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Carbohydrate polymer-based silver nanocomposites: Recent progress in the antimicrobial wound dressings

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ABSTRACT

Wound healing is a dynamic and complex process which affects the quality of life in patients and annually causes high costs for the health system, worldwide. Polymers from natural origins such as polysaccharides have gained particular interest between researchers for wound dressing applications due to their abundance in nature, biocompatibility with human tissues, and ideal physicochemical properties. Aside from their supportive effect in wound care, polysaccharides and their derivatives can actively contribute to the healing process. Silver nanoparticles are widely used noble metal nanoparticles incorporated in wound dressings due to their low toxicity for human cells, naturally availability, and strong antimicrobial effects. In the present study, we will review the most frequently used polysaccharides in wound dressing procedure with silver or silver nanoparticles accommodated. The methods of synthesis, physicochemical properties, healing efficiencies, toxicity against human tissues, antibacterial and antifungal effects of each material will also be discussed.

1. Introduction

The human skin is the outer covering and most significant organ of the body, including three major layers; the epidermis, the dermis, and the hypodermis (Fig. 1). This organ of the integumentary system guards the primary and underlying organs and protects organs against mechanical forces and infections, fluid imbalance and thermal dysregulation (Sorg, Tilkorn, Hager, Hauser, & Mirastschijski, 2017). The human skin has an essential role in preventing pathogens entrance to the body and is a barrier between the human body and the external environment (Proksch, Brandner, & Jensen, 2008). Besides, skin regulates several body functions, especially temperature and support blood

Abbreviations: A. alternata, Alternaria Alternata; AAm, acrylamide; Alg, Alginate; APS, ammonium persulfate; Aniger, Aspergillus niger; B. cereus, Bacillus cereus; B. pumilus, Bacillus pumilus; B. subtilis, Bacillus subtilis; B. fragilis, Bacteroides fragilis; C. albicans, Candida albicans; CPs, carbohydrate polymers; E. aerogeness, Enterobacter aerogeness; E. cloacae, Enterobacter cloacae; E. faecalis, Enterococcus faecalis; E. coli, Escherichia coli; HA, Hyaluronic acid; K. oxytoca, Klebsiella oxytoca; K. pneumonia, Klebsiella pneumoniae; LbL, layer-by-layer; L. monocytogenes, Listeria monocytogenes; MBA, methylenebisacrylamide; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; NFMs, nanofibrous membrane; NPs, nanoparticles; Nic, nicotinamide; PTL, phase-transited lysozyme; PL, platelet lysate; PHEMA, poly 2-hydroxyethyl methacrylate; PAA, poly acrylic acid; PVP, poly(N-vinyl-2-pyrrolidone); PVA, poly(vinyl alcohol); PEG, polyethylene glycol; PU, polyurethane; PVP, polyvinyl pyrrolidone; P. melaninogenica, Prevotella melaninogenica; P. mirabilis, Proteus mirabilis; P. vulgaris, Proteus vulgaris; P., aeruginosa Pseudomonas aeruginosa; ROS, Reactive oxygen species; S. typhimurium, Salmonella typhimurium; S. dysenteriae, Shigella dysenteriae; AgNPs, Silver nanoparticles; S. aureus, Staphylococcus aureus; S. epidermidis, Staphylococcus epidermidis; S. pyogenes, Streptococcus pyogenes; T. viride, Trichoderma viride; TIC, total inhibitory concentration; TCEP, tris(2-carboxyethyl)phosphine; V. cholerae, Vibrio cholerae; Vis, viscous fabrics

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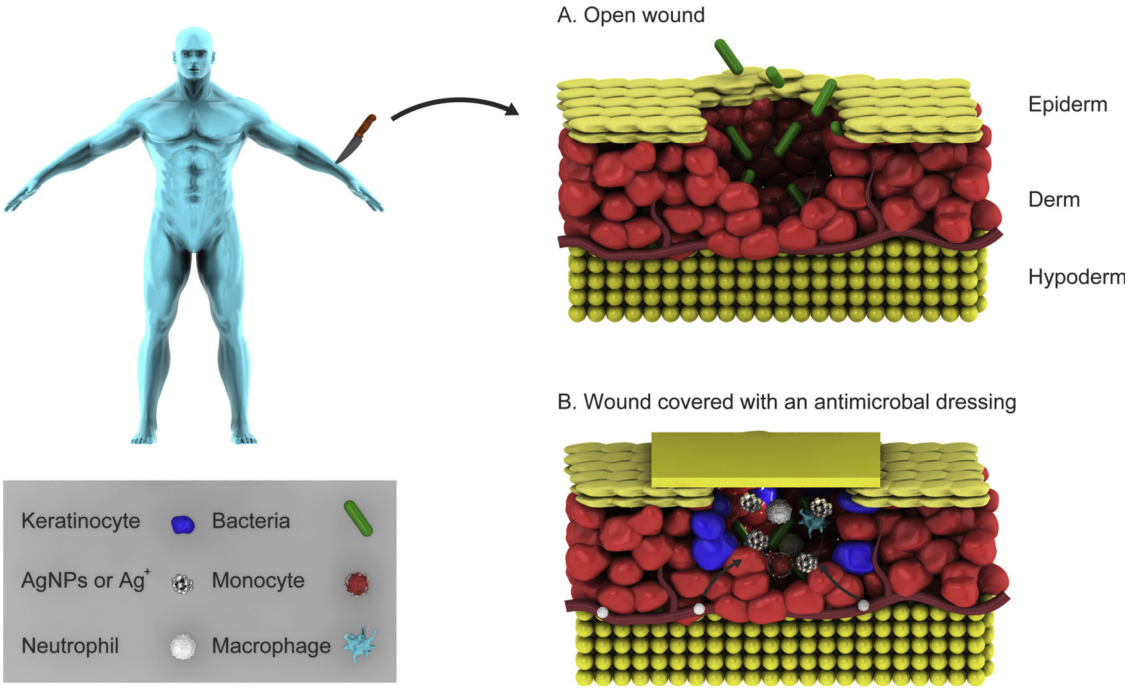

Fig. 1. Carbohydrate polymer-based composites embedded with silver nanoparticles or silver ions as wound dressings for enhancing the wound healing process by prevention of bacteria penetration and releasing antibacterial agents.

vessels and nerves. It acts as an outermost layer to protect the human body with essential importance to human health (Yildirimer, Thanh, & Seifalian, 2012). Therefore, any damage to this protective and vital tissue by external and internal stimuli cause wound formation (a wound is a type of injury and quickly happens when the skin is damaged or cut). The wound may be classified by several methods including; their cause, location, symptoms, severity and tissue loss. It can also be classified as clean, contaminated, infected and colonized (Mellerio, 2010).

The most critical concern in wound care is infections control during its healing procedure which hydrocolloids and films are widely used in wound healing procedure by the physicians since 1970 (Zhou et al., 2018). The wound healing is a multi-step process including inflammation, proliferation and maturation, in which the cells and mediators carry out a lot of reactions and interactions to meet these aims (Janis & Attinger, 2006). Measures that are taking to the wound healing, eventually lead to clean and germ-free conditions for the wounds (Shukrimi, Sulaiman, Halim, & Azril, 2008). It requires active management because of its ability to pose a severe health concern. That is why the whole attention is attracted to the use of new therapeutic approaches (Velnar, Bailey, & Smrkolj, 2009). The wound healing procedure must be done in a moist condition because of an increase in the epithelial cells growth rate (Jones, Grey, & Harding, 2006). Also, it is proven that the wet dressing accelerates the healing process (Muthuramalingam, Choi, Hyun, Kim, & Cho, 2018).

Since ancient times, different materials have been used for wound dressing; several advantages and disadvantages are attributed to each compound (Gudnason et al., 2007). A desirable dressing material must have minimal side effects on the patient's body and be low-cost. In this regard, natural carbohydrate polymers (CPs) including pectin, chitosan, and alginates are widely used individually or in combination with other polymers used as the wound dressing materials (Boateng, Matthews, Stevens, & Eccleston, 2008). The coating of wound bandages with adjuvants or nanoparticles embedded CPs makes them more useful compared to the traditional types (Zahedi, Rezaeian, Ranaei-Siadat, Jafari, & Supaphol, 2010).

Nanotechnology also has a wide range of applications in the current century (Patil et al., 2019; Rahimi, Karimian et al., 2018; Ramos, Cruz, Tovani, & Ciancaglini, 2017). Nanoparticles are approximately 10 − 1000 nm in size, which are available in solid and dispersion modes. Due to their desirable features, they are applied in various biomedical cases extensively (Burdușel et al., 2018; Cardoso et al., 2018; Croissant, Fatieiev, Almalik, & Khashab, 2018; Elahi, Kamali, & Baghersad, 2018; Rahimi, Karimian et al., 2019). Several properties attributed to the biodegradable nanoparticles such as broader access, in-demand encapsulation, control release and less toxicity have caused them to be applied in wound healing procedure (Rajendran, Kumar, Houreld, & Abrahamse, 2018). Many groups of researches have been focused on utilizing various nanoparticles in the carbohydrate-based polymeric matrix for wound healing including silver (Ag), zinc oxide (ZnO), gold (Au), copper (Cu) and Iron(II) oxide (FeO) nanoparticles (Lu et al., 2018; Mehrabani, Karimian, Rakhshaei et al., 2018; Zhai, Xu, Zhou, & Jing, 2018). All nanoparticles (NPs) showed acceptable results in the healing process. However, Ag nanoparticles (AgNPs) have significant antimicrobial effects on a wide range of pathogenic and drug-resistant strains.

The antimicrobial effects and numerous applications of nanoparticles and natural polysaccharides have been discussed in several kinds of literature (El-Batal, Mosalam, Ghorab, Hanora, & Elbarbary, 2018; Lakshminarayanan, Ye, Young, Li, & Loh, 2018; Wang, Hu, & Shao, 2017; Zahran & Marei, 2019). In the current review, we discuss the applications of the CPs in combination with Ag nanoparticles in wound dressing-related to biomedical scope with enhancing the wound healing process (Fig. 1).

2. Silver nanoparticles in biomedical applications

Form the past to present; silver has been used as a valuable metal in different applications. Some of the most important use of silver is the biomedical disinfection of burn wounds, chronic ulcers and traumatic injuries. In the 17th and 18th centuries, silver nitrate was used for ulcer treatment, and its antimicrobial activity was established in the 19th century. In 1884, during childbirth, some drops of aqueous silver nitrate used to pour into the newborn's eyes to prevent the transmission of Neisseria gonorrhoea from infected mothers. Silver became

commonly used during World War I for treatment of wounded soldiers, but after the discovery and synthesis of the antibiotics around the World War II, the use of silver salts as an antimicrobial agent significantly decreased. Nowadays, the most relevant fields of silver and silver nanoparticles are the inspection and application of their biomedical properties.

AgNPs are the clusters of silver atoms ranging in diameter from 1 to 100 nm and has gained extended interests and attention due to their unprecedented properties such as chemical stability (Desireddy et al., 2013), and most importantly antibacterial (Xiu, Zhang, Puppala, Colvin, & Alvarez, 2012), antiviral (Galdiero et al., 2014), antifungal (Panáček et al., 2009), and anti-inflammatory activities (Hebeish, El-Rafie, El-Sheikh, Seleem, & El-Naggar, 2014) incorporated into composite fibres (Park et al., 2012), cosmetic products (Gajbhiye & Sakharwade, 2016), food industry (De Moura, Mattoso, & Zucolotto, 2012), and health industry (Ahamed, AlSalhi, & Siddiqui, 2010). For biomedical applications; silver or AgNPs being added to wound dressings, topical creams, antiseptic sprays and fabrics with significant antimicrobial effects toward a wide range of around 650 microorganisms (Gram-negative and Gram-positive bacteria, fungi and viruses) (Jeong, Yeo, & Yi, 2005). Generally, silver nitrate induces antimicrobial effect, but nano-sized silver has enhanced the available surface area for the microbes to be exposed. Unfortunately, silver use has been limited by the toxicity of silver ions to humans; however, with the aid of nanotechnology, the production of smaller silver particles with increased large surface-area-to-volume ratios, greater efficacy against bacteria and, most importantly, lower toxicity to humans has been facilitated. It is accepted that silver and AgNPs in aqueous solution release silver ions (Ag^+), which are biologically active and mediate the bactericidal effects (Morones et al., 2005; Sanpui, Murugadoss, Prasad, Ghosh, & Chattopadhyay, 2008; Yang et al., 2009).

2.1. Synthesis and properties of AgNPs

Synthesis of AgNPs has a broad generality in various field of science in comparison to other NPs due to its significant antibacterial properties (Saravanan, Arokiyaraj, Lakshmi, & Pugazhendhi, 2018; Xu et al., 2017). Different approaches have been reported for AgNPs preparation, such as physical method (e.g. evaporation-condensation (Natsuki, Natsuki, & Hashimoto, 2015), laser ablation (Ismail, Sulaiman, Mohsin, & Saadoon, 2018), gamma irradiation (Kumar et al., 2015), and lithography (Scuderi et al., 2016)), chemical method (chemical reduction of Ag^+ ions by reducing agents (Khan, Al-Thabaiti, Obaid, & Al-Youbi, 2011), micro-emulsion techniques (Rivera-Rangel, González-Muñoz, Avila-Rodriguez, Razo-Lazcano, & Solans, 2018), and microwave-assisted technique (Parveen, Ahmad, Malla, & Azaz, 2016)) and green synthesis (biosynthesis using plants) (Halawani, 2016) (Table 1). It is expected that each of these methods has its advantages and disadvantages; however, as a secure method for the synthesis of AgNPs, chemical methods have been used more often.

Many research articles are published every year about various synthesis approaches for AgNPs. In the literature, most of the metallic silver applications involved the use of AgNPs in place of silver metal to take benefits of nano-silver's unique properties. Despite all advantages for AgNPs, it has significant concerning impact on the environment. As the synthesis methods have different staring materials, an environmental-friendly method has become a new option in chemistry known as "green chemistry". This new approach consists of reduction and elimination of dangerous substantives for the design of products in the environment (Arokiyaraj et al., 2017; Chowdhury, MacGregor-Ramiasa, Zilm, Majewski, & Vasilev, 2016; Moodley, Krishna, Pillay, & Govender, 2018). However, there are several studies for the preparation of the AgNPs, but the industrial and commercial method is not specified yet.

Table 1
Different preparation methods for the synthesis of AgNPs and their advantages and disadvantages.

Methods For Synthesis of Silver Nanoparticles (AgNPs)		
Methods	Advantages	Disadvantages
Physical	Size and Shape Control	Harmful waste generation and expensive equipment
Chemical	Size and shape control	Harmful waste generation causing environment pollution
Biological	High efficient, low cost, No waste are generated	High dispersion in size and shape

2.2. Antibacterial mechanism of AgNPs

One of the most vital applications of the metal nanoparticles, especially AgNPs, in the field of medicine is using these NPs as antimicrobial agents. After dissolving AgNPs in aqueous solution, Ag^+ ions were leaking to the media to interact with microorganisms. Ag^+ ions have several antibacterial mechanisms; one of them is due to their interaction with sulfur and phosphorus groups in the structure of proteins of the cell wall and plasma membrane of bacteria (Priyadarshini, Gopinath, Priyadharsshini, MubarakAli, & Velusamy, 2013; Yamanaka, Hara, & Kudo, 2005). The Ag^+-membrane interaction leads to dysfunction of the proteins, thereby threatening the organism's life. Ag^+ ions also could bind to negatively charged parts of the microorganism membrane, thus creating holes in the membrane to cause cytoplasmic contents flowing out of the cell. Therefore, the proton gradient dissipates across the membrane and finally cause cell death. After that, the existence of Ag^+ ions inside the cell can disturb the function of electron transport chain of the bacteria (Jung et al., 2008; Slavin, Asnis, Häfeli, & Bach, 2017). It is believed that Ag^+ ions interact with bacterial DNA and RNA and inhibit cell division (Dakal, Kumar, Majumdar, & Yadav, 2016; Yang et al., 2009) (Fig. 2).

Several parameters can effect on the activity of AgNPs and nanoparticles inherent property such as size, shape, and coating. Other parameters attributed to the medium, including the presence of light, oxidative species, presence of other potential ligands for silver, and ionic strength can be altering the activity of AgNPs. These parameters will have an influence on several phenomena that can contribute to the increase or the decrease of the antibacterial activity, along complex pathways, summarized in Fig. 3 (Le Ouay & Stellacci, 2015; Liu, Sonshine, Shervani, & Hurt, 2010).

3. Carbohydrate polymers (CPs) in biomedical applications

Abundant natural sources of CPs are microbial and plants that find broad applications in biomedical materials. However, all CPs consist of repeated saccharide units that are covalently linked with O-glycosidic bonds. Fig. 4 shows the chemical structures, different bioactive functional groups, saccharide units, and the linkage sites of CPs used in biomedical fields (such as agar, alginate, carrageenan, cellulose, chitosan, chitin, hyaluronic acid, pectin and starch). These differences in chemical structure produce different physical properties including mechanical strength, solubility, electrostatic and gelling behaviour, viscosity, and properties at surface and interface (Kives, Orgaz, & SanJosé, 2006; Nakamura, Takahashi, Yoshida, Maeda, & Corredig, 2004; Rioux, Turgeon, & Beaulieu, 2007; Schneeman, 1999; Sriamornsak & Kennedy, 2006). Many efforts in recent decades have caused polymeric materials more interesting in biomedical fields such as drug delivery systems or the therapeutic devices including temporary prostheses and three-dimensional (3D) porous structures, which are used as scaffolds in tissue engineering. (Della Giustina et al., 2019; Hasnain, Ahmad, Chaudhary, Hoda, & Nayak, 2019; Palumbo et al., 2019; Rahimi, Safa, & Salehi, 2017; Rahimi, Shafiei-Irannejad, Safa, & Salehi, 2018).

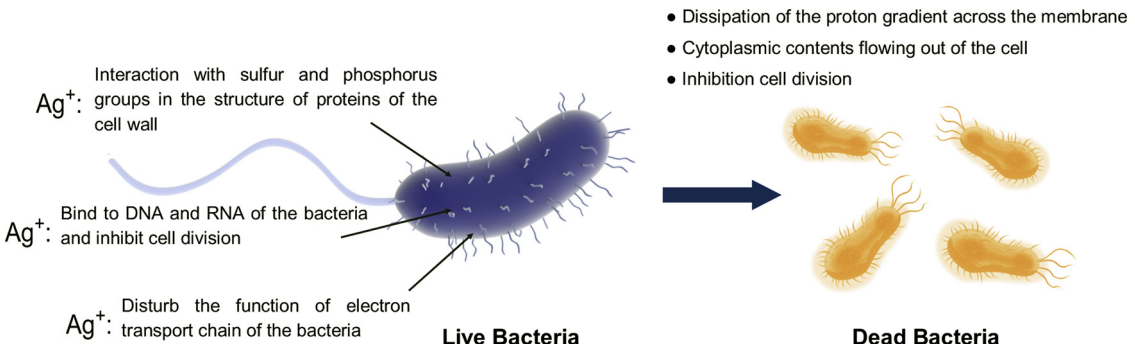

Fig. 2. Different antibacterial mechanisms of Ag^+ ions (Ag-NPs).

3.1. Drug delivery systems

The CPs have been widely used in drug delivery because of their known biocompatibility and biodegradability in the human body (Justin & Chen, 2014; Karimian et al., 2019; Peng et al., 2016; Shafiei-Irannejad et al., 2019). Besides, CPs are diverse in size and charge, highly stable and abundant, and show low toxicity *in vivo*. Naturally, functional groups of many carbohydrates (hydroxyl, carboxyl and amine) can interact with tissue surface allowing the material to have prolonged half-life in the body because of their bio-adhesive property. In overall, CPs afford an effective platform for *in vivo* drug delivery systems and other body-contacting applications (Bhardwaj, Kanwar, Lal, & Gupta, 2000; Pooja et al., 2015; Rahimi, Safa, Alizadeh, & Salehi, 2017; Rahimi Safa, & Salehi, 2017; Swierczewska, Han, Kim, Park, & Lee, 2016; Wang et al., 2006).

3.2. Tissue engineering and regenerative medicine

Natural polymers and their derivatives such as chitosan, hyaluronic acid, and alginates have been successfully employed to provide cell proliferation conditions and tissue regeneration. These polymers have several advantages such as their capability to support cell growth, ability to form hydrogels, non-toxicity, and minimal stimulation to inflammatory or immunological responses of the host tissues due to their extracellular matrix structures (Ciardelli et al., 2005; Sechriest et al., 2000; Wei et al., 2015). The chemical structures of CPs provide unique physicochemical properties and specific advantages for each material in tissue engineering. Unfortunately, most of the CPs have low strength and toughness with no requirements in clinical trials. Thus, the chemical and physical modifications are done on their surface to enhance the bioactivity, strength and toughness. However, both tissue engineering and regenerative medicine fields widely used these natural polymers for their specific aims (Dang & Leong, 2006; Malafaya, Silva, & Reis, 2007; Swetha et al., 2010).

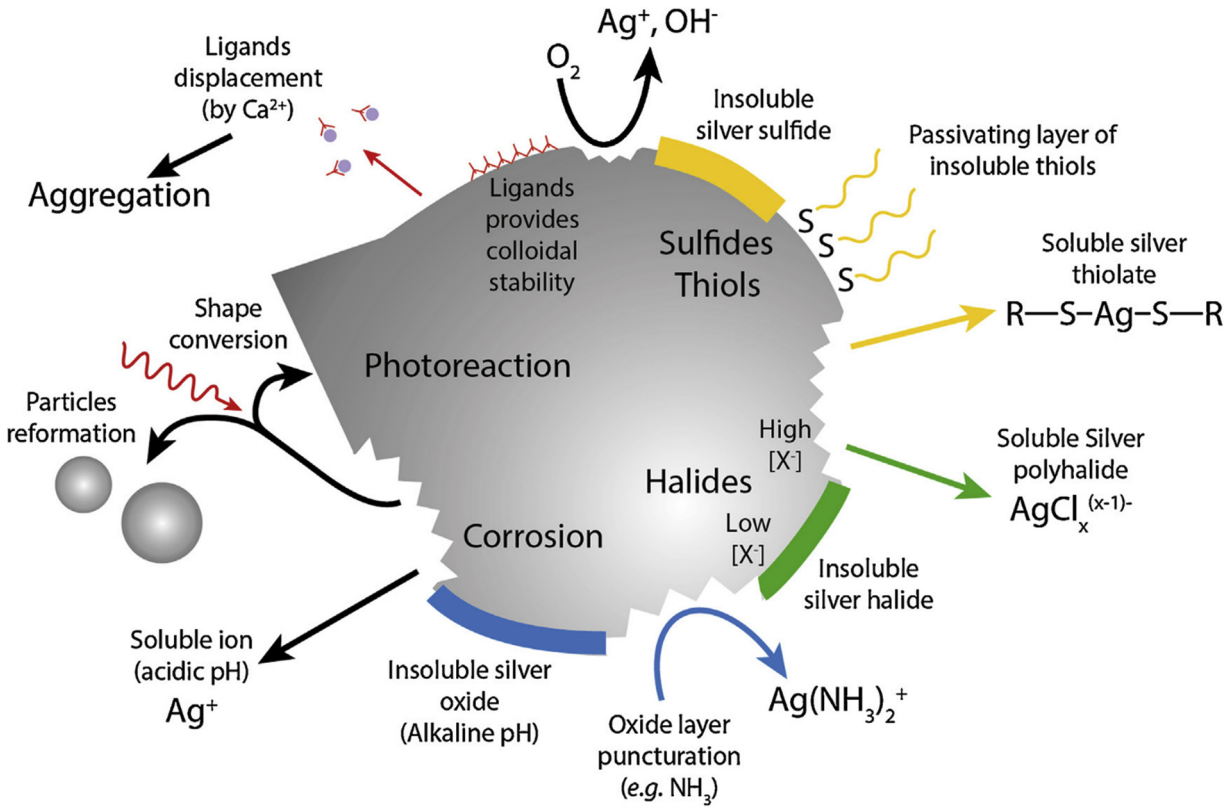

Fig. 3. Visual summary of several phenomena affecting AgNPs dissolution (Reprint license number: adopted from Ref. ((Le Ouay & Stellacci, 2015) with permission number of 4,662,071,365,600).

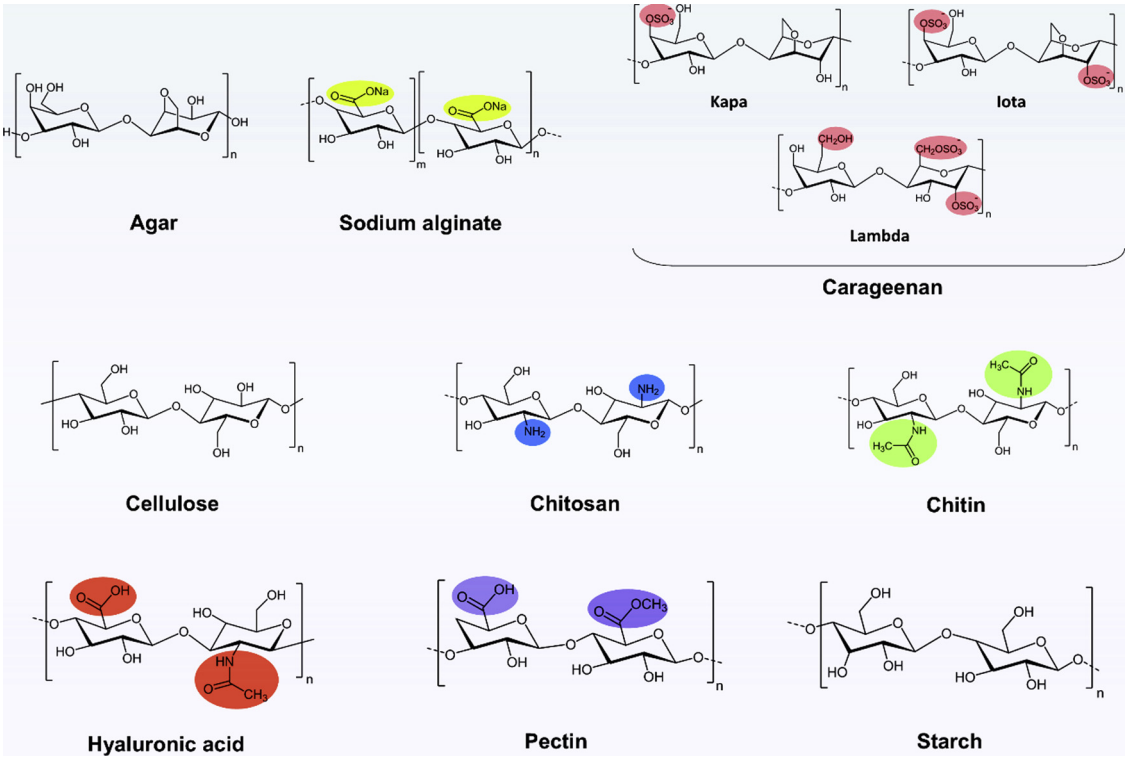

Fig. 4. Structure of conventional CPs (agar, alginate, carrageenan, cellulose, chitosan, chitin, hyaluronic acid, pectin and starch) with different bioactive functional groups used in biomedical applications.

3.3. Wound dressing

The wound dressing is an essential part of the healing process (Atiyeh, Ioannovich, Al-Amm, & El-Musa, 2002). It has many advantages compared to preformed dressings such as conformability without creasing or fluting in the wound bed, and ease of application, which lead to patient's comfort and satisfactory (Balakrishnan, Mohanty, Umashankar, & Jayakrishnan, 2005). The diversity of wounds requires various dressings coated by different materials which are used as a target in the wound bandage. An optimal dressing should achieve quick healing and cost-effective with minimal side effects to the patient (Boateng et al., 2008).

As mentioned above, CPs with various functionalities can be used as the active site for chemical modifications (etherification, esterification, oxidation, cross-linking, ring-opening polymerization, and graft copolymerization) and specific ligands for surface attachments (Masina et al., 2017; Rahimi, Ahmadi, Samadi Kafil, & Shafiei-Irannejad, 2019; Wei et al., 2017). These natural molecules can be modified to change their physical characteristics and, hence, improve the capability for a specific application. Additionally, CPs are naturally occurring biomolecules with several various functions in living organisms. Some of these polymers act as structural components in the plants' cell walls, food reserves, protecting agents of wound region in plants and also lubricating agents in joints. Thus, it was concluded that the structure and function of CPs could be beneficial in a wound management aid or may be useful in the wound healing process (Lloyd, Kennedy, Methacanon, Paterson, & Knill, 1998).

4. Carbohydrate polymer-based silver nanocomposite scaffolds

In general, polymeric nanocomposite refers to a polymer containing dispersed nanofillers with particles size less than 100 nm, which enhanced the properties of both polymer and nanoparticles (Ali & Ahmed, 2018). In the current section, AgNPs containing nanocomposite scaffolds for wound dressing applications is presented as follow.

4.1. Agar

Agar is the combination of the agarose and agaropectin obtained from red algae, and it has been used as a solid substrate and contain culture media for microbiological works (Williams, 2000). Orsuwan and et al. (Orsuwan, Shankar, Wang, Sothornvit, & Rhim, 2016), produced an agar-banana powder blend film reinforced with AgNPs leading to the change of its surface color and transmittance. The resulting composite exhibited distinctive antimicrobial activity against pathogenic bacteria (*E. coli* and *L. monocytogenes*) with stronger antibacterial activity against Gram-negative bacteria than Gram-positive bacteria. Shukla and et al. (Shukla, Singh, Reddy, & Jha, 2012), described the synthesis of a nanocomposite material using agar extracted from the red alga (Gracilaria dura) and AgNPs. The presence of AgNPs enhanced the antibacterial effects to 99.9 % on the bacterium *B. pumilus*. This nanocomposite film with a proven antibacterial property may find applications in food preservation and wound dressing.

4.2. Alginate

Sodium alginate is a polysaccharide which is isolated from brown algae. Since it has negatively charged carboxyl group in its structure, it well dissolved in water and forms a viscous gum. Alginate (Alg) is extensively used in industrial and medicinal fields for its broad utilization such as scaffolds and wound dressings owing to low toxicity and desired mechanical properties (Drury, Boontheekul, & Mooney, 2005; Gombotz & Wee, 1998). It is also widely used in secreted wounds healing. The ion exchange between the calcium ions of the alginate tissue and the sodium ions in the secretion leads to the gel formation on the wound surface. This gel provides a proper moist environment which is required for wound healing (Winter, 1962). The moist environment around the wound could increase and amplify the inflammatory risks, so antimicrobial agents such as Ag and AgNPs are rationally necessary for wound healing. Seo et al. (Seo et al., 2012), synthesized alginate–silver nanoparticles (Alg-AgNPs) composite sponge from AgNPs and viscous

solution of alginate. They used nanoparticle stabilizing property of alginate due to its negatively charged structure, which prevents AgNPs agglomeration. On the other hand, the hydrophilic nature of alginate makes the Alg–AgNPs composite sponge as a moist wound dressing. They chose *S. aureus* and *K. pneumonia* microorganisms to evaluate the antimicrobial activity of synthesized Alg–AgNPs composite sponge. The results showed that the growth of these bacteria was entirely inhibited over the concentration of 200 ppm, which is by the antibacterial effect of the original AgNPs. This excellent disinfection behaviour of Alg–AgNPs sponge is related to alginate hydrophilic nature. Because the alginate fibres absorb water and swell, the empty spaces between the fibres are closed, and any bacteria that are existed in the wound secretions are trapped in the wound dressing. The trapping role of alginate helps microbes and AgNPs fully contact each other to apply a bactericidal effect. Beside excellent antimicrobial activity of Alg–AgNPs sponge, there is a cytotoxic effect on the human fibroblast, which is related to AgNPs. The previous studies revealed that alginate is a biocompatible polymer and had little adverse influence on cell viability and cell proliferation (Wiegand, Heinze, & Hipler, 2009), while AgNPs have interaction with the mitochondria and induce the apoptosis pathway via the production of reactive oxygen species (ROS). Finally, the combination of AgNPs and alginate sponge showed a cytotoxic effect on human fibroblast. The cytotoxicity of the AgNPs decreased the cell viability to 86 % of the control.

Jasmina et al. (Stojkovska, Zvicer, Jovanovic, Mlskovic-Stankovic, & Obradovic, 2012), electrochemically synthesized AgNPs in alginate solution to produce nanocomposite alginate microbeads. They employed the advantage of electrochemical synthesis to control the exact particle size and obtain the pure nanocomposite hydrogel. In this study, the alginate used as a capping agent to prevent AgNPs agglomeration. It has been revealed that the presence of AgNPs in alginate microbeads rarely affected the biomechanical properties of the beds and strengthened the gel under compression (nearly 9 %).

Augustine et al. (Augustine & Rajarathinam, 2012), have synthesized AgNPs by chemical reduction method, and then coated them on the surgical gut suture. After that, the minimum inhibitory concentration of synthesized AgNPs has been determined against both *E. coli* and *S. aureus* bacteria. In the following, the AgNPs immobilized on surgical gut suture by using sodium alginate as a cross-linking agent, and then the release of silver checked *in vitro*. The formation of calcium alginate coating over the suture prepares the moist environment, which facilitates wound healing. Finally, the antimicrobial activity has been evaluated against Gram-negative and Gram-positive bacteria by disk diffusion method. The results showed the sufficient ability of the prepared suture to inhibit the growth of both the Gram-negative and Gram-positive bacteria.

Bojana et al. (Obradovic, Stojkovska, Jovanovic, & Miskovic-Stankovic, 2012), investigated the stabilization process of Alg-Ag solution and preparation of nanocomposite hydrogels of different polymer blends. According to results, AgNPs in alginate colloid solution continue to grow up even after three days and it has been revealed that the Alg-Ag colloid solution remains stable for additional 30–40 days and it could be used in mixtures with aqueous solutions of poly(vinyl alcohol) (PVA) and poly(N-vinyl-2-pyrrolidone) (PVP). The antibacterial tests showed Alg-Ag-PVA beads intense activity against *E. coli* and decreased the concentration of bacteria in suspensions for 99.9 % during 24 h. This strong antimicrobial activity was attributed to the intense release of AgNPs and Ag^+ ions in the bacterial suspension.

Irradiation technology was found a proper technique for *in situ* incorporation of NPs in the polymer matrix and formation of hydrogels in recent years (Nam et al., 2004; Rosiak et al., 2002). Singh et al. (Singh & Singh, 2012), synthesized PVP and alginate hydrogel and used gamma radiation to incorporated AgNPs in the hydrogel network. According to fluid absorption capacity analysis, the absorption capacity and moisture permeability of the prepared PVP-Alg-AgNPs composite hydrogel showed the ability to prevent fluid accumulation in the exudating wound which is an essential parameter for hydrogels used in biomedical and wound dressing application. The antimicrobial tests revealed that PVP-Alg hydrogels are impermeable to various bacilli and cocci bacterial and fungal strain including *P. aeruginosa*, *S. aureus* and *E. coli* bacteria and *C. albicans*.

Ghasemzadeh et al. (Ghasemzadeh & Ghanaat, 2014), recently have synthesized a series of superabsorbent Ag nanocomposites based on sodium alginate and polyvinyl alcohol (PVA) via graft polymerization of acrylamide (AAm) using methylenebisacrylamide (MBA) as a crosslinking agent and ammonium persulfate (APS) as an initiator. The AgNPs were synthesized throw a green synthesis process, and the highly stable AgNPs have been prepared in hydrogel network. In this work, the effect of reaction parameters, including the primary concentration of crosslinker and initiator, reaction temperature, and Alg-PVA weight ratio were inspected on the swelling behaviour and the gel content of the superabsorbent hydrogels. The antibacterial activity of the Ag nanocomposite hydrogels, which evaluated both Gram negative (*E. coli*) and Gram-positive (*S. aureus*) microorganisms have shown excellent antibacterial activity. The result attributed to the release of AgNPs from the hydrogel.

Synthesis of AgNPs by chemical reagents such as sodium borohydride, formamide and triethanolamine is a simple and effective method, but there are some disadvantages such as biological toxicity and environmental hazardous reducing agents. Pankongadisak et al. (Pankongadisak, Ruktanonchai, Supaphol, & Suwantong, 2014), were prepared AgNPs-loaded calcium alginate (Ag-CaAlg) beads by electrospraying technique to control the release of AgNPs from the Ag-CaAlg beads embedded in gelatin (Ag-CaAlg-Gel) scaffolds. In this work, they used UV irradiation technique to reduce the Ag^+ ions in alginate solution to AgNPs and finally, some properties of Ag-CaAlg-Gel scaffolds such as water swelling and weight loss behaviours were investigated. Meanwhile, this research group were evaluated the antibacterial activity of the Ag-CaAlg-Gel scaffolds using both Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria. According to the results, the Ag-CaAlg-Gel scaffolds (without AgNPs) show no activity against the growth of both *E. coli* and *S. aureus* microorganisms. However, with increasing the percentage of AgNPs in the Ag-CaAlg-Gel scaffolds, the antimicrobial activity increased against both Gram-negative and Gram-positive bacteria. Considering the results, the prepared Ag-CaAlg-Gel scaffolds had the most antibacterial effect on Gram-positive bacteria rather than Gram-negative bacteria (Pankongadisak, Ruktanonchai, Supaphol, & Suwantong, 2015).

Another research group (Eghbalifam, Frounchi, & Dadbin, 2015), used a gamma irradiation method to prepare polyvinyl alcohol/sodium alginate/nano-silver (PVA-Alg-Ag) composite films. They have controlled the size and concentration of AgNPs via altering the doses of gamma irradiation from 5 to 15 kGy. Antibacterial tests against *S. aureus* and strains have been set for antibacterial inspection of the prepared composite. The results showed that the inhibition zone against *S. aureus* for PVA-Alg-0.45 %Ag^+/15kGy was 1.5 mm that increased up to 2.1 mm for PVA-Alg-1.33Ag^+/15kGy composite and the inhibition zone against *E. coli* for the above composites containing 0.45 % and 1.33 % Ag^+ was 2.5 and 3.2 mm, respectively. It is good to mention that with increasing gamma radiation dose, the inhibition zone against *E. coli* and *S. aureus* increased from 1.5 to 3.2 and 1 to 2.1 mm, respectively.

In past few years, mesoporous silica materials have received research group's attention due to their potential in biomedical applications and excellent silica properties for better use of metal NPs including rich surface chemistry, high biocompatibility and controllable porosity. Hence, capping AgNPs with mesoporous materials such as silica (SiO_2) is a solution to modify biocompatibility with mammalian cells and on the other hand for better control of Ag^+ ions released from a mesoporous matrix which enhances its therapeutic effect. With this in mind, Pandeya et al. (Pandey & Ramontja, 2016), have synthesized mesoporous silica-capped silver nanoparticles of polyanionic sodium

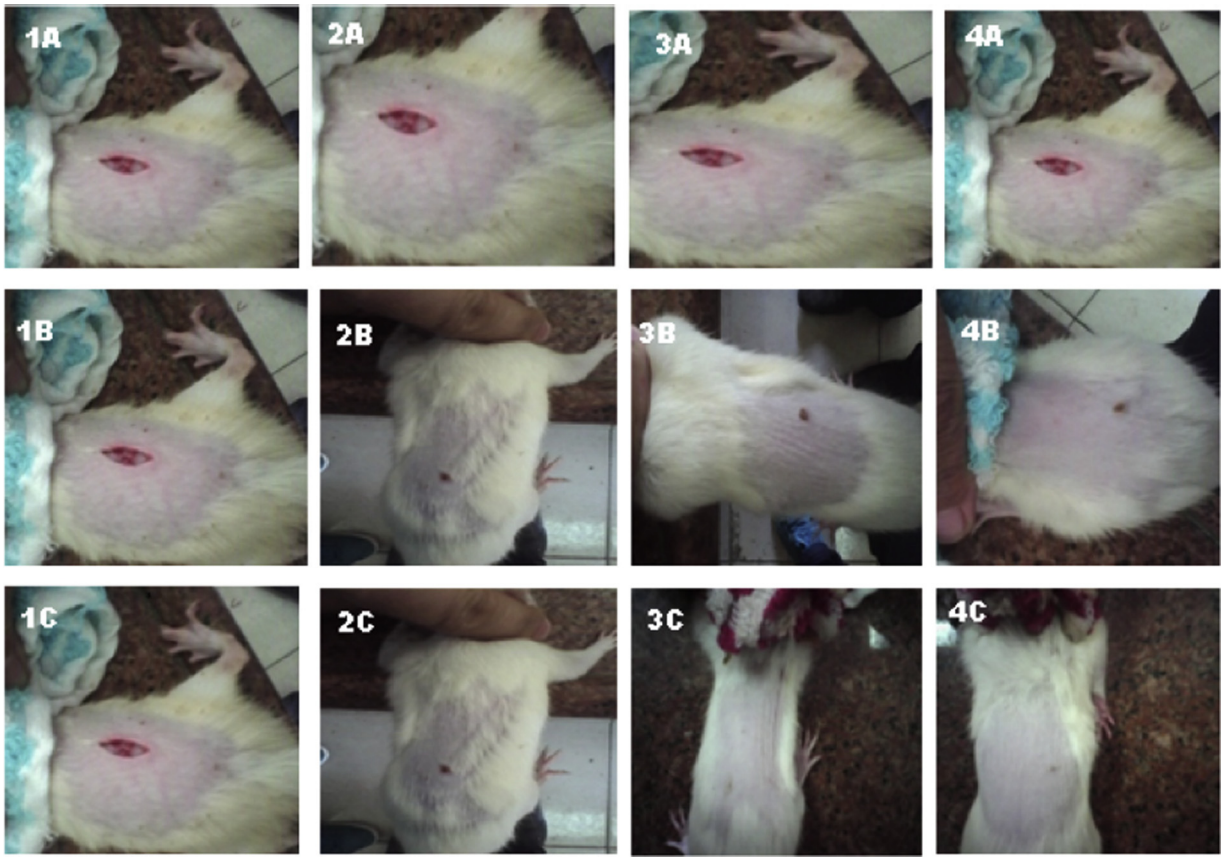

Fig. 5. Selected images for present the effect of the topical bandage type on the wound area healing of viscose nonwoven; (1) Vis; (2) Vis/Alg/AgNPs; (3) Vis/Alg/AgNPs/Nic and (4) Vis/Alg/AgNPs/Nic/$CaCl_2$. (A) Wound area at zero time; (B) wound; (C) wound area at day 10. (Reprint license number: adopted from Ref. (Montaser et al., 2016) with permission number of 4,662,010,363,895).

alginate (Alg-AgNPs-SiO_2 nanohybrid). To evaluate the antibacterial potential of Alg-AgNPs-SiO_2 nanohybrid they tested them against several bacterial strains including Gram-positive bacteria (*S. aureus*, *S. epidermidis*, *B. cereus*, *B. subtilis* and *E. faecalis*) and Gram-negative bacteria (*E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumonia*, *P. mirabilis*, *P. vulgaris*, *P. aeruginosa* and *E. aerogeness*). According to the results, it is evident that the antibacterial effects of AgNPs against all the microorganisms were improved significantly as the particle diameter was reduced from 15 nm to 7 nm in the case of Alg-AgNPs-SiO_2 nanohybrid.

Montaser et al. (Montaser et al., 2016), have used alginate as a reducing and stabilizing agent for the synthesis of AgNPs colloid. They also used nicotinamide (Nic) as a drug for diabetic wound healing and calcium chloride solution (5 % $CaCl_2$) to improve the fixation of nanocomposite/nicotinamide onto viscous nonwoven fabrics (Vis). To evaluate healing properties of viscous fabrics with and without AgNPs and nicotinamide they applied four types of fabrics (1:Vis, 2:Vis/Alg/AgNPs, 3:Vis/Alg/AgNPs/Nic and 4:Vis/Alg/AgNPs/Nic/$CaCl_2$) to four groups of contaminated mice (contaminated by *E.Coli* bacteria and diabetic wound in ten days) (Fig. 5). Considering the results, it was clear that the wound area significantly decreased with the use of AgNPs and nicotinamide loaded fabrics in comparison with blank viscous fabric. Also, a smaller wound area could be achieved from the fourth day to the tenth day for each sample. On the other hand, the best results obtained from a sample which fabric treated loaded with AgNPs, nicotinamide and cross-linked due to the antibacterial effect of AgNPs, anti-inflammatory rule of nicotinamide and presence of calcium which acts as a homeostatic element to blood.

4.3. Carrageenan

Carrageenans are high molecular weight, linear, and sulphated polysaccharides extracted from certain species of red seaweeds (Li, Ni, Shao, & Mao, 2014). They have many applications in various fields including drug delivery, food packaging, tissue engineering and wound dressings and also used as an excipient in the pharmaceutical industry (Noor, 2018; Yegappan, Selvaprithiviraj, Amirthalingam, & Jayakumar, 2018). Besides, carrageenans are biodegradable and biocompatible polysaccharide and exhibit high ductility that allows better skin contact (Kozlowska, Pauter, & Sionkowska, 2018). Therefore, they play a significant role as a major component of wound dressings and are currently promising candidates in tissue engineering and regenerative medicine.

Green synthesis of AgNPs in the plant extracts has an occurrence of subsequent effects during their medicinal applications (Azizi et al., 2016). *Citrullus colocynthis* is a member of the Cucurbitaceae family and is a common used plant in traditional medicine distributed throughout Asia (Kumar, Kumar, Saroha, Singh, & Vashishta, 2008). Azizi et al. (Azizi, Mohamad, Rahim, Mohammadinejad, & Ariff, 2017), synthesized AgNPs with a simple one-step green process using *Citrullus colocynthis* (Fig. 6). They designed a highly safe hydrogel-based antimicrobial bio-nanocomposite via biosynthesized AgNPs method and acted as an antimicrobial agent in the kappa-carrageenan hydrogel matrix. The Ag-containing hydrogel beads have potent antibacterial activity with more inhibition zone against Methicillin-resistant *S. aureus* (*MRSA*), *P. aeruginosa* as well as *E. coli*, in comparison to chemically synthesized Ag-containing hydrogel bead. A biodegradable Ag nanocomposite hydrogel based on carrageenan was reported by Jayaramudu and co-workers (Jayaramudu et al., 2013), which has a potential for

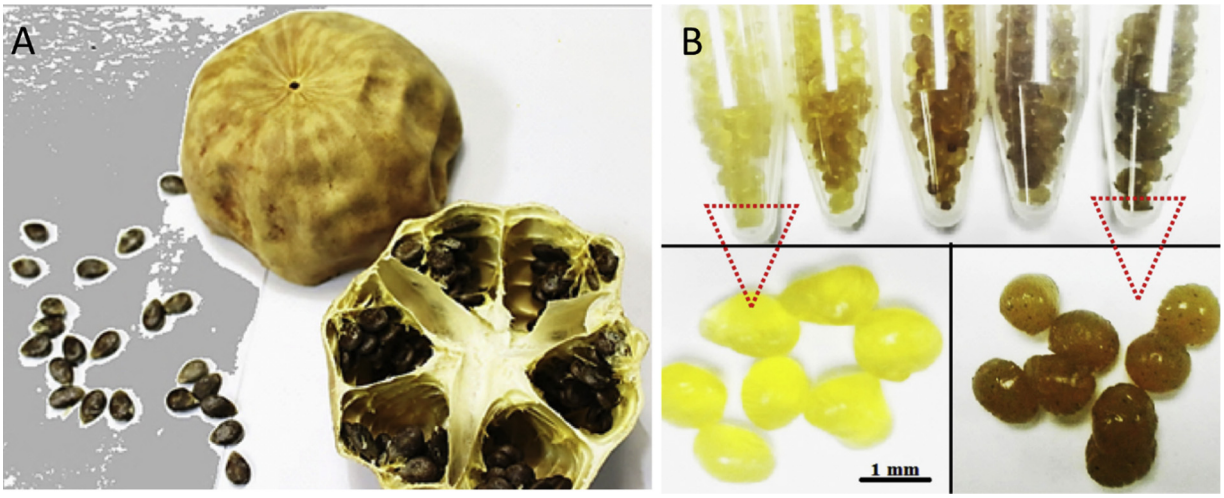

Fig. 6. Photograph of dried *Citrullus colocynthis* (A), and Digital photo of kappa-carrageenan/Ag bionanocomposite hydrogel beads with different ratio of Ag-NPs (B). (Reprint license number: adopted from Ref. (Azizi et al., 2017) with permission number of 4,662,010,078,480).

inactivation of bacteria. The hydrogel was produced by a green approach using acrylamide and iota-carrageenan, which *Azadirachta indica* as the leaf extracts (neem leaf) was used for reducing the Ag^+ ions to Ag in the polymeric network. The antibacterial activities against *Bacillus* and *E. coli* were also studied, and iota-carrageenan combination with Ag nanocomposites showed significant inhibition effects. Zepon and coworkers (Zepon, Marques, da Silva Paula, Morisso, & Kanis, 2018), also introduced a simple, cost-effective green and scalable protocol for preparation of kappa-carrageenan hydrogel membranes containing *in situ* synthesized AgNPs. Due to the controlled release property of the resulting hydrogel, it showed good antimicrobial activity against common bacteria found in wound infections. Furthermore, the flexibility and laminating of the resulting hydrogel it could provide good skin contact for wound dressing applications.

Rhim and Wang (Rhim & Wang, 2014), blended kappa-carrageenan and chemically synthesized AgNPs with clay mineral as the nano-fillers to produce an antimicrobial bio-nanocomposite film. The nanocomposite films exhibited characteristic antimicrobial activity against two pathogenic bacteria (*L. monocytogenes* and *E. coli*), Gram-positive and Gram-negative. Despite the antibacterial activity of AgNPs-included nanocomposite on Gram-negative bacteria, the nano-clay-included nanocomposite showed intense property against Gram-positive bacteria. The presence of alkyl quaternary ammonium salt group on the clay particles provided an antimicrobial activity which bonded irreversibly to the bacterial cell membranes to disrupt the lipid bilayers of the cell membrane, and to cause cell lysis (Obłąk, Piecuch, Rewak-Soroczyńska, & Paluch, 2019).

Synthetic polymers like polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyethylene glycol (PEG), poly acrylic acid (PAA), poly 2-hydroxyethyl methacrylate (PHEMA), and polyurethane (PU) have been used in various forms of hydrogel as a biosynthesis wound dressings (Mir et al., 2018; Zafalon et al., 2018). Hydrogels with the blends of synthetic and natural polymers have considered as the dermal wound healing dressings and can endow the properties ideal for wound repair (Tabasum et al., 2018; Teodorescu, Bercea, & Morariu, 2018; Zia et al., 2018). Durgeshwer Singh and his co-workers (Singh, Singh, & Singh, 2015), fabricated PVP and carrageenan blend hydrogels reinforced with AgNPs in the polymeric matrix by radiation polymerization. No counts for *P. aeruginosa*, *S. aureus*, *E. coli*, and *C. albicans* were observed in the presence of hydrogels containing 100 ppm AgNPs less than six hours. In another study, Fouda et al. (Fouda et al., 2015), formulated kappa-carrageenan biopolymer with the blends of two synthetic polymers, including pyrrolidone and polyethyleneglycol. AgNPs were produced by Honeybee and added to the solution. The obtained films via casting out methods exhibited microbial activity against pathogenic fungi *Asprgillus sp*., *Pencillin sp*. and *F. oxysporum* compared with fluconazole as a commercial fungicide.

4.4. Cellulose

Cellulose is used widely in the wound dressing procedure, individually or in combination with other compounds. Bacterial cellulose as a nanoporous matrix compound and the template is used in the silver nanoparticles synthesize procedure by the chemical reduction. Cellulose nanofibers in combination with nano-silvers are rated to lowest toxicity and display a strong antibacterial effect against the *E. coli*, *S. aureus* and *P. aeruginosa*. Other properties including the quick healing process, involving in epidermal cells growth and attachment and reducing the inflammation are attributed to this combined materials (Wu, Zheng, Song et al., 2014).

Cellulose has no antimicrobial activity to prevent wound infection. To achieve this property, bioactive NPs and polymers were combined with cellulose. A simple method was developed by Maria and et al. (Maria et al., 2010), for loading Ag NPs into the bacterial fibers to obtain a composite with high antibacterial activities against *E. coli*. Sureshkumar and et al. (Sureshkumar, Siswanto, & Lee, 2010), prepared a magnetic bacterial cellulose nanofiber. Then polydopamine was synthesized on the nanofiber via an adherent self-polymerization method. AgNPs were incorporated into the dopamine-treated magnetic bacterial cellulose by soaking in silver nitrate solution. The resulting bacterial cellulose nanocomposite possessed high antimicrobial activity against the model microbes *E. coli* and *B. subtilis*. Raghavendraa and coworkers (Jayaramudu et al., 2013), impregnated AgNPs into the cellulose fibers after successfully developing from a green process where $AgNO_3$ was reduced with natural CPs. Cellulose–silver nanocomposite fibers (CSNCFs) with excellent antimicrobial properties were studied against *E. coli*, with active anti-microbial agents. Hence, the developed CSNCFs can potently use for burn/wound treatments.

Bacterial cellulose (BC) has attracted increasing attention as a novel wound dressing material; however, its antimicrobial activity is not sufficient for use in practical applications. To improve such a deficiency, AgNPs were generated and self-assembled on the surface of BC nanofibers. Jian Wu et al. (Wu, Zheng, Wen et al., 2014), showed that AgNP-BC exhibited significant antibacterial activity against *S. aureus*. Furthermore, AgNP-BC was examined in both *in-vitro* and *in-vivo* models with low cytotoxicity emerge. All results demonstrated that AgNP-BC could reduce inflammation and promote scald wound healing.

Chun-Nan Wu and coworkers (Wu et al., 2018), synthesized

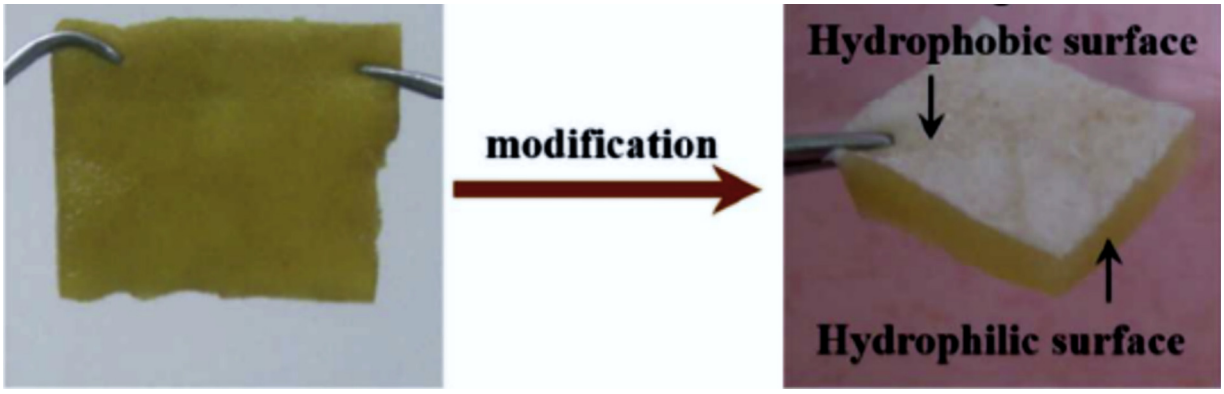

Fig. 7. Photographs of asymmetric wetting modification with hydrophobic and hydrophilic surface (Reprint license number: Adapted with permission from Ref. (Liu et al., 2009) Copyright 2016 American Chemical Society).

TEMPO-oxidized bacterial cellulose (TOBCP) with anionic C6 carboxylate groups. The TOBCP was subsequently ion-exchanged in $AgNO_3$ solution, and AgNPs with diameter of ~16.5 nm were *in situ* synthesized on TOBCP nanofiber surfaces by thermal reduction without using a reducing agent. The prepared nanofiber exhibited high biocompatibility and showed significant antibacterial activities against *E. coli* and *S. aureus* with high potential in wound dressing applications.

4.5. Chitosan

Chitosan is a polymer including the linear and semi-crystalline structure with no natural availability; however, it can be obtained from chitin extraction. The existence of amino groups in chitosan makes it distinctive from chitin and causes unique properties (Croisier & Jérôme, 2013). Chitosan includes a variety of derivatives such as fibers, sponges, membranes and scaffolds. The antibacterial and antifungal properties of these polysaccharides are pertinent to their adhesive nature. The oxygen permeability property is attributed to the use of these biomaterials in the treatment of wound and burn injuries (Jayakumar, Prabaharan, Kumar, Nair, & Tamura, 2011).

Lu and his team (Lu, Gao, & Gu, 2008), constructed an Ag nanocrystalline/chitosan (AgNC-Cs) composite by self-assembly. The prepared composite can promote wound healing and combat infections. Low risk of Ag absorption by skin is an important advantage of this dressing. Readily available materials, simple processing and increasing rate of wound healing are other features of this dressing and could have extensive application in clinical settings. To examine how AgNPs affect the material characteristics, biological activity and antibacterial efficiency of genipin-crosslinked chitosan (Gen-Cs) matrix, Liu et al. (Liu & Huang, 2008), embedded various amounts of AgNPs into biodegradable Gen-Cs films. The antibacterial efficacy of the AgNPs and the biodegradability of the Gen-Cs films were investigated. A new unique hexagonal shape of AgNPs was used in the preparation of chitosan-based nanocomposite, and the results were compared with nanocomposite containing spherical shape. The toxicity of skin cells associated with dermal wound healing was evaluated on both films, and cells had normal enhanced growth on films containing hexagonally-shaped NPs (Levi-Polyachenko, Jacob, Day, & Kuthirummal, 2016).

A chitosan/polyvinyl alcohol (Cs-PVA) composite was fabricated by Vimala and his coworkers (Vimala et al., 2011), in which Ag^+ ions were reduced to AgNPs in an acidic solution of chitosan and PVA by using their intrinsic functional groups ($-OH$, $-COOH$, $-NH_2$ groups). The antimicrobial efficacy of the developed nanocomposite was compared with curcumin encapsulated Cs-PVA-AgNPs nanocomposite, and the results showed that both are potentially useful in preventing/treating infections. Abdelgawad and colleagues (Abdelgawad, Hudson, & Rojas, 2014), also introduced a novel hybrid based on chitosan-AgNPs blended with poly (vinyl alcohol) fibers via a green approach. They founded out that the number of *E. coli* colonies decreased by increasing the chitosan ratio in the fiber blend. The antibacterial activity observed by the nanofiber justified with two mechanisms of actions; interaction of chitosan's protonated amino groups with the negatively charged surfaces of bacteria and attaching AgNPs to the cell walls and disturb the cell wall permeability and cellular respiration. Poly vinyl pyrrolidone (PVP) is a synthetic polymer which has excellent compatibility and used in various fields (Chaudhuri, Mondal, Ray, & Sarkar, 2016). Its blend with other polymers was also studied for antibacterial activity, biocompatibility, and biomedical applications (Ashjaran, Babazadeh, Akbarzadeh, Davaran, & Salehi, 2019; Bonan et al., 2015). Archana et al. (Archana, Singh, Dutta, & Dutta, 2015), prepared wound healing material with chitosan, PVP, silver oxide NPs which showed higher antibacterial activity due to both chitosan as well as silver oxide intrinsic suitable antibacterial activities.

A biopolymer chitosan/montmorillonite nanocomposites were developed by Aguzzi and et al. (Sandri et al., 2014), and blended with Ag sulfadiazine to show antimicrobial activity. The authors studied and investigated designed nanocomposites as well. They also claimed to identify the biocompatibility and investigating on infected wounds in their future works. They made their covenant and evaluated antimicrobial activity assays, cytotoxicity assay for biocompatibility, and cell motility gap closure assay for wound closure effect. The prepared nanocomposite was able to protect fibroblasts from the cytotoxic action and improve its bacteriostatic and bactericidal properties, especially against *P. aeruginosa*, that often complicates skin lesions (Sandri et al., 2014).

Liang et al. (Liang, Lu, Yang, Gao, & Chen, 2016), designed sponge-like AgNPs-chitosan composite as a dressing with asymmetric wettable architecture. The composite has chitosan hydrophilic and a thin layer of stearic acid hydrophobic sides (Fig. 7). The highly hydrophobic surface possessed the properties of self-cleaning by minimizing the water and contaminant adhesion. Whereas, hydrophilic surface give it water-absorbing and hemostatic properties with high water uptake property. Both *in vitro* and *in vivo* investigations on antimicrobial activity against drug-sensitive and drug-resistant pathogenic bacteria were tested and compared with clinically used Acasin™ nano-silver dressing. All results persuaded authors to claimed that the prepared asymmetric wettable composite has high potential application in burn, chronic and diabetic wound infections. In another work on wound dressing films (Liu, Huang, Yao, Fang, & Chang, 2009), they presented a novel dual-layer composite with a soybean protein non-woven fabric and a crosslinked chitosan film (hydrophobic and hydrophilic surfaces, respectively), as a wound dressing material. Both *in vitro* and *in vivo* application of this bilayer composite was performed, and results demonstrated its effectiveness.

4.6. Chitin

Chitin, a natural biopolymer, is vastly produced every year and used in a wide range of biomedical applications (Rameshthangam, Solairaj, Arunachalam, & Ramasamy, 2018). It was discovered by Prof. Henri Braconnot in 1884 which is the most abundant natural polymer in the world after cellulose. Benhabiles et al. (Benhabiles et al., 2012), examined the antibacterial activity of chitin on a wide range of bacterium. As the results showed, chitin had antibacterial activity against three bacterial strains, including *P. aeruginosa*, *S. typhimurium* and *P. melaninogenica*. Among them, *P. aeruginosa* is troublesome with substantial resistance to many antibiotics and the capability to acquire resistance during antibiotic therapy. Chitin exhibited a bacteriostatic effect on Gram-negative bacteria, *E. coli*, *V. cholerae*, *S. dysenteriae* and *B. fragilis*. Thus, the mechanism of antibacterial activity of chitin is by making the bacteria flocculate which kills presumably through lack of nutrients and oxygen (Benhabiles et al., 2012). More flexibility, softness, transparency, and conformability are the other properties attributed to chitin, which are positive features related to wound healing (Yusof, Wee, Lim, & Khor, 2003). Huang et al. (Huang et al., 2014), constructed pure chitin fibers from the chitin solution in NaOH-urea without using a chemical binder. The chitin fiber retained the intrinsic α-chitin structure and its biocompatibility. The prepared fibers as wound dressing showed highly wound-healing effects on rabbits.

A developed nanocomposite based on chitin-AgNPs was obtained by adding different amounts of AgNPs solution to chitin hydrogel and lyophilized by Madhumathid et al. (Madhumathi et al., 2010), which showed bactericidal against *S. aureus* and *E. coli* and good blood clotting ability. The susceptibility of *E. coli* was more than *S. aureus* due to the protection of Gram-positive bacteria by a thick peptidoglycan wall which prevents the penetration of AgNPs. The results of cytotoxic effects on L929 mouse fibroblast revealed that all nanocomposites were cytotoxic. At the relatively same time, Kumar et al. (Kumar et al., 2010), prepared β-chitin-AgNPs composite as a wound dressing scaffolds, according to a published protocol (Madhumathi et al., 2010), and matched with their previous work results. Indirect cytotoxicity study was performed using an Alamar blue assay and showed that nanocomposites were non-toxic to Vero cells. Furthermore, cell attachment was studied and indicated moderate or weak attachment, which would be preferred for the case of wound dressings. Rita Singh and Durgeshwer Singh (Singh & Singh, 2014), developed the chitin membranes containing AgNPs by gamma irradiation (in the presence of sodium alginate as a stabilizer) for use as an antimicrobial wound dressing. *in vitro* antimicrobial analysis were examined on *P. aeruginosa* and *S. aureus*. The membrane with 100 ppm AgNPs showed promising antimicrobial activity against common wound pathogens. Ifuku and et al. (Ifuku et al., 2015), prepared a chitin nanofiber modified with AgNPs by UV light reduction of silver ions. The resulting nanofibers could be efficient substrates to immobilize AgNPs with stable dispersion states and endowed strong antifungal activity to chitin nanofibers. Solairaj and Rameshthangam (Solairaj & Rameshthangam, 2017), focused on the preparation of α-chitin nanoparticles and its nanocomposite impregnated with AgNPs. The antibacterial and antifungal assays revealed that the nanocomposite has an enhanced antimicrobial effect on inhibition of bacteria (*P. vulgaris*, *K. pneumonia* and *S. aureus*) as well as fungi (*C. albicans*, *T. viridae*, *A. niger* and *A. alternate*). It is also proved that the α-chitin NPs could act as stabilizing material by enhancing antimicrobial and mosquito larvicidal activities. All results in this study suggest that the prepared nanocomposite has a potential for further mosquito control applications. Alexandrova (Alexandrova, Shirokova, Bondarenko, & Petrosyan, 2013; Alexandrova, Shirokova, Sadykova, & Baranchikov, 2018), immobilized AgNPs in the carboxymethyl derivative of chitin polymeric matrix in the presence of antioxidants of plant origin by ultrasonic treatment of a heterophase system. The synthesized Ag nanocomposites had a strong bacterial effect on Gram-positive bacteria *S. aureus*, *B. subtilis*, and, to a lesser extent, on Gram-negative bacteria *E. coli* and also showed pronounced fungistatic activity against *A. niger*.

Fibroin is a protein present in silk which extracted silk cocoons of *Bombyx mori* which has good biocompatibility and accelerate the wound healing process by enhancing the adhesion. Regarding this, it is used with blend form with other polymers for biomedical applications. Ghanbari and his colleagues (Mehrabani, Karimian, Mehramouz, Rahimi, & Kafil, 2018), benefited from fibroin advantages and produced a 3D silk fibroin-chitin composite scaffolds incorporated AgNPs as a candidate for wound healing applications.

4.7. Hyaluronic acid

Hyaluronic acid (HA), is an anionic, nonsulfated glycosaminoglycan naturally produced by the human body and distributed widely throughout the body such as connective tissues, eyes and skin. HA is the main component of the extracellular matrix and has a crucial role in tissue regeneration, inflammation response, and angiogenesis, which are phases of skin wound repair (Shaharudin & Aziz, 2016). HA makes wound healing process faster by sending the signal to the body for building more blood vessels around the wounded area (Aya & Stern, 2014; Litwiniuk, Krejner, Speyrer, Gauto, & Grzela, 2016). It also has antibacterial properties, so it can help reduce the risk of infection when applied directly to open wounds (Pirnazar et al., 1999; Romanò, De Vecchi, Bortolin, Morelli, & Drago, 2017).

Anisha et al. (Anisha, Biswas, Chennazhi, & Jayakumar, 2013), developed a composite sponge of chitosan, hyaluronic acid and nanosilver (Cs-HA-AgNPs). They combined the haemostatic properties of Cs, moisture retention ability of HA and antimicrobial potential of AgNPs to prepare this composite for wound dressing of diabetic foot ulcers. Antibacterial activity of prepared sponges against *S. aureus*, *E. coli*, *P. aeruginosa* and *K. pneumoniae* was examined by turbidity assay, and Kirby-Bauer disc diffusion method and the results showed the productive potential of sponge in reducing *in vitro* growth of microorganisms.

Abdel-Mohsen et al. (Abdel-Mohsen et al., 2013), used hyaluronic acid and AgNPs to prepare hyaluronan fibers with incorporated AgNPs (HA-AgNPs). They used the wet-spinning technique for preparation of fibers and used them as capping and stabilizing agent for the preparation of fibers with silver nanoparticles. The antibacterial properties of prepared fibers have been evaluated against *E. coli* and *S. aureus* strains. According to obtained data the produced hyaluronan fiber-silver nanoparticles (HA-AgNPs) had relatively high antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria which is related to the size and the high surface area of the hyaluronan fiber-AgNPs and reached them easily to the bacteria nucleus.

Sandri et al. (Sandri et al., 2013), developed a kind of wound dressing based on silver sulfadiazine (AgSD), loaded in solid lipid NPs (SLNs) and used it in association with platelet lysate (PL) for skin lesions treatments. SLN were prepared by mixing chondroitin sulfate and sodium hyaluronate, as bioactive polymers which have adequate tissue repairing properties (Lin, 2004; Puccio et al., 2011). To prevent the cytotoxic effect of the drug (AgSD), and for enabling the association of the drug with PL, the SLN was loaded in wound dressings based on chitosan glutamate (CS-glu). The bacterial strains such as *S. aureus*, *S. pyogenes*, *E. coli*, *P. aeruginosa* were used to evaluate the antimicrobial properties of drug-loaded dressings. The minimum bactericidal concentration (MBC) values of AgSD-SLN-CS-glu dressing showed significant antimicrobial activities of prepared dressing for all the microorganisms except for *P. aeruginosa*. The increasing of surface area and improving the contact between colloidal particles and microorganisms leads to the enhancement of the antimicrobial properties of the drug by SLN.

Chudobova et al. (Chudobova et al., 2013), prepared the complexes of HA and Cs with silver nitrate and AgNPs for development of antimicrobial polymeric material which is ideal for covering vascular

implants and further use in transplant surgery. The antimicrobial capability of complexes against *S. aureus* strain was determined using the disk diffusion method, minimum inhibitory concentration (MIC) and total inhibitory concentration (TIC) measurements. Testing of antimicrobial activity of HA and Cs in complexes with silver and AgNPs showed that the addition of Ag^+ ions or AgNPs to the complex led to the significant increase in the inhibition of *S. aureus* growth. The greatest inhibitory effect reached with the combination of 9.7 mM Cs with 300 μM Ag^+ ions or AgNPs.

Chen et al. (Chen, Chen, Shalumon, & Chen, 2015), used electrospinning method to prepare a core-sheath structure of hyaluronic acid-polycaprolactone (HA-PCL) nanofibrous membrane (NFMs) embedded with AgNPs. They used NFM with HA as the inner core and the AgNPs-embedded PCL as the outside shell to simulate the functions of the fibrotic and synovial layers in a natural tendon sheath. HA was used for effective lubrication, and AgNPs was used to prevent bacterial infection after tendon surgery. The antibacterial activity of AgNPs in the core-sheath structure was confirmed by observing the inhibition zones against *S. aureus* and *E. coli* strains. The zone of inhibition was 1.66 ± 0.02 cm^2 and 2.21 ± 0.14 cm^2 for *S. aureus* and *E. coli* bacteria, respectively.

The formation of biofilm around implants caused by bacterial colonization after installation is one of the most important reasons for post-operation infection. Initial surface modification is usually required to incorporate antibacterial agents such as silver (Ag) on titanium (Ti) surfaces to inhibit biofilm formation. Considering this, Zhong et al. (Zhong et al., 2016), functionalized the Ti surfaces of the substrates using phase-transited lysozyme (PTL) and tris(2-carboxyethyl)phosphine (TCEP) and further they incorporated AgNPs using Cs and HA via a layer-by-layer (LbL) self-assembly technique to construct multilayer coatings on Ti substrates. The antimicrobial ability of CS-Ag-decorated Ti discs was investigated against *S. aureus* strains over 14 days. The results showed the enhancement of antibacterial properties of Ag incorporated Ti disks in comparison with pristine Ti and Ti-PTL-HA-CS, which confirmed that the modified Ti surfaces with AgNPs were effective in preventing bacterial colonization on the Ti discs.

Lu et al. (Lu et al., 2017), prepared a novel spongy dressing composed of chitosan, L-glutamic acid and hyaluronic acid (Cs-GA-HA). HA was used as a cross-linking agent for reaction with Cs, and Ag^+ was then added to the mixture and reduced to AgNPs with Cs-GA-HA solution by freeze-drying method. *E. coli* and *S. aureus* were used to evaluate the antibacterial activities of prepared composite, and the results revealed that the inhibition zone of bacterial growth increased in a concentration-dependent manner as the concentration of AgNPs increased.

4.8. Pectin

Pectin, a simple polysaccharide with a cytocompatible mechanism, is widely used in the biomedical scope of a particular wound dressing procedure (Yu et al., 2019). It is found in the plant's cell wall and consists of galacturonic acid and low amount of neutral sugars in the side chains (Voragen, Coenen, Verhoef, & Schols, 2009). An anti-bacterial and anti-biofilm based on pectin were fabricated by Pallavicini and et al. (Pallavicini et al., 2017), and pectin-coated spherical silver nanoparticles (P-AgNPs) was obtained. Despite the low free Ag^+ concentration and release rate, the nature of the coating allows P-AgNPs to exert excellent antibacterial and antibiofilm actions, comparable to those of ionic silver, tested on *E. coli* and *S. epidermidis* both on planktonic cells and pre- and post-biofilm formation conditions. A novel *in situ* reduction process has been followed to synthesize oxidized pectin-gelatin-AgNPs with flower-like nano-hydrocolloids. This composite has shown release with a controlled manner like the surrounding biological tissues. Small inhibition zones were observed at all concentrations of pectin-gelatin-AgNPs composite from $3.75 - 10$ μg/cm^2 against *E.coli* as well as *S. aureus* due to the leaching of ionic silver in the culture media. After loading ciprofloxacin hydrochloride, very large zones of inhibition are observed even at a low concentration of 0.5 % against both types of bacteria (Tummalapalli et al., 2016).

4.9. Starch

Nowadays, the mixture of organic polysaccharides, including starch with NPs are being used to reduce their toxic properties. Starch is a well-known and affordable saccharide which is made up of almost 30 % amylose, 70 % amylopectin and a linear (1–4) glucan. The essential property of hydrophilicity in the starch is low; therefore it is not used individually in the wound dressing procedure (Kamoun, Kenawy, & Chen, 2017). However, the gelatinized starch nanocomposites have hydrophilic property (Dean, Yu, & Wu, 2007). Chemically modified starch is more used in the wound dressing scope due to containing more polysaccharide in its structure. The proper cost is another advantage related to this compound (Pal, Banthia, & Majumdar, 2006).

Mandal et al. (Mandal et al., 2014), attempted to produce a collagen-based scaffold impregnated with sago starch capped AgNPs. Antimicrobial activity of resulting scaffold was performed against both Gram-positive and Gram-negative bacterial strains and showed high performance in comparison to collagen scaffolds with uncapped AgNPs. This study revealed that the prepared scaffolds are biocompatible and can be used for tissue engineering applications. Synthesis of hollow polymeric nanocapsules has increased interest in a wide range of applications. Taheri and his co-workers (Taheri et al., 2014), reported a simple method for the synthesis of hybrid starch nanocapsules decorated with silver. AgNPs are formed and embedded in the shell of the nanocapsules during the polyaddition process without using any additional reducing agents. Due to the high antibacterial activity against *S. epidermidis* and *E. coli*, the biocompatible nanostructures are of potential interest for various biomedical applications, especially for medical devices and wound dressings.

The chemical structure, functional groups and antimicrobial activities of discussed carbohydrate polymers-silver or silver nanoparticles composites are shown and summarized in Table 2.

5. Clinical trials

Nowadays, carbohydrate polymer-based wound dressing materials are clinically used with considerable outcomes. With this in mind, chitosan with excellent antimicrobial effects is identified as an active material (with or without AgNPs) in a clinical study for the treatment of chronic periodontitis and wound healing [125]. Recently, an alginate-carboxymethyl cellulose-Ag^+ dressing clinically evaluated on 36 patient with ulcers. The results showed an improvement in wound healing for alginate-carboxymethyl cellulose-Ag^+ dressing (Beele, Meuleneire, Nahuys, & Percival, 2010).

Alginate based dressing are vastly used in clinical trials such as (Askina Calgitrol Ag®), alginate silver wound dressing, which combines the potent broad-spectrum antimicrobial action of silver with enhanced exudate management properties of calcium alginate and polyurethane foam (Opasanon, Muangman, & Namviriyachote, 2010). Besides, hyaluronic acid also has aforementioned biological properties and are commercially available such as Hyalofill® (including Hyalofill-F and Hyalofill-R for the treatment of acute and chronic exuding wounds, and deep exuding wounds, respectively). The combination of dressing with AgNPs illustrated better antibacterial activity in the wound bed with a decreasing inflammatory response (Kumar, Rajendran, Houreld, & Abrahamse, 2018; Sibbald et al., 2007).

Currently, many types of carbohydrate polymers-based containing AgNPs wound dressing materials are commercially available on the market. Some of them include Aquacel Ag® (sodium carboxymethylcellulose), DynaGinate™ (calcium alginate), ALGICELL® (alginate), Biatain Alginate Ag (alginate), ACTICOAT™ (Alginate), and ALGISITE (calcium alginate).

Table 2
Comparison of carbohydrate polymers-silver or silver nanoparticles composites with antimicrobial activities in biomedical applications.

Polymer	Functional Groups	Microorganisms		
Agar	-OH (hydroxyl)	*L. monocytogenes* (Orsuwan et al., 2016) *B. pumilus* (Shukla et al., 2012)	*E. coli* (Orsuwan et al., 2016)	–
Alginate	-COOH (carboxylic acid) -OH (hydroxyl)	*S. aureus* (Augustine & Rajarathinam, 2012; Ghasemzadeh & Ghanaat, 2014; Pandey & Ramontja, 2016; Seo et al., 2012; Shukla et al., 2012) *S. epidermidis* (Pandey & Ramontja, 2016) *B. cereus* (Pandey & Ramontja, 2016) *B. subtilis* (Pandey & Ramontja, 2016) *E. faecalis* (Pandey & Ramontja, 2016)	*E. coli* (Augustine & Rajarathinam, 2012; Ghasemzadeh & Ghanaat, 2014; Montaser et al., 2016; Obradovic et al., 2012; Pandey & Ramontja, 2016; Shukla et al., 2012) *K. pneumonia* (Pandey & Ramontja, 2016; Seo et al., 2012) *P. aeruginosa* (Pandey & Ramontja, 2016; Shukla et al., 2012) *E. cloacae* (Pandey & Ramontja, 2016) *K. oxytoca* (Pandey & Ramontja, 2016) *P. mirabilis* (Pandey & Ramontja, 2016) *P. vulgaris* (Pandey & Ramontja, 2016) *E. aerogeness* (Pandey & Ramontja, 2016)	*C. albicans* (Shukla et al., 2012)
Carrageenan	-OSO_3^- (sulphonate) -OH (hydroxyl)	*S. aureus* (Singh et al., 2015) *MRSA* (Azizi et al., 2017) *B. subtilis* (Jayaramudu et al., 2013) *L. monocytogenes* (Rhim & Wang, 2014)	*E. coli* (Azizi et al., 2017; Jayaramudu et al., 2013; Rhim & Wang, 2014; Singh et al., 2015) *P. aeruginosa* (Azizi et al., 2017; Singh et al., 2015)	*C. albicans* (Singh et al., 2015) *Aspergillus* (Fouda et al., 2015) *Penicillium* (Fouda et al., 2015) *F. oxysporum* (Fouda et al., 2015)
Cellulose	-OH (hydroxyl)	*S. aureus* (Wu, Zheng, Song et al., 2014) *B. subtilis* (Sureshkumar et al., 2010)	*E. coli* (Maria et al., 2010; Shen, Zhang, Huang, Xu, & Song, 2014; Sureshkumar et al., 2010; Wu, Zheng, Song et al., 2014) *P. aeruginosa* (Wu, Zheng, Song et al., 2014)	–
Chitosan	-NH_2 (amine) -OH (hydroxyl)	–	*E. coli* (Abdelgawad et al., 2014) *P. aeruginosa* (Sandri et al., 2014)	–
Chitin	-NH-$COCH_3$ (amide) -OH (hydroxyl)	*S. aureus* (Alexandrova et al., 2013; Kumar et al., 2010; Singh & Singh, 2014; Solairaj & Rameshthangam, 2017) *B. subtilis* (Alexandrova et al., 2013, 2018)	*E. coli* (Alexandrova et al., 2013, 2018; Benhabiles et al., 2012; Madhumathi et al., 2010) *P. aeruginosa* (Benhabiles et al., 2012; Singh & Singh, 2014) *S. typhimurium* (Benhabiles et al., 2012) *P. melaninogenica* (Benhabiles et al., 2012) *V. cholera* (Benhabiles et al., 2012) *S. dysenteriae* (Benhabiles et al., 2012) *B. fragilis* (Benhabiles et al., 2012) *P. vulgaris* (Benhabiles et al., 2012; Solairaj & Rameshthangam, 2017) *K. pneumonia* (Solairaj & Rameshthangam, 2017)	*C. albicans* (Solairaj & Rameshthangam, 2017) *T. Viride* (Solairaj & Rameshthangam, 2017) *A. niger* (Alexandrova et al., 2013, 2018; Solairaj & Rameshthangam, 2017) *A. alternate* (Solairaj & Rameshthangam, 2017)
Hyaluronic acid	-COOH (carboxylic acid) -NH-$COCH_3$ (amide) -OH (hydroxyl)	*S. aureus* (Abdel-Mohsen et al., 2013; Anisha et al., 2013; Chen et al., 2015; Chudobova et al., 2013; Lu et al., 2017; Sandri et al., 2013; Zhong et al., 2016) *S. pyogenes* (Sandri et al., 2013)	*E. coli* (Abdel-Mohsen et al., 2013; Anisha et al., 2013; Chen et al., 2015; Lu et al., 2017; Sandri et al., 2013) *P. aeruginosa* (Anisha et al., 2013; Sandri et al., 2013) *K. pneumonia* (Anisha et al., 2013)	–
Pectin	-COOH (carboxylic acid) -$COOCH_3$ (carboxylate)	*S. aureus* (Tummalapalli et al., 2016) *S. epidermidis* (Pallavicini et al., 2017)	*E. coli* (Pallavicini et al., 2017; Tummalapalli et al., 2016)	–
Starch	-OH (hydroxyl)	*S. epidermidis* (Taheri et al., 2014)	*E. coli* (Taheri et al., 2014)	–

6. Conclusions

During the past few years, the field of wound dressing has improved a lot since newly designed dressings are not considered as just simple coverings, but also materials with high technology and biologic properties. It is essential to choose the correct material for wound dressing applications. As discussed in above-mentioned studies, polysaccharide-based materials are ideal dressings due to their biocompatibility, biodegradability, minimal cytotoxicity, and carrying various functional groups to gain multiple biologic and healing properties. They also can carry multiple bioactive compounds with different healing and antimicrobial characteristics. As discussed, silver nanoparticles are among the widely used compounds incorporated in polysaccharide-based dressings to enhance their antibacterial and antifungal properties. Despite the advances in the development of proper and ideal dressings, there are still some disadvantages to each of these substances and might be more evident in the prospective studies as well. Overall, for more attributed advantages they may need new modifications to minimize the patients and physicians troubles much more. To achieve the unique features of biodegradable polymers, it is suggested to use other compounds by more diverse techniques and also using other natural polymers in combination with polysaccharides to meet the cost-effective wound healing process and appropriate in terms of medicine.

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