water poses a challenge for bonding with cellulose and tea and coffee compounds. Learning how to develop novel strategies by using simple methods and selecting appropriate materials is vital. Therefore, knowledge of the characteristics of raw materials is important for producing ideal wound dressing composites.

Cellulose is a hydrophilic biopolymer that does not readily bind to hydrophobic active constituents. Therefore, it is necessary to add an emulsifier or modify the cellulose to be more hydrophobic, and an understanding of the hydrophilicity of other biopolymers that need to be considered as cellulose composites to be explored. The nature of the active ingredients will also impact the drug release rate. One of the conditions for an ideal wound dressing is to absorb excess exudate. This aspect should be considered in selecting and studying the active ingredients and biopolymers and their release profile. This is where the importance of modifying the properties of cellulose to be highly hydrophilic is. The dosage of active

Table 5 Summary of characteristics of coffee, tea, and cellulose as wound dressing materials

Materials	Reported compounds	Properties
Coffee	Chlorogenic, caffeine, caffeic acid, diterpenes (kahweol and cafestol), melanoidin, caffeine–isophthalic acid, theophylline–trimesic acid, caffeine–trimesic acid cocrystals protocatechuic acid, gallic acid, pyrogallol, trigonelline, and formation of other compounds produced during roasting, such as the Maillard reaction, caramelization of carbohydrates, and product decomposition	• Lowering MMP-1 levels • Anti-inflammatory • Accelerating epithelialization • Antioxidant • A pleasing odor (especially roasted coffee) • Increased wound dressing longevity • Absorption capacity to maintain a moist wound environment (coffee powder) • Autolytic debridement capacity • Minimal adverse reactions • Acidity effect • Antagonist negates the adenosine receptors, limits keratinocyte cell proliferation, and inhibits epithelialization depending on the dose (caffeine) • Antitumorigenic (cafestol) • Anti-angiogenesis (cafestol and kahweol) • Antimicrobial
Tea	Polyphenolic, flavonoid, catechins, theaflavins, thearubigins, epigallocatechin, epigallocatechin-3-gallate, epicatechin-3-gallate, epicatechin, gallocatechin, gallocatechin gallate, caffeine, polysaccharide conjugates, amino acids, and vitamins	• Antioxidant • Anti-inflammatory • Antimicrobial • Anticarcinogenic • Anti-diabetic • Antimutagenic • Reducing adhesion formation • Promote angiogenesis • Accelerate advanced tissue granulation, epithelialization formation, and activation of transglutaminase expression epidermal morphogenesis (green tea polyphenol)
Cellulose	Structure and functional groups	• Biocompatible • Biodegradable • Low toxicity (depending on preparation) • Easy to modify • Hydrophilic • High absorption capacity • Nanostructure (especially BC) • High porosity • Purity (especially BC) • Permeability to gases and liquids • Mechanical resistance

ingredients and their level of toxicity also need to be studied in formulating wound dressing biomaterials.

6. Conclusions

Cellulose is a natural biopolymer that has demonstrated its biocompatibility in tissue engineering applications. On the other hand, the problem of antimicrobial, reactive oxygen, and antibiotic resistance has also become a focus for biomaterials synthesis for biomedical applications. In general, the bioactive constituents of coffee and tea have demonstrated their activity in wound healing through clinical studies (Table 5), including antimicrobial and antioxidant studies. Considering the perspectives and challenges ahead, the combination of cellulose with the active ingredients of coffee and tea shows its potential as a promising novel wound dressing.

Abbreviation

BC	Bacterial cellulose
CMC	Carboxymethyl cellulose
DDS	Drug delivery system
APIs	Active pharmaceutical ingredients
MRSA	Methicillin-resistant *S. aureus* (MRSA)
GTE	Green tea extract
ROS	Reactive oxygen species
ABTS	2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
DPPH	1,1-diphenyl-2-picrylhydrazyl
MEP	2-methyl-D-erythritol 4-phosphate

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by Direktorat Jenderal Pendidikan Tinggi, Riset, dan Teknologi, Kementrian Pendidikan, Kebudayaan, Riset, dan Teknologi, Republic of Indonesia.

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