Sodium alginate for wound healing applications: A review

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Abstract

Sodium alginate (SA) is a polysaccharide biopolymer widely used in wound healing applications due to its beneficial role in the hemostatic, inflammatory, and proliferative phases of tissue repair. Its hydrophilic nature supports the wound healing process by enabling efficient absorption of wound exudate and maintaining a moist microenvironment conducive to tissue regeneration. Moreover, SA can form highly porous structures that promote oxygen diffusion and provide a suitable scaffold for neovascularization and new tissue formation. This review summarizes recent advances in the application of SA in wound dressings. A bibliometric analysis of Scopus data using the keywords "sodium alginate" AND "wound healing" reveals a growing number of publications in recent years, highlighting the increasing scientific interest in this field. The expanding utilization of SA in wound healing may be attributed to its favorable properties, including biocompatibility, biodegradability, and low toxicity.

Key words: wound healing, sodium alginate, biopolymer, alginic acid, porous materials

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Introduction

Biopolymers can be extracted from bio-based materials using various techniques. They can also be produced biotechnologically or synthesized directly from building blocks derived from living organisms. Thus, in general, nature is the primary source of biopolymers.[1] Jabeen and Atif defined biopolymers as macromolecules that are primarily composed of monomeric units of natural origin.[2] Biopolymers are advantageous due to their environmentally friendly nature.[3] Nitta and Numata discussed the classification of biopolymers, which are mainly divided into 3 types: polysaccharides, nucleic acids, and proteins.[4] In the huge family of polysaccharides, one can find starch, cellulose, chitin, chitosan, and many more, for example, alginate.[5]

The primary sources of alginate reported are brown seaweed and marine algae.[6,7] Alginate has a unique non-toxic nature and biocompatibility, which make this biopolymer attractive for biomedical and cosmetic applications.[8,9] It exhibits bioadhesivity, which is the primary reason for its widespread use in pharmaceutical applications.[10] It may form sponge-like structures that are capable of absorbing water.[11] Alginate-based hydrogels are formed through ionic crosslinking.[12] Salarvand et al. reported the presence of hydroxyl and carboxyl groups in alginate, which gives the possibility of hydrogen bond formation.[13] Moreover, alginate contains negative ions capable of further interactions.[14] Wang et al. reported that sodium alginate (SA) and its oxidized derivatives show good cytocompatibility.[15] Alginate-based nanofibers are widely utilized in biomedical applications, especially in tissue engineering and wound healing.[16,17] It has recently been observed that SA applications in various areas are growing, particularly in wound healing.

Sodium alginate

The properties of SA are widely studied. Phùng et al. mentioned the water solubility of SA,[18] whereas Yan et al. reported that SA is insoluble in ethanol.[19] Sodium alginate is highly preferred in several applications due to its outstanding ability to form films.[20,21] Yan et al. described SA as a low-cost polymer presenting high potential.[19] The presence of functional groups, such as hydroxyl and carboxyl groups, makes it easy to modify.[22] Belalia and Djelali reported the rheological behavior of SA. In their research, it was concluded that it presents shear-thinning non-Newtonian flow behavior in its aqueous form.[23] Viscosity was reduced with an increase in shear rate; this behavior has been reported as shear-thinning behavior in the literature.[24]

In the structural formula of SA, the main constituents are α-L-guluronic acid and β-D-mannuronic acid.[25,26] ChemDraw 25.0.2 software (Revvity Signals Software) was used to draw the structural formulas of SA and its constituents, which are presented in Fig. 1. The "Structure" tab of the ChemDraw software was selected, and in this tab, "Convert Name to Structure" was chosen to draw the structural formulas of SA and its constituents. The names used are also presented in the figure alongside their corresponding structural formulas. Therefore, in short, SA is a combination of 2 uronic acids. Sodium alginate sourced from algae contains a significant portion of other cations: Ca (calcium), Mg (magnesium), and Sr (strontium), which are treated with hydrochloric acid (HCl) to obtain alginic acid through a liquid wash mechanism.[27]

The addition of sodium carbonate (Na_2CO_3) leads to a pH range of 9–10. Na_2CO_3 can also be replaced with alternatives such as sodium hydroxide (NaOH), sodium bicarbonate ($NaHCO_3$), or sodium chloride (NaCl). This leads to the conversion of alginic acid (which is water-insoluble) to SA (a water-soluble form).[28] It can be followed by either the Ca-alginate or the alginic acid route. The route considering alginic acid involves the treatment of SA with HCl. The 2nd route is the Ca-alginate route, which involves the addition of calcium chloride to SA to form Ca-alginate.[29] Ca-alginate is further treated with HCl to obtain alginic acid. The alginic acid obtained from these 2 routes is further treated with Na_2CO_3 to produce SA in its pure form.[30]

Porosity of sodium alginate materials

Sodium alginate materials can be fabricated into gels. Abka-Khajouei et al. reported that alginate gels presented pores, with the pore size specified in their research ranging

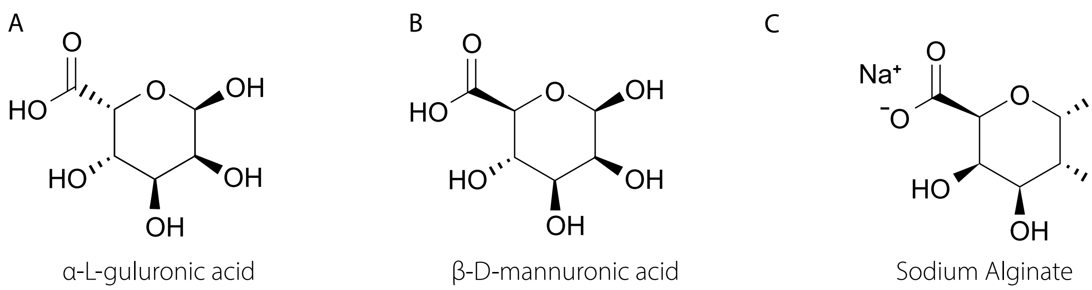

Fig. 1. Structural formulas of (A) α-L-guluronic acid, (B) β-D-mannuronic acid, and (C) sodium alginate

from 5 nm to 200 nm. They mentioned electron microscopy for pore size demonstration.[31] Da Silva et al. reported that as the SA concentration increases, it causes a decrease in the material's porosity. Therefore, an inverse relationship between SA concentration and material porosity was presented. Porosity in wound dressings is preferred because it facilitates the process of oxygenation.[32] Sinha et al. reported that wound dressings with the highest porosity had the greatest tendency to absorb wound exudate.[33] Liu et al.[34] also demonstrated that SA gel presented pores. They conducted field emission electron microscopy (FE-SEM) on SA gels with the addition of calcium ions (Ca^{2+}) to demonstrate the pores.

MATLAB and Python are referred to as programming languages.[35,36] They are effectively utilized for the visualization and demonstration of pores. Jenkins et al. were the developers of PoreScript (a MATLAB algorithm), and PoreScript was used to determine pore size from scanning electron microscopy (SEM) images.[37] Polez et al. utilized SEM images to determine porosity using PoreSpy,[38] a Python package that characterizes porous materials from 3D images.[39] Negut and Bita reported the use of a convolutional neural network (CNN) to identify pore size distribution in hydrogels.[40] Zhang et al. reported CNN as a deep learning model.[41] El Naqa and Murphy described deep learning as a sub-classification of machine learning, and stated that deep learning has the capacity to be trained from raw data.[42] Machine learning has been referred to as a field within artificial intelligence.[43] Three types of machine learning are reported in the literature: supervised learning, unsupervised learning, and reinforcement learning.[44,45]

Supervised machine learning utilizes labeled data.[46] Unsupervised learning is based on unlabeled data.[47] Reinforcement learning allows an agent to take actions.[48] Correct actions in reinforcement learning lead to earning rewards, whereas wrong decisions result in failure.[49] Saberian et al. utilized ImageJ software (National Institutes of Health (NIH), Bethesda, USA) to measure pores based on SEM images. The hydrogel utilized in their research was based on alginate/chitosan and also included honey and aloe vera. The prepared hydrogel was intended for use as a wound dressing.[50] Olevsky et al. developed PoreVision using a Python script. PoreVision utilizes Python libraries, primarily OpenCV, NumPy, and Pandas. It was used to measure pore size from SEM images and can be utilized for gels and porous materials, as indicated in their research.[51] Shkarin et al. developed quanfima, a Python-supported package that can be used to analyze the morphology of biomaterials, including porosity.[52] MICPY has been highlighted for pore analysis and has been reported as a Python-supported package. It can analyze SEM images.[53,54] Nair et al. utilized CTAnalyzer software for pore size determination, which was made possible by using a 3D object analyzer within the software.[55] Karaca and Aldemir Dikici utilized a deep learning model, which they named Pore D^2. In their study, YOLOv5 was used for object detection, and SEM images were utilized as the input. EasyOCR has been used to extract text from images, and it is a Python library that employs a deep learning approach. The output layer provided accurate information on pore size.[56]

Wettability of sodium alginate materials

The hydrophilicity of the material's surface may be a reason for better cell adhesion. Yuan and Lee presented the relationship between the water contact angle and wettability in the context of liquid–solid interaction. According to their research, contact angles below 90° exhibited the highest wettability. A contact angle greater than 90° was a clear indication of low wettability.[57] Kumar and Prabhu described reactive and non-reactive wetting. A reaction occurring between the spreading liquid and the substrate material impacts the mechanism of wetting, which is reported as reactive wetting. If no reaction occurs between the spreading liquid and the substrate material, it is reported as inert or non-reactive wetting.[58] Xie et al. conducted contact angle analysis for membranes made of SA, and SA 100 and SA 200 were named for the lower amounts of guluronic acid. Manugel DMB was named for a higher amount of guluronic acid. A Milli-Q water drop was utilized to obtain contact angle measurements, and the analysis was conducted on alginate–chitosan–alginate (ACA) membranes. The water contact angle for SA 100, as reported in their study, was 65.9 ±1.0°. SA 200 presented a water contact angle of 68.5 ±2.4°. The water contact angle of Manugel DMB recorded in their research was 77.7 ±3.3°. These values are reported as mean ± standard error (SE). The number of analyses specified in their study was 3. In short, their results showed that an increase in guluronic acid content led to a reduction in hydrophilicity.[59] Karmakar et al. analyzed the contact angle of a hydrogel composed of SA and carboxymethyl cellulose in a 1:1 ratio, reporting a contact angle value of 48.32 ±1.5°. Contact angle measurements were recorded using distilled water, and 3 measurements were taken to obtain the mean value.[60] Mujawar et al. conducted contact angle measurements on 3D-printed samples, including those made from SA–gelatin and SA–gelatin–*Aloe barbadensis* extract. Six contact angle measurements were taken using water as the probe liquid. The recorded water contact angle for 3D-printed SA–gelatin was 42.31 ±3.23°. The water contact angle reported for SA–gelatin–*Aloe barbadensis* extract was about 53.2 ±4.7°.[61] Sisakht et al. prepared a hydrogel with a 50:50 weight ratio of SA and poly(acrylic acid). They utilized both SA and poly(acrylic acid) at a concentration of 2% wt/vol. They also analyzed the contact angle in combination with fibroblast growth factor (FGF1). Deionized water was used as the probe liquid for the contact angle analysis. Three measurements were recorded for the samples. The contact angle reported for SA was 57.87°. In the case of the SA–poly(acrylic acid) hydrogel, the reported contact angle was 18.52°. The SA–poly(acrylic acid) hydrogel in combination with FGF1 exhibited a water contact angle of approx. 62.56°.[62] Hosseini et al. prepared a hydrogel composed of carboxymethyl cellulose and SA. Subsequently, they combined it with simvastatin, resulting in a final form known as the carboxymethyl cellulose/SA–simvastatin hydrogel. The recorded water contact angles for carboxymethyl cellulose–SA and carboxymethyl cellulose/SA–simvastatin were 43.3 ±2° and 59.1 ±4°, respectively. They utilized water as the probe liquid, and 3 measurements were recorded for each sample.[63] Table 1 presents a summary of the contact angle measurements for SA-based materials. Isa Rahim et al. specified that contact angles lower than 90° were indicative of hydrophilicity, and contact angles between 90° and 150° were indicative of hydrophobicity.[64] Chen et al. specified that a surface with a contact angle higher than 150° can be reported as superhydrophobic.[65] Choi et al. reported the use of SA for wound dressings, and the reason given in their study was its hydrophilicity.[66] Jin et al. examined the impact of hydrophilic polymers on swelling, and their study concluded that SA presented the maximum swelling among the analyzed hydrophilic polymers.[67] Feng and Wang highlighted the use of hydrogels with maximum swelling capacity for wound healing due to their ability to absorb wound exudates.[68] Singh and Pramanik reported better cell adhesion for polymeric films composed of SA and chitosan than for alginate itself, and it was also mentioned in their study that the contact angle was lower than 90°.[69]

Sodium alginate wound healing

Zahid et al. indicated that the use of SA for wound healing applications is promising due to its liquid absorption.[70] The stages of wound healing have been demonstrated in various studies and include hemostasis, inflammation, proliferation, and remodeling phases.[71–73] Hemostasis is the first stage of wound healing, and in this phase, blood clot formation takes place.[74] Periayah et al. explained the blood coagulation mechanism in significant detail. Their study indicated the key role of platelets in thrombus formation.[75] Zhang et al. demonstrated that platelets play a vital role in vascular repair.[76] Huang et al. reported that SA can enhance platelet concentration.[77] Zhang et al. recommended SA for blood coagulation applications.[78] Chen et al. reported in their study the preparation of a hemostatic powder, which involves the presence of SA, $CaCl_2$, graphene oxide, and cerium nitrate. The concluding remarks in their study indicated that the hemostatic powder presented the ability to absorb water, resulting in a shorter hemostatic time. The hemostatic powder effectively decreased blood loss and enhanced the wound healing mechanism due to the presence of Ce^{3+} (which acts as a free radical scavenger).[79] Zhou et al. analyzed the blood coagulation of a gelatin sponge individually and in combination with SA, and their study summarized that blood coagulation was enhanced due to the presence of SA.[80] Wang et al. prepared a powdered composite that included SA and poly(γ-glutamic acid) (PGA). The prepared powdered composite was found to arrest or block bleeding.[81] Li et al. presented a material composed of SA, silk fibroin, and thrombin. It was mentioned that the prepared material could promote hemostasis.[82] Xie et al. prepared a hydrogel containing SA, chitosan, and oxidized dextran. Their study results showed that the prepared hydrogel reduced blood loss, which significantly supports the basis for improved hemostasis.[83] Khattak et al. mentioned that persistent inflammation was a significant reason for the slowing down or delay of the wound healing mechanism.[84] Zhang et al. reported that inflammation was a notable challenge in wound healing.[85] Liu et al. highlighted that the anti-inflammatory effect was essential for wound healing.[86] Summa et al. prepared a wound dressing material composed of SA and povidone–iodine.

Table 1. Contact angle measurements for sodium alginate (SA)-based materials

SA 200	3	Milli-Q water	68.5 ±2.4°	59
SA–carboxymethyl cellulose (1:1 ratio)	3	distilled water	48.32 ±1.5°	60
SA–gelatin–*Aloe barbadensis* extract	6	water	53.2 ±4.7°	61
SA–poly(acrylic acid) (50:50)	3	deionized water	18.52°	62
Carboxymethyl cellulose–SA	3	water	43.3 ±2°	63

The results of their study indicated that the prepared material exhibited an anti-inflammatory effect.[87] Zhao et al. formulated a composite that included low-viscosity SA combined with titanium dioxide and temozolomide nanoparticles. Their study reported the anti--inflammatory effect of the designed composite. Their research summarized that the anti-inflammatory effect was enhanced due to the prominent presence of SA.[88] Karmakar et al. initially prepared a SA and carboxymethyl cellulose composite, which was then crosslinked to a decellularized extracellular matrix. The crosslinker used in their study was calcium chloride, resulting in a final hydrogel composed of SA, carboxymethyl cellulose, and decellularized extracellular matrix. According to their research, the prepared hydrogel exhibited anti-inflammatory properties.[60] Zhang et al. prepared a blend of SA and carboxymethyl chitosan, which was then loaded with curcumin. Sr^{2+} was used for the crosslinking of the polymers. The prepared hydrogel exhibited anti-inflammatory activity, leading to an enhanced wound healing mechanism.[89] Raguvaran et al. prepared hydrogels composed of SA and gum acacia, which were incorporated with zinc oxide nanoparticles. Their research concluded that polymers in combination with zinc oxide nanoparticles tend to boost the proliferation of fibroblasts.[90] Song et al. demonstrated that fibroblast proliferation is essential to promote the wound healing mechanism.[91] Harper et al. presented fibroblast migration as a component of the proliferative phase of wound healing.[92] Kibungu et al. reported that fibroblast cells assist in the production of collagen.[93] AlShaali et al. also described that granulation tissue starts to form during the proliferation stage.[94] Zhu et al. utilized a hydrogel based on SA, which was incorporated with *Capparis spinosa* L., and the incorporated hydrogel exhibited biocompatibility. It also boosted cell proliferation.[95] Zhou et al. reported that enhanced cell proliferation encouraged wound healing.[96] Ma et al. synthesized a nanocomposite based on SA, polyvinyl alcohol, and graphene oxide. Their research summarized that nanocomposites may result in enhanced cell proliferation.[97] Dodero et al. prepared electrospun membranes of SA, which were crosslinked with divalent cations such as Ca^{2+}, Sr^{2+}, and Ba^{2+}. In the final step, they prepared electrospun mats of SA loaded with zinc oxide nanoparticles, which were crosslinked with Sr^{2+} ions due to excellent cell adhesion. The electrospun mat prepared in their research was recommended for wound healing applications.[98] Ding et al. utilized electrostatic spinning to synthesize a membrane based on SA and polyvinyl alcohol. Shikonin was incorporated into the electrospun membrane. It was found that the shikonin-loaded membrane boosted vascular endothelial growth factor A (VEGF-A) in the proliferative stage of wound healing.[99] Liu et al. reported shikonin as a naphthoquinone pigment useful in the preparation of shikonin-based nanomedicine.[100] Guo et al. highlighted *Lithospermum erythrorhizon* as the source of extraction for shikonin.[101] Lin et al. referred to *Lithospermum erythrorhizon* as a Chinese medicinal herb.[102] Tian et al. reported the antimicrobial and anti-inflammatory properties of shikonin in their research.[103] Guo et al. mentioned the antioxidant and antithrombotic properties of shikonin.[101] Ye et al. reported the anti-tumor effect of shikonin.[104] Several studies reported shikonin as an ideal option for the treatment of diabetic wounds.[105–107] Eming et al. described VEGF-A in relation to angiogenesis in wound healing.[108] DiPietro presented that angiogenesis results from hypoxia.[109] In the case of injury, hypoxia is primarily responsible for the recruitment of hypoxia-inducible factors such as HIF-1. It supports the mechanism of angiogenesis during wound healing.[110] Dawood et al. highlighted angiogenesis as a key feature linked to the proliferative phase of wound healing.[111] Bahadoran et al. referred to the proliferative phase by another name, the growth phase of wound healing.[112] Çerçi et al. utilized amoxicillin in combination with SA and polyvinyl alcohol. Polyvinyl alcohol was employed at a concentration of 12% wt/vol. Sodium alginate was utilized at a concentration of 1% wt/vol. The ratio selected for polyvinyl alcohol and SA was 2:1 (vol/vol) for the electrospinning solution, and 6.4 mg of amoxicillin trihydrate was added to the electrospinning solution. The electrospun nanofibrous mats were prepared by electrospinning. According to their research conclusions, the amoxicillin-loaded electrospun nanofibrous mat exhibited antibacterial properties. Based on their in vitro studies, the prepared nanofibrous mat loaded with amoxicillin was recommended for wound dressing applications.[113] Kaur et al. reported amoxicillin as an antibiotic belonging to the penicillin class.[114] Ayavoo et al. reported that the remodeling phase of wound healing was responsible for the conversion or transformation of fibroblasts into myofibroblasts.[115] The remodeling phase of wound healing tends to remodel collagen III to collagen I.[116] Yang et al. recommended a scaffold composed of SA, silk fibroin, and hyaluronic acid for extracellular matrix remodeling.[117]

Bibliometric analysis

The bibliometric analysis was conducted using the R software v. 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and VOSviewer (https://www.vosviewer.com/). Initially, the “bibliometrix” package was installed, followed by loading the library (bibliometrix). The biblioshiny() function was used to open the web-based interface for bibliometrix. Bibliometrix and biblioshiny were developed by Aria and Cuccurullo.[118] The data were obtained from Scopus, and the document search was conducted using the terms “Sodium Alginate” AND “Wound Healing”, with the search restricted to “Article title, Abstract, Keywords” from 2010 to 2025 (access date: 27 June 2025). A total of 944 documents were generated from the search for "Sodium Alginate" AND "Wound Healing". The annual scientific production data from Scopus for the specified search are presented in Fig. 2. The analyzed data show that the number of articles from 2018 to 2024 increased continuously, indicating the growing prominence of the presented research in recent years. The most relevant sources are depicted in Fig. 3. It represents the *International Journal of Biological Macromolecules*, the leading journal presenting pertinent articles, with 159 publications. The 2nd most relevant source was *Carbohydrate Polymers*, with 37 articles. The 3rd most relevant source was *ACS Applied Materials and Interfaces*, with 24 articles reported. The most globally cited papers were analyzed using Scopus data, and the results are presented in Fig. 4, which shows the papers with the most significant global citation impact. The impact of local citations was also investigated, and the highest number of locally cited documents was 32, as depicted in Fig. 5. Van Eck and Waltman developed VOSviewer for bibliometric mapping.[119] The Scopus data file was imported into VOSviewer, which helped identify relevant keywords through co-occurrence analysis. The co-occurrence analysis is presented in Fig. 6.

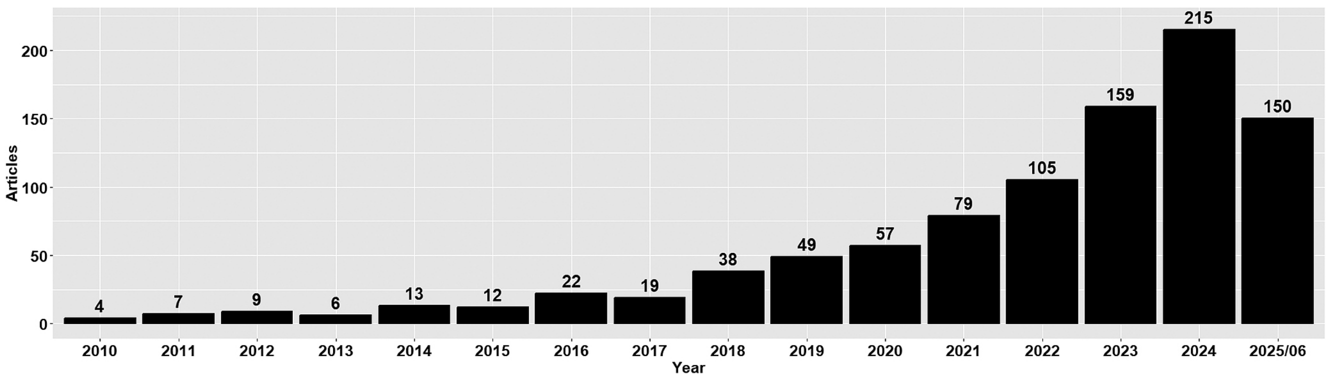

Fig. 2. Annual scientific production ("Sodium Alginate" AND "Wound Healing" search within Scopus; access date: June 27, 2025)

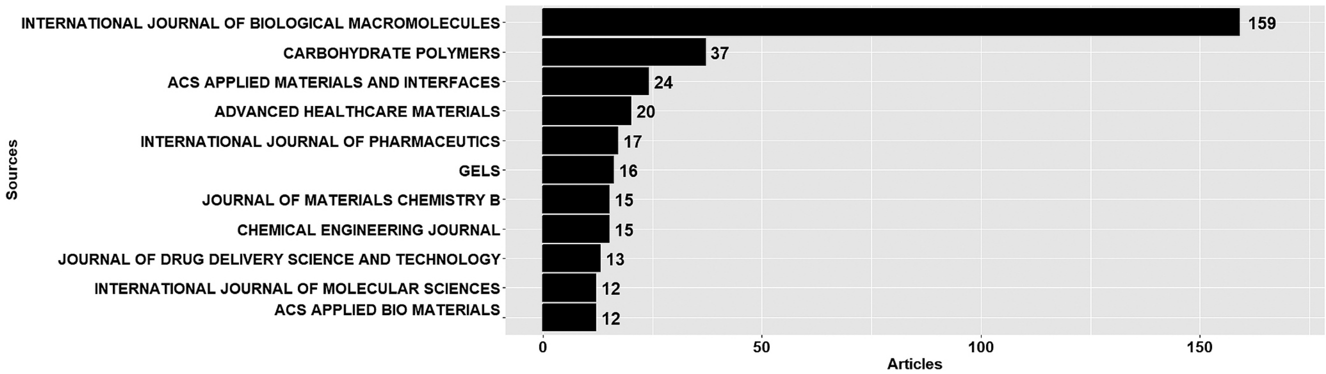

Fig. 3. Most relevant sources with the number of articles ("Sodium Alginate" AND "Wound Healing" search within Scopus; access date: June 27, 2025)

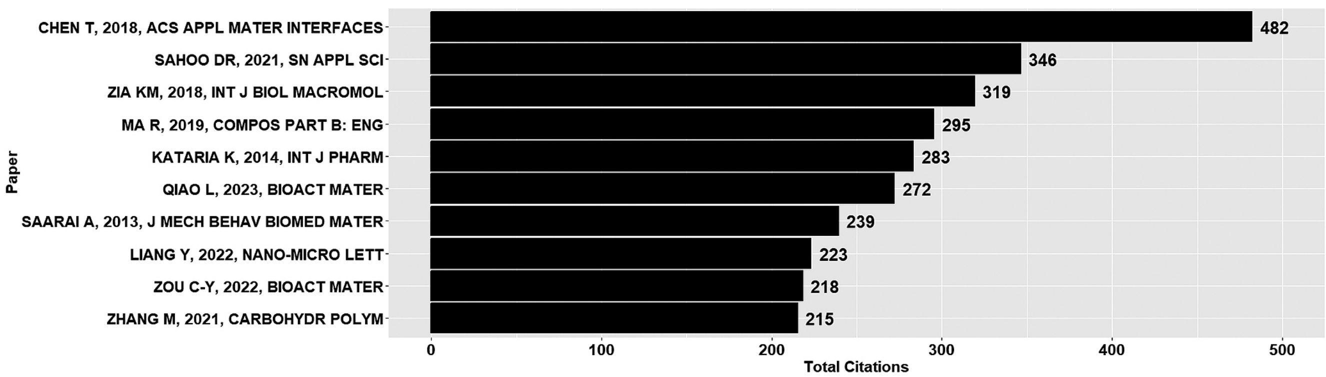

Fig. 4. Most globally cited papers ("Sodium Alginate" AND "Wound Healing" search within Scopus; access date: June 27, 2025)

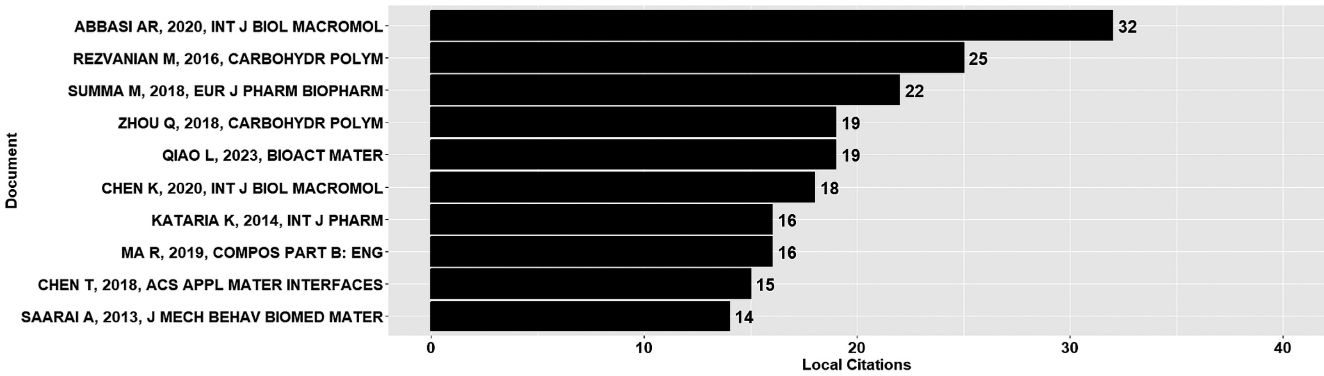

Fig. 5. Most locally cited documents ("Sodium Alginate" AND "Wound Healing" search within Scopus; access date: June 27, 2025)

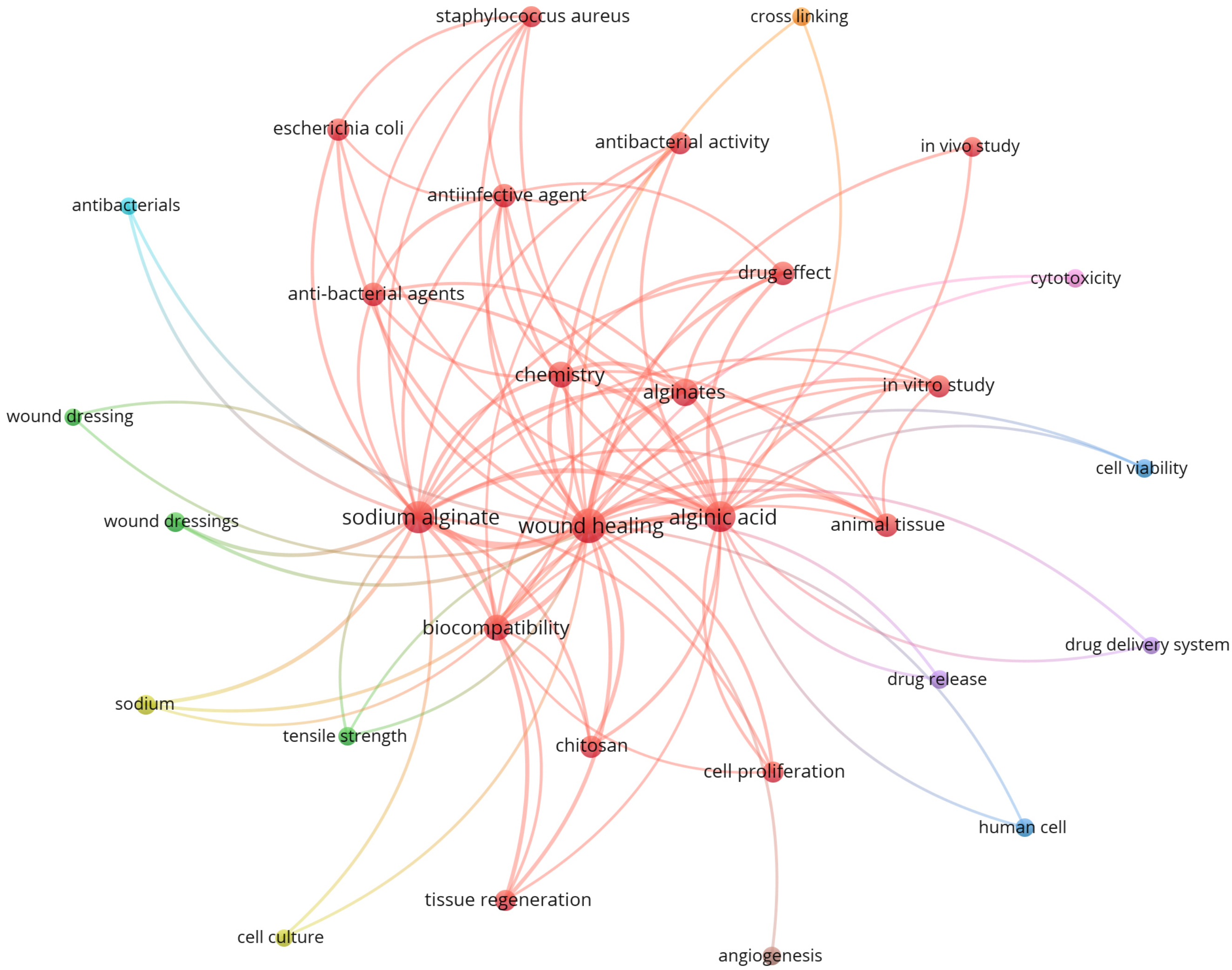

Fig. 6. Co-occurrence of keywords ("Sodium Alginate" AND "Wound Healing" search within Scopus; access date: June 27, 2025)

Conclusions and future outlook

Several factors must be considered in the wound healing mechanism, including the hydrophilicity, porosity, and biocompatibility of wound dressing materials. Sodium alginate is primarily used in hemostatic powders for blood coagulation, as blood coagulation is the initial phase of wound healing. Wound healing is often delayed due to prolonged inflammation. Sodium alginate exhibits significant anti-inflammatory properties, facilitating early wound healing. The proliferation phase of wound healing is the combined result of angiogenesis, fibroblast migration, and collagen deposition. Sodium alginate can effectively promote the proliferative phase of wound healing by contributing to tissue granulation. Sodium alginate scaffolds also promote extracellular matrix remodeling. Machine learning is widely used to explore porous material structures. In the future, there is a need to develop an application programming interface (API) to facilitate data communication, particularly an API for the porosity of SA-based materials. Bibliometric analysis also revealed that open-access journals are focusing on promoting research related to SA wound healing applications. Although many papers regarding the application of SA have been published so far, it can be expected that more research articles on this material will be published in the future, as many research groups worldwide are working on alginate and its combinations with other macromolecules.

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