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MICROBIAL EXOPOLYSACCHARIDE-BASED HYDROGELS FOR BURN WOUND HEALING

This review examines innovative approaches to the treatment of burn injuries through the use of microbial polysaccharides, highlighting their unique properties such as wound infection prevention, moisture retention, and acceleration of tissue regeneration. The development of novel, natural-based pharmaceutical formulations in a patient-friendly dosage form is necessitated by the complexity and high cost of burn treatment, which, in severe cases, may result in fatal outcomes.

An analysis of the pharmaceutical market in Kazakhstan reveals a shortage of multifunctional anti-burn drugs and a limited utilization of natural-origin active compounds (17.6% natural components, 82.4% synthetic components). Hydrogels, as a dosage form, offer notable advantages due to their unique physicochemical properties. They maintain a moist wound environment, regulate the release of active substances, ensure direct contact with the injured area, and act as a protective barrier against infection.

Microbial polysaccharides, owing to their ability to form three-dimensional network structures, are particularly promising as a foundational material for hydrogels. A detailed examination of the composition and properties of hydrogels based on microbial polysaccharides underscores the potential of biopolymeric compounds in the development of accessible and effective wound-healing formulations. Special attention is given to pullulan, dextran, alginate, and hyaluronic acid, with a discussion on their biomedical applications and potential for integration into polymeric composites with enhanced healing and antimicrobial properties.

Key words: burn wound healing, microbial exopolysaccharide, hydrogels, pullulan, dextran, alginate, hyaluronic acid.

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Күйіктерді емдеуге арналған микробтық полисахаридтер негізіндегі гидрогельдер

Осы шолуда микробтық полисахаридтердің бірегей қасиеттерін пайдалана отырып, күйік жарақаттарын емдеудің инновациялық тәсілдері қарастырылады. Бұл қасиеттерге жараның инфекциялануын болдырмау, оның ылғалдануын сақтау және регенерация процестерін жеделдету жатады. Пациенттер үшін қолайлы дәрілік формадағы табиғи негіздегі жаңа препараттарды жасау күйіктерді емдеу үдерісінің күрделілігі мен жоғары құнына байланысты, өйткені ауыр жағдайларда бұл өлімге әкелуі мүмкін.

Қазақстанның фармацевтикалық нарығын талдау көпфункционалды күйікке қарсы препараттардың жетіспеушілігін және табиғи негіздегі белсенді қосылыстардың төмен пайызын көрсетті (17,6% – табиғи компоненттер, 82,4% – синтетикалық компоненттер). Гидрогельдер дәрілік форма ретінде қолдануға ыңғайлы және ерекше физика-химиялық қасиеттерге ие. Олар жараның айналасында ылғалды орта сақтауға, белсенді заттардың бөлінуін реттеуге және оларды зақымдалған аймақпен тікелей байланыстыруға, инфекция көздерінен қорғаныс тосқауылын жасауға қабілетті.

Микробтық полисахаридтер үш өлшемді торлы құрылымдар түзе алады, сондықтан олар гидрогельдер үшін перспективті негіз болып табылады. Микробтық полисахаридтер негізінде жасалған гидрогельдердің құрамы мен қасиеттерін зерттеу биополимерлік қосылыстардың қолжетімді әрі тиімді дәрілік формаларды әзірлеуге әлеуетті екенін көрсетеді. Бұл шолуда лан, декстран, альгинат және гиалурон қышқылына ерекше назар аударылып, олардың биомедициналық қолдану мүмкіндіктері мен жараны жазатын және микробқа қарсы қасиеттері бар полимерлік композициялар жасау жолдары талқыланды.

Түйін сөздер: күйікті емдеу, микробтық экзополисахаридтер, гидрогельдер, пуллулан, декстран, альгинат, гиалурон қышқылы.

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Гидрогели на основе микробных полисахаридов для лечения ожогов

В данном обзоре рассматриваются инновационные подходы к лечению ожоговых травм с использованием полисахаридов микробного происхождения за счёт их уникальных свойств: предотвращение инфицирования раны, её увлажнение и ускорение процессов регенерации. Разработка и создание новых препаратов на природной основе в удобной для пациентов лекарственной форме обусловлено сложностью и затратностью процессов лечения ожогов, способных привести к летальному исходу.

Анализ фармацевтического рынка Казахстана показал недостаток многофункциональных противоожоговых препаратов и низкий процент использования активных соединений на природной основе (17,6% – природные компоненты, 82,4% – синтетические компоненты). Гидрогели, как лекарственная форма, являются удобными в применении и обладают уникальными физикохимическими свойствами. Они способны сохранять влажную среду вокруг раны, контролировать высвобождение активных веществ и обеспечивать их контакт с травмированной зоной, создавать барьер для источников инфицирования раны.

Способность микробных полисахаридов к образованию трёхмерных сетчатых структур делает их перспективными агентами в качестве основы для гидрогелей. Исследование состава и свойств гидрогелей на основе микробных полисахаридов демонстрирует потенциал биополимерных соединений для создания доступных и эффективных лекарственных форм. Особое внимание было уделено пуллулану, декстрану, альгинату и гиалуроновой кислоте. Были обсуждены перспективы их применения в биомедицине и возможности создания полимерных композитов с заживляющими и противомикробными свойствами.

Ключевые слова: лечение ожогов, микробные экзополисахариды, гидрогели, пуллулан, декстран, альгинат, гиалуроновая кислота

Introduction

Burn injuries are severe and common types of injuries and their treatment remains quite complex and costly. According to WHO data from 2018, burn injuries pose a significant threat and are one of the causes of fatal cases [1]. The consequences of even small in depth and area burns can lead to functional disorders, affect the quality of life and social adaptation of victims. One of the modern trends in the treatment of burns is the use of microbial polymers, the main advantages of which are stability, non-toxicity, biocompatibility and repeatability [2].

Rapid and timely restoration of the skin for the treatment of burn injuries is one of the primary objectives of modern combustiology. Substances of natural origin are currently attracting great interest among researchers and clinicians, as some polymeric substances can be used in regenerative medicine to stimulate reparative processes [3].

Hydrogels are colloidal materials that play a significant role in the healing process of burn wounds, skin ulcers and pressure sores, and can provide relief to the patient. The unique properties of wound cooling and pain reduction inherent in gel bandages. Hydrogel dressings based on microbial polysaccharides have the following advantages for damaged areas of the body: mechanical strength along with elasticity and softness, preventing excessive fluid loss, barrier to bacterial penetration, ensuring oxygen penetration to the wound, transparency, which allows to see the wound, lack of difficulties in treating the wound with additional drugs, hypoallergenic, anesthesia and stimulation of regeneration, tight fit to the skin area without sticking, sterility and ease of use [4].

The investigation of natural polysaccharides as hydrogels is compelling because of their abundance in nature, enhanced biocompatibility and biodegradability. In addition, the various active hydroxyl, carboxyl and amino groups present in monosaccharide units provide opportunities for derivatisation [5, 6]. This facilitates a variety of crosslinking processes to form hydrogels and imparts unique characteristics that allow interaction with living organisms [7, 8, 9]. Polysaccharide-based hydrogels can maintain localised concentrations of bioactive substances over long periods of time through suitable release mechanisms including diffusion, swelling, chemical factors and control of certain environmental stimuli. This ensures precise and controlled release of drugs or nutrients, emphasising the inherent advantages of polysaccharide-based hydrogels as carriers for encapsulation of such substances [10, 11]. Moreover, polysaccharide-based hydrogels exhibit impressive mechanical properties and biological activity, making them effective for cell culture and tissue regeneration [12]. As research on polysaccharide-based hydrogels derived from natural sources continues, their exceptional biological activity is increasingly recognised in the scientific community [13].

Analysing the pharmaceutical market in Kazakhstan

In the State Pharmacopoeia of the Republic of Kazakhstan, the register of the National Centre for Drug Expertise and the Kazakhstan National Drug Formulary, burn drugs are not identified as a separate category due to the wide variety of mechanisms of action, which include cooling, wound healing, antiseptic and analgesic effects. In the Kazakhstan National Drug Formulary, burn drugs can be found in three categories of medicines: preparations for the treatment of wounds and ulcers (preparations promoting tissue regeneration are included), antibiotics and chemotherapeutic preparations for dermatological use (preparations with antibacterial and antiseptic effects for burns are included), preparations for local treatment of joint and muscle pain (gels and ointments with cooling effect are included, which are also indicated for burn injuries) [14].

According to the State Pharmacopoeia of the Republic of Kazakhstan, the active ingredients of soft medicines are intended to have a protective or emollient effect. They should have transdermal or topical effect and be homogeneous. The bases of topical preparations may be single- or multiphase and consist of natural or synthetic components. Only sterile preparations are intended for use on severely damaged skin or open wounds [15].

Soft medicines include: patches, creams, pastes, ointments or gels. Plasters are designed to be applied to the wound and keep the active ingredient in contact with the skin. Creams are multiphase preparations consisting of two phases: aqueous and lipophilic. Pastes contain solid components in significant quantities dispersed in the base. Ointments, unlike creams, include a single-phase base. Ointments are divided into hydrophobic (with a small amount of water), water emulsion (with a large amount of water and emulsifiers) and hydrophilic (with a water-miscible base). Gels are liquids with the addition of gelling agents. The base of lipophilic gels often consists of fatty oils or paraffin, while the base of hydrophilic gels includes propylene glycol, glycerin or water. Silicates, carbomers, cellulose derivatives or starch are commonly used as gelators [15].

In the register of the 'National Centre for Expertise of Medicines and Medical Devices' of Kazakhstan, 98 trade names of medicines are classified as 'gel', of which 8 are wound-healing. The pharmaceutical form 'ointment' includes 136 trade names of medicinal products, of which 9 are wound healing (Table 1). In the category 'Medicinal products of biological origin' no anti-burn or wound-healing medicinal products are displayed [16].

Table 1 – Description of medicinal products with wound healing effect according to the register of the National Centre for Expertise of Medicines and Medical Devices

Trade name of the anti-burn/wound-healing drug	Dosage form	Active compound	Pharmacological action
Solcoseryl	Gel	Deproteinized dialysate from the blood of healthy dairy calves	Acceleration of cellular regeneration processes
Contractubex	Gel	Sodium heparin, allantoin, onion extract	Anti-inflammatory, keratolytic, antithrombic action
Contubel	Gel	Sodium heparin, allantoin, onion extract	Anti-inflammatory, keratolytic, antithrombic action
Fenistil	Gel	Dimetindene maleate	Local anesthetic effect

Continuation of the table

Trade name of the anti-burn/wound-healing drug	Dosage form	Active compound	Pharmacological action
Curiosin	Gel	Zinc hyaluronate	Angiogenesis, accumulation of collagen fibers
Cholisal	Gel	Choline salicylate	Local analgesic and anti-inflammatory effect
Dekstanol	Gel	Dexketoprofen trometamol	Anti-inflammatory effect
Korneregel	Gel	Dexpanthenol	Increased fibroblast proliferation
Deflamol	Ointment	Vitamins A and D	Tonic effect on the epithelium
Levomekol	Ointment	Methyluracil	Anti-inflammatory and antimicrobial effects
Vegaderm	Ointment	Betamethasone dipropionate, clotrimazole	Anti-inflammatory, antimicrobial action
Methyluracil	Ointment	Methyluracil	Acceleration of cellular regeneration processes
Bepanthen	Ointment	Dexpanthenol	Acceleration of cellular regeneration processes
Sulphargin	Ointment	Silver sulfadiazine	Antimicrobial action
Zinc ointment	Ointment	Zinc oxide	Anti-inflammatory and antiseptic effect
Apiphyt	Ointment	Polyphyte oil «Kyzyl Mai»	Anti-inflammatory, analgesic, antimicrobial and analgesic effects
Streptocid ointment	Ointment	Sulfanilamide	Antimicrobial action

The active substances of preparations indicated for burn injuries (from the categories of wound healing, antimicrobial and cooling agents) are silver sulfathiazole, zinc bacitracin, zinc hyaluronate, zinc oxide, dexapanthenol, vaseline, furacilin, sulphonamide, silver sulphadiazine, dioxomethyltetrahydropyrimidine (methyluracil), gentamicin sulphate, choline salicylate, allantoin, sodium heparin, dimethindene, mupirocin, dexketoprofen or refined resin (Figure 1).

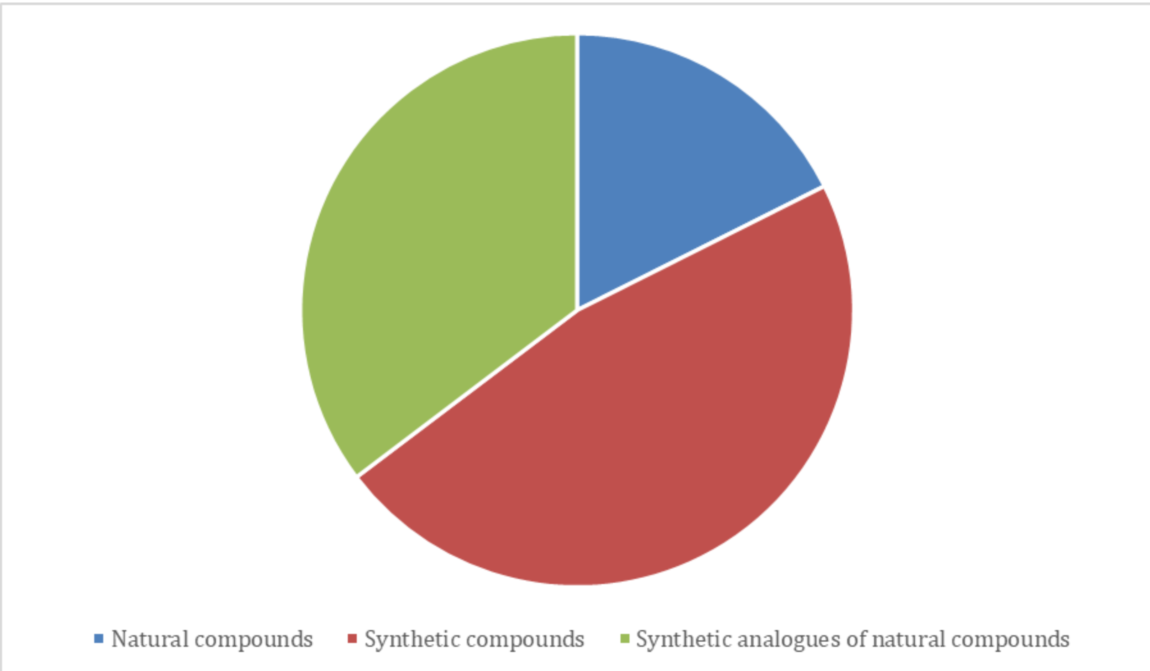

Figure 1 – Types of active ingredients of anti-burn ointments by origin

Of the listed active compounds, 17.6% are natural components, 47.1% are exclusively synthetic, and the remaining part was originally of natural origin but is currently synthesised artificially in the pharmaceutical industry [17].

The pharmacological actions of the listed active compounds include acceleration of regeneration, bacteriostatic action, anti-inflammatory action, rapid skin absorption, softening and moisturising and normalisation of tissue blood supply through receptor irritation [16].

Due to the fact that most of the used active substances of wound-healing ointments and gels are not natural components, makes it promising to create new drugs on a natural basis.

Polymeric materials are already used in medicine as medical devices that promote wound healing. Thus polymers act as an alternative to suture materials due to their adhesive properties, ability to isolate the wound, hold its edges and prevent bleeding. Polysaccharide polymers (hyaluronic acid, alginate, chitosan and dextrin) are also used to create wound dressings. Their natural origin and biocompatibility prevent inflammatory reactions, some of them (chitosan) have antimicrobial activity [18].

Hydrogels in the treatment of burn wounds

Important factors during the burn healing period are the maintenance of a moist environment and the bacterial barrier, as the injured skin loses its defence function [19]. Infected skin does not pass through the healing stage in time due to high bacterial load, which favours the transition of the wound into a chronic form [20]. Preventing infections allows the wound to heal faster, as infectious agents can impede healing and increase treatment time and costs [21]. Topical treatment reduces the infectious load without interfering with the body's internal mechanisms [20].

Internal body functions such as haemostasis, angiogenesis, and collagen production play a major role in the healing process of traumatised skin. Therefore, it is necessary to create an environment that supports recovery. Hydrogels, due to their high water content, slow moisture loss and biocompatibility, serve as an optimal way to provide an environment favourable for recovery [22].

Equally important in the healing process to maintain the environment around the wound surface is pH, both intracellular and extracellular. Accordingly, the acidity of wound healing preparations should not be lower than 4 and not higher than 6. This is the pH of intact skin; after injury, the pH becomes more alkaline, favouring the active development of bacteria on the wound surface [23].

Hydrogels are currently of particular interest in the treatment of burns. Their three-dimensional structure with its unique properties and layering ability is an optimal method of combating bacterial colonisation. Hydrogels maintain a moist environment for traumatised skin, the dryness of which is a consequence of burns. Additional compounds ranging from small molecules to polymers to large particles can be incorporated into hydrogels to improve their wound healing properties or to add new properties that promote repair and rapid delivery of bioactive compounds to the wound [24]. Accordingly, functionality lends itself to pre-design. The mechanical properties of hydrogels allow them to be compatible with biological tissues. They leave the wound moist and, if a dressing is required, if it is replaced in time, the wound will not be re-injured with damage to the newly formed epithelium sticking to the bandage due to drying. Hydrogels are biodegradable, their porous structure resembles the structure of the extracellular matrix, which does not prevent cell migration into the injured skin area [25].

Due to the necessary level of acidity, oxygen, moisture and antimicrobial properties (polysaccharides themselves or active components included in the hydrogel on a polysaccharide matrix), the healing process of burn wounds is accelerated. And the dosage form in the form of hydrogel will keep the wound sufficiently hydrated [26, 27].

The widespread use of antibiotics has already led to drug resistance, making it impossible to use them to create wound healing ointments with bacteriostatic action. The addition of chemically synthesised antimicrobials to wound dressings entails cytotoxic effects, which prolongs the healing process. Consequently, there is a growing need for natural products [28].

A wide variety of polysaccharide materials, including sodium alginate, chitosan, hyaluronic acid, chondroitin sulfate and carrageenan, have now been found to have extensive and important applications in tissue engineering [29]. Among natural polysaccharides, polysaccharides produced by microorganisms hold particular promise.

Currently, microbial exopolysaccharides find wide application in various industries from food production (emulsifiers, thickeners, gelling agents) to medicine (healing agents) [30, 31, 32]. Their high hydrophilicity, presence of functional groups and flexible polymer chain structure account for their adsorption properties [33, 34].

Microbial polysaccharides are renewable, biocompatible and biodegradable polymers that are competitive with polysaccharides of plant and animal origin due to rapid accumulation, non-necessity of arable land and ease of isolation and purification [35, 36]. Creating a blend of microbial polysaccharides with natural polymers (gelatin+pullulan, chitosan+pullulan) leads to synergistic [35]. The production of polysaccharides with biological activity is simple and cheap, which allows their widespread use.

Since polysaccharides are constituents of the extracellular matrix, hydrogels based on them can mimic the same function for accelerated healing of skin lesions [37].

Microbial polysaccharides as the main components of anti-burn agents

Despite the wide application of microbial polysaccharides in various industries, only a few of them are used in medicine. In this review, the microbial polysaccharides that fulfil the requirements for wound healing hydrogels are: pullulan, dextran, alginate and hyaluronic acid [38].

Pullulan, a microbial polysaccharide with unique physicochemical properties is of interest in pharmacy and biomedicine [39, 40]. Pullulan has antitumour properties as confirmed by the studies of Hossam E. Emam et al, where breast cancer cell culture was exposed to Pullulan-based carbon quantum dots for 48 hours. The viability of tumour cells was checked by adding WST-1 (Water-Soluble Tetrazolium-1) reagent. This method is based on the ability of living cell lines to reduce tetrazolium salt by mitochondrial dehydrogenases to a stained formazan product. The result of the study was a reduction in cancer cell viability from 98.5% at a pullalan concentration of 10 μg/ml to 42.1% at a pullalan concentration of 100 μg/ml. It is assumed that pullulan quantum dots also have an antiviral effect by stimulating the production of interferons, which subsequently inhibit the development of viral diseases. Studies have shown that the LD50 of a MERS-CoV (coronavirus) viral culture was achieved at a pullulan concentration of 4 mg/litre [41].

Due to the possibility of modifying the pullulan molecule and creating derivatives, the polysaccharide is able to possess additional properties such as anticoagulant and anti-inflammatory [42]. For example, Masoud Hamidi et al. synthesised a sulphated pullulan derivative and subjected it to caogulometric tests, which showed the ability of the derivative to prolong the prothrombotic time by interacting with positively charged amino acid residues of proteins of the coagulation cascade with subsequent inhibition of their activity [36].

Microbial polysaccharides, in addition to having active properties, are able to stabilise metal nanoparticles (silver, gold, zinc, copper, etc.), thus preserving the 'green' concept of drug delivery to the body. Pullulan based nanoparticles were tested by Ganduri et al. by agar diffusion method for antibacterial activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Serratia marcescens* and *Escherichia coli*). Pullulan silver nanoparticles showed a pronounced antibacterial effect against *Bacillus subtilis* and *Staphylococcus aureus*, but all cultures had clear zones of inhibition after 24-h incubation. The diameter of the zone of inhibition was directly proportional to the dose of nanoparticles added to the wells [43].

The wound healing properties of pullulan-based dressings and hydrogels are summarised in Table 2.

Table 2 – Properties of Pullulan-based wound healing preparations

Medicinal product	Properties that promote wound healing	Source
Wound dressings based on pullulan and chitosan	Hemostatic, antibacterial	[44]
Hydrogel based on pectin and carboxymethylpullulan with addition of polyvinylpyrrolidone (povidine)-iodine.	Antimicrobial, highly efficient release of the active ingredient from the hydrogel matrix	[45]
Hydrogel based on pullulan and collagen	Accelerated wound healing in a mouse model, reduced scarring	[46]
Pullulan and gelatin based hydrogel	Anti-inflammatory, angiogenesis-stimulating	[47]
Sponge dressings based on succinyl pullulan and carboxymethyl chitosan	Maintenance of moist environment, stimulation of fibroblast proliferation	[48]
Pullulan hydrogel without additional agents	Antioxidant, energetic (energy source for fibroblasts), hygroscopic (dehydration of bacteria and wound fluid), oxygenation of cells	[49]

The above conclusions based on pullulan studies allow us to recognise microbial polysaccharides as universal compounds for use in medicine for the treatment of burn injuries.

Dextran is an electrically neutral polymer synthesised by bacteria and capable of binding water [50]. Its molecule consists of α-1,6-linked glucose monomers and branched α-1,3 chains, which allows the molecule to exhibit the properties of biocompatibility and biodegradability. The ability of the hydroxyl groups of dextran to partially oxidise to aldehyde groups affects its adhesive properties. The oxidised dextran by Schiff base reaction cross-links with amino groups of skin tissues, spreading even on uneven skin surface with defects, thus allowing local controlled release of additional active compounds and promoting wound healing without noticeable scarring [51]. The adhesive prevents wound infection as it inhibits the ability of bacteria to penetrate deep into the wound tissue [52].

As the wound healing process requires innovative materials that mimic natural tissue and maintain a moist environment around the wound, the hydrogel dosage form is becoming an interesting formulation to study. However, conventional hydrogels lack mechanical strength, antimicrobial activity and controlled release of active ingredients [53]. The efficacy of hydrogel dressings is enhanced by the addition of dextran due to the strength, swelling and accelerated degradation of the material [54]. Hydrophilic polymers in dressings are able to absorb significant amounts of exudate and are suitable for rehydration of necrotised tissues [55].

Another interesting gel-forming natural polysaccharide is alginate. It can be produced not only from the cell walls of algae, but also from bacterial strains-producers such as *Acetobacter* and *Pseudomonas* [56].

It is recognised as a safe, biodegradable and biocompatible polymer, which, in addition to tissue engineering and wound care, is used in the cosmetics industry and in drug delivery systems. The polymer fulfils the requirements for wound dressing materials due to its high water absorption and porosity, prolonged release of active compounds [57, 58]. To create alginate-based pharmaceuticals, manufacturers most often use silver ions as an additive compound to treat wounds of moderate to severe exudation to enhance the antibacterial effect (Coloplast (Denmark), Hartmann (Germany)) [59].

Hyaluronic acid is a non-protein compound having repeating β-1,4-D-glucuronic acid and β-1,3-N-acetylglucosamine links [60]. In addition to hyaluronic acid production by animal and human organs and tissues, it is produced by microorganisms *Streptococcus zooepidemicus*, *Escherichia coli*, and *Bacillus subtilis* [61]. Hyaluronic acid, which is part of the extracellular matrix, has biocompatibility, moisture retention properties, hygroscopicity and viscoelasticity. It is therefore involved in various cellular processes: cell proliferation and differentiation, joint lubrication and hydration balance. A clinical study by Juhász I showed that in 93.3% of 60 patients, the size of a thermal wound decreased by 50% within 5 days of topical application of hyaluronic acid with zinc supplementation [62]. In other experimental studies, the application of hyaluronic acid demonstrated accelerated wound healing, improved microvascular elasticity, and moisture retention, creating a favourable environment for collagen and elastin synthesis [63].

Conclusion

This review presents the prospects for the use of microbial polysaccharides in the treatment of burn wounds. Analyses have shown that microbial polysaccharides such as pullulan, dextran, alginate and hyaluronic acid have high hydrophilicity, biocompatibility and antimicrobial properties. Their ability to inhibit infection, provide accelerated wound healing and support optimal moisture levels makes microbial polysaccharides promising components for the development of anti-burn hydrogels. This dosage form can reduce the risk of scarring and alleviate the patient's condition. The possibility of incorporation of additional components into polymeric matrices makes polysaccharides universal carriers of active compounds for their delivery and timely release.

Despite their significant potential, large-scale introduction of microbial polysaccharides into medical practice requires additional research: optimisation of production methods and detailed study of interaction with living tissues. Research in this direction can contribute to the development of affordable and effective wound healing agents, which is relevant in the context of increasing resistance of microorganisms in the modern world.

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