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SEAGRASSES: A PROMISING SOURCE OF BIOACTIVE COMPOUNDS FOR HUMAN HEALTH APPLICATIONS

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ABSTRACT

Seagrasses are unique marine flowering plants that provide critical ecological services and can serve as valuable reservoirs of bioactive compounds with potential health benefits. This review explores the bioactive metabolites found in four seagrass species native to European marine waters: Cymodocea nodosa, Posidonia oceanica, Zostera marina, *and* Nanozostera noltei. *These species exhibit diverse chemical properties, including antioxidants, antimicrobials, and anti-inflammatory agents, making them promising candidates for pharmaceutical, nutraceutical, and cosmetic applications. Despite their promising applications in biotechnology, their full potential remains underexplored due to research and technological limitations. Future studies should focus on optimizing extraction methods, exploring synergistic interactions, and ensuring sustainable utilization of these valuable marine resources.*

Key words: seagrasses, European marine waters, bioactive compounds, human health applications

FANEROGAME MARINE: UNA PROMETTENTE FONTE DI COMPOSTI BIOATTIVI PER APPLICAZIONI NEL CAMPO DELLA SALUTE UMANA

SINTESI

Le fanerogame sono piante marine che forniscono servizi ecologici critici e possono servire come preziosi serbatoi di composti bioattivi con potenziali benefici per la salute. Questa rassegna esplora i metaboliti bioattivi trovati in quattro specie di fanerogame native delle acque marine europee: Cymodocea nodosa, Posidonia oceanica, Zostera marina e Nanozostera noltei. *Queste specie presentano diverse proprietà chimiche, tra cui antiossidanti, antimicrobici e agenti antinfiammatori, che le rendono promettenti candidati per applicazioni farmaceutiche, nutraceutiche e cosmetiche. Nonostante le loro promettenti applicazioni in biotecnologia, il loro pieno potenziale rimane poco esplorato a causa delle limitazioni tecnologiche. Gli studi futuri dovrebbero concentrarsi sull'ottimizzazione dei metodi di estrazione, sull'esplorazione delle interazioni sinergiche e sull'utilizzo sostenibile di queste preziose risorse marine.*

Parole chiave: fanerogame, acque marine europee, composti bioattivi, applicazioni per la salute umana

INTRODUCTION

Seagrasses are the only group of marine flowering plants, uniquely adapted to thrive in underwater environments. Their morphological, physiological, ecological, and genetic adaptations facilitate survival in these habitats, including underwater pollination, internal gas transport, and the presence of epidermal chloroplasts (Hemminga & Duarte, 2000). Originating from terrestrial species, seagrasses have transitioned to marine habitats, forming vast meadows in shallow waters (Papenbrock, 2012). These meadows provide essential ecosystem services, serving as key feeding and breeding grounds for marine organisms (Ruiz-Frau *et al.*, 2017). Referred to as the "lungs of the sea," seagrasses contribute significantly to oxygen production and carbon sequestration, mitigating climate change through the blue carbon storage (Papenbrock, 2012; Bedulli *et al.*, 2020; James *et al.*, 2023). Indeed, seagrass ecosystems are estimated to sequester approximately 140 megagrams of organic carbon (C_{org}) per hectare within the top meter of soil (Fourqurean *et al.*, 2012). This accumulation occurs over centennial to millennial time scales, making seagrass up to 40 times more effective at capturing organic carbon compared to terrestrial forest soils. (Serrano *et al.*, 2021). Additionally, they stabilize sediments, filter pollutants, and enhance water quality (Reynolds *et al.*, 2016; Bonanno & Orlando-Bonaca, 2017). As a result, seagrass meadows are recognized as one of the priority habitats in Europe within the EU Habitat Directive (HD, 92/43/EEC) and the evaluation of their status is crucial for the implementation of the EU Water Framework Directive (WFD), and the Marine Strategy Framework Directive (MSFD) (Orlando-Bonaca *et al.*, 2015). Moreover, they are among the least conserved marine ecosystems (Hu *et al.*, 2021).

Beyond their ecological significance, seagrasses are gaining attention for their rich diversity of bioactive compound with antioxidant, anti-inflammatory, cytotoxic and antimicrobial activities (Ameen *et al.*, 2024). Despite increasing interest in marine-derived bioactives, research on seagrasses remains limited, presenting an opportunity for further exploration (Ribas-Taberner *et al.*, 2025). In recent years, there has been growing interest in seagrass-derived bioactive compounds for biotechnological applications (Rotter *et al.*, 2021, 2023). However, challenges such as preservation of their ecological stability and technological limitations hinder their full integration into biotechnology (Rotter *et al.*, 2021; Gono *et al.*, 2022).

This review provides an in-depth examination of the bioactive compounds of biotechnological relevance in the biomedical field, isolated and characterized from four native seagrass species in European marine waters: *Cymodocea nodosa* (Ucria) Ascherson, *Posidonia oceanica* (Linnaeus) Delile, *Zostera marina* Linnaeus, and *Nanozostera noltei* (Hornemann) Tomlinson & Posluszny. The paper also highlights some areas for future research on these seagrass species that could improve their use for human health while maintaining sustainable practices.

MATERIAL AND METHODS

A systematic literature review was conducted to gain insights into the breadth of studies published on the bioactive compounds of the four European seagrass species and their potential benefits. The literature search, covering 2004–2025, was performed in Scopus Advanced search, VOSviewer and Google Scholar, focusing on peer-reviewed articles and excluding grey literature. The keywords employed in the search included seagrass, *Cymodocea nodosa*, *Posidonia oceanica, Zostera marina* and *Nanozostera noltei,* biotechnology, bioactive compounds, bioactive molecules, bioactive potential, health, pharma and biomedicine.

RESULTS AND DISCUSSION

Bioactive compounds in *Cymodocea nodosa*

Cymodocea nodosa (commonly known as Lesser Neptune grass) is the most common species in shallow, sheltered to semi-exposed Mediterranean sites, forming meadows that can be either mono-specific or mixed with *N. noltei* (Buia *et al.*, 1985). This species has its origins in tropical regions and is currently confined to the Mediterranean Sea and some areas in the North Atlantic, extending from southern Portugal and Spain to Senegal, including the Canary Islands and Madeira (OSPAR, 2010). It can be found in coastal waters, coastal lagoons, inlets and estuaries and other sheltered and semi-exposed habitats (Ivajnšič *et al.*, 2022). It is recognized as a pioneer species, adept at rapidly colonizing bare patches of the sea floor, since its rhizome can grow several meters annually (Boudouresque *et al.*, 1994).

C. nodosa contains several bioactive metabolites with potential pharmaceutical applications (Tab. 1; Fig. 1). Among them, diarylheptanoids and terpenoids have demonstrated antibacterial activity, particularly against mycobacterial strains and methicillin-resistant strains of Staphylococcus aureus (MRSA) (Kontiza *et al.*, 2008). The relatively simple structures of these metabolites also suggest they could be targets for further chemical modification to enhance their antibacterial properties (Kontiza *et al.*, 2008). In addition, diarylheptanoids, especially cymodienol, have shown strong cytotoxicity (Kontiza *et al.*, 2005).

Tab. 1: Bioactive compounds extracted from the four European marine seagrasses and their reported bioactivities. CN =** Cymodocea nodosa**; ZM =** Zostera marina**; PO =** Posidonia oceanica**; NN=** Nanozostera noltei**.

Tab. 1: Bioaktivne spojine, pridobljene iz štirih evropskih morskih cvetnic, in njihove potrjene bioaktivnosti. CN =** Cymodocea nodosa**; ZM =** Zostera marina**; PO =** Posidonia oceanica**; NN =** Nanozostera noltei**.

Compound	Bioactivity	Seagrass species	References
Terpenoids	Antibacterial	CN	Kontiza *et al.* (2008)
Diarylheptanoids	Antibacterial, anticancer/ cytotoxic	CN, ZM	Kontiza *et al.* (2005); Kontiza *et al.* (2008); Li *et al.* (2021); Cacciola *et al.* (2024)
Polysaccharides	Antioxidant, antimicrobial, cytotoxic, antihypertensive, anti-obesity, antidiabetic	CN, PO, ZM	Kolenchenko *et al*. (2005); Berfad & Alnour (2014); Kolsi *et al.* (2015, 2016, 2017a, 2017b, 2018); Benito-Gonzalez *et al*. (2019); Perumal *et al*. (2021); Ribas-Taberner *et al*. (2025)
Phenolics	Antidiabetic, anti-inflammatory, antioxidant, analgesic, antihypertensive, antirheumatic, anti-arthritic, antimicrobial, anticancer/ cytotoxic	CN, PO, ZM, NN	Rees *et al.* (2008); Choi *et al.*, (2009); Subhashini *et al.* (2013); Berfad & Alnour (2014); Barletta *et al.* (2015); Custódio *et al.* (2015); Grignon-Dubois *et al.* (2015); Kolsi *et al.* (2017b); Manck *et al.* (2017); Styshova *et al.* (2017); Farid *et al.* (2018); Leri *et al.* (2018); Benito-Gonzalez *et al.* (2019); Sevimli-Gur & Yesil-Celiktas (2019); Vasarri *et al.* (2020); Ammar *et al.* (2021); Mechchate *et al.* (2021); Vasarri *et al.* (2021); Razgonova *et al.* (2022); Abruscato *et al.* (2023); Grignon-Dubois & Rezzonico (2023); Vasarri *et al.* (2023); Chabbani *et al.* (2024); Kevrekidou *et al.* (2024); Micheli *et al.* (2024); De Leo *et al.* (2025)
Proteins and peptides	Antioxidant, antimicrobial	PO	Berfad & Alnour (2014); Benito-Gonzalez *et al*. (2019); Punginelli et al. (2023)

Furthermore, sulfated polysaccharides derived from *C. nodosa* exhibit a diverse range of bioactive properties, including significant antioxidant, antimicrobial, cytotoxic, antihypertensive activity, anti-obesity and anti-diabetic properties (Kolsi *et al.*, 2015, 2016, 2017a; Perumal *et al.*, 2021; Ribas-Taberner *et al.*, 2025; see Tab. 1). Sulfated polysaccharides derived from *C. nodosa* warrant special attention also for treating male infertility and enhancing sperm quality due to their antioxidant capabilities (Kolsi *et al.*, 2018; Ribas-Taberner *et al.*, 2025).

Among phenolic compounds, the chicoric acid, that was found to be abundant in *C. nodosa*, has high potential for management of metabolic alterations, thus representing a target for treatment of diabetes and its complications (De Leo *et al*, 2025). The hydroalcoholic extract of *C. nodosa* containing phenolic compounds exhibits significant antioxidant activity, which may protect against oxidative stress and be applied for managing metabolic disorders, particularly diabetes, by enhancing insulin secretion and reducing hyperglycemia and lipid levels in the blood (Kolsi *et al.*, 2017b). More recently, Chabbani *et al.* (2024) identified additional phenolic compounds in *C. nodosa*, including sinapic acid, myricetin, and quercetin-3-O-rutinoside, which demonstrate potential therapeutic properties, aimed at combating oxidative stress and inflammation. The extract's safety profile, with no cytotoxic effects observed, further supports its application in skincare products (Chabbani *et al.*, 2024).

Bioactive compounds in *Posidonia oceanica*

Posidonia oceanica (the Neptune grass) is the most important Mediterranean endemic seagrass species, that forms meadows extending from the surface to depths of 40–45 m (Telesca *et al.*, 2015). These meadows provide multiple ecosystem services, including protection of coastlines from erosion, provision of breeding and nesting habitats for economically important species, and serving as a vital source of oxygen while facilitating high carbon sequestration within the matte (consisting of intertwined remnants of roots, rhizomes, and leaves, which effectively trap sediment and organic carbon, creating stable substrates) (Pergent-Martini *et al.*, 2021). The widespread distribution of *P. oceanica* in the Mediterranean Sea suggests that these meadows are the product of ecological and evolutionary processes that have unfolded over centuries (Giakoumi *et al.*, 2013; Telesca *et al.*, 2015).

Extracts of *P. oceanica* have shown anti-diabetic, antioxidant, vasoprotective and antimicrobial activities (Gokce & Haznedaroglu, 2008; Ozbil *et al.,* 2024). Phenolic compounds, such as chicoric, gentisic, ferulic and caftaric acid have potential analgesic, anti-inflammatory, antirheumatic, anti-arthritic and anticarcinogenic activities (Grignon-Dubois & Rezzonico, 2015; Mechchate *et al.,* 2021; Micheli *et al.,* 2024), see Tab. 1. These were also observed in *C. nodosa* and such phenolic similarities between *P. oceanica* and *C. nodosa* imply a possible evolutionary connection that may suggest that these families possess adaptive traits developed in response to comparable environmental pressures (Grignon-Dubois & Rezzonico, 2015). Polyphenols including gallic acid, catechin, epicatechin and chlorogenic acid that were isolated in *P. oceanica* extracts were able to inhibit the expression and activity of gelatinases MMP-2 and MMP-9 (enzymes that break down the extracellular matrix), which are associated with cancer cell invasion and metastasis (Barletta *et al.*, 2015). Additionally, Leri *et al.* (2018) highlighted the significant antioxidant properties of these bioactive metabolites, with potential use in therapeutic applications against malignancies and other chronic conditions due to their ability to impair malignant cell migration through autophagy modulation. Furthermore, the (hydro)alcoholic extracts of *P. oceanica* leaves containing phenols has potential anticancer applications, given their antioxidant, anti-inflammatory and anti-glycation properties (Farid *et al.,* 2018; Sevimli-Gur & Yesil-Celiktas, 2019; Abrsucato *et al.,* 2023; Vassari *et al.,* 2023; Kevrekidou *et al.,* 2024)

Cornara *et al.* (2018) reported that the extract of *P. oceanica*, rich in CA, exhibits significant radical scavenging activity and lipolytic activity. Regarding skin protection, the polyphenols of *P. oceanica* have potential therapeutic applications in treating conditions like psoriatic skin inflammation, indicating its potential use in complementary medicine for inflammatory skin diseases (Micheli *et al.*, 2024). Messina *et al.* (2021) concluded that the phenolic compounds found in *P. oceanica* are also promising candidates for applications particularly in cosmeceuticals and as protective agents against oxidative stress and UV-induced damage. They highlighted that the dried leaves of *P. oceanica* demonstrated significantly higher antioxidant activity that fresh leaves.

P. oceanica butanol extract containing phenolic acids and flavonoids, encapsulated in gelatin nanoparticles, as a promising and effective antidiabetic therapy (Ammar *et al.*, 2021). Additionally, the extract from *P. oceanica* egagropiles (round-shaped conglomerations created by the progressive disintegration of fibrous material sourced from its foliage and transported to nearby coastal areas by waves) showed a moderate inhibition against H5N1 virus (Farid *et al.*, 2018).

P. oceanica extracts containing phenols and flavonoids exhibit anti-inflammatory activities (Vasarri *et al.*, 2020), while those containing polyphenols, polysaccharides and proteins exhibit antioxidant and antimicrobial activities (Berfad & Alnour, 2014; Benito-Gonzalez *et al.,* 2019). The main polysaccharide known from angiosperm land plants in the cell walls is cellulose; however, it is currently lacking biotechnologically relevant biological activity properties for biomedical purposes (Pfeifer & Classen, 2020). The polysaccharides identified in *P. oceanica* that have bioactive qualities include galacturonic acid and xylose, which are components of pectin and hemicellulose. These polysaccharides contribute to the antioxidant, antifungal, and antiviral properties of the extracts, making them potential candidates for use in food and pharmaceutical applications (Benito-Gonzalez *et al.*, 2019).

Bioactive compounds in *Zostera marina*

Zostera marina (commonly known as Eelgrass) is one of the world's most widespread marine phanerogams, predominantly found along the temperate and cold coasts of the Northern Hemisphere, but it is also present in the Mediterranean Sea, where its distribution is more limited. The species fulfils important roles as an ecosystem engineer in estuarine and coastal waters, enhancing biodiversity, contributing to sediment stability, and carbon and nutrient

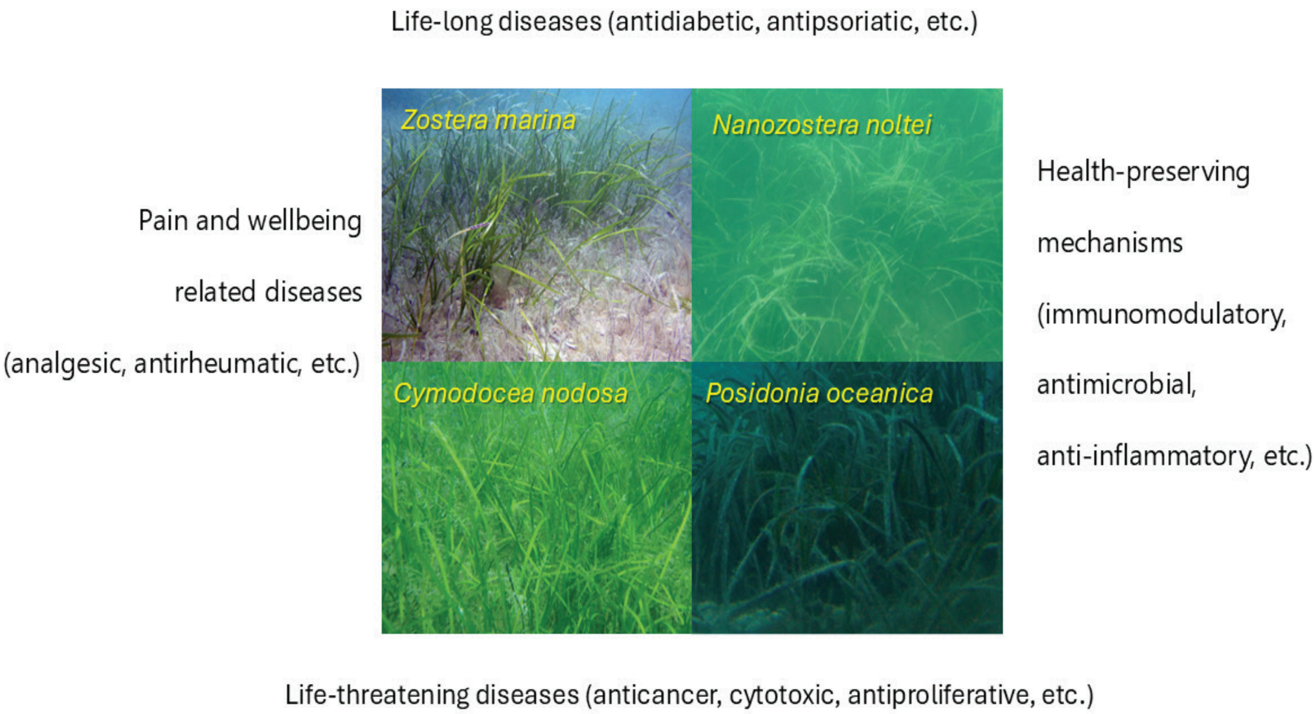

Fig. 1: Potential bioactive properties of the four European marine seagrasses (photos: Tihomir Makovec).
Sl. 1: Potencialne bioaktivne lastnosti štirih evropskih morskih cvetnic (slike: Tihomir Makovec).

storage (Duarte *et al.*, 2013; Blok *et al.*, 2018). Distinct life history strategies and a wide tolerance to a range of salinity and temperature conditions allow this seagrass species to exploit areas from brackish estuaries to open oceans over a large geographical range (Nejrup & Pedersen 2008).

Z. marina leaves decay very slowly and indeed, extracts from this seagrass exhibited antimicrobial and antioxidant activities (Zheng *et al.*, 2014). Polysaccharides from *Z. marina* exhibit significant antioxidant activities (see Tab. 1). An example is zosterin, a low-etherified pectin with potential in reducing lipid peroxidation products, suggesting its use in therapeutic applications for oxidative stress-related conditions (Kolenchenko *et al.*, 2005). Additionally, zosterin has been associated with various pharmacological effects, including hypocholesterolemic, antibacterial, antiviral, and immunomodulating properties, indicating its broad potential in medical applications (Kolenchenko *et al.*, 2005).

Phenolics, such as zosteric acid and others, have shown potential as antimicrobial agents (Rees *et al.,* 2008; Choi *et al.,* 2009). Rosmarinic acid (RA) from *Z. marina* was also recognized for its antioxidant properties (Custódio *et al.,* 2016). Rosmarinic acid and flavonoids extracted from *Z. marina* have also evidenced therapeutic potential in the treatment of type 2 diabetes and hyperlipidemia, due to their antioxidant, anti-inflammatory, and immunomodulatory activities (Styshova *et al.*, 2017). Several polyphenols from *Z. marina* (chicoric, p-coumaric, rosmarinic, benzoic, ferulic and caffeic acids) exhibited significant cytotoxic effects against various cancer cell lines, indicating their potential use as chemotherapeutic agents in cancer treatment and as preventive supplements in oncology (Sevimli-Gur & Yesil-Celiktas, 2019). *Z. marina* polyphenols also have potential applications in pharmaceutical industry due to their antioxidant and anti-inflammatory properties (Grignon-Dubois & Rezzonico, 2023; Razgonova *et al.*, 2022).

Diarylheptanoids extracted from *Z. marina* exhibited selective cytotoxic effects and significant inhibition of the HCT116 colon cancer cell line and potential for reducing tumor growth *in vivo* (Li *et al.,* 2021; Cacciola *et al.,* 2024).

Bioactive compounds in *Nanozostera noltei*

Nanozostera noltei (the dwarf eelgrass) is widely distributed along the northeastern Atlantic coasts, from Norway to Mauritania, and in the Mediterranean and Black Seas (Short e*t al*., 2007). This species frequently thrives in meadows of *C. nodosa* in the infralittoral belt, but it can be found in a variety of habitat types with variable salinity. In lagoonal systems, it establishes a narrow band within the mediolittoral zone, demonstrating its ability to endure partial desiccation (Lipej *et al*., 2006).

Only in recent decades several studies have examined the phenolic profile of this species (see Tab. 1), with rosmarinic, caffeic and zosteric acids having antioxidant properties (Grignon-Dubois *et al.,* 2012; Subhashini *et al.,* 2013). Phenolic compounds, flavons and flavonoids from *N. noltei* suggest potential applications in pharmaceuticals (Manck *et al*., 2017).

Extracts of *N. noltei* are notable for their ability to chelate both copper and iron ions, potentially aiding in the reduction of oxidative stress and associated conditions (Custódio *et al*., 2016). This seagrass has demonstrated significant toxicity to various cell lines, suggesting promising applications in cancer research, particularly in targeting hepatocarcinoma cells, and may also contribute to alleviating Alzheimer's disease (Custódio *et al*., 2016).

Sourcing and extraction of biotechnologically relevant bioactive compounds

Despite the ample evidence that indicates seagrasses as a resource for novel health and pharmaceutical formulations, it is important to highlight that seagrasses provide an excellent substratum for epiphytic organisms (such as bacteria, fungi, protozoa and algae), making these organisms an integral component of seagrass ecosystems (Borowitzka *et al*., 2006). In addition, distinct microbial communities within the seagrass leaves, roots, flowers, fruits, seeds and the rhizosphere are likely involved in ecologically important processes that benefit plants (Tarquinio *et al*., 2021). These microbial communities may be promoting the production or might be the main source of biotechnologically relevant secondary metabolites (Panno *et al.,* 2013; Rotter *et al.,* 2021). When bioprospecting for novel compounds, it is therefore important to sterilize the seagrass surfaces (targeting epiphytes) and conduct molecular analyses to assess the presence of microbial genetic markers. This can identify the producer organism of the biotechnologically relevant compound.

Regardless of the source of the main biological activities, it is important to again highlight that seagrass ecosystems are now recognized as critical habitats supporting biodiversity and ecosystem services (Duarte *et al*., 2025). Hence, when confirming the bioactivity and target sector for compounds from seagrasses, sustainable sourcing of the biomass and supply of biomolecules must be considered to maintain the ecological stability of these fragile communities (Rotter *et al*., 2020, 2021). In the case of seagrasses, research can rely on harvesting or beach wrack, provided that their harvesting is sustainable and does not affect the ecosystem balance in coastal areas (Rudovica *et al*., 2021). Wherever possible, harvesting can also be substituted/complemented by modern biotechnology approaches including systems biology and metabolic engineering (Rotter *et al*., 2024). Finally, to contribute to environmental sustainability to an even higher degree, besides sourcing, extraction methods should be improved by means of greener methodologies avoiding the use of toxic organic solvents (Benito-González et al., 2019).

CONCLUSIONS

Seagrass meadows are among the most essential and productive yet threatened benthic habitats, warranting significant scientific attention, particularly in the field of biotechnology. The bioactive metabolites found in marine plants have been shown to address various human health concerns, including several diseases, and hold promise for developing new natural-based therapeutic products.

The bioactive compounds found in the reviewed seagrass species exhibit a diverse array of health-promoting properties, positioning them as significant resources for the development of novel therapeutic drugs. Their bioactive potential highlights their ability to act as inhibitors of various harmful pathogens within the pharmaceutical sector. These compounds also show promise in treating metabolic disorders and cancers. Nevertheless, this review does not cover the literature on human clinical trials involving bioactive molecules derived from seagrasses or the sustainable production of drugs, considering the yield, maintenance of ecological balance or the use of green extraction processes, as this represents a separate and extensive area of research. Many bioactive metabolites from seagrasses remain unidentified, and ongoing research aims to uncover all relevant compounds that contribute to human well-being. Future research should focus on environmentally and economically sustainable extraction methods for metabolites with significant therapeutic potential.

Further studies should investigate the long-term stability and shelf life of seagrass extracts and their use in various formulations. Additionally, future research should explore the potential synergistic effects of various seagrass bioactive compounds, both among themselves and in combination with other ingredients, to enhance product effectiveness. Finally, as the extraction of bioactive compounds from marine resources continues to expand globally, it is crucial to assess the environmental impact of harvesting seagrass meadows. This will ensure that sustainable practices are upheld while utilizing this valuable resource. Hence, extraction from seagrasses or their epiphytes should be complemented by using metabolic engineering and chemical synthesis.

MORSKE CVETNICE: OBETAVEN VIR BIOAKTIVNIH SPOJIN ZA UPORABO V ZDRAVSTVU

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POVZETEK

Morske cvetnice so edinstvene morske rastline, ki zagotavljajo ključne ekološke storitve in lahko služijo kot dragoceni viri bioaktivnih spojin s potencialnimi koristmi za zdravje ljudi. Ta pregled obravnava bioaktivne metabolite, prisotne v štirih vrstah morskih trav, ki so domorodne v evropskih morskih vodah: Cymodocea nodosa, Posidonia oceanica, Zostera marina *in* Nanozostera noltei. *Te vrste izkazujejo raznolike kemijske lastnosti, vključno z antioksidativnim, protimikrobnim in protivnetnim delovanjem, zaradi česar so obetavne za uporabo v farmacevtski, nutracevtski in kozmetični industriji. Kljub njihovemu potencialu v biotehnologiji pa ta ostaja premalo raziskan zaradi raziskovalnih in tehnoloških omejitev. Prihodnje študije bi se morale osredotočiti na optimizacijo metod ekstrakcije, raziskovanje sinergijskih učinkov ter zagotavljanje trajnostne uporabe teh dragocenih morskih virov.*

Ključne besede: morske trave, evropske morske vode, bioaktivne spojine, uporaba za zdravje ljudi

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