The profound potential of fungal β-glucans in animal skin wound healing

O profundo potencial das β-glucanas fúngicas na cicatrização de feridas cutâneas em animais

Rafaela Caldas de Paula[1,2]
Crystian Bartsch Parodi[2,3]
Nicoly Subtil de Oliveira[1,2]
Pedro Andrade de Souza[3]
Luiz Fernando Bianchini[2]
Edvaldo Antonio Ribeiro Rosa[1-3*]

[1] Graduate Program in Animal Science (PPGCA), Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil
[2] Xenobiotic Research Unit (UPX), Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil
[3] Graduate Program in Dentistry (PPGO), Pontifícia Universidade Católica do Paraná (PUCPR), Curitiba, PR, Brazil

***Correspondence:** edvaldo.rosa@pucpr.br
Received: 2025 May 13 | **Accepted:** 2025 May 15
DOI: http://dx.doi.org/10.7213/acad.2025.23101
Rev. Acad. Ciênc. Anim. 2025;23:e23101

Abstract

β-glucans have a recognized broad potential for immunomodulation, re-epithelialization, and inflammation mitigation. In veterinary medicine, their role in wound healing is particularly relevant due to these re-epithelializing and anti-inflammatory properties. This study conducted a literature review to evaluate the use of β-glucans in healing cutaneous wounds in animals. The databases PubMed, Web of Science, Scopus, and Embase were searched for relevant studies. Only articles published between January 2013 and March 2023 that specifically reported the use of β-glucans as a therapeutic agent for skin wound healing were included. A total of 237 articles were initially identified, but only 17 met the inclusion criteria and methodological standards for analysis. Among these studies, mice were the most frequently used animal model, and β-glucans were most commonly applied in hydrogel formulations. The compiled findings demonstrate that β-glucans contribute positively to the wound healing process by accelerating tissue regeneration and reducing the overall time required for wound closure, showing superior outcomes compared to many conventional treatments.

Keywords: βeta-glucans. Re-epithelialization. Wounds. Dermal injuries.

Resumo

Os β-glucanos têm um amplo potencial reconhecido para imunomodulação, reepitelização e mitigação da inflamação. Na medicina veterinária, seu papel na cicatrização de feridas é particularmente relevante devido a essas propriedades reepitelizantes e anti-inflamatórias. Este estudo conduziu uma revisão de literatura para avaliar o uso de β-glucanos na cicatrização de feridas cutâneas em animais. As bases de dados PubMed, Web of Science, Scopus e Embase foram pesquisadas em busca de estudos relevantes. Apenas artigos publicados entre janeiro de 2013 e março de 2023 que relataram especificamente o uso de β-glucanos como agente *terapêutico para cicatrização de feridas cutâneas foram incluídos. Um total de 237 artigos foram inicialmente identificados, mas apenas 17 atenderam aos critérios de inclusão e aos padrões metodológicos para análise. Entre esses estudos, camundongos foram o animal mais frequentemente utilizado, e β-glucanos foram mais comumente aplicados em formulações de hidrogel. Os resultados compilados demonstram que β-glucanos contribuem positivamente para o processo de cicatrização de feridas, acelerando a regeneração do tecido e reduzindo o tempo total necessário para o fechamento da ferida, apresentando resultados superiores em comparação a muitos tratamentos convencionais.*

Palavras-chave: *βeta-glucanas. Reepitelização. Feridas. Lesões dérmicas.*

Introduction

A β-glucans are biologically active polysaccharides found in the cell walls of cereals, fungi, some types of seaweed and bacteria, and have D- glucose monomers joined by β-glycosidic bonds in their constitution. Glycosidic bonds of the β-1,3 and β-1,4 types are predominant in cereals (Henrion et al., 2019), whereas, in filamentous fungi and mushrooms, β-1,3 and β-1,6 bonds are responsible for the linear structures chains and branches, respectively (Stier et al., 2014; Bai et al., 2019). Yeasts also produce molecules with β-1,3 and β-1,6 bonds; however, the β-1,3 type is found more frequently in about 85% of cases (Manners et al., 1973).

These polysaccharides are considered functional, tolerable and safe immune adjuvants (Błaszczyk et al., 2019) and have a wide range of therapeutic applications, highlighting immunomodulation (Blanchard et al., 2006), re-epithelialization (Micháľová et al., 2019), and the ability to mitigate inflammation (Lin et al., 2021).

In veterinary medicine, these polysaccharides have already been evaluated for their applicability in polyvalent and anti-rabies vaccination in dogs, inducing a high adaptive response mediated by B lymphocytes (Altuğ et al., 2010; Paris et al., 2020); in the activation of interferon and interleukins involved in the innate response against spring viremia of carp virus (Medina-Gali et al., 2018); in the stimulation of anti-*Actinobacillus pleuropneumoniae* sIgA secretion on in the colostrum and milk of vaccinated sows (Chau et al., 2009); in increasing the efficacy of the vaccine against the infectious bursal disease virus in broiler chickens (Rajapakse et al., 2010); in the decrease of deleterious effects in panga fish (*Pangasianodon hypophthalmus*) caused by cold stress (Soltanian et al., 2014); and in the prevention and treatment of canine obesity with the reduction of serum cholesterol (Ferreira et al., 2018).

Another application derives from its stimulating regenerative capacity in wounds. Once the dectin-1 receptor is activated in keratinocytes, these migrate through skin lesions to reconstruct the lost epithelium (Stojadinovic et al., 2012; van den Berg et al., 2014). In humans, activating macrophages via dectin-1 has increased nitric oxide production and secretion of IL-10, TNF-α and IL-1β (Vetvicka et al., 2013; Jellmayer et al., 2017). Fungal β-glucans can also increase collagen synthesis (Portera et al., 1997; Wei et al., 2002; Seo et al., 2019), collaborating in the repair process.

The application of β-glucans directly on chronic wounds, "difficult-to-heal" wounds, or those caused by burns is a simple therapeutic strategy (Delatte et al., 2001; Majtan and Jesenak, 2018; Rajarajaran and Dakshanamoorthy, 2020), less expensive (Cutting, 2017), and is quite effective in repair (Grip et al., 2021), in relatively short periods (Zykova et al., 2014).

Animals have been used as a study model for evaluating the healing potential of β-glucans, with very promising results (El Hosary et al., 2020); however, such studies seek the development of products for human use, and little has been targeted towards the development of medications aimed at veterinary applications.

The present review was conceived and conducted to compile data about β-glucans in healing animal skin wounds. This review focused on the most common application forms, the most used animal models, and therapeutic efficiency due to the reduced wound healing times.

Material and methods

This review was conducted to verify the potential of β-glucans in healing animal wounds. For this, keywords were chosen that would allow achieving these objectives, namely "healing", "beta-glucans", AND "animal". These words were chosen based on the Mesh Terms. The bibliographic search used Pub Med, Web of Science, Scopus, and Embase databases. The search was carried out from February 1 to March 31, 2023.

The screening was performed on all articles retrieved from the consulted databases. In each of them, filters were applied to limit the period of publication of articles to ten years, from January 2013 to the end of March 2023. Only articles published in English were accepted (Sharil et al., 2022). Titles and abstracts of all articles were read so that more refined inclusion and exclusion criteria could be applied. At this stage, articles involving clinical trials, randomised clinical trials and case-control studies performed in vivo were accepted. Inclusion and exclusion criteria are detailed in Table 1.

The data of interest plotted were the type of study, animal characteristics (species, lineage, sex, and some disease reported), wound healing capacity (initial size of the wound and estimated time until complete healing), and use of β-glucan (origin, formulation, dosage, frequency and time of use of the formulation). Bibliometric information [author(s), title, year, database] was also listed.

Table 1 - Inclusion and exclusion criteria used for papers selection

Inclusion	Exclusion
Papers in English	Non-English written papers
Only complete articles with case studies and clinical trials	Review articles, book chapters, news journals, patents, conference proceedings, theses, dissertations, and monographs
Articles that mention β-glucans acting directly in the healing of skin wounds in animals	Articles that do not mention β-glucans in the healing of skin wounds in animals

Results

Applying Mesh Terms in the databases generated a list of 237 articles that met the initial search criteria. Embase provided 53.16% (126/237), PubMed furnished 27.42% (65/237), Scopus generated 17.29% (41/237), and Web of Science contributed 2.10% (5/237) of the items raised. After applying the inclusion and exclusion criteria and removing duplicate articles, 17 articles were defined, entirely fitting the research objectives. Two independent reviewers (R.C.P. and C.B.P.) evaluated them.

Two independent reviewers (R.C.P. and C.B.P.) evaluated the effectiveness of the time required for the complete healing of wounds to occur, accelerated by exposure to β-glucans compared to control groups. It is notable that β-glucan treatments considerably reduced wound closure times.

Regarding the animals used, 14 (82.35%) experiments used mice, two (11.76%) involved fish, and one (5.88%) was a clinical case in which the efficiency of β-glucans in treating a large wound in the paw of a domestic cat was presented.

The most evaluated forms of application were hydrogel-based ointments (5/17; 29.41%), dressings (4/17; 23.53%), aqueous solutions (2/17; 11.76%), immersion in baths (2/17; 11.76%), hydrogel sprays (3/17; 17.64%), and sponge (1/17; 5.88%). Table 2 summarizes information about the studies, showing which animals were involved, the forms of application of β-glucans, the controls for comparison purposes, the initial dimensions of the induced/observed injuries, and the outcomes of these studies.

Discussion

The use of β-glucans in veterinary medicine has been expanding positively due to the various advantages that justify their prophylactic or therapeutic indication for companion, working, production, and even wild animals (Vetvicka and Oliveira, 2014; Błaszczyk et al., 2019; Picetti et al., 2021; Kilburn-Kappeler and Aldrich, 2023).

Table 2 - Main information extracted from the 17 selected papers

Article	Population	Intervention	Wound	Outcome
Qiu et al., 2022	• Mice • Prague-Dawley • Females	**Treatment:** Hybrid sponge of collagen I and aminated β-glucan **Control:** Not treated **Time of treatment:** 14 days	Dorsal dermatotomies of 10 mm in diameter	Re-epithelialization of 95.5% of the area (treated) and 87.6% (non-treated)
Nissola et al., 2021	• Rats • Wistar • Males	**Treatment:** Hydrogel with lasiodiplodan (β-glucan) **Control:** Hydrogel without lasiodiplodan **Time of treatment:** 14 days	Dorsal dermatotomies of 10 mm in diameter	Almost complete re-epithelialization with 67% increase in thickness (treated)
Lin et al., 2021	• Mice • BALB/c • Males	**Treatment:** Hydrogel com curdlan and silver nanoparticles **Control:** Not treated **Time of treatment:** 10 days	Dorsal dermatotomies of 10 mm in diameter	Bactericidal action, inhibition of the development of inflammation and acceleration of healing
El Hosary et al., 2020	• Mice • Males	**Treatment:** Hydrogel with crude β-glucan **Control:** Not treated **Time of treatment:** 10 days	Interescapular dermatotomies of 15 × 15 mm	Re-epithelialization of 99% of the area (treated) and 25.5% (not treated)
Voloski et al., 2019	• Catfish (*Rhamdia quelen*)	**Treatment:** Daily immersion for 1 h in yeast β-glucan 500 μg L^{-1} **Control:** Not treated **Time of treatment:** 28 days	Bilateral excisions in the dorsal region near the central fin of 3 mm in diameter and 5 mm in depth	Dermis recovery in 100% of the area (treated) and 30-60% (not treated)
Micháľová et al., 2019	• Cat • Female • 9 years old	**Treatment:** Hydrogel with β-glucan and chlorhexidine. Oral administration of β-glucan **Control:** Clinical case **Time of treatment:** 35 days	Animal with post-traumatic necrosis in the skin and subcutaneous structures of the right front limb	Complete wound healing with hair growth after healing
Fusté et al., 2019	• Mice • C57BL/6	**Treatment:** Barley β-glucan aqueous solution **Control:** Water **Time of treatment:** 12 days	Dorsal dermatotomies of 10 mm in diameter	Early healing in the treated group
Muthuramalingam et al., 2019	• Mice	**Treatment:** Hydrogel with PVA/β-glucan **Negative control:** Not treated **Positive control**: MeditouchH **Time of treatment:** 14 days	Dorsal dermatotomies of 5 mm in diameter	Epidermal cells migrated 1.5-fold faster in the treated group
Grip et al., 2018	• Mice • Males • Diabetic	**Treatment:** Nanofiber ressings with β-glucan **Control:** Nanofiber dressings without β-glucan **Time of treatment:** 8 days	Dorsal dermatotomies of 10 × 10 mm	Re-epithelialization of 100% of the area (treated) and 50% (not treated)

Table 2 - Main information extracted from the 17 selected papers (continued)

Article	Population	Intervention	Wound	Outcome
Veerasubramanian et al., 2018	• Rats • Wistar • Males • Diabetic	**Treatment:** Konjac glucomannan dressings (KGM) with oat β-glucan **Control:** Cotton gauze dressings **Time of treatment:** 24 days	Dorsal dermatotomies of 20 × 20 mm	Fast and complete wound healing
Wu et al., 2016	• Mice • Kunming • Males	**Treatment:** Transparent β-glucan nanofiber dressings and non-transparent β-glucan dressings **Control:** Not treated **Time of treatment:** 14 days	Dorsal dermatotomies of 10 × 10 mm	Re-epithelialization of 83.1% of the area (treated with a non-transparent dressing), 57.5% (treated with a transparent dressing), and 50% (not treated)
Hsiao et al., 2016	• Rats • Wistar • Males	**Treatment:** Spray with β-glucan and hydroxyethyl cellulose (HEC) **Control 1:** PBS **Control 2:** HEC **Time of treatment:** 29 days	Dorsal dermatotomies of 15 × 15 mm	Early rethelialization in the presence of β-glucans
Przybylska-Diaz et al., 2013	• Carps (*Cyprinus carpio*)	**Treatment:** Daily immersion for 1 h in yeast β-glucan 100 μg L^{-1} **Control:** Not treated **Time of treatment:** 14 days	Dorsal dermatotomies of 5 mm in diameter and 2.5 mm in depth	Expressive reduction in wound size in the treated group
Yun et al., 2015	• Mice • Males • Diabetic	**Treatment:** Aqueous solution of β-glucans **Control:** Madecassol® **Time of treatment:** 20 days	Dorsal dermatotomies of 10 mm in diameter	Complete healing in the β-glucans treated group on the 16th day and in the control group after the 20th day
Grip et al., 2021	• Mice • Males	**Treatment:** Spray and hydrogel with β-glucan **Positive control:** Platelet-derived growth factor and TGF-α **Negative control:** Water **Time of treatment:** 24 days	Dorsal dermatotomies of 10 × 10 mm	Spray and gel treated groups showed very similar accelerated wound closure profiles
Yasuda et al., 2018	• Mice • Males	**Treatment:** β-glucan film dressings (Paramylon) **Control:** Cellulose film **Time of treatment:** 5 days	Dorsal dermatotomies of 8 mm in diameter	Greater lesion reduction in the treated group on the 5th day
Grip et al., 2017	• Mice • Males • Diabetic	**Treatment:** Spray with β-glucan (1%) in Carbopol hydrogel **Positive control:** Platelet-derived growth factor and TGF-α **Negative control:** Hydrogel base **Time of treatment:** 24 days	Dorsal dermatotomies of 10 × 10 mm	The beneficial effects of β-glucan did not overcome the deleterious effects of the excipient Carbopol, which caused ischemia and tissue maceration

This review aimed to increase veterinarians' knowledge about β-glucans by proving that formulations containing these polysaccharides can favour the re-epithelialization and healing wounds in animals of different species.

As seen here, the most common form of use is the incorporation of bioactives in hydrogels. This pharmaceutical form comprises hydrophilic and cross-linked polymers that absorb a large amount of water (Kashyap et al., 2005) and in which a reasonable amount of soluble principles can be dispersed (Shoukat et al., 2021). β-glucans can serve as gelling agents for formulating hydrogels if their concentration in the formulation is increased (Park et al., 2018), thus exerting simultaneous dual activity of carrier and drug.

Hydrogels are versatile forms that ensure good coverage of the area affected by the lesion, remaining adhered while maintaining the interface of action, guaranteeing a high rate of hydration of the injured tissue, allowing diffusion of oxygen and carbon dioxide, favouring the growth of adjacent cells, reducing the possibility of microbial contamination, and absorbing exudate (Brumberg et al., 2021; Savina et al., 2021). This myriad of benefits makes this a preferred way of delivering β-glucans.

The possibility of incorporating other therapeutic activities adds advantages, as seen in the article (Lin et al., 2021). Silver nanoparticles inhibit bacterial growth, which implies a lower exudative inflammatory response, and synergistically reflects in the reduced repair time of injured tissues. In the clinical case (Micháľová et al., 2019), incorporating chlorhexidine into the hydrogel inhibited microbial growth, accelerating wound repair.

Sprays containing β-glucans were formulated with gelling agents that, once applied to the lesions, formed a covering film similar to hydrogels, such as hydroxyethyl cellulose and carboxymethyl cellulose. Using spray-spreadable hydrogels ensures a simple application with reduced contact pressure, favouring quick applications (Geh et al., 2019) and a lower risk of painful discomfort (Grip et al., 2021). However, similar formulations based on Carbopol, an acrylic acid polymer, are completely contraindicated, as they promote oedema, ischemia, apparent loss of viability, and skin erosion in the peripheral region of the lesions (a.k.a. maceration) (Grip et al., 2017). In the study (Grip et al., 2018), a formulation containing a high concentration of β-glucan and a low concentration of Carbopol accelerated the epidermal repair process without these reported side effects.

Studies that evaluated the effectiveness of dressings containing β-glucans showed that these could be produced by inclusion (Grip et al., 2018), co-polymerization (Veerasubramanian et al., 2018), esterification (Wu et al., 2016), or by forming retentive films (Yasuda et al., 2018). Regardless of how they are produced, a common feature is that all these dressings have a high capacity for absorbing water and forming hydrogels that cover wounds, promoting the repair of injured tissues. Thus, the dressings begin to function a posteriori as the strictu sensu hydrogels described above.

A mechanism of action proposed for Paramylon dressing, a β-glucan from *Euglena gracilis* (freshwater single-celled alga), was based on the finding of inhibition of the inflammatory response in lesions in mice by inhibiting the elevation of pro-inflammatory cytokines, which would have accelerated wound repair (Yasuda et al., 2018).

Incorporating aminated β-glucans with type I collagen generated a spongiform application form favouring macrophage activation and accelerated the repair process (Qiu et al., 2022). This application can be quite interesting, as the drug remains immobilised on the wound, reducing the need for reapplication.

Immersion in β-glucan solutions has also been evaluated as a way to treat wounds (Przybylska-Diaz et al., 2013; Voloski et al., 2019). It can be considered a viable option for wounds that are difficult to treat with topical therapies, especially in fish and other animals that need to stay immersed. The solution can be easily applied to more extensive or harder-to-reach areas. In the two studies investigating the application of β-glucans by immersion, more significant collagen deposition was detected, which is implicated in the acceleration of healing. Furthermore, β-glucans organise the immune response to facilitate the healing of injured tissues in carp (Dalmo and Bøgwald, 2008). It is likely that during immersion, animals absorb β-glucans through the digestive tract or any other mucosal tissue, leading to reduced stress in fish (Vetvicka and Oliveira, 2014), with consequent reduction of cortisol. This hormone hinders the repair process (van den Berg et al., 2014).

Still, about immersion, β-glucans also mediated muscle tissue regeneration in fish. The β-glucans may have bound to dectin-1 of M2 CD206 or similar macrophages, which produce growth factors favouring muscle regeneration in injured muscles (Sakaguchi et al., 2014; Rőszer, 2015). In addition to growth factors, angiogenic factors derived from these macrophages may have contributed to this regeneration (Jetten et al., 2014). Added to this is that in sites of muscle injury treated with β-glucans, IL-8 expression was increased (Przybylska-Diaz et al., 2013). In humans and rats, this interleukin is intrinsically related to muscle development and repair (Akerstrom et al., 2005; Ahn and Kim, 2020; Hong and Tian, 2020).

Instilling aqueous solutions of β-glucans directly on the wounds proved feasible and satisfactory. This resource has been used for a long time (Kenyon, 1983; Kenyon and Michaels, 1983), but it has the inconvenience of needing multiple applications during the day since the exudate can leach the applied molecules. Applications of hydrogels and other formulations that form hydrogels ensure drug retention for a longer time, generating greater dosage comfort (Pal et al., 2009).

Some of the studies sought to work with diabetic mice as a model for treating wounds in humans; however, the positive and promising results obtained can be transferred to other species, such as dogs and cats, which can develop wounds that are difficult to heal (Schaer, 1995; Bennett, 2002). Studies of this nature and in these species must be conducted to confirm this assumption assertively.

Worthy of mention is the clinical case in which an in-house hydrogel containing β-glucan, chlorhexidine digluconate and *Apis melifera* honey was experimentally used and which stimulated a regenerative response with neo-growth of skin covered by hair to a large extent. That had been removed due to a traumatic accident (Micháľová et al., 2019). This result shows that an association of a regenerating agent (β-glucan) with an antimicrobial agent (chlorhexidine) can be very advantageous in the treatment of very extensive lesions that are susceptible to microbial contamination. However, the use of bee honey as a retentive agent may be advised against as it may contain dormant spores of pathogenic bacteria such as *Bacillus* spp., notably antiseptic resistant (Snowdon and Cliver, 1996).

Most of the selected studies used rodents as a model to test the epithelial regenerative capacity mediated by β-glucans. Notably, these studies aimed not to contribute to developing products for animal use but for human use. Only two experimental studies with fish (Przybylska-Diaz et al., 2013; Shoukat et al., 2021) and a clinical case involving a feline (Micháľová et al., 2019) were exclusively directed to animals. However, the results obtained with rodents showed that these polysaccharides can accelerate re-epithelialization in mammals with high tissue complexity, and this can serve to develop products aimed at animals.

Conclusion

The studies listed in this review are unanimous in concluding that β-glucans significantly improve the healing process of dermal wounds. Reduced wound closure time, with minimal inflammation, was a standard feature. Several application forms were presented, but the results showed no differences between them. Although several of these studies have used animals as experimental models for an alleged extrapolation to humans, the results strongly suggest that β-glucans can be applied in wound healing and regeneration of cutaneous and subcutaneous tissues of animals of different species, which justifies a new proposition of use in veterinary medicine.

Acknowledgments

The authors would like to thank the Coordination for the Improvement of Higher Education Personnel – Brazil (CAPES) - Financing code 001 for financial support and scholarships.

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