β-glucan extracts as a high-value ingredient for skin health and disease: A review

Pedro Sousa [a], Diana Tavares-Valente [b], Manuela Amorim [a], João Azevedo-Silva [a], Manuela Pintado [a], João Fernandes [a b *]

[a] Universidade Católica Portuguesa, CBQF—Centro de Biotecnologia e Química Fina—Laboratório Associado, Escola Superior de Biotecnologia, Rua Diogo Botelho 1327, 4169-005 Porto, Portugal

[b] Amyris Bio Products Portugal, Unipessoal Lda, Rua Diogo Botelho 1327, 4169-005 Porto, Portugal.

[*]Author to whom correspondence should be addressed (jcfernandes@ucp.pt)

Abstract

β-glucans, which are naturally present in cereals, yeast, and mushrooms, have gained attention as a potential natural source for functional foods and pharmaceuticals. Due to the availability of β-glucans from several sources, different extraction methods can be employed to obtain high purity extracts that can be further modified to enhance their solubility or other biological properties. Apart from their known ability to interact with the immune system, β-glucans possess specific properties that could benefit overall skin health and prevent age-related signs, including soothing and antioxidant activities. As a result, the use of β-glucans to mitigate damage caused by environmental stressors or skin-related issues that accelerate skin aging or trigger chronic inflammation may represent a promising, natural, eco-friendly, and cost-effective approach to maintaining skin homeostasis balance. Therefore, this review aims to summarize β-Glucans extraction methodologies, molecular structure, and potential chemical modifications. Additionally, it explores the biological properties of β-Glucans that could be utilized for skin applications and provides an overview of marketed products containing this polysaccharide.

Keywords: Beta Glucans; Extraction; Chemical modification; Biological Properties; Immunomodulation; Skincare

1 - Introduction

Human skin serves as a natural physical barrier against various external factors, including ultraviolet radiation, urban air pollution, pathogens, and toxins, while also regulating body temperature and water loss (Abdo et al., 2020; Maarouf et al., 2019). Skin structure can be divided into three main layers: the epidermis, dermis, and hypodermis. Each of these layers supports a large number of different skin cells and more than 300 molecules present in the extracellular matrix (ECM). These molecules include fiber-forming molecules (e.g., collagen), non-fiber forming molecules (e.g., hyaluronan), and matricellular proteins (e.g., periostin) that contribute to the support, elasticity, strength, and homeostasis of the skin (Huang et al., 2022). The epidermis is the outermost layer of the skin and is mainly composed of keratinocytes (approximately 90%), as well as a smaller number of Langerhans cells, melanocytes, and Merkel cells (Mohamed & Hargest, 2022). Within this layer, keratinocytes can be found in various stages of differentiation, ranging from undifferentiated keratinocytes (innermost layer of the epidermis) to terminally differentiated non-nucleated dead keratinocytes (outermost layer of the epidermis) (Scieglinska et al., 2019). Langerhans cells are the only dendritic cells present in the epidermis. These are immune cells with antigen-presenting capacity, playing a crucial role in adaptive immune defense. Melanocytes are responsible by the production of melanin, which is transferred to keratinocytes and accumulates in the supranuclear region, providing protection against UV radiation (Correia et al., 2018). Finally, Merkel cells constitute a unique population of postmitotic cells scattered along the dermo-epidermal junction. It is believed that these serve as adapting mechanoreceptors.

Within the epidermis, various types of keratins (KRT) and laminins (LM) are present, contributing to its strength (Pfisterer et al., 2021). According to Dyring-Andersen et al.'s review (2020), this layer contains 47 different identified keratins, with KRT-1, 5, 10, 14, and 6A being the most abundant. Increased levels of certain keratins (KRT-6, 16, and 17) are also associated with cell proliferation and inflammation, which is a natural response to skin barrier damage or specific skin diseases like psoriasis. LM 332, 511, and 521 are the most prevalent laminins in the epidermis, particularly near the epidermal-dermal junction. These laminins are involved in wound repair processes, with LM 332 being synthesized by keratinocytes in the initial stages of wound healing (Rousselle et al., 2019).

The dermis is the region where skin fibroblasts reside. These are responsible for producing the molecules found in the ECM. The dermis also contains pericytes, which possess mesenchymal

capacity and play an important role in tissue regeneration (Bodnar et al., 2018). Additionally, immune cells, endothelial cells, and cells that produce cytokines and chemokines are present in the dermis, contributing to immune responses (Rognoni & Watt, 2018; Sanchez et al., 2019). Collagen is the primary component of the ECM in the skin and is predominantly represented by fibrillary collagen. Collagen type-I is the most abundant type, followed by collagen type-III, and smaller amounts of collagen type-V. These collagens provide structural support and tensile strength to the skin. Elastic fibers (e.g., elastin), glycoproteins (e.g., fibronectin), and other molecules (e.g., hyaluronan) also contribute to the elasticity and stabilization of the skin (Pfisterer et al., 2021). The hypodermis, also known as the subcutaneous layer, serves as an insulator and protects the organs underneath (Supe & Takudage, 2021). It is primarily composed of blood vessels and adipocytes, which have various functions such as energy storage, synthesis of triglycerides, tissue regeneration by facilitating the recruitment of fibroblasts, and nutrient homeostasis (Gupta, 2014; Yucha et al., 2019). Given the importance of this organ, it is essential to minimize skin degradation by promoting the synthesis of vital skin components or mitigating the adverse effects of factors such as sun exposure or air pollution (Piquero-Casals et al., 2023; Zouboulis et al., 2019). In recent years, consumers' interest in innovative skincare products containing natural, bioactive compounds has surged (Ahsan, 2019a). These products, known as cosmeceuticals, may contain ingredients that occur naturally (e.g., minerals, plant extracts, products from microorganisms) or are chemically synthesized.

One of the most essential and widespread classes of bioactive compounds is polysaccharides, which play a crucial role in the structure of animal cell membranes, microbes, and plant cell walls, and possess well-known biological properties. Polysaccharides can be obtained from a wide variety of sources, including plants, algae, microorganisms, and animals (Li et al., 2018; Ullah et al., 2019; Yu et al., 2018). Several studies have indicated the use of polysaccharides extracted from natural sources as bioactive ingredients in skincare products (Du et al., 2014; Kanlayavattanakul & Lourith, 2015; Fernando et al., 2019). One such polysaccharide with bioactive properties is β-glucan (BG), a structural polymer found in plants and fungi, which has documented biological activities suitable for skincare applications, such as wound healing, anti-wrinkle, and antioxidant activities (Du et al., 2014). BG can be obtained and isolated from cereals, mushrooms, or microorganisms, in different conformations (Kaur et al., 2020).

Products containing BG are commercially available and are present in the normal diet of many consumers due to their natural presence in oats and barley (Hughes & Grafenauer, 2021). Recently, some authors have pointed out BG as an excellent compound with applicability in skincare, not only due to its direct impact through antioxidant mechanisms or antimicrobial properties but also due to its indirect effect on the modulation and stimulation of the immune system and wound healing (Divya et al., 2020; Huang & Huang, 2021; Vetvicka et al., 2019). Numerous chemical functionalization strategies have been extensively employed to modify the inherent structure of specific types of glucans, with the aim of enhancing their physicochemical and biological properties. These modifications can considerably improve BG solubility and increase the potential use of these molecules as a bioactive ingredient (Liu et al., 2021; Yuan et al., 2019). In this case, certain properties demonstrated by functionalized BG, such as antioxidant (Calegari et al., 2017; Theis et al., 2019), antibacterial (Wan-Mohtar et al., 2016), wound healing (Yasuda et al., 2018), ultraviolet radiation (UV) protection (Zülli et al., 1998) and antiaging (Pillai et al., 2005), can be promptly used for skincare application.

This review comprehensively describes different BG extraction methodologies applied to various sources and the types of chemical functionalization typically employed to improve its solubility and biological properties. In the context of skincare, we will also review the relevant properties that have been reported for BG, which have potential applicability as a bioactive ingredient. The final chapter of this review will analyze the potential application of this molecule and the current availability of skin products enhanced by the presence of BG in their formula or its use as an ingredient.

2 - β-Glucans extraction, structure and functionalization

2.1 - Extraction methods

The extraction of BG can be achieved through various methods, however, they can affect BG's primary physical properties, such as viscosity, molecular weight, and solubility. These methods include chemical extraction using acid, alkaline, and organic solvents, enzymatic treatment, autolysis, mechanical methods, or a combination of these to improve BG purity and remove impurities such as lipids (Kaur et al., 2020; Yuan et al., 2019).

Regarding yeast, several approaches have been reported, including enzymatic hydrolysis, autolysis, chemical treatments, or ultrasounds, mainly used to break down the cell wall

(Avramia & Amariei, 2021; Liu et al., 2021). Purified BG from spent yeast from a brewing process with a final yield of 11% comparing with the initial mass of yeast, was obtained from the *Saccharomyces cerevisiae* yeast (Liu et al., 2008). The authors applied a methodology that consisted of autolysis for 24 hours at 55 °C followed by a short heat treatment at 85 °C. The pellet was then subjected to a hot water treatment (autoclave) for 4h, homogenization by high pressure, lipid extraction, protein hydrolysis, and spray drying as a final process. The dry weight content of BG and total carbohydrates increased from 21% and 35% (spent yeast) to 93% and 96% (purified BG) at the end of the process. A more in-depth study was conducted to evaluate the best methods to disrupt this yeast cell wall, analyzing various methodologies such as hot water treatment (autoclaving), autolysis, bead mill, sonication, and more than one of these conditions simultaneously. After comparing and analyzing all the results, the authors reported that bead milling alone, autolysis followed by bead milling, and sonication were the most efficient methods to extract BG from yeast, obtaining extracts with a high quantity of saccharides and low protein content. All the extraction methods tested obtained a BG content ranging from 6% (autoclaving in deionized water/buffer) to 15% (autolysis + bead milling in deionized water) (Bzducha-Wróbel et al., 2014). Applying a "greener" approach, (Magnani et al., 2009) demonstrated that it is also possible to extract insoluble BG from *Saccharomyces cerevisiae* yeast without producing harsh residues. For this, an initial autolysis of 24 hours at 55 °C followed by a high-temperature procedure in an autoclave for 4 hours was performed. Afterward, three more processes took place: sonication to break the cell wall, lipid extraction using isopropanol and petroleum ether, and a final protein hydrolysis with protamex (proteolytic enzyme) to cleave the residual protein remaining in the insoluble fraction. This extraction method had a yield of 11% and a BG recovery of 94%, compared with the amount of BG from the original yeast. In most cases, simple methods are not enough to destroy the cell wall structure, explaining the need to complement more than one method, such as heat treatment followed by acid-base extractions (Avramia & Amariei, 2021).

In order to obtain BG from cereals, various extraction conditions can be applied, such as alkaline extraction, acid extraction or enzymatic hydrolysis (Ahmad et al., 2010). Some authors observed that the most efficient condition to extract BG from oat was a simultaneous hot-water treatment and a thermostable α-amylase hydrolysis for 3 hours at 100°C, following an initial reflux of oat brans in ethanol (82%) for 2 hours to inactivate native enzymes. This method resulted in a yield of 76% (Ragaee et al., 2008). In a different study, two proteolytic enzymes,

pancreatin and papain, were tested separately, resulting in two final BG concentrates with 57% BG content and a protein content of 18% and 6%, respectively (Immerstrand et al., 2009). Another study evaluated four types of extraction (alkaline, acidic, hot-water and enzymatic), following an initial reflux of barley flour in ethanol (80%) for 6 hours. The authors reported that hot-water extraction was the best condition, recovering 83% of BG from the original source and an extraction yield of 5%, when compared with the other conditions studied (Ahmad et al., 2009). The same authors made a similar analysis for oat BG. In this case, the enzymatic procedure was the condition that obtained the highest yield, with a recovery of 87% and an extraction yield of 5%, when compared to alkaline and acid extractions, as hot-water extraction was not performed (Ahmad et al., 2010).

In another study, the impact of increasing concentrations of HCl [0.1-0.5 M] was evaluated for primary acid hydrolysis and an alkaline extraction with NaOH [1 M] to extract BG from barley. Then, the supernatant was hydrolyzed with α-amylase and later precipitated with ethanol (80%) overnight at 4°C. The authors concluded that as HCl concentration increased, the amount of total and soluble BG decreased, but the purity of both fractions increased. The molecular weight and viscosity of the soluble BG also decreased (Lee et al., 2015). BG was also extracted from *Eleusine coracana* seeds flour through an initial reflux with 80% ethanol and NaOH [1 M] for 8 hours. Then, the sample was stirred at 45 °C for 90 min, and the insoluble fraction was incubated overnight with 80% ethanol. The final purified BG from this plant seeds presented a value of 8% (Divya et al., 2020).

The drying process is equally important to the extraction method when it comes to achieving high purity. According to recent research by Zeko-Pivač et al. (2023), spray-drying has been identified as the most suitable method for preserving the structure of BG compared to lyophilization, which can cause agglomeration and result in a porous sheet-like surface, or air drying, which leads to the formation of larger, granular BG particles.

As summarized in Table 1, various approaches can be used to disrupt the matrix, although researchers typically begin with similar steps, which typically include: (I) Autolysis or autoclave treatment - to break down the cell wall and inactivate native enzymes; (II) Acid or alkaline extraction - primarily aimed at removing lipids and proteins; (III) Enzymatic hydrolysis - specifically targeting the breakdown of α/β glycosidic linkages or the removal of specific chemical components; (IV) Spray-drying method - used to obtain a fine and stable

powder of BG. It is important to note that these methods, particularly the harsh chemical extractions, may gradually break down and alter the conformation of polysaccharides, potentially resulting in a BG extract with a lower molecular weight. Depending on the desired degree of purification, additional steps such as sonication, organic solvent treatments, or other complementary methods (e.g., acid-base extraction) may be included.

Table 1 – Methods used for the extraction and purification of BG obtained from different sources.

Source	Method(s)	β-Glucans (%)	Reference
Bacteria	Basic extraction Acid precipitation Dialysis	-	(Shih et al., 2009)
	Ethanol precipitation Fractionation	>90	(Luo et al., 2019)
Algae	Acid/Water extraction Ethanol precipitation	4 - 5	(Kadam et al., 2015)
	Acid extraction Autoclave Filtration	-	(Garcia-Vaquero et al., 2019)
	Water extraction Ethanol precipitation	-	(Cuong & Xuan, 2020)
Fungi	Alkaline extraction Organic solvent extraction Autoclave	-	(Ishibashi et al., 2004)
	Autolysis Autoclave High Pressure homogenization Organic solvent treatment Protease treatment	34 - 93	(Liu et al., 2008)
	Autolysis Autoclave Sonication Lipid extraction Enzymatic hydrolysis Dialysis	-	(Magnani et al., 2009)

	Autolysis Autoclave Bead mill Sonication	6 - 15	(Bzducha-Wróbel et al., 2014)
	Hot water extraction Ethanol precipitation Dialysis	9 - 17	(Khan et al., 2017)
	Autoclave Ethanol precipitation	3 - 48	(Vetvicka et al., 2019)
	Alkaline extraction Acid extraction	-	(Amer et al., 2021)
	Mechanical cell lysis Alkaline extraction Acid extraction	79	(Avramia & Amariei, 2022)
Cereals	Ethanol reflux Alkaline extraction Acid extraction Enzymatic hydrolysis	-	(Ahmad et al., 2009)
	Ethanol reflux Hot water extraction Ultrasound Autoclave Enzymatic hydrolysis Dialysis Ethanol precipitation	57	(Immerstrand et al., 2009)
	Ethanol reflux Alkaline extraction Acid extraction Hot water extraction Enzymatic hydrolysis	-	(Ahmad et al., 2010)
	Acid extraction Alkaline extraction Enzymatic hydrolysis Ethanol precipitation	1 - 7	(Lee et al., 2015)
	Ethanol reflux Alkaline extraction Ethanol precipitation	8	(Divya et al., 2020)
	Organic solvent extraction	81	(Chen et al., 2021)

	Enzymatic hydrolysis Ethanol precipitation Ammonium sulfate precipitation Dialysis		
	Ethanol reflux Hot water extraction Enzymatic hydrolysis Ethanol precipitation Dialysis	77 - 80	(Li et al., 2023)

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196 **2.2 - Molecular structure**

197 Glucans consist of several glucose units linked by both alpha and beta glycosidic linkages, and
198 the number of monomers directly affects its molecular weight (Ruiz-Herrera & Ortiz-
199 Castellanos, 2019). Depending on its source, BG can have a linear or branched structure with
200 different types of glycosidic linkages: β-(1→3), β-(1→4), and β-(1→6) (Figure 1). In the
201 specific case of yeast, BG is composed of a backbone of β-(1→3)-Glucan with long β-(1→6)-
202 Glucan branches. However, recent reports highlight the presence of a mix of (α1→4)- and β-
203 (1→4) linked cell wall glucans (Bastos et al., 2022). In mushrooms, BG has a backbone of β-
204 (1→3)-Glucan with short β-(1→6)-Glucan branches, while in cereals BG has a linear structure
205 consisting of linked β-(1→4)-Glucan and β-(1→3)-Glucan (Du et al., 2019).

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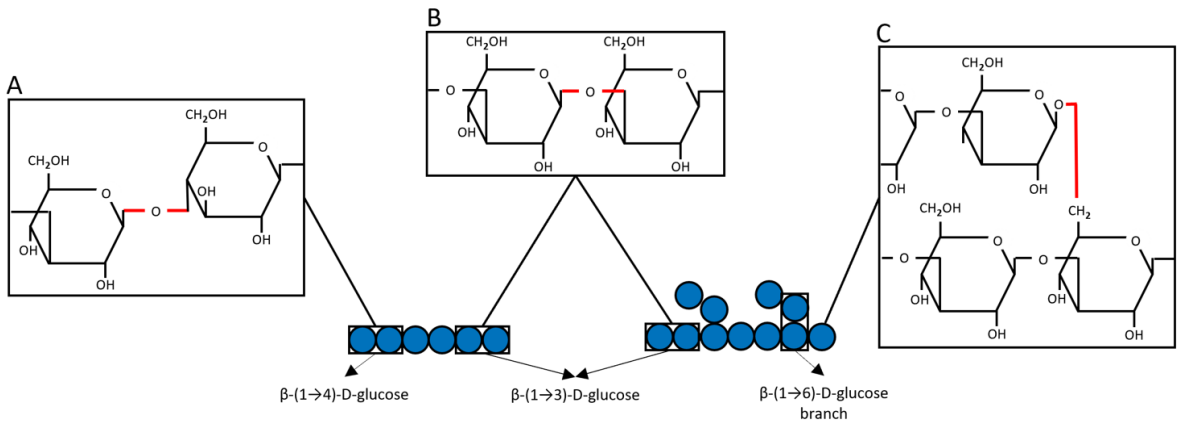

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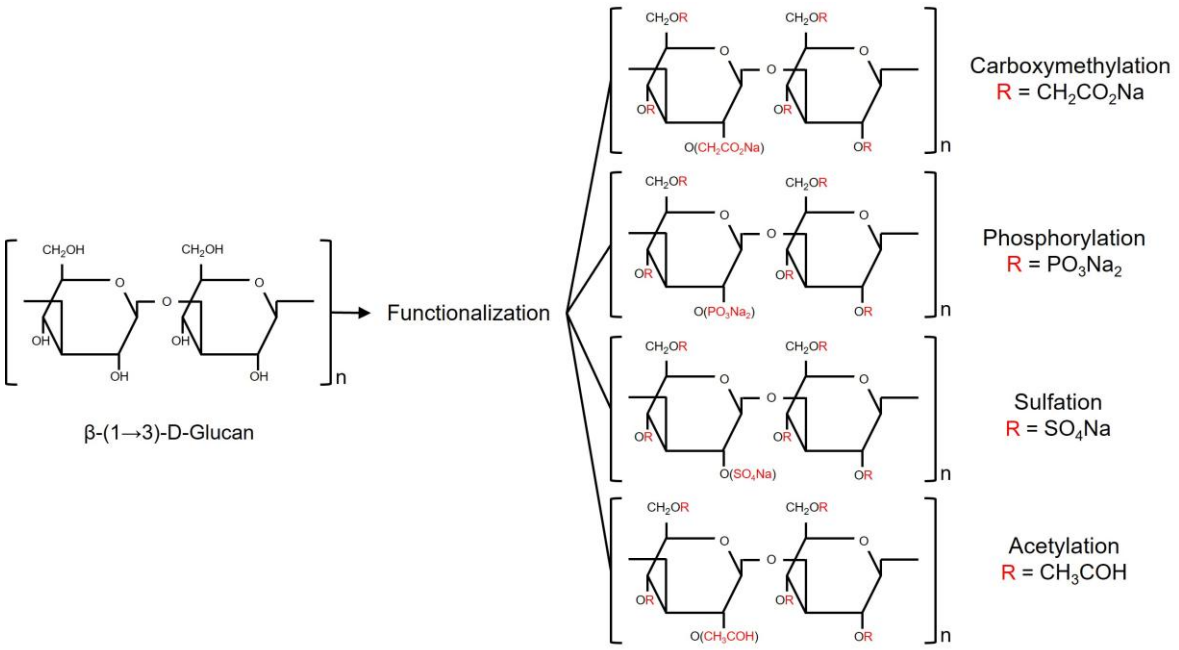
Figure 1 – Types of linkages that can be found in β-Glucans between glucose monomers: (A) β-(1→4)-D-glucose; (B) β-(1→3)-D-glucose; (C) β-(1→6)-D-glucose. These linkages are naturally found in cereals (A and B) or in yeast (B and C).

BG solubility is mainly affected by its degree of polymerization (DP), since a better solubility indicates a lower DP (Du et al., 2014; Yuan et al., 2019). Considering their linkages, BG are typically water-insoluble when their structure is mainly composed by β-(1→3)-Glucans with few or no β-(1→6)-Glucans, as seen in curdlan. Conversely, a more branched structure composed of the same linkages, such as lentinan, can be dissolved in water (Chen et al., 2022). Therefore, the solubility of BG is influenced by the frequency and distribution of side-chain branches within their molecular structure (Bacic et al., 2009).

2.3 - Chemical modification

Chemical modifications of BG can be achieved by altering its structure through processes such as carboxymethylation, sulfation, phosphorylation, or acetylation. These modifications can enhance the solubility and biological activity of BG. Less commonly, amination or gamma irradiation have been utilized to functionalize β-glucan (Kaur et al., 2020; Khan et al., 2016). Moreover, besides modifying the structure of BG itself, it is possible to functionalize it by conjugating it with other molecules. For example, for skincare applications, BG can be conjugated with chitin (Gautier et al., 2008), while for drug delivery purposes, it can be linked with silica (Hwang et al., 2018). These conjugations allow for the incorporation of additional properties or functionalities into BG, expanding its potential applications. These substitutions, as depicted in Figure 2, can have a significant impact on the properties of BG. The type and number of substituents linked to the structure will modify its biological capacity, molecular weight, and branching ratio (Huang & Huang, 2021).



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237 **Figure 2 –** Examples of most used chemical modifications of β-(1→3)-D-Glucans through the
238 addition of functional chemical groups.

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240 Carboxymethylation and sulfation are the most commonly used methodologies for modifying
241 BG, based on the available literature. Carboxymethylation provides an effective and low-cost
242 way to functionalize BG while potentially enhancing its biological activity (Chakka & Zhou,
243 2020). This process involves replacing hydroxyl groups on the polysaccharide chain with
244 carboxymethyl groups. It typically involves three main steps: (I) formation of alkoxide groups
245 through the reaction of the polysaccharide in a highly alkaline environment; (II) addition of a
246 carboxymethylation agent, usually monochloroacetic acid, in a highly alkaline environment;
247 (III) reaction of the polysaccharide with the carboxymethylation agent, resulting in the addition
248 of carboxymethyl groups to the alkoxide groups.

249 Sulfation is another commonly used method, chosen for the resulting immunomodulatory
250 properties observed in chemically modified polysaccharides (Huang et al., 2019). Sulfation
251 involves the addition of sulfate groups by substituting hydroxyl groups in the polysaccharide.
252 Various methods can be employed, but they generally follow a similar methodology (Kaur et
253 al., 2020; Y. Liu et al., 2014; Ray et al., 2013; Zhang et al., 2017): (I) dissolution of glucans in
254 formamide or dimethyl formamide; (II) addition of a sulfation agent, such as sulfuric acid,
255 sulfur trioxide-dimethylacetamide, or chlorosulfonic acid; (III) reaction of the polysaccharide

with the sulfation agent, leading to the addition of sulfate groups into the polymer chain. The degree of substitution (DS) is a critical parameter used to evaluate the efficiency of these functionalization processes. It represents the average amount of functional groups inserted into the molecule.

Various DS values have been reported for carboxymethylated BG extracts obtained from different sources. For example, fungal exocellular Lasiodiplodan (*Lasiodiplodia theobromae*) showed a DS range of 0.32-0.68 (Theis et al., 2019) and Qingke barley (*Hordeum vulgare* L.) exhibited a range of 0.32-0.88 (Guo et al., 2020). BG extracted from yeast (*S. cerevisiae*) also showed varying DS values depending on the method specifications, such as 0.43 (Machová et al., 2014) or 0.80-1.03 (Ma et al., 2022). Many of these studies have indicated a potential correlation between a higher degree of substitution and improved biological activity, including enhanced antioxidant capacity, which can be further potentiated by reducing the molecular weight of BG (Ma et al., 2022).

Sulfated BG can also be obtained with high DS values, with variations depending on the modification methods and the sources of extraction. Examples include oat (*Avena sativa* L.) with a DS of 0.68 (Yun et al., 2006), Qingke barley with a range of 0.25-0.58 (Guo et al., 2019), and mushroom sclerotia (*Pleurotus tuber-regium*) with a range of 1.14-1.74 (Zhang et al., 2003). For yeast-derived BG (*S. cerevisiae*), different studies have reported DS values such as 0.16-0.27 (Lei et al., 2015), 0.75 (Zhang et al., 2017), 0.16 (Wang et al., 2016, 2019). While a definitive relationship between the DS value and the biological activity of sulfated BG cannot be confirmed due to discordance in the results reported by various authors, there has been an observed relationship between lower molecular weight of BG and higher biological activity, independent of the DS value (Lei et al., 2015).

Other chemical methods, such as phosphorylation, acetylation, and amination, can also be employed to modify BG. These methods function similarly to carboxymethylation and sulfation by introducing functional groups into the polysaccharide chain. For fungal phosphorylated BG, two studies reported DS values of 0.06-0.15 for a *Poria cocos* extract (Chen et al., 2009) and 0.77-2.09 for a *S. cerevisiae* extract by Shi et al. (2014). Acetylated BG showed DS values of 0.03-0.12 for oat BG (Souza et al., 2015). BG was obtained by Shin et al. (2005) from oat with a DS value of 0.48, and more recently, *S. cerevisiae* BG was successfully modified with DS values of 0.55-1.15 (Qiu et al., 2022).

As observed, various methods can be utilized to chemically modify BG from different sources, leading to improved solubility and enhanced biological activity. The choice of method depends on the complexity of the functionalization process. Among all the methods, carboxymethylation appears to be the most commonly used due to its simplicity, requirement of fewer reagents, and lower overall cost of the resulting modified molecule.

3 - Biological properties for skin application

Native BG has been found to exhibit bioactive properties naturally, but the addition of functional groups can significantly enhance BG solubility and improve bioactive properties (Divya et al., 2020; Calegari et al., 2017). Therefore, some biological active properties, reported for both native and chemically modified BG, with potential use in skin care products, are summarized in Table 2.

Table 2 – Skin-applicable properties of various modified and non-modified β-Glucans and their sources.

Source		Chemical modification	Properties	Reference
Bacteria	*Alcaligenes faecalis* (Curdlan)	Native	Wound healing	(Berg et al., 2014)
Fungi	*Agrocybe chaxingu*	Native	Anti-inflammatory	(Lee et al., 2009)
	Amanita muscaria	Native	Anti-cancer	(Zavadinack et al., 2021).
	Lasiodiplodia theobromae (Lasioplodan)	Native	Antioxidant	(Kagimura et al., 2015; Theis et al., 2017, 2019)
		Carboxymethylation		
		Sulfation	Antioxidant	(Calegari et al., 2017)
		Native		
	Schizophyllum commune	Native	Wound healing	(Seo et al., 2019)
	Cordyceps militaris	Native	Anti-inflammatory	(Smiderle et al., 2014)

	Saccharomyces cerevisiae	Sulfation	Antioxidant	(Lei et al., 2015; Zhang et al., 2017)
		Carboxymethylation	Antioxidant	(Ma et al., 2022; Machová et al., 2014)
			UV Protection	(Zülli et al., 1998)
		Native	Wound healing	(Medeiros et al., 2012)
			Antioxidant	(Khan et al., 2016)
	Schizophyllum commune	Native	Wound healing	(Seo et al., 2019)
			Anti-inflammatory	(Cao et al., 2021)
	Aureobasidum pullans	Native	Anti-inflammatory	(Choi et al., 2016)
Algae	*Euglena gracilis* (Paramylon)	Native	Anti-inflammatory Wound healing	(Yasuda et al., 2018)
	Laminaria digitate (Laminarin)	Native	Anti-inflammatory Antioxidant	(Ozanne et al., 2020)
Cereals	Barley	Sulfation	Antioxidant	(Guo et al., 2019)
		Native	Wound healing	(Fusté et al., 2019)
	Oat	Native	Anti-wrinkle	(Pillai et al., 2005)
			Anti-cancer	(Choromanska et al., 2015; Parzonko et al., 2015)
	Eleusine coracana	Native	Antioxidant	(Divya et al., 2020)

3.1 - Antioxidant

The use of ingredients with antioxidant capacity in skincare products is important for reducing skin damage caused by oxidative stress. Reactive oxygen species can be produced directly and indirectly in our body. Various mechanisms can generate radical species such as superoxide by the electron transport chain in the mitochondria or hydrogen peroxide by peroxisomes in the endoplasmic reticulum (Rinnerthaler et al., 2015). The human body can protect itself by enzymatic and non-enzymatic mechanisms against ROS generated by endogenous factors (e.g., genetics) and exogenous sources (e.g., environment). However, the inclusion of topical antioxidants like vitamin C and E in skincare products can provide additional protection against these free radicals. Nevertheless, there are certain drawbacks associated with these antioxidants, such as molecular instability. This has opened up new possibilities for utilizing

polysaccharides for this purpose (Chen et al., 2012; Krutmann et al., 2021; Ngoc et al., 2023). Polysaccharides are known to possess antioxidant activity, although their efficacy is influenced by factors like molecular structure and chemical characteristics, including solubility and the presence of negatively and positively charged groups (Fernandes & Coimbra, 2023).

The antioxidant potential of BG extract obtained from a native Brazilian mushroom (*Geastrum saccatum*) was evaluated, and it was observed that this extract highly inhibited superoxide radicals and was efficient against hydroxyl radicals and lipid peroxidation in a dose-dependent manner (Dore et al., 2007). The antioxidant capacity was also analyzed for BG extracted from three mushroom species (*Agaricus bisporus*, *Coprinus atramentarius*, and *P. ostreatus*). According to the results obtained, *C. atramentarius* demonstrated the best antioxidant capacity against ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) and DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals, as well as reducing power and chelating ability. On the other hand, BG from *P. ostreatus* demonstrated the best lipid peroxidation inhibition (Khan et al., 2017). Laminarin, a β-(1→3)-D-glucan obtained from the seaweed *Laminaria digitate*, was reported as a great protector against ROS formation in HDFa cells and normal human epidermal keratinocyte cells (NHEK) upon exposure to hydrogen peroxide and UV-A radiation (Ozanne et al., 2020).

Antioxidative properties were also reported for γ-irradiated (5 to 50 kGγ) BG extracted from *S. cerevisiae*. According to the authors, irradiated BG demonstrated scavenging capacity against ABTS, DPPH, and hydroxyl radicals, as well as lipid peroxidation inhibition and ferrous-ion chelating properties. The authors pointed out that this antioxidant capacity increased with the amount of radiation used (Khan et al., 2016). BG from barley (*Hordeum vulgare*), when γ-irradiated (2, 4, and 8 kGγ), also demonstrated increased antioxidant capacity (Shah et al., 2015).

Lasioplodan is a β-(1→6)-D-glucan obtained from the fungi *Lasiodiplodia theobromae*, which has been shown to be an interesting choice for developing antioxidant compounds through chemical modification. By adding carboxymethyl groups to the molecular structure of lasiodiplodan, its capacity to scavenge hydroxyl radicals was improved compared to its native form. The authors observed a positive correlation between the increase of the DS value of the derivatives and this scavenging capacity, although the native BG performed better for hydrogen peroxide scavenging and reducing power (Theis et al., 2019). These improvements were

corroborated by the results obtained for carboxymethylated lasiodiplodan through the evaluation of ABTS and DPPH scavenging capacity and ferric reducing ability of plasma (FRAPS) (Kagimura et al., 2015). According to the results obtained, the modified derivative obtained great results for the FRAPS assay when compared with the native form, although its scavenging capacity for the other assays was relatively similar.

In a study by Ma et al. (2022), the antioxidant capacity of carboxymethylated *S. cerevisiae* BG with three different molecular weights was investigated against hydroxyl radical and ABTS radical. The results indicated that the molecular weight had a notable impact on the antioxidant capacity. The fraction with the lowest molecular weight demonstrated the highest activity, and higher concentrations of BG (1-10 mg/mL) exhibited increased antioxidant activity. For instance, at a concentration of 1 mg/mL, the smallest molecule showed a scavenging percentage of 91% against the hydroxyl radical and 45% against the ABTS radical, whereas the largest fraction exhibited values of 7% and 8% for the same assays and concentration. Another study demonstrated that sulfation, as a way to modify lasiodiplodan, increased the overall antioxidant properties and reducing power when compared to its native form, by scavenging hydroxyl radicals in 74% and 44% and peroxide hydrogen radicals in 5% and 0%, at a concentration of around 0.9 mg/mL for the sulfated BG and the native BG, respectively (Calegari et al., 2017). Using the same modification method, hulless barley BG had its antioxidant capacity improved against DPPH and nitric oxide radicals and reducing power when compared with the native form, with this activity increasing with the DS value of the sulfated BG (Guo et al., 2019). Sulfated BG from *S. cerevisiae* also demonstrated strong antioxidant activity against DPPH, superoxide and hydroxyl radicals. Although the authors reported an inverse correlation between the DS value/molecular weight and antioxidant ability (Lei et al., 2015). Although no studies were done evaluating antioxidant activity by a direct topical application of BG, it was observed that sulfated BG from *S. cerevisiae* increased the activity of catalase and superoxide dismutase, enzymes responsible for the defence against free radicals and reactive species in the human body (Limón-Pacheco & Gonsebatt, 2009), when administered intragastrically to mice (Lei et al., 2015; Zhang et al., 2017).

In general, BG obtained from different sources demonstrate great *in vitro* antioxidant capacity, and in some cases, this capacity can be improved by chemical modification. Further in vivo studies should be done to understand the topical applicability of BG as an antioxidant ingredient for the skin in clinical trials.

3.2 - Immunomodulation

Inflammation is a complex biological response that involves both the innate and adaptive immune systems in response to stimuli such as infection or injury. Generally, an inflammatory process begins with the recognition of the stimulus, followed by the activation of inflammatory pathways, the release of inflammatory mediators, and immune cell proliferation. Numerous molecules are involved in the inflammation process, such as transcription factors (e.g., nuclear factor-κB), enzymes (e.g., cyclooxygenase-2), pro-inflammatory cytokines (such as interleukin IL-1β/6/8 and tumor necrosis factor [TNF]), anti-inflammatory cytokines (such as IL-10/11 and transforming growth factor [TFG]), and reactive oxygen species (ROS) (Chen et al., 2018). Typically, a compound demonstrates anti-inflammatory properties by suppressing pro-inflammatory cytokines, enzymes, and inflammation-related proteins (Xu et al., 2019). Immunomodulators such as BG are compounds capable of stimulating or suppressing the natural response of the immune system, such as inflammation, by modulating adaptive or innate immunity (Byrne et al., 2020).

BG is recognized by the innate immune system through pattern recognition receptors (PRRs) due to its conserved structures named pathogen-associated molecular patterns (PAMPs), which are naturally present in microorganisms. This causes a response from the innate system by interacting with BG and activating macrophages (Vetvicka et al., 2019). Macrophages, an important and ubiquitous type of cells in the innate immune system, when activated, exert their phagocytic activity, release cytokines (e.g., IL-1β), generate ROS and nitric oxide (NO) (Schepetkin & Quinn, 2006). BG can bind to dectin-1, toll-like receptors (TLRs), complement receptors-3 (CR-3), lactosylceramide, and scavenger receptors present in various immune cells, such as macrophages or dendritic cells, triggering a response from the immune system (Chan et al., 2009; Kim et al., 2011). In topical applications, BG can bind to the receptors present in the skin resident cells, promoting an inflammatory response by immune cells, cytokine production by macrophages, and cell proliferation by non-immune cells such as keratinocytes and fibroblasts for skin repair (Majtan & Jesenak, 2018).

According to the literature, BG obtained from the mushroom *Agrocybe chaxingu* led to a reduction in the production of NO and the expression of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) *in vitro* in murine macrophages stimulated with lipopolysaccharide

(LPS) (Lee et al., 2009). The same pattern in NO production was observed, with reduced NO levels as BG concentration increased, for BG obtained from black yeast (*Aureobasidum pullans*) when exposing macrophages to the same inflammatory stimulus (Choi et al., 2016). It was also found that BG extracted from mushroom (*Cordyceps militaris*) could reduce the impact of LPS on the expression of IL-1β, TNF-α, and COX-2 in macrophage cells (Smiderle et al., 2014). Laminarin, a BG obtained from seaweed, demonstrated the capacity to reduce the production of IL-6 by 27% and 54% in human dermal fibroblast cells (HDFa) and normal human epidermal keratinocytes, respectively, when exposed to LPS (Ozanne et al., 2020).

In an *in vivo* assay, BG was applied one hour after the application of 12-O-tetradeca-noylphorbol 13-acetate (TPA) on the mice ear for two days, which caused a reduction in monocyte infiltration and ear weight and thickness compared to untreated mice with TPA-induced inflammation (Lee et al., 2009). To evaluate the potential use of BG for treating skin wounds in mice, dressing films containing BG were analyzed for their impact on the release of inflammatory cytokines, such as interferon gamma (IFN-γ), IL-6, and vascular endothelial growth factor (VEGF) in the mouse serum at 3 and 5 days after wounding. The results showed that BG maintained a modest cytokine production initially but tended to reduce and normalize in the following days, indicating their potential use for skin application (Yasuda et al., 2018). This may be due to the initial higher inflammatory response promoted by BG, as evidenced by the upregulation of pro-inflammatory cytokines, followed by a reduction and stabilization of inflammatory cytokine production (Russo et al., 2017).

3.2.1 - BG as therapy in skin cancer

Tumors are characterized as a mass of malignant transformed cells that communicate and induce recruitment of other cells, distorting their behavior (Balkwill et al., 2012). This extensive network of intracellular communications, such as cytokine release, occurs among various immune cells, both malignant and non-malignant, and is known as the tumor microenvironment (TME) (Arneth, 2019). In the skin, cancer is typically divided into two broad categories: melanoma and non-melanoma cancer (Khan et al., 2022). Melanoma is associated with mutations in melanocytes, while non-melanoma cancer involves other types of cancer, such as squamous cell and basal cell carcinomas (Dhanyamraju & Patel, 2022; Woo et al., 2022). The main reason for using BG for this type of disease is their capacity to modulate

the immune system, as previously detailed, and interact with various immune cells, altering their behavior. In addition to immunomodulation, BG can also be utilized to transport specific molecules or anti-tumor drugs, such as single-stranded DNA (ssDNA) or doxorubicin, to target tumors (Geller et al., 2019).

Nine different glucans, including curdlan, zymosan, and yeast BG, were also analyzed for their anti-tumor capacity. The authors demonstrated that these BG were able to modulate tumor-associated macrophages (TAMs), immune suppressive cells, into a more pro-inflammatory phenotype (M1). They observed an increase in chemoattractant production, such as CCL3, by TAMs and TAMs derived from melanoma, which may help in understanding the role of BG in anti-tumor therapies (Graaff et al., 2021). Additionally, the ability of BG to polarize macrophages into an M1-like phenotype is significant, as M1 macrophages are associated with a more favorable prognosis in cancer patients and may result in tumor regression (Zhou et al., 2020).

Low molecular weight oat BG has also demonstrated in vitro anticancer properties by reducing the viability of human melanoma and human epidermoid carcinoma cells. It induces high levels of caspase-12 expression, leading to cell death due to oxidative stress in both cell types (Choromanska et al., 2015). Another study tested human melanoma cells to analyze the potential pro-apoptotic effects of *Avena sativa* BG. According to the authors' observations, these oat glucans induced cell cytotoxicity and demonstrated anti-proliferative and pro-apoptotic capacities (Parzonko et al., 2015).

BG obtained from the mushroom *Amanita muscaria* were reported to selectively reduce the proliferation of murine melanoma cells but not fibroblasts (normal cells around the tumor). They also exhibited the ability to inhibit colony formation when cells were pre-treated with or in the presence of the BG extract (Zavadinack et al., 2021).

A nanocomplex of carboxymethylated BG from the mushroom P. tube-regium and iron oxide nanoparticles (IONPs) was also reported to have a combined effect of stimulating the polarization of pro-inflammatory M1 macrophages, increasing cancer cell apoptosis, and suppressing melanoma growth. This study observed the capacity of BG to stimulate the immune system and serve as a vehicle for IONPs (Su et al., 2022, 2023). Another study investigated the potential tumor treatment using water-soluble BG (*Aureobasidium pullulan*) combined with a blocker of programmed death-ligand 1 (PD-L1), evaluating the synergistic

effect of both compounds against melanoma (Hu et al., 2023). According to their findings, BG induced the production of cytokines, such as IL-6, by converting the phenotype of peritoneal exudate macrophages (CD11b+ cells). However, BG also enhanced the expression of programmed cell death protein 1 (PD-1) and PD-L1, two immune checkpoints known to negatively regulate the immune response (Zou & Yaguchi, 2023). To overcome this issue, the authors combined BG with a PD-L1 blocker for use in a mouse melanoma model. They observed that the anti-tumor capacity of BG was improved by initially changing the phenotype of CD11b+ cells to a pro-inflammatory state, blocking PD-1/PD-L1, and boosting T-cell function to inhibit tumor growth and metastasis.

Considering these studies, BG can potentially be used for melanoma skin cancer therapy as an active molecule or as a vehicle to transport specific anti-cancer drugs into tumors. However, it is important to consider and evaluate the different types of BG for both uses since their interactions with the immune system can vary based on their chemical characteristics. For example, soluble and insoluble BG from the same yeast may exhibit different interactions in cancer therapy (Qi et al., 2011).

3.3 - Wound healing and tissue repair

3.3.1 - Wound healing capacity

Wound healing is a regenerative process that occurs through four main events: coagulation, inflammation, proliferation, and remodelling. These events are accompanied by the release of a cascade of numerous signalling molecules, such as cytokines, chemokines, and growth factors, to promote tissue regeneration (Larouche et al., 2018).

In a study analyzing the effects of four BG obtained from different sources (black yeast, barley, *Schyzophilum commune*, and *Euglena gracilis*) on immortalized human keratinocytes (HaCaT) and HDFa, it was found that there was no cytotoxicity in these cells and an increase in HaCaT migration was observed when exposed to all the BG studied at a concentration of 20 µg/mL. It was concluded that BG obtained from *S. commune* presented the best results, including promoting of cell migration and dermal contraction and in vivo properties, such as re-epithelialization capacity, wound closure, and scab loss observed in mice skin wounds (Seo et al., 2019). Similar results were obtained for *in vivo* studies, after monitoring a mouse wound

for two weeks treated with aqueous BG (Barley origin) solution. A notable wound healing ability was observed after topical application of the BG solution, which may be related to the promotion of human fibroblast cell migration (Fusté et al., 2019). Another study evaluated if dectin-1 activation would induce cellular proliferation and migration. The authors observed that human keratinocytes had their proliferation, migration, and wound closure increased by Curdlan BG (*Alcaligenes faecalis*) exposure, *in vitro* and *ex vivo* (Berg et al., 2014). Yeast BG can also be an interesting wound healing agent, as it showed a capacity to promote proliferation and increased the number of inflammatory cells recruited to ulcer area (Medeiros et al., 2012). The same study also observed that BG could reduce the wound area in over 60% of a patient with a non-healing wound for over 15 years, which reinforces the potential use of this molecule for wound healing. These results are consistent with the ones obtained from the analysis, through a clinical study, of the impact of soluble BG from yeast (*S. cerevisiae*) applied as a topical wound healing promoter in diabetic patients with foot ulcers. It was concluded that BG were safe and successfully promoted skin healing, probably due to the interaction with various immune cells (e.g., macrophages), and it may accelerate the closure of leg ulcers (Zykova et al., 2014).

3.3.2 - BG in wound dressings

The capacity of BG to be used as immune modulators and wound healing agents has boosted research on these molecules for medical and pharmaceutical applications. Several reports have shown promising results using BG incorporated into composite scaffolds, such as collagen or chitin, for tissue repair (Reddy et al., 2021). Hydrogels, in particular, are highly useful for treating wounds due to their versatility, biodegradability, biocompatibility, and compatibility with a wide range of bioactive molecules (Firlar et al., 2022). However, the application of hydrogels may be limited in wounds where greater adsorption or adhesion is required (Latiyan et al., 2023). In such cases, BG can also be applied in other types of wound dressings, such as sponges (Zhou et al., 2023).

As a biopolymer, BG can also serve as a structural element rather than an active molecule in hydrogels and film dressings for wounds. For example, BG can be linked with collagen to explore the potential antioxidant and antibacterial properties of tannic acid (Michalska-Sionkowska et al., 2021a) or combined with glycerol to analyze the capacity of nanostructured

zinc oxide as an antibacterial agent (Pino et al., 2023). Additionally, BG imparts physical properties to these hydrogels, improving material stability and rigidity (Choi et al., 2021; Michalska-Sionkowska et al., 2021b).

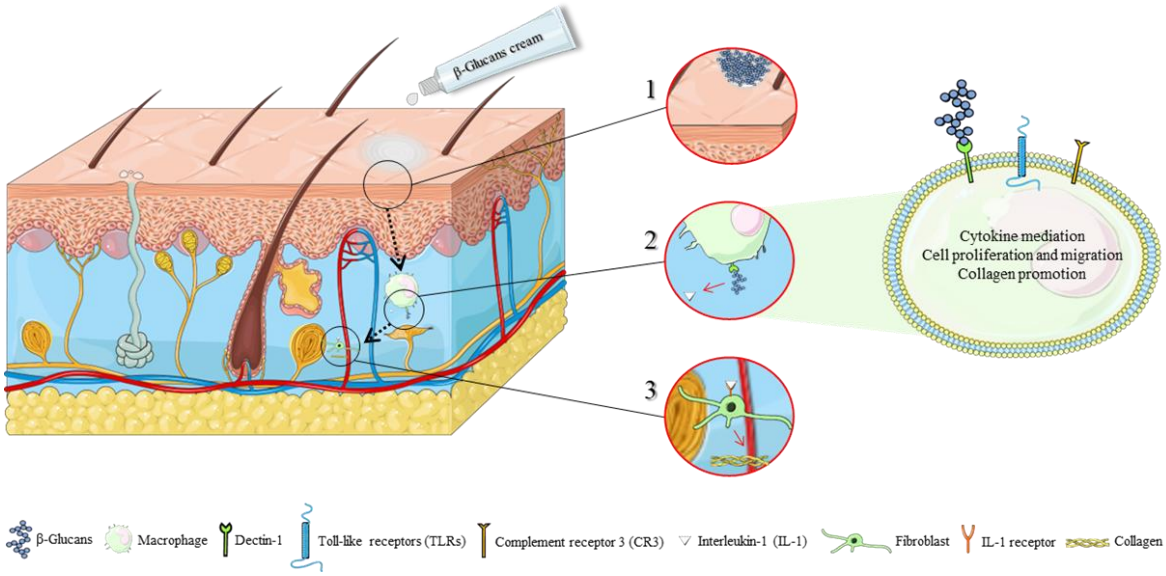
BG can also act as an active compound in hydrogels due to its biological potential. One study explored a sprayable hydrogel composed of yeast soluble BG, which demonstrated the capacity to promote wound closure in a diabetic mice model (Grip et al., 2021). Another study demonstrated the wound healing capacity of a BG hydrogel and its ability to inhibit scarring by modulating the production of skin extracellular matrix components such as collagen type-III and keratin-14/keratin-15 (Kang et al., 2022). A mixture of BG extracted from *Schizophyllum* spp. and polyvinyl alcohol (PVA) hydrogel was reported to promote human dermal fibroblast migration and wound closure in mice when treated for two weeks. It also exhibited a significant anti-scarring effect in the wound area (Muthuramalingam et al., 2019). Another hydrogel containing lasioplodan was found to be highly effective for wound application. This formulation demonstrated antioxidant capacity, promoted in vivo mice wound closure, initiated collagen type-III production, which later matured to collagen type-I, and stimulated keratinocyte proliferation (Nissola et al., 2021). Pullulans in gel form were studied for their wound healing capacity by applying them to excision wounds in mice. The results showed that the gel positively influenced all stages of the wound healing process, accelerating wound closure, promoting blood vessel formation, and stimulating collagen type-III biosynthesis (Thangavel et al., 2020).

In addition to hydrogels, BG films and sponges are also potential candidates for wound repair. Barley BG films were found to promote HaCaT cells growth, contributing to wound closure (Michele et al., 2023). The wound healing ability induced by BG extracted from *E. gracilis*, using a film dressing with paramylon, was also demonstrated. These films exhibited significant wound healing capacity by reducing the initial wound area in mice skin by half after 5 days (Yasuda et al., 2018). A sponge incorporated with carboxymethyl yeast BG was evaluated for wound healing. According to the authors, this sponge accelerated blood coagulation, controlled hemorrhage through *in vivo* mice wounds, and considerably improved wound repairing properties, such as *in vitro* cell migration, compared to native water-insoluble BG (Zhou et al., 2023).

The immunomodulatory capacity of BG plays a significant role in the process of wound healing, primarily through its interactions with skin and immune cells, thereby enhancing the cascade of events involved in skin regeneration. As discussed in a review by Majtan and Jesenak (2018), BG has a direct influence on keratinocytes, fibroblasts, and macrophages, leading to enhanced reepithelialization by stimulating cellular proliferation and migration through dectin-1 receptors. Additionally, the interaction between BG and fibroblasts stimulates collagen production, facilitating the restoration of the extracellular matrix and promoting wound closure and tissue repair (Pillai et al., 2005).

3.4 - Antiaging

Skin aging can be influenced by both intrinsic, natural aging processes that occur throughout life and extrinsic factors such as air pollution, smoking, or exposure to ultraviolet radiation. These factors contribute to the development of wrinkles, primarily caused by a thinner epidermis and the breakdown of ECM components like elastin (Graf, 2005). Furthermore, they promote the generation of ROS and trigger inflammation processes (Zhang & Duan, 2018). To reduce the impact of these factors, the antioxidant and immunomodulatory capacity of BG, paired with its anti-aging properties such as UV protection (Zülli et al., 1998) or wrinkle reduction (Pillai et al., 2005), demonstrate the potential of this molecule for anti-aging purposes. A representation of how BG interrelate with our skin is explained in Figure 3.



582

583 **Figure 3 –** Overview of β-glucans cream impact upon skin application and potential cellular
584 mechanisms regarding its use as a skincare product (Cordier-Dirikoc et al., 2022; Majtan &
585 Jesenak, 2018; Pillai et al., 2005). (1) A topical formulation containing β-glucans could boost
586 skin permeation and allow the passage of this molecule through epidermis. (2) Once β-Glucans
587 reach the dermis, they are recognized by macrophages receptors (e.g., dectin-1) and initiate an
588 immune response, releasing interleukins (e.g., IL-1) and starting an inflammatory cascade. (3)
589 This immunomodulatory capacity could lead to activation of several other skin cells, such as
590 dermal fibroblasts inducing the production of ECM components (e.g., collagen deposition) or
591 epidermal keratinocytes prompting migration and proliferation in a wound closure scenario.
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594

595 The protective capacity of carboxymethylated BG obtained from *S. cerevisiae* against UV
596 radiation was analyzed *in vitro* and *in vivo*. According to the results obtained, pre-treatment
597 with the modified BG effectively protected human keratinocyte cells from UV-A radiation. For
598 the *in vivo* test, the authors observed a concentration-dependent reduction in squalene
599 hydroperoxides when using an oil-in-water emulsion with BG at 0.04% and 0.2%, after pre-
600 treating the volunteer's skin for 5 days before exposing it to the UV-A stimulus (Zülli et al.,
601 1998). Oat β-glucan has demonstrated potential anti-wrinkle capacity by reducing wrinkle
602 height and depth, as well as skin roughness, in 27 subjects over 8 weeks (Pillai et al., 2005).
603 Additionally, the same study concluded that β-glucan could penetrate deeply into the skin

604 layers, explaining its ability to reach the dermis and epidermis and interact with skin cells in
605 these layers, thereby reducing wrinkles and improving skin elasticity.

606 Zhu et al. (2023) evaluated the potential of a water-soluble BG produced by the bacteria
607 Agrobacterium sp. and Panthenol (pro-vitamin B5) spray formulation to alleviate itchy and
608 inflamed skin using an in vivo model. They induced chronic pruritus in mice with an acetone-
609 ether solution and observed several positive effects. The authors noted a reduction in
610 transepidermal water loss (TEWL), decreased inflammation indicated by lower levels of
611 cytokines such as IL-1β and TNF-α, and a decrease in scratching bouts, indicating relief from
612 itching sensation. This suggests that incorporating BG into a spray formulation with common
613 skin moisturizers can provide a feasible solution for skin itching and irritation. Corroborating
614 these findings, Cao et al. (2021) also found that a cream containing BG from *Schizophyllum*
615 *Commune* is effective in reducing TEWL and improving skin erythema in patients undergoing
616 fractional laser therapy, a procedure that naturally induces skin inflammation and irritation.

617 Potential to be used as a moisturizer is also a great property to maintain our skin healthy. Skin
618 outer layer can be affected the same factors causing aging (e.g. UV exposure) or low humidity,
619 which can impact normal enzymatic processes, causing flaky and dry skin (Rittié, 2016). The
620 first study evaluated the potential use of a chitin-glucan formulation and concluded that it
621 caused no harmful effects in volunteers with sensitive skin, and improved skin firmness,
622 tonicity, SC hydration, and roughness compared to the placebo (Gautier et al., 2008). In the
623 second study, a formulation containing a plant extract, plant oil, BG, and sodium hyaluronate
624 was effective in improving skin hydration and texture in subjects with sensitive skin (Wang et
625 al., 2018).

626 Overall, several BG from different sources, extracted by diverse methodologies and with
627 unequal chemical properties, water-soluble, water-insoluble, or chemically modified, have
628 demonstrated throughout the years a very interesting potential to be used in skin (Figure 4).

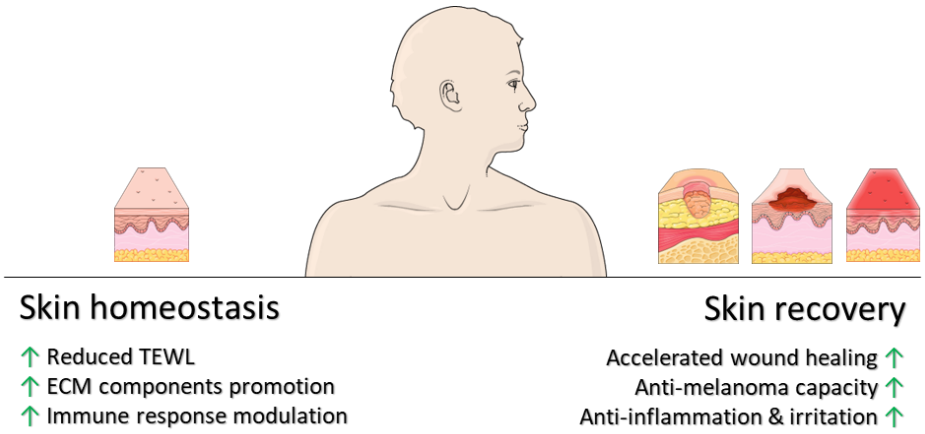

Figure 4 – Beneficial properties of BG molecules in maintaining skin homeostasis, such as preventing TEWL or by applying it in skin disorders, such as wounds, melanoma, and inflammation. This figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

BG not only significantly contributes to skin homeostasis by forming a protective layer that reduces water loss and promotes collagen deposition but also has potential applications as a natural compound to accelerate wound closure and in tumor therapies. Its strong immunomodulatory capacity and easy recognition by various cellular receptors expressed in skin and immune cells make it highly versatile. Consequently, the broad applicability of BG positions this polysaccharide as a valuable ingredient skincare, biomedical or cosmetic industry.

4 - β-Glucans as an ingredient for skincare

Due to increasing consumers' interest in how skin products impact their health, their choice is changing towards the use of these products with natural bioactive ingredients, which have a beneficial effect when compared with synthesized ones (Ahsan, 2019b; Bilal & Iqbal, 2019). Additionally, was observed a preference for "green" products obtained from natural sources without preservatives (Rizzi et al., 2021). Interestingly, yeast and oat BG seem to be heavily used in skin products, as shown in Table 3, with a broad diversity of biological properties described.

652 **Table 3** – Examples of commercial BG used for skincare products as a multipurpose bioactive
653 ingredient.

Product name	BG source	Manufacturer	Described properties available in their website	Reference
PromOat Oat BG	Oat	Lantmännen Oats	• Thickener and emulsion stabilizer	(Lantmännen Oats, 2023)
SWEOAT Flours	Oat	Swedish Oat Fiber	• Skin protectant and moisturizer • Repairing, rejuvenating and anti-aging capacity • Anti-inflammatory, anti-itchy and soothing properties • Skin pH stabilizer	(Swedish Oat Fiber, 2023)
SymGlucan	Oat	Symrise	• Cellular renewal (*in vitro*) • Moisture, firmness and elasticity enhancer (*in vivo*) • Fades wrinkles, skin smoother and improve skin recovery (*in vivo*)	(Symrise, 2023)
IMoist BG	Oat	Bioalkemia	• Anti-aging, anti-irritant and non-greasy • Wrinkles improvement and accelerate wound healing • Attenuate sunburns and protects against UV light redness • Skin moisturizer	(Bioalkemia, 2023)
Yeast essence glucare C90	Yeast	Angel Yeast	• Enhances natural skin self-protective capacity • Improves skin recovery and wound healing • Restores skin moisture barrier • Repair damage induced by sun light • Anti-aging and anti-radiation	(Angel Yeast, 2023)
Herbex Yeast BG	Yeast	Biospectrum	• Immune cells mobilization • Phagocytic capacity of immune cells to destroy pathogens	(Biospectrum, 2023)

			• UV protection and sunburn recovery	
CM-Glucan forte	Yeast	Mibelle AG Biochemistry	• Reduces the release/expression of inflammatory cytokines • Inhibits the adhesion of *S. aureus* to skin • Reinforce the skin barrier • Alleviate 6 symptoms of skin eczema	(Mibelle Biochemistry, 2023a)
CM-Glucan granulate			• Soothes capacity • Protection against skin dehydration after stress • Accelerates skin regeneration • Protects against UV damage, preventing loss of firmness and skin lipids degradation • Reduces wrinkle depth	(Mibelle Biochemistry, 2023b)

654

655

656 Considering consumers opinion in cosmetic products, BG seems to be a perfect candidate for
657 this purpose, since it is a molecule possible to be extracted from a wide variety of natural
658 sources with exploitable bioactive properties for skincare. In some cases, by-products from
659 already stablished industrial processes, such as spent yeast generated in beer production, can
660 be used as sustainable source. As Thomas et al. (2022) emphasize, industrial waste should be
661 the main choice for the extraction of these type of bioactive compounds, prioritizing
662 sustainability, and a circular economy, protecting the environment. Therefore, spent yeast
663 seems to be the obvious choice to extract BG, since its produced in relatively large quantities,
664 can be obtained in a pure form, creating value in a by-product that is mostly discarded (Caruso
665 et al., 2022).

666 As mentioned previously, BG can be obtained from a wide variety of sources, in some
667 instances, subjected to carboxymethylation to enhance solubility and modify specific bioactive
668 properties, as discussed earlier. Due to the diverse sources from which BG can be obtained,
669 including by-products like spent yeast, the extraction of this polysaccharide can remain
670 relatively cost-effective and may be optimized to reduce expenses and increase purity.

671 However, it is important to note that the extraction methods for BG cannot be universally
672 applied to all sources, which poses challenges in reproducing large-scale extractions of this
673 compound when multiple sources are utilized (Zhu et al., 2016). This diversity of extraction
674 methods also complicates the comparison of the chemical structure of BG in its native and
675 functionalized forms, as well as its potential for skin care applications across the numerous
676 available studies. To mitigate this heterogeneity, it would be beneficial to employ more
677 standardized extraction methods specific to each source, resulting in less variability in the
678 obtained results. Further research is required to comprehensively understand the true impact of
679 BG on more complex systems, such as 3D cell models or ex vivo skin models, and how BG
680 interacts with different layers of the skin to maintain or enhance skin health. Additionally, there
681 is a paucity of information regarding the utilization of BG for skin diseases like atopic
682 dermatitis or psoriasis and how it can positively modulate the inflammatory response in such
683 cases. These areas warrant additional investigation to fully explore the potential benefits of BG
684 in managing and treating various skin conditions.

685

686

4 - Conclusion

The development of new products enriched with novel ingredients that promote skin health may represent a significant step forward for the skincare or biomedical industry. β-Glucans, due to their biological properties (e.g., wound healing) and immunological relevance related to skincare, have great potential to be used in such products. This polysaccharide can be obtained from a wide range of natural products (e.g., cereals) or by-products (e.g., brewer's spent yeast), and in some cases, it can be chemically modified to adjust or improve its innate characteristics and biological capacity. Already, some products containing BG as a natural, bioactive, and innovative ingredient are commercially available in a growing market. However, practical formulations and *in vivo* studies must be conducted to ensure that their *in vitro* properties are transposable and comparable with what would occur in human skin without losing their biological capacity. Nonetheless, BG are a promising skin health enhancer with a strong scientific background supporting their potential use in the skin related industries.

Author contributions:

Pedro Sousa: Conceptualization, Writing - Original Draft and Writing - Review & Editing. Diana Tavares-Valente: Conceptualization, Writing - Original Draft, Writing - Review & Editing and Supervision. Manuela Amorim: Conceptualization, Writing - Original Draft, Writing - Review & Editing and Supervision. João Azevedo-Silva: Writing - Review & Editing. Manuela Pintado: Project administration and Funding acquisition. João Fernandes: Writing - Review & Editing and Supervision.

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Conflicts of Interest:

All the authors declare no conflicts of interest.

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