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Emerging Sources of Glycosaminoglycans: Can Fungi Be the New Alternative?

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Abstract

Glycosaminoglycans (GAGs) are polysaccharides that are widely studied for their medicinal properties, such as anticoagulant, antitumor, and immunomodulatory effects, as well as for their use in cosmetic products. Although GAGs have traditionally been sourced from animals such as cattle, pigs, sheep, and marine organisms, evidence suggests that certain fungi can also produce GAGs or GAG-like compounds, thereby expanding the potential resource base. Given the high market value of GAGs and their broad industrial applications, the limited supply from current sources is insufficient to meet global demand, particularly for non-animal, vegetarian, or vegan products. This review provides a comprehensive overview of the occurrence, structural diversity, and health benefits of both animal- and fungal-derived GAGs. It also discusses their potential uses in medicine, nutraceuticals, and biotechnology, and outlines current market trends, future opportunities, and gaps in existing research. By highlighting the role of fungi as renewable and versatile GAG producers, this work offers a new perspective on sustainable alternatives to traditional animal-based production systems.

Keywords – Bioactive compounds – Fungal glycosaminoglycans – Medicinal mushrooms – Polysaccharides

Introduction

Glycosaminoglycans (GAGs) are negatively charged polysaccharides (Afratis et al. 2012). They belong to a class of complex, polydisperse, highly sulfated linear polysaccharides made up of repeating disaccharide units of hexuronic acid and hexosamine (Pérez et al. 2020, Yang et al. 2024). The functions and bioactivities of GAGs are well studied. Their capacity to bind and modulate enzymatic activity or to initiate protein–protein interactions has made them significant in determining cellular responsiveness during development, homeostasis, and disease (Shi et al. 2021). There are two types of GAGs: sulfated and non-sulfated types. Sulfated GAGs include chondroitin sulfate, dermatan sulfate, heparin, heparan sulfate, and keratan sulfate (Prydz 2015, Casale & Crane 2019). Hyaluronic acid or hyaluronan is the only reported non-sulfated natural glycosaminoglycan (Srimasorn et al. 2022).

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GAGs are present across different groups of organisms, including invertebrates, vertebrates, and marine sources (Sahu et al. 2023, Hou et al. 2025). They are present in all mammalian tissues, with various functions (Sahu et al. 2023). They are critical structures of the extracellular matrix at cell surfaces and inside cells, where they have been found in animals' nuclei and are important participants in many aspects of biological processes (Esfandiari & Loewen 2019, Anderegg et al. 2021).

Research on GAGs has advanced significantly over the past few decades, and these macromolecules are now recognized as key components of vital biological processes that regulate cell characteristics, tissue growth and remodeling, homeostasis, and the progression of various diseases (Perez et al. 2023). GAGs have demonstrated a range of bioactivities, including anticoagulant, anti-inflammatory, antioxidant, cell proliferative, immunomodulatory, neuroprotective, and wound-healing effects (Gao et al. 2022, Yang et al. 2024). GAGs have garnered significant interest due to their broad applications in cosmetics, healthcare, and the clinical management of arthritis and cancer (Liu et al. 2023, Sun et al. 2024).

Fungi, especially mushrooms, have a long history of use in traditional medicine, especially in East Asia, where their medicinal qualities are highly valued (Szychowski et al. 2021, Ray et al. 2024). Recent studies on mushrooms have revealed that the secondary metabolites from various species exhibit strong biological activities (Ślusarczyk et al. 2021, Karunarathna et al. 2025). As the search for sustainable sources of bioactive compounds intensifies, mushrooms and other microfungi stand out not only for their ecological roles (Branco et al. 2022, Niego et al. 2023a) but also for their potential to contribute significantly to the pharmaceutical, nutraceutical (functional food and dietary supplements) (Niego et al. 2023b, Bumbu et al. 2024), and cosmetic industries (Hyde et al. 2019, Badalyan et al. 2022, Dewanjee et al. 2024). Increasing attention is being given to these naturally derived active compounds as potential alternatives to synthetic drugs (Bhambri et al. 2022, Niego et al. 2023b). More recently, mushrooms have been investigated as possible ingredients in cosmetics (Li et al. 2019a, Sangthong et al. 2022) and as cosmeceuticals (Bandara et al. 2015, Badalyan et al. 2022). A variety of macrofungi and their constituents have been shown to have positive effects on skin and hair (Wu et al. 2016, Dewanjee et al. 2024).

Due to the important biological functions of GAGs, their production methods are crucial. Traditionally, GAGs are extracted from animal tissues, but this approach has drawbacks, including contamination, endotoxins, and the risk of viral or prion infections. To overcome these issues, researchers are exploring alternative methods, such as chemical and chemoenzymatic syntheses, and bioengineering using microorganisms, such as yeasts and bacteria, to establish biosynthetic pathways for GAG production (Jin et al. 2021a). Although GAGs are predominantly studied from animal sources, some fungal species have been identified as promising alternative sources of these important compounds (Choocheep & Nathip 2018, Krishnan et al. 2025, Liu et al. 2025). This study pioneers a comparative approach to understanding GAGs derived from animals and fungi, highlighting fungi as novel and sustainable sources, citing recent research findings and discussing their implications for health and medicine. It provides an in-depth examination of fungi as sources of GAGs, exploring their potential uses in medicine, cosmetics, and biotechnology, while highlighting market trends, future prospects, and existing research gaps.

Classification, structure, and biological functions of GAGs

Chondroitin sulfate

Chondroitin sulfate (CS) is a type of sulfated glycosaminoglycan, a negatively-charged polysaccharide composed of D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc) linked together through an alternating β-1,3 and β-1,4 glycosidic bond (Fig. 1) (Chaplin 1981). CS is produced through the action of chondroitin sulfotransferases, which act on an unsulfated chondroitin or a dermatan polysaccharide precursor (He et al. 2017). Depending on the source, these repeating disaccharide units can differ in degree of sulfation. For instance, in terrestrial animal sources such as bovine, porcine, and chicken, CS is exclusively composed of non-sulfated

and monosulfated units, with sulfate groups found on either or both of the C-4 and C-6 of GalNAc units (Higashi et al. 2015, Valcarcel et al. 2017). The polysaccharide backbone of marine sources typically contains over-sulfated disaccharide units with additional sulfate groups on GlcA units at C-2, as in sharks and rays, or C-3, as in crabs, squid, and octopus (Higashi et al. 2015, Valcarcel et al. 2017), and sometimes at both C-2 and C-3 positions, like in shrimps (Vessella et al. 2021). Furthermore, CS chains in marine sources tend to be longer (e.g., 70 kDa CS from sharks) than in terrestrial sources (Valcarcel et al. 2017).

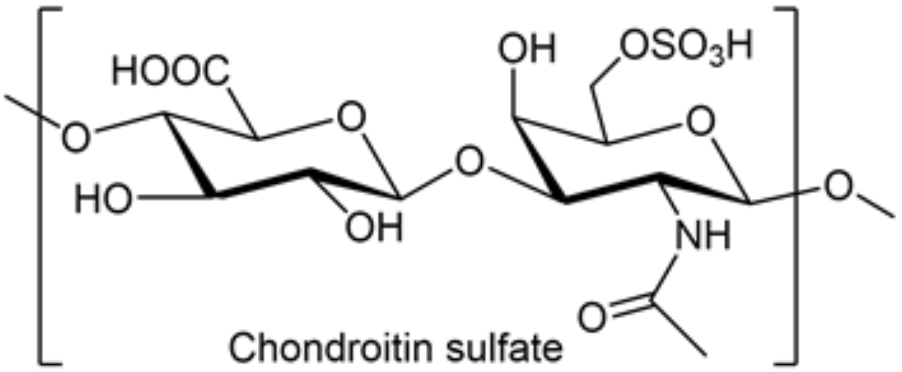

Fig. 1 – Chemical structure of chondroitin sulfate generated using ChemDraw.

Biological functions of chondroitin sulfate

Many free carboxyl and sulfate groups were present in the CS chain, allowing them to easily interact with positively charged substrates and metal ions to form complexes (Shen et al. 2023). When CS binds to calcium (Ca^{2+}) or magnesium (Mg^{2+}) ions, it has been shown to increase radical scavenging activity, also known as antioxidant activity (Ajisaka et al. 2016). These complexes, i.e., chondroitin sulfate calcium, chondroitin sulfate magnesium, and chondroitin sulfate strontium, can also stimulate the growth of chondrocytes or osteoblasts (Li et al. 2019b, Shen et al. 2021). Besides metal ions, other substances can interact with CS to form a conjugate that resembles an analogous complex and strengthens the original substrate's properties. For instance, CS is used as a reducing or stabilizing agent in the synthesis of gold nanoparticles and in the creation of the CS-capped gold nanoparticle system, which can be used to deliver insulin (Cho et al. 2014).

The interaction of CS with membrane receptors, such as the Cell Surface Glycoprotein Cluster Differentiation 44 (CD44), prevents hyaluronan (HA) binding. Consequently, this will inhibit the phosphorylation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase. There will also be a decrease in the nuclear translocation of NF-κB, which could prevent the expression of multiple genes that support inflammation (Muran et al. 2023, Shen et al. 2023). In combination with glucosamine sulfate, it increases type II collagen and proteoglycan synthesis, slowing the progression of deterioration in synovial joint cells (Henrotin et al. 2014). This mode of action could account for CS's effectiveness in conditions with significant inflammatory components. Additionally, it indicates that CS is a crucial dietary supplement recommended by the European League Against Rheumatism Committee for the treatment of osteoarthritis, with a suggested dosage of 1200 mg per day for pain relief (Shen et al. 2023). Other bioactivities of CS and its applications in clinical settings have yet to be tested in humans, as studies have been limited to cell cultures and animals (Shen et al. 2023).

Heparin

Heparin, also known as heparin sodium and heparin calcium, having Chemical Abstracts Service Registry Number (CAS) 9041-084 and CAS 37270-89-6, respectively, is a sulfated polysaccharide belonging to the class GAGs (Acquisto 2014, Casu et al. 2015). It is composed of mixed disaccharides such as hexosamine and uronic acid arranged in a linear sequence one disaccharide over the other (Fig. 2) (Casu et al. 2015, Banik et al. 2021).

Heparin comes with a hydrophilic parent chain, also with varying chain length of negatively-charged saccharides, by which the majority is composed of trisulfated disaccharide (TSD) – $IdoA2SO_3$–$GlcNSO_3$,$6SO_3$ – covering up to 90% from beef lung preparation and about 75% of heparin from porcine source (Casu et al. 2015, Zare et al. 2024). The remainder to 100% is composed of repeating –GlcA–GlcNAc–sequences. The composition suggests that heparin is microheterogeneous in structure to varying degrees (Casu 1985, Casu et al. 2015).

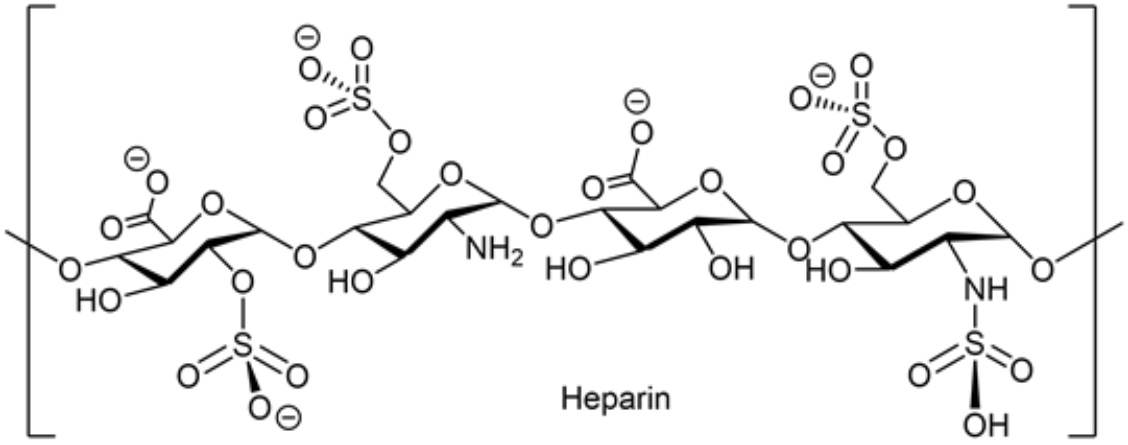

Fig. 2 – Chemical structures of heparin.

Biological functions of heparin

Heparin plays a significant biological role in relation to coagulation, inflammation, and angiogenesis in addition to its biological characteristics such as biocompatibility, biodegradability, and nontoxicity in endogenous substances (Paluck et al. 2016, Sun et al. 2018). The primary function of heparin is to regulate the coagulation cascade (Bhaskar et al. 2012). The anticoagulant action of heparin proceeds by combining with antithrombin III (AT III), a plasma enzyme that deactivates components of the coagulation cascade, via lysine residues to form a reversible complex. The formed complex primarily exposes the active arginine site of AT III, resulting in rapid fusion with activated proteinases such as thrombin (factor IIa), factor IXa, Xa, XIa, and XIIa. Consequently, the integration accelerates the anticoagulation factor (by approximately a thousand times), thereby preventing fibrin clot formation (Acquisto 2014, Zang et al. 2022).

Heparin, an anticoagulant, is a naturally occurring polyanionic polysaccharide. Its sulfated amide and ester compounds eject protons and drag balancing cations, producing heparin salt. As a result, the formation of new blood clots and the propagation of already formed clots are terminated under physiological conditions (Hansen et al. 2015, Baytas & Linhardt 2020, Zare et al. 2024). Furthermore, the anticoagulation activity of heparin occurs when the lysine in antithrombin binds to the pentasaccharide sequence of heparin, which induces an irreversible conformational change in antithrombin. This alteration at the arginine-reactive site enhances the binding affinity between thrombin and antithrombin several-fold. As a result, thrombin is inactivated, thereby effectively inhibiting fibrin formation (Nahain et al. 2018, Tang et al. 2021).

The heparin released from mast cells in response to inflammation supports the concept of heparin's anti-inflammatory activity (Casu 1985). Additionally, heparin can bind with chemokines to exert anti-inflammatory effects (Zang et al. 2022). Chemokines are bands of cytokines related to inflammation as well as angiogenesis promotion (Linhardt & Toida 2004). Furthermore, non-anticoagulant heparins were found to inhibit heparanase (Naggi et al. 2005, Casu et al. 2015). Heparanase is an enzyme that promotes the production of angiogenic growth factors, which support tumor development by degrading heparan sulfate into smaller oligosaccharides (Zhu et al. 2020). On the other hand, heparin can inhibit the action of the heparanase enzyme by using chemoenzymatically synthesized heparin oligosaccharides (Casu et al. 2015), which have been found to be effective antimetastatic and anticancer agents (Casu et al. 2015). Moreover, the

multiple processes underlying the anti-inflammatory and anti-tumor effects of heparin are not yet fully understood and require further elucidation (Oduah et al. 2016).

Heparan sulfate

Heparan sulfate (HS) is a highly acidic, linear polysaccharide characterized by substantial structural variability. It is an evolutionarily conserved subgroup of glycoproteins, and is closely related to, though less sulfated than heparin (Li & Kusche-Gullberg 2016, Ravikumar et al. 2020). HS is widely distributed—being present on the cell surface and within the extracellular matrix (Sarrazin et al. 2011, Davis & Parish 2013).

The structural diversity of HS results from tissue-specific and frequently incomplete enzymatic modifications of its precursor polymer, which is initially composed of alternating 1→4-linked N-acetyl-α-d-glucosamine (GlcNAc) and β-d-glucuronic acid (GlcA) residues (Fig. 3) (Staples et al. 2010, Zulueta et al. 2018).

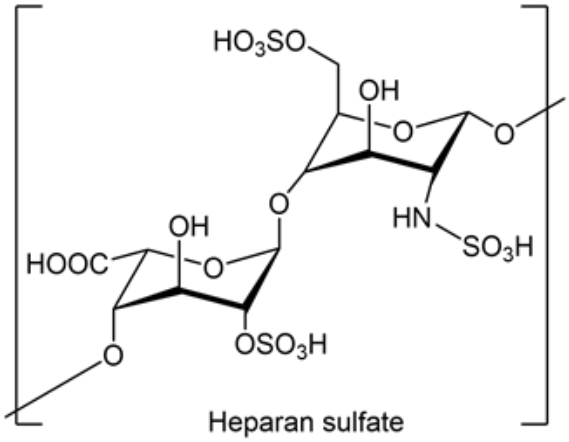

Fig. 3 – Chemical structures of heparan sulfate.

In its basic structure, each repeating disaccharide unit consists of a GlcA residue connected to a GlcNAc residue through a β1,4 glycosidic linkage. During post-polymerization processing, selected GlcA units are epimerized to iduronic acid (IdoA), a form that is especially prone to 2-O-sulfation. Additional sulfation can occur at the N, C6, and—less commonly—the C3 positions of the glucosamine residue (Shriver et al. 2011, Ravikumar et al. 2020).

Biological functions of heparan sulfate

The structural diversity of HS complexes is examined in relation to their biological activities (Xu et al. 2021, Matsuzaka & Yashiro 2024). The side chains of HS are the main functional factor, with a strong anionic chain, a structurally varied polysaccharide, and a regular overall pattern, classified into strongly, moderately, and faintly sulfated areas (Li & Kusche-Gullberg 2016, Matsuzaka & Yashiro 2024). In addition, the HS chain can interact with a vast range of ligands which significantly influence adhesion, proliferation, migration, and survival (Park 2018, Matsuzaka & Yashiro 2024).

HS is pivotal in the innate immune response. It helps during extravasation of leukocytes, and acts as a scaffold for chemokines binding with leukocyte receptors during inflammation (Li & Kusche-Gullberg 2016, Krüger-Genge et al. 2019, Wang et al. 2021). HS functions as coreceptor between fibroblast growth factor (FGF) and FGF receptor, wherein, FGF showed dependence on HS to interact with its receptor resulting to increased cell population (Fuster & Esko 2005, Li & Kusche-Gullberg 2016, Wang et al. 2021). Furthermore, current studies show that many viral species involve HS to initiate infection. The cationic regions of viral protein surface reacts with the anionic side of HS, thereby giving viral access to the host cell surface (Li & Kusche-Gullberg 2016, Matsuzaka & Yashiro 2024).

Studies on HS demonstrate its significance on mammalian physiology. The structural complexity enables a wide range of functions and protein interactions, requiring in-depth investigation of HS in various biological processes (Davis et al. 2013, Li & Kusche-Gullberg 2016, Wang et al. 2021).

Hyaluronic acid

Hyaluronic acid (HA), also called hyaluronan, is a naturally occurring glycosaminoglycan usually found in vertebrate connective tissues, epithelial, nerves, and skin tissues (Salih et al. 2024). It was first isolated from a cow's eye by scientists Karl Meyer and John Palmer in 1934 (DrugBank 2025a). HA is a megadalton glycosaminoglycan component critical for maintaining the integrity of the extracellular matrix and plays an important role in biological processes, including CD44-mediated cell signaling, wound reparation, and tissue regeneration (Stern 2008, Dicker et al. 2014, Salih et al. 2024). HA has the simplest structure of all GAGs, consists of consecutively bound glucuronic acid and N-acetylglucosamine residues (Ghiselli 2017) (Fig. 4).

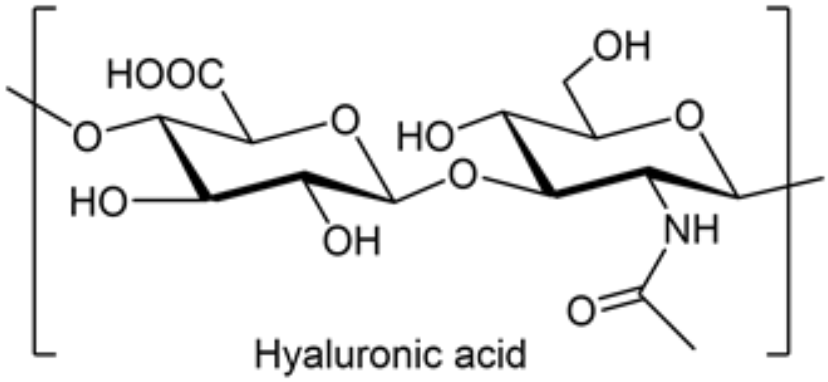

Fig. 4 – Chemical structures of hyaluronic acid.

Biological functions of hyaluronic acid

Hyaluronic acid is a naturally occurring polysaccharide found in the body that plays a vital role in skin health and beauty. It has multifunctional roles in living organisms in controlling different biological processes such as skin healing, cancer detection, anti-inflammatory reactions, and immune regulation (Bukhari et al. 2018). In many cases, it acts as a lubricant (joints), a structure stabilizer, an organ space filler (skin), and a shock absorber (cartilage). HA is significant in the cellular functions of living organisms by maintaining tissue hydration, promoting cell growth and differentiation, and regulating inflammatory responses. It is important in dermal wound healing and tissue regeneration (Aya & Stern 2014, Frenkel 2014). High molecular weight (HMW)-HA exhibits immunosuppressive and anti-inflammatory effects, whereas low molecular weight (LMW)-HA contributes to immuno-stimulation and thus inflammation (Kaul et al. 2021).

HA is also well-known for its role in skin hydration and joint lubrication (Moreira et al. 2024). As we age, the amount of HA produced in our skin decreases, leading to skin aging (Serra et al. 2023). Skin aging is associated with the loss of HA and collagen, leading to the appearance of wrinkles and a loss of facial volume (Bukhari et al. 2018). HA has a high water-retention capacity, biocompatibility, and biodegradability (Moreira et al. 2024). It demonstrates valuable bioactive properties, exceptional viscoelasticity, and moisturizing qualities that are beneficial in numerous clinical applications (Gupta et al. 2019). HA is a highly sought-after substance in medicine and cosmetics due to its distinct biological and rheological characteristics (Shikina et al. 2022). The anionic properties of HA are responsible for water retention which encourage swelling thereby increasing tissue volume which increase skin structural integrity (DrugBank 2025a).

HA also has significant therapeutic potential. It is considered a key regulator of cell proliferation, migration, and invasion, essential mechanisms underlying inflammatory responses and cancer development (Misra et al. 2015). HA achieves its therapeutic effects by binding to three

main types of cell surface receptors namely CD44 (a non-kinase transmembrane glycoprotein), the receptor for hyaluronate-mediated motility (RHAMM), and the Intercellular Adhesion Molecule 1 (ICAM-1) (Wolf et al. 2020, Shan et al. 2022).

Of the three HA receptors, CD44 is the most studied and recognized as the main HA signaling pathway. HA is important for wound healing, tissue regeneration, and cancer treatment because it controls cellular behavior through processes, such as adhesion, migration, proliferation, and survival, via its interaction with receptor CD44 (Misra et al. 2015). It has also been shown that the HA-CD44 interaction modulates immune activity and reduces inflammation (Misra et al. 2015). Another receptor, RHAMM, is strongly implicated in cell migration, blood vessel formation, and cystoskeleton organization; abnormal RHAMM activity has been associated with aggressive cell behavior in cancer (Fujisawa et al. 2024). When HA binds to RHAMM, it stimulates cell migration, blood vessel formation, and tissue recovery (Hinneh et al. 2022). In addition, ICAM-1, a cell-surface glycoprotein functioning as an adhesion receptor, plays a crucial role in HA-mediated regulation of immune and inflammatory pathways, injury resolution, and tumorigenesis (Bui et al. 2020). Its interaction with HA promotes leukocyte adhesion and migration, thereby supporting immune surveillance and tissue repair. HA can also modulate ICAM-1 levels through NF-κB signaling, thereby affecting inflammatory responses in conditions such as kidney damage and autoimmune disorders (Oertli et al. 1998, Marinho et al. 2021). HA's interactions with these receptors highlight its potential for therapies that regulate inflammation and immune responses.

Sources of glycosaminoglycans

Animal-sourced chondroitin sulfate

Chondroitin sulfate is a natural biomacromolecule widely studied in vertebrates and invertebrates due to its multiple functions and bioactivities (Table 1). It mainly functions to cushion joints and provides elasticity and resistance to compression (Shen et al. 2023). Thus, most CS are extracted from cartilage and other connective tissues, mainly bovine (Fardellone et al. 2013, Zhou et al. 2020), porcine (Wildi et al. 2011), and galline (Fardellone et al. 2013). Marine sources such as sharks, rays, and other fish are also being exploited for the same purpose (Sim et al. 2007, Medeiros et al. 2021, Pang et al. 2024). Other animals, such as crocodiles, are also being explored as alternative sources (Garnjanagoonchorn et al. 2007). CS from marine sources has a higher molecular weight and disulfated disaccharides, which can limit its potential bioactivities and bioavailability (Narayanan et al. 2017). For instance, Ticar et al. (2020) extracted GAGs from heads of silver-banded whiting fish (*Sillago argentifasciata*; Martin & Montalban 1935) and subjected them to size-exclusion chromatography, in which fraction 1 was elucidated as HA (190 kDa), and fractions 2 (82 kDa) and 3 (64 kDa) were both CS using 1D and 2D NMR spectroscopy. The extracts were subjected to biocompatibility testing in accordance with ISO 10993, including intracutaneous irritation, maximization sensitization, systemic toxicity, and cytotoxicity. Preliminary results of this testing suggest that silver-banded whiting fish heads are suitable alternatives for soft tissue augmentation, although further biocompatibility studies would still be required.

Other invertebrates and marine organisms were also explored for the presence of CS (Cássaro & Dietrich 1977, Yamada et al. 2007, Yuvashri et al. 2020) (Table 2). The study of Cássaro and Dietrich (1977) showed that the dark-brown ant (*Camponotus rufipes*) possesses the highest percentage yield of CS (95%), followed by squid (*Loligo brasiliensis*) (91%) and shrimp (*Penaeus brasiliensis*) (66%). Other terrestrial invertebrates that contain CS were the termite (*Cornitermes cumulans*), the cockroach (*Cornitermes cumulans*), and the spider (*Nephila clavipes*) (Cássaro & Dietrich 1977, Yuvashri et al. 2020). Moreover, marine invertebrates such as crab (*Callinectes sapidus*), lobster (*Scyllarides brasiliensis*), mussel (*Perna perna*), sponge (*Spongiaria* sp.), and tunicate (*Ascidia nigra*) were also potential sources of CS (Cássaro & Dietrich 1977, Yuvashri et al. 2020)

Table 1 Animal sources of chondroitin sulfate and their bioactivities and applications.

Sources	Bioactivities	Applications	Current Status	References
		Vertebrates		
Bovine	Anti-inflammatory, Analgesic, Mineral binding	Symptom-modifying drugs for osteoarthritis with structure-modifying effects, joint care supplement	Available as oral over-the-counter drug: Chondrosulf (IBSA Institut Biochimique SA); Chondrosan (Bioiberica, S.A.) Food supplement: Pureflex Chondroitin sulfate (TSI Health Sciences, Australia)	Bourgeois et al. (1998), Bucsi & Poór (1998), Uebelhart et al. (2004), Kahan et al. (2009), Gabay et al. (2011), Zegels et al. (2013), Fardellone et al. (2013), Henrotin et al. (2014), Fransen et al. (2015), Reginster & Veronese (2021)
Porcine	Anti-inflammatory, Analgesic, Mineral binding	Symptom-modifying drugs for osteoarthritis	Available as oral over-the-counter drug: Chondrosan (Bioiberica, S.A.); Pureflex Chondroitin sulfate (TSI Health Sciences, Australia)	Fuentes & Diaz (1998), Volpi (2007), Wildi et al. (2011), Möller et al. (2016), Monfort et al. (2017)
	Anti-aging	Component in various skincare and cosmetic products as moisturizer, hair conditioning products	Not stated	Min et al. (2020)
Galline (Chicken)	Anti-inflammatory, Analgesic, Antioxidant	Symptom-modifying drugs for osteoarthritis, joint care supplement for osteoporosis	Available as oral over-the-counter drug: Structum (Laboratoires Pierre Fabre)	Fuentes & Diaz (1998), Luo et al. (2002), Volpi (2004), Garnjanagoonchorn et al. (2007), Mazières et al. (2007), Schneider (2012), Railhac et al. (2012), Fardellone et al. (2013)
Shark/Ray	High binding affinity, Anti-angiogenic and antitumor activities	Potential for drug delivery and tissue engineering, Food supplement	Exploratory: interaction with bovine serum albumin Available as varying food supplements	Fuentes & Diaz (1998), Berbari et al. (1999), González et al. (2001), Volpi (2004), Sim et al. (2007), Wang & Tang (2009), Pang et al. (2024)
Fish	Anti-oxidant	Component in various skincare and cosmetic products as moisturizer, hair conditioning products	Not stated	Ajisaka et al. (2016)
	Anti-coagulant	Not stated	Not stated	Krichen et al. (2018)
Crocodile	Not stated	Not stated	Exploratory: alternative source of chondroitin sulfate	Garnjanagoonchorn et al. (2007)
Multiple animal sources	Surface coating	Use in phacoemulsification cataract surgery	Ophthalmic Viscosurgical Devices (OVDs) such as: VISCOAT, DuoVisc, DisCoVisc (Alcon Laboratories, Inc., Belgium)	Glasser (1989), Moschos et al. (2011), Papaconstantinou et al. (2014), Hsiao et al. (2023)

Table 1 Continued.

Sources	Bioactivities	Applications	Current Status	References
		Vertebrates		
	Anti-oxidant	Component in various skincare and cosmetic products as moisturizer, hair conditioning products	Companies producing Chondroitin sulfate for skincare and cosmetic products: Chondroitin sulfate (HorseTeach, USA), Chondroitin Sulfate Sodium Salt (Spectrum Chemical Mfg. Corp., USA), Chondroitin Sulfate USP (McKinley Resources, USA)	Metoree (2025)

Table 2 Other invertebrate sources of chondroitin sulfate.

Sources	% Yield of chondroitin sulfate	References
Ant (*Camponotus rufipes*)	95	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Crab (*Callinectes sapidus*)	43	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Cockroach (*Cornitermes cumulans*)	17	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Feather duster worm (*Eudistylia polymorpha*)	2.5	Person & Mathews (1967), Yuvashri et al. (2020)
Freshwater polyp (*Hydra magnipapillata*)	<1	Yamada et al. (2007), Böttger et al. (2012, Yuvashri et al. (2020)
Lobster (*Scyllarides brasiliensis*)	17	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Mussel (*Perna perna*)	12	Cássaro & Dietrich (1977), Yuvashri et al. (2020), Pai et al. (2024)
Sea cucumber (*Thelenata ananas*)	0.7	Wu et al. (2012), Yuvashri et al. (2020)
Squid (*Loligo brasiliensis*)	91	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Shrimp (*Penaeus brasiliensis*)	66	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Spider (*Nephila clavipes*)	38	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Sponge (*Spongiaria* sp.)	48	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Termite (*Cornitermes cumulans*)	35	Cássaro & Dietrich (1977), Yuvashri et al. (2020)
Tunicate (*Ascidia nigra*)	16	Cássaro & Dietrich (1977), Pavão et al. (1995), Yuvashri et al. (2020), de Sousa et al. (2020)

Chondroitin sulfate in microorganisms

Interestingly, CS has also been reported in microorganisms, such as bacteria (Badri et al. 2021) and fungi (Narayanan et al. 2017). *Flavobacterium heparinum* and *Proteus vulgaris* isolated from soil and estuaries were extensively screened for commercial CS production. However, productivity remains low with high production costs (Blain et al. 2002). In a recent study by Badri et al. (2021), *Escherichia coli* was engineered to simplify CS production, marking an important step in animal-free production.

Extraction of chondroitin sulfate

CS is extracted in various ways depending on the type of materials and the desired yield and purity (Saha et al. 2024). More commonly, CS is extracted by hydrolyzing the biomass chemically using acids (e.g., hydrochloric acid, sulfuric acid) and alkaline (e.g., sodium hydroxide, potassium hydroxide, urea, guanidine) solutions to dissolve the tissue component in cartilages. Enzymes, on the other hand, can also be used in combination to hydrolyze tissues such as papain, trypsin, pepsin, and alcalase, which can efficiently yield high GAG (Urbi et al. 2022). However, the process requires a significant amount of enzyme, additional buffer solution, and an extended reaction time

to hydrolyze tissues, making it more expensive (Abdallah et al. 2020, Shen et al. 2023, Saha et al. 2024).

Recently, combined chemical and physical methods (e.g., ultrasonication, microwave digestion, high-pressure water/steam) have been suggested as an alternative (Chang-yu et al. 2011, Tsai et al. 2023, Saha et al. 2024). The process will accelerate tissue hydrolysis while using lower chemical concentrations. At the same time, it will allow for higher yield and purity and will be able to reduce operating costs compared to conventional chemical extraction (Saha et al. 2024). In some samples, such as fish, a delipidation process follows after hydrolysis, using chloroform and acetone or methanol; samples were also dried before extraction (Abdallah et al. 2020, Urbi et al. 2022). Once hydrolyzed, CS is purified using water or buffer solution, precipitated by alcohol (ethanol, isopropanol), and cationic quaternary ammonium salts (sodium acetate, trichloroacetic acid, cetylpyridinium chloride). The purification steps may be combined with gel filtration, ion-exchange chromatography, or size-exclusion chromatography (Abdallah et al. 2020, Saha et al. 2024).

Animal-sourced heparin

Heparin is found in mast cells and is present in multiple tissues across various animal species (i.e., abundant in the blood, liver, lung, and muscle) (Lee et al. 2020) (Table 3). While the majority of pharmaceutical heparin today is sourced from porcine intestines, it was historically produced from bovine lungs and ovine intestines (Fu et al. 2013, Guan et al. 2016). Pharmaceutical-grade heparin is obtained from the mucosal tissues of animals, such as pigs and cattle, that are processed for meat (Zhang et al. 2023a). The study of Lee et al. (2020), established the average amount of heparin extracted per kilo from different pig tissues. The liver had the highest heparin concentration (439 mg/kg), followed by the heart (398 mg/kg), stomach (261 mg/kg), and large intestine (239 mg/kg) (Table 3).

Currently, Chinese industries use porcine intestines as raw materials, producing approximately 60% of the heparin consumed in the world (Tovar et al. 2016). Heparin derived from the aforementioned sources showed different disaccharide content and chain lengths, with an average molecular weight ranging from 10 to 20 kDa, in accordance with the variable methods of preparation (Acquisto 2014).

Table 3 Animal sources of heparin.

Source	Body parts	Average amount of heparin extracted per kilogram of by-products (mg/kg)	References
Bovine (cattle)	Intestine mucosa	Not stated	Fu et al. (2013)
Bovine (cattle)	Lung	Not stated	Nagasawa & Uchiyama (1984), Guan et al. (2016)
Ovine (sheep)	Intestine mucosa	Not stated	Fu et al. (2013)
Porcine (pig)	Intestine mucosa	Not stated	Nagasawa & Uchiyama (1984), Fu et al. (2013), Tovar et al. (2016)
Pig	Liver	439	Lee et al. (2020)
	Lung	127	
	Heart	398	
	Stomach	261	
	Small intestine	197	
	Large intestine	239	

Other possible sources of heparin included marine organisms such as clams, mussels, snailfish, and whales (Table 4). The giant clam (*Tridacna maxima*) and green mussel (*Perna viridis*) can yield 260 mg/kg and 248 mg/kg of heparin from their soft tissue (Arumugam et al. 2009). Both species exhibited antiproliferative activity in crude and purified fractions, with *P. viridis* showing higher activity (39,000 USP units/kg and 75 USP units/mg) compared to *T. maxima* (20,128 USP units/kg and 7.4 USP units/mg). Antiproliferative assays using pulmonary

artery smooth muscle cells revealed dose-dependent inhibition, with *P. viridis* demonstrating stronger effects than *T. maxima*.

The anticoagulant activity of heparin (Table 5) is measured in United States Pharmacopeia (USP) units per milligram. Heparin from hog intestines and bovine lungs, studied by Nagasawa and Uchiyama (1984), showed anticoagulant activities of 167 and 149 USP units/mg, respectively. These values suggest moderate anticoagulant potency, with hog-intestinal heparin exhibiting slightly higher activity. Similarly, whale-intestinal heparin showed higher activity in the 1.5 M fraction (174 USP units/mg) than in the 1.25 M fraction (60 USP units/mg), highlighting significant differences within fractions from the same source (Nagasawa & Uchiyama 1984). Baig et al. (2020) support the study by Nagasawa and Uchiyama (1984) wherein bovine heparin exhibited anticoagulant activity of 130-15- USP units/mg.

Table 4 Other non-conventional animal sources of heparin and heparin-like compounds.

Source	Body parts	Average amount of heparin extracted per kilogram of by-products (mg/kg)	References
Dog	Liver	Not stated	Linhardt (2003),
	Spleen	Not stated	Middeldorp (2008)
	Pancreas	Not stated	
Giant clam (*Tridacna maxima*)	Soft tissue	260	Arumugam et al. (2009)
Clam (*Ruditapes philippinarum*, formerly *Tapes philippinarum*)	Soft tissue	2.1	Cesaretti et al. (2004)
Crab (*Goniopsis cruentata*)	Tissue	Not stated	Andrade et al. (2013)
Green mussel (*Perna viridis*)	Soft tissue	248	Arumugam et al. (2009)
Mollusk (*Coelomactra antiquata*)	Soft tissue	Not stated	Du et al. (2019)
Mollusk (*Callista chione*)	Soft tissue	1.9	Luppi et al. (2005)
Bivalve Mollusk (*Nodipecten nodosus*)	Soft tissue	4.6 mg/g	Gomes et al. (2010)
Snail fish (*Liparis tessellatus*)	Eggs	Not stated	Ticar et al. (2015)
Whale	Intestine	Not stated	Nagasawa & Uchiyama (1984)

Meanwhile, ovine mucosal heparin, as investigated by Kouta et al. (2019), exhibited superior anticoagulant activity at 200 ± 1.2 USP units/mg, which is consistent with the findings of Baig et al. (2020), who reported 190 USP units/mg. In comparison, Jaques et al. (1942) identified dog liver-derived heparin as the most potent, with an activity of 240 USP units/mg. Variation in anticoagulant activity across different sources may reflect differences in molecular structure, degree of sulfation, and composition, all of which are critical determinants of heparin's biological activity.

Furthermore, Oliveira et al. (2022) investigated the anticoagulant activity of heparins obtained from different animal sources and demonstrated that their biological efficacy is not determined by a single structural feature but rather by a synergistic interplay of multiple physicochemical factors. The study highlighted that variations in sulfation patterns, molecular weight distribution, and conformational flexibility collectively influence the interaction of heparins with antithrombin and other coagulation-related proteins. These differences explain the observed variability in anticoagulant potency among heparins derived from porcine, bovine, and ovine tissues. The findings underscore the importance of considering the holistic structural profile of heparins rather than focusing solely on individual molecular attributes, providing insights valuable for quality control and the development of alternative non-animal sources of heparin.

Heparin-like compounds were found in some marine organisms. For instance, a heparin-like compound from the crab *Goniopsis cruentata* was found to be rich in disulfated disaccharides but contained fewer trisulfated units than mammalian heparin (Andrade et al. 2013). It showed negligible anticoagulant activity and low bleeding potential, highlighting its potential as a safer template for developing heparin-based therapeutics.

Another heparin-like anticoagulant polysaccharide was also extracted from *Liparis tessellatus* eggs by using an enzyme-assisted extraction technique employing ALcalase®2.4L, Flavourzyme® 500 mg, and Protamex®. The heparin-like nature of this polysaccharide was also confirmed by digestion with heparinases, and the extract showed anticoagulant activity at increasing concentrations (Ticar et al. 2015).

In the study of Gomes et al. (2010), heparin-like glycans with strong anticoagulant activity were also identified in the marine bivalve *Nodipecten nodosus*. Structural analysis revealed a HS-like glycosaminoglycan as the main component (~4.6 mg/g dry tissue), composed of glucuronic acid and glucosamine residues with variable sulfation. The mollusk HS exhibited anticoagulant activity (36 IU/mg), lower than porcine heparin (180 IU/mg), but effectively inhibited factor Xa and thrombin in the presence of antithrombin. *In vivo*, it suppressed thrombus growth without causing bleeding, kallikrein activation, or cytotoxicity, highlighting its potential as a safer antithrombotic agent.

Table 5 Animal sources of heparin with anticoagulant activity.

Animal Source	Anticoagulant Activity (USP units/mg)	References
Hog-intestinal heparin	167	Nagasawa & Uchiyama (1984)
Bovine-lung heparin	149	
Whale-intestinal heparin		
1.5 M fraction	174	
1.25 M fraction	60	
Ovine mucosal heparin	200	Kouta et al. (2019)
Dog livers heparin	240	Jaques et al. (1942)
Porcine heparin	200	Baig et al. (2020)
Ovine heparin	190	
Bovine heparin	130–150	

Heparin from microorganisms

A study by Deng et al. (2024) reports the synthesis of animal-free heparins using bacteria. The authors also utilized *Escherichia coli* K5 to facilitate sulfation in N-trifluoroacetylglucosamine. The *E. coli* K5 produced the polysaccharide backbone for heparin synthesis (Vaidyanathan et al. 2017). Then, the Protein Repair One-Stop Service-Focused Rational Iterative Site-specific Mutagenesis (PROSS-FRISM) strategy was adopted, leading to enhanced sulfation. This method allows for the generation of active heparin from bioengineered heparosan, resulting in increased anti-FXa and anti-FIIa activities (Deng et al. 2024).

Extraction of heparin

There are multiple processes available for extracting heparin from the by-products of porcine and bovine. Recently, DuPont (2023) developed an ion-exchange resin that can extract heparin via adsorption. The concept was based on the nature of heparin, which contains negative charges (Zare et al. 2024). The DuPont™ AmberLite™ FPA98 Cl ion-exchange resin contains quaternary amine functional groups in a macroporous matrix, which are responsible for effective heparin adsorption (DuPont 2023). The matrix is made of an acrylic polymer that mitigates organic fouling and consequently aids desorption or regeneration. The macroporous matrix has been used in different heparin extraction and purification processes (Gu 2015).

Another method of extracting heparin is the use of enzymes, as investigated by Lee et al. (2020). The said work employed trypsin, papain, and alkaline-AK enzymes. The pig by-products underwent a defatting process using mainly Folch I solution, followed by dehydration at low temperature. The dried by-products were prepared for enzyme addition, after which heparin was extracted. The extracted heparin was quantified using high-performance liquid chromatography (HPLC). Trypsin, which is widely used for the extraction of heparin, yielded 1718 mg of heparin per 1 kg of pig by-products. On the other hand, 1697 mg of heparin was extracted using papain

enzyme. Meanwhile, 1905 mg of heparin was obtained from the same amount of pig by-products using alkaline-AK enzyme. The latter enzyme was recommended because it is 1.3 million times cheaper than trypsin and 2000 times cheaper than papain.

Animal-sourced hyaluronic acid

Hyaluronic acid is naturally present in animal connective tissues and vertebrate body fluids, particularly concentrated in synovial fluid, vitreous fluid of the eye, umbilical cords, and other body tissues, as well as in some bacteria and fungi (Fraser et al. 1997). Animals rich in HA are cattle, rabbits, rats, roosters, and sheep (Table 6). Animal connective tissues, including skin and cartilage, have been found to contain HA, which fills in intercellular gaps and mostly preserves the tissues' flexibility and structure (Hussain et al. 2017). Historically, Healon® was among the first commercial medical HA products developed in the 1970s as an injectable HA solution extracted from rooster combs and became a breakthrough in ophthalmic surgery (Balazs et al. 1986). Rooster combs contain the highest HA concentration, reaching up to 7.5 g/kg (Kalantarmahdavi et al. 2022).

HA occurs naturally within the human body in the highest concentration within the extracellular matrix of soft connective tissue, synovial fluid, and life-critical tissues like skin, and eyes, where it assists in holding water and aiding cellular function (Menaa et al. 2011, Salih et al. 2024).

Table 6 Animal sources of hyaluronic acid.

Sources	Occurrence	Average amount of HA extracted per kilogram of by-products (g/kg)	References
Cattle	Bovine nasal cartilage	Not stated	Roughley & Mason (1975)
Rabbits	Renal papillae, kidney, vitreous body, muscle, liver	Not stated	Valachová et al. (2016)
Rats	Lung, kidney, brain, liver	Not stated	Valachová et al. (2016)
Roosters	Rooster comb	1.0	Kang et al. (2010), Serra et al. (2023)
Roosters	Rooster comb	7.5	Kalantarmahdavi et al. (2022)
Sheep	Synovial fluid, medulla cortex, lungs	Not stated	Fraser et al. (1997)

Hyaluronic acid in microorganisms

Recent years have seen increased interest in the study of microbial synthesis of HA. HA can be manufactured by fermentation of specific bacteria, including the Gram-positive Streptococcus zooepidemicus, which is widely used for the commercial production of HA for medical and cosmetic applications (Serra et al. 2023, Zhang et al. 2023c). However, the introduction of recombinant HA production attracted increasing attention due to the avoidance of potential toxins, with Novozymes being able to produce HA on an industrial scale using recombinant *Bacillus subtilis* (Liu et al. 2011). Several heterologous hosts, particularly those classified as Generally Regarded as Safe (GRAS), including *Bacillus subtilis* (Jia et al. 2013, Jin et al. 2016), *Corynebacterium glutamicum* (Cheng et al. 2016), *Lactococcus lactis* (Sheng et al. 2015), and *Pichia pastoris* (now referred to as *Komagataella pastoris*) (Jeong et al. 2014), have recently been developed as alternative biological platforms for HA production (Kang et al. 2018b).

Extraction of hyaluronic acid

Hyaluronic acid can be extracted from animal tissues or produced via microbial fermentation, with the chosen method influencing its yield, molecular weight, and purity. Traditionally, animal-derived HA is obtained from rooster combs or bovine vitreous humor through mechanical disintegration, proteolytic digestion to remove proteins, and precipitation using ethanol or cetylpyridinium chloride, followed by purification steps such as dialysis (Necas et al. 2008). HA extraction from animal sources, such as rooster combs, involves a series of steps designed to

remove proteins, lipids, and other macromolecules while maintaining the polymer's high molecular weight and bioactivity. Protease digestion or chloroform denaturation of the protein are two methods for completing this step. Combinations of organic solvents are used to remove lipids. Lastly, dialysis or precipitation of HA with ethanol or isopropyl alcohol may be necessary to eliminate low-molecular-mass contaminants.

Specifically, fresh tissues are cleaned with cold saline, mechanically homogenized, and subjected to proteolytic digestion with enzymes such as papain or trypsin under controlled temperature and pH to degrade structural proteins and release HA. Lipids are removed using organic solvents, and centrifugation separates insoluble residues from the HA-rich aqueous phase. The polymer is then precipitated using cationic detergents such as cetylpyridinium chloride or cold alcohols, followed by purification via dissolution–reprecipitation, dialysis, and, occasionally, activated carbon treatment to remove pigments and small impurities. Finally, the purified HA is lyophilized to preserve its structure and stored under sterile, dry conditions to maintain quality and prevent contamination (Necas et al. 2008, Rodriguez-Marquez et al. 2022).

Extraction from animal sources has long been regarded as a classic way to obtain HA; however, it is no longer associated with large-scale production (Shikina et al. 2022). Microorganisms such as bacteria and yeast have been used to produce HA through fermentation. *Streptococcus zooepidemicus*, a Gram-positive bacterium, is one of the most commonly used organisms for HA production due to its easy cultivation and high HA production rate (Pan et al. 2019). In recent years, this microbial fermentation has become the preferred approach due to its safety, improvements in physicochemical, sensory, and nutritional attributes, scalability, and avoidance of animal-borne contaminants (Siddiqui et al. 2023). Extraction of HA via microbial fermentation typically involves fermentation under optimized conditions, cell removal, HA precipitation, ultrafiltration, and chromatographic purification to achieve pharmaceutical-grade quality (Rodriguez-Marquez et al. 2022). Advanced separation technologies, including tangential flow filtration and membrane-based purification, are increasingly applied to enhance recovery efficiency while preserving HA's structural integrity (Zhou et al. 2006).

Fungi as a potential source of GAGs

Glycosaminoglycans in fungi

Polysaccharides are the most effective compounds obtained from mushrooms for various physiological activities, including anticarcinogenic, anti-inflammatory, antimicrobial, antioxidant, antiviral, immunomodulatory, and neuroprotective properties (Varghese et al. 2019, Sandargo et al. 2019, Wang et al. 2023). Fungal cell walls are structurally composed of polysaccharides (Gow et al. 2017). The two main forms of polysaccharides that make up a fungal cell wall are matrix-like β-glucan, α-glucan, and glycoproteins, and a stiff fibrillar of chitin (Kang et al. 2018a).

GAGs, which are negatively-charged polysaccharide molecules, are also referred to as mucopolysaccharides (Casale & Crane 2019). Although GAGs are found on cellular membranes and in the extracellular matrix of almost all mammalian tissues some microfungi and macrofungi also possess these compounds (Choocheep & Nathip 2018). GAGs have been found in a variety of mushroom species, as evidenced by the study by Choocheep & Nathip (2018), and they may offer advantages comparable to or even greater than those of their animal counterparts. Thailand harbors a variety of mushrooms (Fig. 4). Choocheep & Nathip (2018) investigated several mushroom extracts for GAGs. Study found presence of GAGs in 10 wild mushrooms in Thailand: hygroscopic earthstar (*Astraeus hygrometricus*), Jew's ear (*Auricularia* sp.) (Fig. 5a), shitake mushroom (*Lentinula edodes*), log black fungi (*Lentinus polychrous*), sajor-caju mushroom (*Lentinus sajor-caju*), bolete (*Phlebopus portentosus*) (Fig. 5c), milk white russula (*Russula* sp1.) (Fig. 5d), rosy russula (*Russula* sp2.) (Fig. 5e), and straw mushroom (*Volvariella volvacea*) (Choocheep & Nathip 2018).

The detection of GAGs in mushroom extracts was conducted by utilizing the 1,9-dimethylmethylene blue (DMMB) dye-binding assay of Farndale et al. (1982) with CS as

a standard. In addition, UV-Vis spectrophotometry was used to further examine GAGs in mushrooms in absorbance mode. The aforementioned study found that *Astraeus hygrometricus* contained the most GAGs. However, the authors did not identify the specific GAG types present in these macrofungi. The various GAGs mentioned in the study that may be present in mushrooms include heparin, CS and HA (Choocheep & Nathip 2018). Moreover, a heteroglycan known as OL-1 was a primary water-soluble polysaccharide extracted from the sclerotia of *Omphalia lapidescens* and purified using DEAE-cellulose chromatography and zone electrophoresis (Miyazaki & Nishijima 1981).

Microfungi are also thought to produce GAGs (Tithi et al. 2024). The cell wall of *Schizosaccharomyces pombe* primarily comprises (1→3)-α-glucan and (1→3)-β-glucan, with some (1→6)-β linkages. Although hydrolyzed samples reveal only trace amounts of glucosamine, this amino sugar likely plays a key role as a component of a glucosaminoglycan/glucan complex (DrugBank 2025b). This compound has also been shown to exist in the cell walls of several filamentous fungi (Patel & Free 2019), and is also suggested to be present in the lateral walls of budding yeasts, such as *Saccharomyces cerevisiae* (Mol & Wessels 1987) and *Candida albicans* (Surarit et al. 1988).

Fig. 5 – Commonly collected wild local mushrooms in Thailand. a. *Auricularia auricula-judae* b. *Lentinus squarrosulus* c. *Phlebopus portentosus* d. *Russula* sp. 1 (milk white) e. *Russula* sp. 2 (rosy) f. *Termitomyces* sp. (Photo credit: A.G.T. Niego).

Yeast as a heterologous host for chondroitin biosynthesis

There is a lack of comprehensive research on the natural synthesis of CS in fungi, with most existing studies on CS biosynthesis focusing on animal-derived sources, particularly from cartilaginous tissues of bovine, porcine, and marine organisms (Fardellone et al. 2013, Pang et al. 2024). Although some fungi can synthesize sulfated polysaccharides (Cheng et al. 2012), including those with potential structural similarities to CS, the specific pathways and enzymes involved in CS synthesis in fungi remain largely unexplored. Biotechnological chondroitin production from microorganisms is typically achieved by cultivating the pathogenic bacterium *Escherichia coli*

O5:K4:H4, which naturally synthesizes a fructosylated variant of chondroitin (Cimini et al. 2015). Numerous attempts have been undertaken to engineer safer microorganisms for chondroitin production; however, the resulting yields have fallen short of meeting the increasing demand (Couto et al. 2024). The exploration of eukaryotic microorganisms in chondroitin production still remains limited. A genetically engineered yeast, *Piccia pastoris* was once studied in the biosynthesis of CS from methanol. A study of Jin et al. (2021b) developed a sustainable alternative by engineering *Pichia pastoris* to synthesize non-animal CS from methanol. The exogeneous genes, kfoC and kfoA from *Escherichia coli* K4 and tuaD from *Bacillus subtilis* were introduced to *P. pastoris* to create a chondroitic synthesis pathway which initially yielded 5.5 mg/L chondroitin and later was enhanced to 189.8 mg/L through codon optimization. Further optimization with Kozak sequences, promoters, and chondroitin-4-O-sulfotransferase expression enabled the production of 182.0 mg/L chondroitin sulfate A (CSA) with 1.1% sulfation, later increased to 2.8% by boosting PAPS supply. In fed-batch cultivation, the system achieved 2.1 g/L CSA with 4.0% sulfation, demonstrating the potential of *P. pastoris* as a green platform for producing sulfated GAGs.

Another yeast, *Saccharomyces cerevisiae*, has been shown to be a promising heterologous host for chondroitin biosynthesis. In a recent proof-of-concept study, Couto et al. (2024) successfully engineered a biosynthetic pathway in *S. cerevisiae*, offering a promising alternative for chondroitin production. This highlights the feasibility of engineering yeast, specifically *Saccharomyces* species, for the synthesis of GAGs. Moreover, this genus is among the most explored microorganisms in industrial biotechnology due to its rapid growth rate, ease of genetic engineering, and safe applications in food, beverages, and pharmaceutical production (Parapouli et al. 2020). It offers a significant advantage in metabolic engineering due to its ability to perform eukaryotic post-translational modifications, such as glycosylation, which are essential for the synthesis of functional recombinant proteins and complex carbohydrates (Parapouli et al. 2020). Leveraging these yeast systems for chondroitin production could provide a sustainable and animal-free source of CS, offering significant advantages for pharmaceutical, nutraceutical, and biomedical applications.

Bioengineered heparin production using yeasts

Advancements in metabolic engineering have enabled the development of yeast-based platforms for the scalable, high-fidelity biosynthesis of bioengineered heparin, offering an animal-free alternative to conventional extraction from porcine mucosa (Sultana & Kamihira 2024). Saribaş et al. (2004) successfully expressed the bifunctional N-deacetylase/N-sulfotransferase-1 (NDST-1) in *Saccharomyces cerevisiae*, overcoming a major limitation in heparosan modification. HS/heparin N-deacetylase/N-sulfotransferase-1 (NDST-1) plays a critical role in the structural modification of the HS/heparin backbone during its biosynthesis. Moreover, Zhou et al. (2011) achieved secreted expression of multiple human HS sulfotransferases in *Kluyveromyces lactis* (formerly *Saccharomyces lactis*) alongside scalable preparation of the essential cofactor 3′-phosphoadenosine-5′-phosphosulfate (PAPS), thereby establishing practical methods for chemoenzymatic conversion of heparosan into heparin. The use of yeasts in heparin synthesis via metabolic engineering was further supported by more recent studies. Zhang et al. (2022) demonstrated an important achievement by using *Pichia pastoris* to express C5-epimerase and a full complement of essential sulfotransferases, enabling both a cell-free lysate-based enzyme cascade and a functional yeast cell factory capable of producing bioengineered heparin at titers of approximately 2.08 g/L in fed-batch fermentation. The bioengineered heparin produced using *Pichia pastoris* demonstrates anticoagulant activity comparable to that of animal-derived commercial heparin. Furthermore, the industrial relevance of yeast as a host system was evident in the recent filing of a patent for methods of production of heparosan, HS, and heparin in yeast, *S. cerevisiae* (WO2023110854; EP4198139) (Korner 2022). Together, these scientific and technological developments position yeast as a versatile and sustainable platform for next-generation heparin manufacturing.

Heparin-like compound from fungi

Atromentin has an anticoagulant effect similar to that of heparin (Khanna et al. 1965). Elkhateeb et al. (2019) reviewed the literature on the anticoagulant properties of several medicinal mushrooms, including *Auricularia auricula-judae*, *Geastrum fimbriatum*, *Hydnellum peckii* (formerly *Hydnellum diabolus*), and *Ganoderma lucidum* (Khanna et al. 1965, Bian et al. 2020). Mushroom species, especially *Hydnellum peckii* and *Thelephora aurantiotincta* were found to produce atromentin, a heparin-like compound (Khanna et al. 1965, PubChem 2025). Atromentin is a known natural pigment, a chemical compound found in some Agaricomycetes fungi in Agaricales and Thelephorales (Khanna et al. 1965, Sullivan et al. 1971). In a living organism, 1 mg of *Hydnellum peckii* 70% ethanolic extract had the same anticoagulation effect as 0.58 heparin units. Meanwhile, 2.3 mg of the same extract contained 1 mg of atromentin, equivalent to 5.1 heparin units in a laboratory setting (Khanna et al. 1965). At the same time, the alkali extracts of *A. auricula-judae* also reveal an anticoagulant property (Jeong et al. 2004). The mechanism of the anticoagulation effect of *A. auricula-judae* extract was based on the catalytic action of thrombin restriction via antithrombin. This process differs from that of cofactor II of heparin; thus, the active compound might not be heparin but rather one with the same bioactivity (Yoon et al. 2003). Atromentin was also found in both 30- and 45-day-old cultures of *Omphalotus subilludens* (formerly *Clitocybe subilludens*) (Sullivan & Guess 1969, Sullivan et al. 1971). These data suggest that atromentin could function as a precursor of thelephoric acid, given that the presence of the latter (terphenylquinone) coincides with the disappearance of the former (Sullivan et al. 1971).

Moreover, studies on the antithrombotic action of bioactive compounds from medicinal plants and mushrooms are ongoing (Mehta 2020). This is due to the inherent risk of bleeding of antithrombotic drugs classified as anticoagulant drugs (as acetylsalicylic acid, namely aspirin) and antiplatelet drugs (heparin) (Watson 2002). In this context, Choi et al. (2020) conducted a study on the antithrombotic action and antiplatelet factors of *Cordyceps militaris*, which revealed a potential antithrombotic effect. The findings were attributed to the antiplatelet effect and not to anticoagulation. Furthermore, *C. militaris* ethanol extract has a promising effect on improving blood circulation and the healing of injured vessels.

Hyaluronic acid presence in fungi

There are reports of mushrooms producing HA and related polysaccharides (Wu et al. 2016). The HAs are significant components of the *Auricularia cornea* polysaccharide and have extremely high medicinal value (Li et al. 2021). The most studied genus is *Tremella*, which produces abundant, adaptable, and biologically active natural compounds with a distinctive structure that are used in the food, everyday chemical, and pharmaceutical industries (Ma et al. 2021, Latimer 2025). *Tremella* species have been used since ancient Chinese times as a beauty product because they produce natural HA. *Tremella fuciformis*, commonly known as snow fungus, is particularly rich in HA. It is one of the greatest natural beauty foods for skin because of its capacity to replace HA in the body (FRWRD Skincare 2025, Three Ships 2025). This was supported by a recent study that isolated HA from *T. fuciformis*, based on the study by Galla et al. (2025). Chemical characterization of the molecule extracted from this mushroom showed that HA was the most prevalent polysaccharide in the extract, accounting for ca. 87.76% of the extract, with molecules weighing more than 2000 kDa. Furthermore, the presence of non-animal HA in *T. fuciformis* extract was verified by ATR/FTIR, NMR, and MALDI-TOF spectroscopy.

There are some patented methods for extracting HA from a fungus in the Basidiomycota (Cerana & Bos 2021). Based on the patented method of Cerana and Bos (2021), the process for extracting HA from mushrooms involves several precise steps. Initially, *T. fuciformis* is identified and, if desired, pulverized. The mushroom material undergoes enzymatic hydrolysis with enzymes such as pectinase, cellulase, or proteinase in water at temperatures ranging from 10°C to 90°C. This mixture is then extracted with water at 91°C to 110°C to obtain an aqueous extract. The addition of alcohol, such as ethanol or isopropanol, is required to precipitate HA, as it is poorly soluble in these solvents. The solvent is then evaporated under reduced pressure. The last step is drying, usually

freeze-drying, to produce HA with a molecular weight ranging from 10 kDa to 600 kDa. The process enables the production of high-quality, mushroom-derived HA for many applications. Not only is the process sustainable, but it is also free of contamination and ethical issues surrounding animal-derived HA.

It is also important to take note that some microfungi also possess HA. The yeast *Cryptococcus neoformans* produces HA, a component of its capsule (Jong et al. 2007). The study of Jong et al. (2007) indicates that this fungus synthesizes HA through the CPS1 gene, which plays a crucial role in the organism's ability to adhere to host cells, particularly during brain invasion due to its neurotropism. Furthermore, when CPS1 is expressed in *Saccharomyces cerevisiae*, HA can be detected in the cells. *Pichia pastoris* (now referred to as *Komagataella pastoris*) (Jeong et al. 2014) has recently been developed as an alternative biological platform for HA production (Kang et al. 2018b).

Pathogenic enzymes: Hyaluronidase and chondroitin sulfatase

It is also important to note that some yeasts, especially *Candida* spp. (*Candida albicans, C. guilliermondii*, *C. krusei*, *C. parapsilosis,* and *C. tropicalis*) are producing hyaluronidase and chondroitin sulfatase (Shimizu et al. 1995). Hyaluronidase and chondroitin sulfatase are key pathogenic enzymes that contribute to the pathogenesis of infectious diseases (Shimizu et al. 1995). According to Narayanan et al. (2017), the utilization of HA and CS in the environment determines the invasiveness and pathogenicity of these microbes. For instance, gram-positive bacteria that cause infections on the skin or mucosal surfaces produce hyaluronidases, enzymes that break down hyaluronate to initiate infections (Hynes 2000). *Candida albicans* is believed to use periodontal tissue, particularly HA and CS, as a nutrient source for growth (Shimizu et al. 1995).

Fungi capable of producing enzymes that degrade and utilize CS have been isolated from infected patients and animals. These include *Aspergillus niger*, *Candida* sp., *Paracoccidioides brasiliensis*, and *Malassezia pachydermatis*. Their pathogenicity is closely linked to their ability to metabolize CS. In opportunistic fungi such as *Candida* and *Malassezia*, CS is involved in the early stage of infection as a receptor or signal modulator. The interaction of these species with skin cell lines induces transcriptional alterations in different genes (CHSY1, CHSY3, and CHPF) involved in the polymerization and modification (i.e., sulfation pattern of the chains) of CS. Thus, increasing the binding affinity to their host cells (Ordiales et al. 2022a, b, Shen et al. 2023)

Market value and industrial applications of GAGs

Glycosaminoglycans are a significant part of the global biomedical, nutraceutical, pharmaceutical, and cosmetic industries due to their diverse biological functions and therapeutic applications. The global market for GAGs, including well-known compounds such as CS, heparin, and HA, has experienced significant growth in recent years (Nikitovic & Pérez 2021, Credence Research 2025). This is primarily fueled by the growing need for anti-aging cosmetics, osteoarthritis therapies, and anticoagulant treatments. The global GAG market was valued at approximately USD 9,214.53 million in 2023 and expected to grow at 8.67% from 2023 to 2032 (Credence Research 2025).

Looking ahead, fungal roles in the extraction of GAGs as sources and bioengineered hosts for biosynthesis have great potential for scalability and sustainability. Biotechnology and extraction process improvements will probably render fungal sources commercially feasible (Crognale et al. 2022). Mushrooms can be produced on a large scale with low environmental impact, providing a renewable and inexpensive alternative. Besides, as research continues to streamline the extraction process and learn more about the molecular structures of GAGs from mushroom origin, even greater applications can be envisioned in medical treatments and cosmetics. This can open up new frontiers in drug discovery, technologies for wound healing, and other biomedical applications, thus rendering fungal-derived GAGs as a valuable resource for future industrial applications (Iozzo & Schaefer 2015).

Chondroitin sulfate

Chondroitin sulfate and heparin are important contributors in the medicinal and pharmaceutical industries, particularly in the treatment of diseases such as osteoarthritis and thrombosis, respectively. CS, used extensively as a supplement for joint health, accounted for a significant portion of the market, especially in the U.S.A., Europe, and Asia (Volpi 2007, Brito et al. 2023). The global market for CS was valued at USD 1,249.4 million in 2022 and is expected to grow at a CAGR of 3.1% between 2023 and 2030 (Coherent Market Insights 2024). However, CS supplements, used in many countries, are not controlled, wrongly labelled, and claimed to have high levels of purity (Brito et al. 2023).

Pharmaceutical CS, such as *Structum* (Laboratoires Pierre Fabre) and *Chondrosulf* (IBSA Institut Biochimique SA), are used as symptomatic slow-acting drugs for osteoarthritis (SYSADOA). *Structum* has been internationally approved since 1993, containing CS from avian origin (Schneider 2012). On the other hand, *Chondrosulf* is a common prescription medication in Europe that contains fish-derived CS. These drugs provide relief and increase joint mobility after being taken for a few months/years (Reginster & Veronese 2021). In the United States, other CS are controlled as dietary supplements sourced from terrestrial and marine sources, typically in conjunction with glucosamine. There are no laws governing CS as an additive because the FDA recognizes it as a food ingredient and considers it to be "generally recognized as safe." However, the FDA disapproves the proposed use of a dietary supplement called CS as a way to stop joint degeneration (U.S. Food and Drugs Administration 2025).

In addition, CS is also being used as a component of Ophthalmic Viscosurgical Devices (OVDs) approved by the FDA. In particular, DuoVisc System (MyAlcon Professionals 2025) contains 4% CS combined with 1% sodium hyaluronate. The combination creates a triple-negative-charged product that improves adhesion to endothelial tissue. Thus, it is indicated for use during cataract surgery to protect the eye (Espíndola et al. 2012, MyAlcon Professionals 2025). The demand for CS in skin care products and cosmetics has also increased recently as it has been found to have anti-aging properties (Min et al. 2020, Ewald 2021). It is currently available in the market as toners, moisturizers, serums, masks, cleansers, and lip and hair care products (INCIDecoder 2024). Many other uses of CS are being investigated, such as an antithrombotic agent (Fonseca & Mourão 2006, Vessella et al. 2020), anti-cancer activity (Kantor et al. 2016), treatment of gastroesophageal reflux disease and extravasations (Palmieri et al. 2013), and as an emerging biomaterial for drug delivery and tissue engineering (Sharma et al. 2022). However, all are still in preclinical and clinical trials.

Currently, CS sources satisfy the present global demand (Badri et al. 2018). However, it is not a sustainable solution because of problems with extracted CS quality control (which determines its effectiveness), scarcity of source tissues (sources utilized mainly for food), and specific processes (such as pre-treatment and extraction) that have adverse environmental effects (Shen et al. 2023). More sustainable alternatives for producing GAGs are required. Therefore, finding GAGs in mushrooms may offer a non-animal source of GAGs, including CS. In order to successfully develop alternative production methods and use new synthetic biology tools, more research on GAGs is required, particularly in non-animal sources.

Heparin

The demand for heparin, an essential anticoagulant, is also increasing due to the growing incidence of cardiovascular diseases. The worldwide heparin market size was valued at USD 9.83 billion in 2023 and is projected to grow from USD 10.21 billion in 2024 with a CAGR of 4.4% (Fortune Business Insight 2025).

Heparin is functional for prevention as well as treatment of thromboembolic ailment owing to its quick onset action (Acquisto 2014, Zang et al. 2022). The ultralow molecular weight heparin (ULMWH), commercially known as Arixtra® (fondaparinux), is commonly used for thromboembolic events. Fondaparinux is a preferred heparin derivative for the following reasons: its production characteristics, ease of alteration and functional group derivatization, stable structure,

and stable properties. This kind of heparin derivative is chemically synthesized from pentosan methyl of an active fragment of low molecular weight heparin and unfractionated heparin (Baytas & Linhardt 2020).

Heparin administration varies on a case-by-case basis. For an instance, moderate conditions of pulmonary embolism undergo different heparin treatment compared with extreme risk cases. These extreme risk cases include patients with pulmonary embolism initiated by hypertension or shock. In addition, special incidents such as cancer patients and pregnant women with thrombotic pulmonary embolism go through heparin treatment of particular approach (Fransson et al. 2013, Cohen et al. 2014, Konstantinides et al. 2014, Onishi et al. 2016).

The plurality of anti-inflammatory mechanisms of heparin is complicated and partly explained (Oduah et al. 2016, Zang et al. 2022). Despite this fact, the administration of heparin along with its derivatives show effective anti-inflammatory action in acute lung injury, allergic rhinitis, asthma, chronic obstructive pulmonary disease, sepsis, and diseases related to allergic responses (Mahmoud Abd-Elaty et al. 2007, Suleimani et al. 2008).

The source, size length, and structure of heparin affects its anti-inflammatory effects (Tandon et al. 2021). Regardless of high and repeated doses of heparin, the clotting parameters are undisturbed, hence, the bleeding side effects of heparin is mitigated (Martin et al. 2001, Onishi et al. 2016). The presence of heparin in mast cells give away the concept of its immunomodulatory properties such that it hinders the inflammatory reaction, fix impaired endothelial cells, and repair vascular barrier function (Zang et al. 2022).

According to existing studies, there is a distinction between the anti-angiogenic property and the anticoagulant activity of heparin (Lapierre et al. 1996, Kragh et al. 2005). Hence, tumor growth which is related to angiogenesis is inhibited by heparin at the same time decreasing the risks of bleeding (Oduah et al. 2016). In this context, non-anticoagulant heparin (NACH) was produced to further decrease the bleeding risk while enhancing the anti-cancer properties (Oduah et al. 2016, Banik et al. 2021). Additionally, studies on modifying heparin molecular structure via binding with hydrophobic compounds such as bile acids and cholesterol resulted to improved anti-cancer factor while simultaneously decreasing the anti-coagulation effect (Park et al. 2006, 2010). Furthermore, the inhibition of heparin on tumor-related clots promotes better effect on radiotherapy and chemotherapy drugs to cancer patients (Smorenburg & Van Noorden 2001).

The anti-tumor action of heparin spurred up studies on nano-formulations to enhance target drug delivery and increase circulation times for improved therapeutic effects for cancer treatment (Lim et al. 2019, Park et al. 2019, Rajora et al. 2020, Meher et al. 2024). Applications of heparin in blood-related environment, such as drug delivery vehicle and diagnostic agent, are widely accepted due to its anticoagulant properties (Zare et al. 2024).

Furthermore, heparin's ability to bypass the liver and its antimetastatic and antiproliferative properties make it useful for drug delivery (Zare et al. 2024). By combining hydrophobic compounds with hydrophilic heparin (Qiu et al. 2021), researchers created nanoparticles through self-assembly (Nurunnabi et al. 2012). Various heparin conjugates, such as bisdeoxycholyl–heparin, heparin-chlorambucil, heparin-biotin, and heparin-pyropheophorbide (Andrgie et al. 2019, Wu et al. 2021) are successfully formed nanomaterials and nanospheres in aqueous solutions, improving oral absorption and delivery efficiency (Banik et al. 2021).

Under other conditions, studies on employing heparin-based nanotechnology for antimicrobial and bioimaging applications are limited, making these areas promising for future investigation to develop beneficial and commercially viable materials (Zare et al. 2024). The contribution of heparin on functionality enhancement of nanocarriers has been thoroughly reviewed (Thacker et al. 2014). Overall, it is evident that many heparin-based nanoparticles possess intriguing characteristics suitable for medical treatments. Given the advancements in nanotechnology and heparin-based biomolecules, further investigation into heparin nano-formulations is needed (Banik et al. 2021).

Bioengineered heparin (BH) is a synthetic heparin sourced from non-animal materials. The development of bioengineered heparin relies on the chemoenzymatic synthesis and the

configuration must be equal with animal-sourced heparin (Bhaskar et al. 2012, 2013). Works in this context has promised to address the concerns on supply, at the same time quality of heparin active pharmaceutical ingredient (API) (Onishi et al. 2016). On the other hand, there are multiple issues existing under BH synthesis such as the complex and expensive multi-step process, its competition with low-cost heparin API, as well as the regulatory challenges (Onishi et al. 2016).

The advancements of bioengineering and synthesizing heparin molecules are open for improvement. This will further address the needs on supply shortages, synthesis refinement, and clear structure-function of heparin. Wherefore, expanding heparin's applications in various areas as such anti-tumor, anti-inflammatory, and infectious disease treatments (Onishi et al. 2016, Oduah et al. 2016).

Hyaluronic acid

Hyaluronic acid being an important contributor to increased GAG value with a market value at USD 10.04 billion in 2023 (Grand View Research 2024), attributed to its wide use in cosmetic procedures and skincare products (Juncan et al. 2021). As the global population ages and the demand for aesthetic and medical treatments rises, the market is expected to continue expanding at a compound annual growth rate (CAGR) of 7.7% from 2024 to 2030 (Grand View Research 2024).

HA exhibits significant biological activities with applications in cosmetics, skin care, and aesthetic anti-aging (Ye et al. 2025). Numerous HA-based biomedical products have been created because of its non-toxicity, biodegradability, biocompatibility, and non-immunogenicity (Iaconisi et al. 2023). Furthermore, the potential applications of mushroom-derived HA extend beyond cosmetics. In the medical field, it shows promise in wound healing, osteoarthritis treatment, medical orthopedic repair, gynecological cancer monitoring, other pathological conditions and as a drug delivery agent (Ye et al. 2025). HA represents a significant advancement in biotechnology and sustainable resource utilization. HA has been a major component of biomedical research and has seen application in several fields such as tissue engineering and cancer treatments through a multitude of different forms (Dovedytis et al. 2020). Among protein-based hydrogel-forming polymers, different salts of HA, also known as hyaluronan or sodium hyaluronate, are utilized in tissue engineering due to their excellent biocompatibility and biodegradability (Menaa et al. 2011). When chemically modified, HA can take various forms, such as hydrogels, fibers, fibrillar sponges, sheets, and nanoparticulate fluids, making it useful in both research and medical applications (Burdick & Prestwich 2011). HA is also explored in drug delivery systems to treat cancer, ophthalmological diseases, joint conditions, and cosmetic defects (Fallacara et al. 2018). HA is classified as a bioactive, biodegradable, non-immunogenic, and non-thrombogenic substance (Sudha & Rose 2014). It has the ability to spot overexpressed receptors on the surface of the tumor cells, thus can be used to target these abnormal cells to better kill them. With this characteristics, HA has been recognized as drug delivery vehicle (Huang & Huang 2018).

Numerous beauty products with infusion of HA in tropical, oral, as well as injectable forms have been in the market and have been popular in recent years to treat aging-related skin imperfections and wrinkles (DrugBank 2025a). For instance, dermal fillers of HA help in imparting youthful and healthy appearance by replacing the lost tissue volume. Dermal fillers have increased demand in the US market since the introduction of bovine collagen-based dermal fillers in the 1980s (Brandt & Cazzaniga 2008). HA-based dermal fillers becomes the fastest non-invasive esthetic procedure in the US (Wise & Greco 2006). They are resistant to various form of physical and chemical breakdowns, thus have a longer youthful effects to skin elasticity (Matarasso et al. 2006). They helped in the increased production of fibroblasts, fast wound healing, and offers relief from irritated and inflamed skin (Bukhari et al. 2018, American Board of Cosmetic Surgery 2025).

Mushrooms can be a source of HA. For instance, the company, Alpha Environmental which supplies ingredients to the cosmetic and personal care industry is producing HA extracted from *Tremella* (Ultrus Prospectus 2025). Some polysaccharides produced by *Tremella* has water retention capacity comparable to HA. *Tremella* polysaccharide can be used as a moisturizing additive, or it can be a replacement of HA to be used in cosmetics and receive good economic value

(Hui & He 2012). It can reduce the cost by 86% with the same effect when compared with the traditional HA moisturizer (Liu & He 2012). It has been shown in previous research that HA and HA-like substances extracted from mushrooms like *Trametes versicolor* can induce cell proliferation and migration, an important key to tissue regeneration and repair (Teymoorian et al. 2024). As research progresses, it is likely that mushroom-derived HA will be increasingly explored in various applications, due to their unusual skincare and health-promoting properties (Paterska et al. 2024), thus, supporting the expansion of market for ethical and natural products. These results imply that HA obtained from mushrooms may be a good substitute for conventional sources, providing sustainability and effectiveness.

Mushroom-derived HA is a major breakthrough in biotechnology and green resource utilization. With further research, mushroom-derived HA will increasingly be used in a wide range of applications, from cosmetics to medicine. This technology not only fits into the trend towards natural and ethical products but also provides new opportunities for improving human health and well-being through sustainable means.

Challenges and research gaps in animal-derived glycosaminoglycan production and fungi as a sustainable alternative

Glycosaminoglycans, including CS, heparin, and HA, are most often obtained from animal-derived tissues such as those from bovine, ovine, porcine, and various marine species (Sahu et al. 2023, Hou et al. 2025, Oliveira et al. 2025). Animal-based extraction, despite its drawbacks, continues to monopolize and dominate the rapidly expanding glycosaminoglycan production industry (Badri et al. 2018). While these sources provide high yields, they present substantial biosafety concerns. Animal tissues can harbor viruses, bacteria, and prions, increase the risk of zoonotic transmission and initiate thorough regulatory review (Volpi 2007, Wildi et al. 2011). Incomplete purification may result in the presence of residual proteins or nucleic acids, which can elicit immune responses (Song et al. 2021). Such contamination risks demand extensive purification and rigorous quality control processes, thereby increasing production expenses and making pharmaceutical-grade approval more challenging. Furthermore, reliance on animal products also raises sustainability and ethical concerns, as evidenced by the overuse of organisms such as marine species for cartilage extraction and the environmental stresses associated with livestock rearing (Hampton et al. 2021). Traditional sources, like marine life and animal tissues, particularly shark cartilage, are susceptible to ecological problems like overfishing, seasonal variations in availability, and contamination risks (Cobbinah-Sam & Ekaette 2025). Furthermore, there are ethical concerns about the treatment of animals and the environmental impact of sourcing these materials when using GAGs made from animals (Kiani et al. 2022). The extraction process, which generates waste and adds to environmental pollution, also uses hazardous chemicals. Market instability, caused by livestock supply fluctuations and disease outbreaks, further threatens the global GAG supply (Kappes et al. 2023). For instance, in the heparin industry, the heavy reliance on porcine intestinal mucosa as the primary raw material source presents significant vulnerabilities (Fareed et al. 2019). Currently, pig's intestinal mucosa is the only approved source for pharmaceutical-grade heparin in the United States (Al-Hakim 2021). This reliance on a single animal source creates a vulnerable supply chain, as a disease outbreak among pigs could lead to global shortages of this crucial medication. In addition, fungal-derived GAGs offer a more sustainable and ethically acceptable option, as they are free from cultural and religious restrictions limiting animal-derived sources. Unlike porcine or bovine GAGs, which are prohibited by Islam and Hinduism respectively, fungal-based production ensures universal acceptability among diverse populations.

Historical precedents, such as the 2008 heparin crisis triggered by over-sulfated chondroitin sulfate (OSCS) contamination in China, highlight the public health risks associated with relying on a single source for critical pharmaceutical ingredients (Hedlund et al. 2013). This incident, which resulted in serious adverse reactions and deaths, highlighted the vulnerabilities of a globalized supply chain and the need for diversification and stringent quality control measures, according to

medical and pharmaceutical publications. Similarly, animal-derived HA sources such as rooster combs and bovine vitreous humor offer high bioactivity but face contamination, degradation, and scalability issues (Necas et al. 2008, Fallacara et al. 2018). For many years, animal-derived extraction was the conventional approach to obtaining HA; however, it is no longer favored for large-scale production. (Liu et al. 2018).

Apart from biosafety concerns, variability in product composition remains a significant limitation. For example, CS preparations from different organisms and tissues vary in molecular weight, sulfation pattern, and impurity profile, all of which influence biological activity and clinical efficacy (Zhang et al. 2023b). Extraction methods such as enzymatic digestion, alkaline treatment, and proteolysis can alter GAG chain length and sulfation distribution, resulting in inconsistencies between batches that compromise reproducibility (Shen et al. 2023).

Current exploration of fungi in both industrial applications and scientific research is driving the search for more sustainable sources of valuable biomolecules (Hyde et al. 2024). Chemical synthesis, chemo-enzymatic approaches, and biosynthesis using GAG-producing cells including genetically engineered recombinant fungal strains are currently being explored (De Pourcq et al. 2010, Badri et al. 2018). Fungal biotechnology emerges as a highly promising yet underutilized approach to addressing the challenges associated with animal-based glycosaminoglycan production (De Pourcq et al. 2010, Tiwari & Park 2024). Many fungi naturally synthesize GAG-like polysaccharides and possess eukaryotic post-translational modification machinery, enabling the production of structurally complex and functionally active molecules comparable to animal-derived GAGs (Hyde et al. 2019). There are certain advantages to using fungi compared to animal sources and bacteria. As the demand for recombinant proteins and glycoproteins continues to rise, research efforts are increasingly directed toward identifying cost-effective host expression systems. Yeasts and other fungi present attractive alternatives, offering affordable and efficient platforms capable of performing essential eukaryotic post-translational modifications (De Pourcq et al. 2010). Unlike bacterial systems, fungi can glycosylate proteins and modify carbohydrate chains in ways that closely mimic mammalian pathways, making them ideal for producing biologically active GAG analogs (Martínez-Duncker et al. 2014). Yeasts and other fungi naturally add heterogeneous high mannose glycans to their glycoproteins, a feature that can negatively impact the pharmacokinetics of therapeutic proteins and hinder downstream processing efficiency. This limitation can be overcome by engineering their glycosylation pathways to generate more uniform, and when required, human-like glycan structures (De Pourcq et al. 2010).

Another advantage of using fungi in GAG production is their ability to grow and be cultivated on low-cost agricultural byproducts, reducing production expenses while avoiding the ethical and environmental drawbacks of animal harvesting (Borkertas et al. 2025). Mushrooms can be cultivated under controlled conditions using low-cost lignocellulosic substrates, providing a scalable and eco-friendly alternative to animal-based production systems (Hyde et al. 2010). Yeasts and filamentous fungi have been effectively utilized as cell factories for the production of specialized, high-value chemical compounds (Martins-Santana et al. 2018). Large-scale submerged fermentation of fungi offers consistent yields with minimal batch-to-batch variability, and metabolic engineering can be used to optimize biosynthetic pathways for desired molecular weight and sulfation profiles (Martins-Santana et al. 2018). By integrating fungal genomics, synthetic biology, and bioprocess optimization, fungi have the potential to replace or at least significantly supplement animal sources in the global GAG supply chain, ensuring safer, more sustainable, and more resilient production systems.

Future perspective of GAGs from fungi

With regard to commercial GAG safety and possible scarcity, the industry has moved from conventional animal-based processes toward biomanufacturing. Synthetic biology is an emerging approach for optimizing pathways and advancing metabolic engineering (Vaidyanathan et al. 2017, Birchfield & McIntosh 2020, Jin et al. 2021a). It is now feasible to metabolically engineer new capacities in plants or fungi and effectively engineer entire pathways into microbial systems

following the clarification of biosynthetic routes and regulatory variables (Birchfield & McIntosh 2020, Zou et al. 2023). Synthetic biology has promise for the development of fungal chassis cells, biosynthetic gene cluster mining, precision breeding, and cell factories for high-value products such as GAGs (Zou et al. 2023). Despite these considerable successes and advantages in using high-tech approaches the world-wide demands for GAGs still cannot be met. Traditionally, HA was extracted from rooster combs; however, it is now primarily produced through microbial fermentation using yeasts and bacteria, which results in reduced production costs and less environmental pollution (Liu et al. 2011). The recent gram-scale chemoenzymatic synthesis of a heparin dodecasaccharide indicates its potential as an alternative to animal-derived low molecular weight heparin (LMWH) (Jin et al. 2021a).

Further studies of fungal resources are also still required because they have yet to be exhaustively investigated. Investigations on GAGs isolated from mushrooms are still sparse. Although GAGs, such as heparin, CS, and HA, are already popular in their properties related to animal connective tissue, cellular communication, and the immune system, their presence and prospects in fungi are not commonly studied. The conventional sources of GAGs, which are largely obtained from animal tissues, have sustainability, ethical, and safety issues. Such issues, along with the contamination risk associated with animal-derived products, have initiated a transition to seek alternative sources of GAGs, such as those derived from non-animal origins such as fungi (Bhilegaonkar et al. 2014).

Earlier studies suggest that some mushrooms may contain GAG-like compounds with potential bioactivities and therefore be worth considering in the pharmaceutical, cosmetic, medical, and nutraceutical industries (Choocheep & Nathip 2018). However, due to the heterogeneity of mushroom species and variations in growth and extraction techniques, isolation, characterization, and functional assessment of mushroom-derived GAGs are required to analyze their biochemical features and worthiness for applications. This study may open new avenues for the discovery of bioactive compounds in mycology.

The GAG market produced from fungi is greatly promising since the use of fungi is a sustainable, ethical, and environment-friendly source of bioactive substances. Mushrooms have a rich polysaccharide content, and certain species have shown the ability to produce GAGs similar to those found in animal tissues. These fungal GAGs could serve as alternatives for pharmaceutical and cosmetic applications, offering the same functional benefits while addressing the growing consumer demand for cruelty-free and sustainable products as well as the development of products of non-animal origin for various religious and ideological (veganism) reasons worldwide (Choocheep & Nathip 2018, Bhambri et al. 2022). As research into GAGs derived from mushrooms advances, extraction procedures are expected to become more efficient, eventually reducing manufacturing costs and enabling fungal GAGs to compete with conventional sources. In any case, it is necessary to protect the various fungal resources and develop the production of GAGs by biotechnological means respecting environmental standards.

The market value of mushrooms was USD 50.3 billion in 2021 and projected to increase up to USD 115.8 billion by 2030 (Grand View Research 2025). The market potential for mushrooms, as possible sources of GAGs, is likely to expand in the future, especially as they attract more attention as a source of healthy food, meat alternative, and bioenergy as biotechnology and extraction methods improve (Niego et al. 2023b, Llanaj et al. 2023). Increased attention and growing trends towards vegan and ethical products, coupled with the limitations of animal-derived GAGs, have made mushroom-derived GAGs an important innovation for the future. Since mushrooms can be cultivated, they can be a sustainable source of GAGs. Businesses investing in the production of GAGs from mushrooms may benefit from rising consumer and industry interest in sustainable products for skin care, pharmaceuticals, medicinal, and nutraceutical applications. Moreover, with advances in genetic engineering and fermentation technologies, opportunities exist to enhance GAG production in fungi, thereby broadening their industrial applications. This new market has the potential to contribute meaningfully to the overall GAG industry, particularly in markets were ethical and environmental issues influence consumer behavior.

Conclusions

Fungi represent potential sources of GAGs with diverse bioactivities and medical and therapeutic applications. They can also be bioengineered to serve as hosts for GAG synthesis. Further work is needed to fully characterize the structure and mechanism of action of fungi-derived GAGs and to develop effective extraction and purification protocols. More studies are proposed to examine other wild and cultivated mushroom species and microfungi as potential candidates for industrially produced GAGs. Exploring fungi as sources of GAGs not only expands the potential of natural products in medicine but also offers eco-friendly alternatives to traditional synthetic production methods, thus preserving the environment and reducing dependence on limited resources, including animal resources. This review provides context for future studies on the uses of fungal GAGs and their effects in areas that have hitherto focused on their animal-derived equivalents. Our in-depth review of fungi as sources of GAGs also explores their potential uses in medicine, cosmetics, and biotechnology, while highlighting market trends for animal-free products, future prospects, and current research gaps. This perspective highlights the importance of GAGs from fungi and the need for further research on their biochemical activities, with potential for new applications in pharmaceutical, nutraceutical, and related industries, particularly in pharmacology, tissue engineering, and the discovery of bioactive compounds. This review fills knowledge gaps, provides a basis for future research on the potential of fungi for GAG production, and anticipates societal evolution in the use of non-animal GAGs.

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