

A NARRATIVE REVIEW ON THE OCCURRENCE, BIOSYNTHESIS AND APPLICATIONS OF RARE SIMPLE SUGARS DERIVED FROM MACROALGAE

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ABSTRACT

Macroalgae are abundant in bioactive compounds, and their unique polysaccharide content, which includes rare sugars with potential industrial applications, has garnered significant attention in recent years. This review aims to occurrence and applications of rare sugars by examining their occurrence and biosynthesis in macroalgae. A comprehensive analysis of the biosynthetic pathways that lead to the formation of these sugars is essential for understanding their presence in marine organisms. The study emphasizes the importance of precise structural characterization for the identification and quantification of rare sugars, detailing advanced analytical techniques used in this process. It also discusses the challenges associated with extraction and purification, underscoring the need for scalable and cost-effective methods for industrial production. The potential applications of rare sugars span various industries, including food and pharmaceuticals, highlighting their significance in health-related contexts. The review addresses critical issues such as low yields, storage stability, and regulatory challenges, providing a comprehensive overview of the current state of research on rare sugars and their applications.

Keywords: Simple sugars, macroalgae, bioactive molecules, occurrence, applications

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INTRODUCTION

Marine macroalgae and other macroalgae have emerged as promising sources of valuable nutrients and bioactive substances, with applications ranging from food ingredients to nutritional supplements and cosmetics. Despite the fact that oceans cover over 70% of Earth's surface, only a small number of marine organisms have been thoroughly studied and identified. The cell walls of macroalgae contain commercially significant polysaccharides that serve various biological functions. Marine macroalgae, or macroalgae, are rich in diverse polysaccharides that play critical roles in

structural integrity and energy storage within their cells [1-4].

Different types of algae exhibit distinct polysaccharide compositions: brown algae are primarily composed of alginates, which provide structural support and flexibility while storing energy in the form of laminarin; red algae are characterized by carrageenans and agar, sulfated polysaccharides that contribute to cell wall integrity and gel-like properties; and green algae primarily utilize cellulose as a structural component, much like land plants. Storage polysaccharides such as laminarin and floridean starch act as

energy reserves that can be metabolized when needed. Beyond their biological functions, these polysaccharides have attracted significant interest for various human applications, including food production, pharmaceutical research, biomaterial development, and potential nutraceutical innovations. The complexity and versatility of marine macroalgal polysaccharides underscore the remarkable biochemical adaptations of these organisms, revealing that these compounds are dynamic molecules with multiple critical functions.

Fucoidan, predominantly found in brown algae, exhibits variations in molecular characteristics, including length, branching patterns, monomer fractions, and sulfate levels. These structurally variable fucoidans, also known as fucose-containing sulfated polysaccharides, demonstrate bioactive properties influenced by species, thallus age, seasonal variations, and extraction techniques. Although fucose is the predominant sugar, other monomers such as galactose, mannose, glucose, and uronic acids are also present, with some sulfated galactofucans showing comparable ratios of galactose to fucose [5].

Macroalgae are abundant in bioactive compounds like vitamins, minerals, antioxidants, and rare sugars. These components exhibit anti-inflammatory and immune-supporting properties, which are currently being investigated for their potential health benefits. In addition to basic nutrition, macroalgae provide essential proteins, fiber, and omega-3 fatty acids that contribute to overall health and well-being when included in diets. The development of sustainable cultivation techniques, such as offshore farming and integrated multitrophic aquaculture, is underway. However, challenges in market development, environmental impact assessment, and regulatory frameworks remain. Addressing these challenges requires collaboration

among governments, businesses, and the scientific community, along with innovative technologies and sustainable practices [6]. Rare sugars represent a unique class of compounds distinct from common sugars like glucose and sucrose. Characterized by unique molecular arrangements, these molecules show promise in applications including pharmaceutical formulations, skincare products, and wound dressings. Their potential also extends to biotechnological processes such as enzyme synthesis and biofuel production. Ongoing research continues to explore their chemical structures, biosynthesis pathways, and physiological roles. Cultivating macroalgae for rare sugar production aligns with sustainable practices, requiring minimal resources while enabling rapid growth [7-11]. Environmental impact assessments and sustainable practices are essential for minimizing ecological effects. Understanding the potential of rare sugars can benefit industry stakeholders, highlighting opportunities for market expansion, product innovation, and economic development.

The commercial landscape for rare sugars is undergoing significant transformation, driven by increasing market interest in biotechnological and pharmaceutical applications. Macroalgae-derived rare sugars represent an emerging field with substantial potential, evidenced by their diverse applications across multiple industries. This manuscript highlights the growing commercial interest in these compounds, noting their potential uses in functional foods, nutraceuticals, pharmaceuticals, and specialized chemical sectors. Although current commercial products are limited, ongoing research and advancements in extraction technologies suggest promising future developments. The versatility of rare sugars from marine macroalgae—encompassing their potential as low-calorie

sweeteners, bioactive compounds, and precursors for various industrial applications—positions them as a strategic area for biotechnological innovation. This review aims to provide an in-depth exploration of rare sugars from macroalgae, their occurrence and applications.

OCCURRENCE OF RARE SUGARS IN MACROALGAE

The distribution of rare sugars in nature, particularly in various macroalgae species, is notably diverse. While these sugars are less prevalent than more common sugars like glucose and sucrose, they play crucial roles in biological processes and offer potential applications across multiple industries. The occurrence of rare sugars can differ among macroalgae species and even within the same species, influenced by factors such as environmental conditions, geographic location, and growth stage [12]. Understanding the distribution of rare sugars is essential for industries aiming to exploit these compounds for applications in food, pharmaceuticals, and cosmetics. Furthermore, ongoing research enhances our understanding of the bioactive compounds in macroalgae and their potential health benefits [13-17].

These seven sugars—D-glucose, D-fructose, D-xylose, L-arabinose, D-ribose, D-mannose, and D-galactose—are the most commonly utilized in carbohydrate-based refineries. In contrast, most other sugars exhibit an inherent “rarity,” including all forms of monosaccharides and their derivatives, such as uronic acids, sugar alcohols, and modified sugars (deoxygenated, aminated, and methylated), as identified by the International Society of Rare Sugars. While small amounts of these rare sugars exist in nature, primarily in terrestrial plants, they hold significant value, particularly in the pharmaceutical and nutraceutical industries. Due to their generally low-calorie content, they serve as

sweeteners, replacing more common sugars like sucrose, D-glucose, and D-fructose. Rare sugars have demonstrated various physiological effects, including prebiotic properties (sugar alcohols), anti-caries effects (sugar alcohols), anti-diabetic properties (D-tagatose), anti-hyperlipidemic and anti-atherosclerotic effects (D-allulose), anti-inflammatory effects (D-allose), and neuroprotective properties (D-allulose). Recent evidence suggests that rare sugars could serve as a new platform chemical in carbohydrate-based refineries.

Uncommon sugars are typically produced through enzymatic or microbiological processes grounded in the systematic relationships of all potential sugar monomers, following the “Izumoring” concept. This method involves intramolecular reduction-oxidation reactions and regio-selective epimerization/isomerization through enzymatic mechanisms. Although the Izumoring process entails multiple steps, it effectively synthesizes uncommon sugars from the aforementioned seven common sugars. For instance, an enzymatic reaction involving “phosphorylation → dephosphorylation” at 37–45°C over 12–36 hours can preferentially convert aldoses to ketoses with over 90% efficiency [18-20].

BIOSYNTHESIS, EXTRACTION AND IDENTIFICATION OF RARE SUGARS

The process of biosynthesis of rare sugars refers to the enzymatic or microbial synthesis of sugars that are not commonly found in nature. These rare sugars can be advantageous for various industries, including food, cosmetics, and pharmaceuticals. Numerous microorganisms, such as yeast, fungi, and bacteria, are capable of synthesizing these uncommon sugars. Researchers often identify and isolate organisms that either naturally produce the desired rare sugars or can be genetically modified to do so [21-23]. Once a suitable source organism is selected, scientists

examine the biosynthetic pathways involved in synthesizing the target rare sugar. This process includes identifying the genes and enzymes responsible for the synthesis of the sugar. Genetic engineering techniques are frequently employed to enhance the production of rare sugars, which may involve modifying the metabolic pathways of the source organism to increase yield. Using recombinant DNA technology, specific genes can be added, removed, or altered through genetic manipulation.

A common step in the biosynthesis process is fermentation, where the chosen microorganism is cultivated in a controlled environment. The fermentation medium is designed to supply the necessary nutrients and conditions for the microorganism to thrive and produce the desired rare sugar. In addition to microbial fermentation, enzymatic synthesis is another method for producing rare sugars. This approach utilizes specific enzymes that catalyze the conversion of more accessible substrates into the rare sugar. After fermentation or enzymatic synthesis, the rare sugar must be extracted and purified from the fermentation broth or reaction mixture. Various separation methods, including chromatography and crystallization, can be employed to isolate the target compound [24]. The isolated rare sugar is then analyzed and characterized to confirm its identity and purity, often using analytical techniques such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry. After optimizing the biosynthesis process on a small scale, efforts are made to increase production for commercial purposes. This involves enhancing strain performance, maximizing fermentation conditions, and ensuring cost-effective production. Rare sugars have applications in several industries; for example, they can serve as building blocks for bioactive compound synthesis, sweeteners, or prebiotics in the

pharmaceutical sector. The biosynthesis of rare sugars is an interdisciplinary field that integrates genetics, biochemistry, microbiology, and bioprocess engineering, with ongoing advances in genetic engineering and bioprocess optimization aimed at developing sustainable and economical production processes [25-30].

The extraction of macroalgal polysaccharides may involve several phases. These steps include pre-treating the macroalgae, preparing the biomass, employing extraction techniques (traditional solvent extraction versus innovative methods such as ultrasound, microwave, and enzyme-assisted extractions), and applying purification techniques.

Identifying and quantifying rare sugars can be challenging due to their low abundance and structural complexity. Enzymatic techniques and high-performance liquid chromatography (HPLC) are widely used. Since 2004, enzymatic techniques have grown in popularity, especially in human studies. HPLC is a quick and efficient method for detecting the concentration of uncommon sugars, and a simpler reverse phase HPLC method has been devised for distinguishing rare sugars like D-psicose from D-fructose. Another well-established approach for measuring uncommon sugars is to determine sugars in molasses using HPLC after solid-phase extraction. However, several methods have been developed to address these challenges [30-36].

APPLICATIONS

Rare sugars, although found in small quantities in nature, have attracted considerable attention in biotechnology due to their unique properties and potential applications. Their biotechnological uses are diverse, spanning the food and pharmaceutical industries, materials science, and more. As research in this area progresses, it is likely that new and innovative

applications for rare sugars will emerge, further advancing various industries [37-39].

Rare Sugars in Macroalgae-Based Products

The following table provides a comprehensive overview of the major polysaccharides and sugars derived from red, brown, and green macroalgae, highlighting their associated bioactive applications. It summarizes the key biochemical components of each macroalgae type and outlines their uses in various areas, including skin whitening, anti-inflammatory, anti-aging, and pharmaceutical developments [40-44].

Macroalgae extracts are hydrocolloids derived from macroalgae that serve as gelling and thickening agents in a variety of food, pharmaceutical, and biotechnological applications. Approximately 80% of agar is extracted from the macroalgae *Gracilaria*, while around 80% of carrageenan comes from the species *Eucheuma* and *Kapahulu*. Agar (or agar-agar) is a gel-like substance derived from the cell walls of red macroalgae, specifically *Gracilaria*. Nutritionally, agar is a good source of iron and magnesium and offers benefits for digestive, bone, and brain health, as well as aiding in weight loss. Carrageenan, made from edible red macroalgae, promotes gut health and is rich in antioxidants [45].

Health and Nutritional Values

Recent research has examined the chemical properties and biological effects of macroalgae sugars, revealing that the structure and composition of these molecules are crucial in regulating plant defense signaling pathways. Fucans and carrageenans, which contain sulfate groups, are known to activate the salicylic acid signaling pathway and can reduce cholesterol absorption in the gut. Acidic polysaccharides, such as alginic acids and carrageenans, form indigestible ionic colloids, while neutral polysaccharides like agars exhibit water dispersibility. The biological activities of

sulfated macroalgae polysaccharides, including fucoidans, ulvans, and ulvan-derived oligosaccharides, are of particular interest due to their notable antioxidant properties, which help prevent diseases related to free radicals. Fucoidans derived from *Laminaria japonica* have been shown to reduce lipid peroxidation and protect cellular membranes [46-48]. The antioxidant activity of fucoidans is influenced by their molecular weight and sulfate concentration. Additionally, ulvans and ulvan-derived oligosaccharides from the green macroalgae *Ulva pertusa* exhibit antioxidant properties and have been found to lower serum total cholesterol, LDL cholesterol, and triglyceride levels, all significant risk factors for cardiovascular diseases. Sulfated polysaccharides have also been associated with anticoagulant, antithrombotic, and antiviral properties, including effectiveness against HIV, herpes, and hepatitis viruses. Their health benefits have been extensively studied, with biological activity varying based on composition and sulfate levels.

Commercial Benefits

The economic potential of rare sugars derived from macroalgae is gaining traction, particularly for applications in the chemical and pharmaceutical sectors. Macroalgae, which are rich in carbohydrates, have long been recognized as a valuable source for extracting uncommon sugars such as sugar alcohols, deoxy sugars, and sugar acids. Although the market currently offers limited commercial products based on macroalgae polysaccharides, the unique properties of these rare sugars suggest promising opportunities for the development of specialized and platform chemicals [48-51]. Research indicates that macroalgae are a viable source of economically valuable uncommon sugars due to their high carbohydrate content. For instance, the significant presence of mannitol, a rare sugar alcohol, in certain macroalgae species

highlights its potential for commercial use. Despite the current lack of widespread commercial products, increasing global macroalgae production and ongoing research into macroalgae biorefineries indicate a growing interest in harnessing the economic potential of rare sugars from macroalgae. Consequently, while the commercialization of rare sugars from macroalgae is still in its infancy, their distinctive characteristics and potential applications make them a promising area for future industrial development [52-54].

CHALLENGES AND FUTURE PROSPECTS

Research and development are currently focused on the challenges and future prospects of rare sugars derived from macroalgae. Macroalgae, especially green varieties, are rich in carbohydrates and have been explored for their potential applications, including the production of rare sugars. Among these, the polysaccharides found in green macroalgae like *Ulva* spp. are particularly noteworthy due to their ability to yield rare sugars. The versatility, rapid growth, and sustainability of macroalgae have positioned it as a promising resource, drawing increased interest in its applications. However, the specific biologically active components of green macroalgae, particularly rare sugars, have not been thoroughly studied, indicating a need for further research and development in this area [55, 56].

Recent advancements in macroalgae biorefineries have highlighted the potential of carbohydrate-rich macroalgae as a feedstock for bioethanol production, showcasing the feasibility of extracting rare sugars. Nevertheless, current research does not adequately address the challenges and future opportunities associated with these sugars. While the potential for rare sugar production from green macroalgae is recognized, the specific obstacles and prospects in this field remain underexplored. Continued research and development in macroalgae biorefineries

and rare sugar extraction are essential to fully understand and harness the potential of these valuable marine resources.

CONCLUSION

The discovery of rare sugars in macroalgae presents new opportunities that could significantly impact various industries. A thorough investigation of their occurrence and biosynthesis has unveiled the complex biochemistry of macroalgae polysaccharides. To fully leverage the potential of these sugars, it is vital to utilize biotechnological approaches, such as advanced extraction techniques and scalable production methods. Rare sugars possess unique properties and structural diversity, making them valuable for pharmaceutical, food, and other industrial applications. As our understanding of their biological functions grows, so do the possibilities for therapeutic applications and health benefits. However, challenges persist, including the need for standardized analytical methods and achieving high yields in large-scale production. Addressing these challenges necessitates ongoing interdisciplinary collaboration, innovative research strategies, and a commitment to environmentally sustainable practices.

To facilitate the acceptance and integration of rare sugars from macroalgae into diverse products, raising awareness and understanding among stakeholders is crucial. Future research efforts should focus on enhancing our understanding of the intricate relationships between rare sugars and living organisms, optimizing production processes for commercial viability, and exploring new applications in the rapidly evolving field of biotechnology. The quest to harness the potential of rare sugars from macroalgae is an exciting and dynamic journey, filled with opportunities that could transform industries and promote sustainable practices globally.

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