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Identification of Active Compounds of *Eucheuma spinosum* as Antidiabetic and Antioxidant Candidates

Metabolomic and In Silico Approaches

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ABSTRACT

Diabetes mellitus (DM) is a non-communicable disease with an increasing global prevalence, and the long-term use of synthetic antidiabetic drugs is often associated with adverse side effects. Therefore, the exploration of natural antidiabetic agents with high efficacy and minimal toxicity is urgently needed. Red algae *Eucheuma spinosum* has been reported to contain bioactive metabolites with various pharmacological activities; however, its antidiabetic and antioxidant potential remains insufficiently explored. This study aimed to evaluate the antidiabetic and antioxidant activities of *E. spinosum* through integrated in vitro and in silico approaches. Metabolite profiling using LC-HRMS identified 2,373 compounds in the alga extract. Antioxidant assays revealed strong activity with an IC_{50} value of 97.72 ppm. In vitro antidiabetic assays demonstrated inhibitory activity against α-amylase and α-glucosidase enzymes. Eighteen compounds with the highest abundance were selected for molecular docking and molecular dynamics simulations against 1B2Y, 5NN8, and 1CB4 target proteins. The results indicated that Undecyl 3,4,5-trihydroxybenzoate and nobiletin exhibited strong binding affinity and stable interactions with all three receptors. These findings suggest that E. spinosum is a promising source of natural antidiabetic and antioxidant compounds, particularly Undecyl 3,4,5-trihydroxybenzoate and nobiletin, which warrant further investigation.

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Introduction

Diabetes mellitus (DM) is a major non-communicable metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin secretion, insulin action, or both [1]. The global incidence of DM continues to increase annually, making it a significant public health concern. Diabetes is often referred to as a silent killer because it can progressively affect multiple organ systems and present with symptoms such as polyphagia, polydipsia, polyuria, paresthesia, and unintended weight loss [2]. Persistent hyperglycemia induces endothelial dysfunction through glucose autooxidation, leading to oxidative stress and excessive production of free radicals, which contribute to the development of diabetic complications and increased morbidity and mortality [3].

According to the International Diabetes Federation (IDF), approximately 589 million people worldwide are currently living with diabetes, with a substantial proportion residing in the Western Pacific Region, including Indonesia, where diabetes prevalence has increased markedly over the past decade. Despite the widespread use of synthetic antidiabetic drugs, their long-term administration is frequently associated with adverse side effects, prompting growing interest in safer natural therapeutic alternatives [4]. Marine algae have emerged as promising sources of bioactive compounds with diverse pharmacological properties, including antioxidant and antidiabetic activities. Indonesia hosts approximately 45% of the world's seaweed biodiversity, with red algae being particularly rich in structurally diverse secondary metabolites such as terpenoids, polyethers, acetogenins, and other halogenated compounds that are attractive candidates for drug discovery [5]–[13].

Eucheuma spinosum, a red alga abundantly distributed in South Sulawesi, remains relatively underexplored despite evidence suggesting its broad biological activities [13],[14]. From a bioinformatics-driven drug discovery perspective, the integration of metabolite profiling with structure-based computational approaches enables efficient screening of natural compounds against key molecular targets involved in diabetes pathogenesis. Inhibition of carbohydrate-hydrolyzing enzymes such as α-amylase and α-glucosidase, along with modulation of oxidative stress–related pathways, represents a rational strategy for identifying potential antidiabetic and antioxidant agents from natural sources. Although marine-derived natural products have gained attention for diabetes management, studies on red algae—particularly Eucheuma spinosum—remain largely limited to preliminary bioactivity assessments or partial chemical characterization. Integrated investigations linking comprehensive metabolite profiling with molecular-level mechanistic evaluation are still scarce. Therefore, this study seeks to bridge this gap by employing an integrative approach that combines metabolomic analysis and in silico modeling to elucidate the therapeutic potential of Eucheuma spinosum.

This study addresses this gap by combining LC-HRMS–based metabolite profiling with in vitro antidiabetic and antioxidant assays and in silico structure-based analyses, including molecular docking and molecular dynamics simulations targeting key diabetes-related enzymes. This integrative framework enables a systematic assessment of the chemical composition, biological relevance, and potential molecular interactions of E. spinosum metabolites, thereby providing a more mechanistic basis for evaluating its potential as a source of natural antidiabetic and antioxidant candidates

Material And Methods

This study was conducted from July to October 2025 at the Pharmacology Laboratory, Megarezky University, and the Radiation Chemistry Laboratory, Hasanuddin University. *Eucheuma spinosum* was collected from Topejawa, Takalar, South Sulawesi, Indonesia. Analytical-grade solvents and reagents, including methanol, chloroform, n-hexane, ethyl acetate, acids, α-amylase, α-glucosidase, ABTS, quercetin, and gallic acid, were used. Instruments included an analytical balance, vortex, centrifuge, water bath, oven, rotary evaporator, UV–Vis spectrophotometer, and LC-HRMS. Computational analyses employed high-performance hardware (Intel® Core™ i9-14900K, NVIDIA RTX 5070, Apple M1) and software/web platforms: PubChem, PDB, PreADMET, PyMOL, VMD, DOCK6, AMBER Tools, and Toxtree.

The study employed integrated in vitro and in silico approaches. Dried Eucheuma spinosum was macerated in methanol, and metabolite profiling was conducted using LC-HRMS. Antidiabetic activity was evaluated via α-amylase and α-glucosidase inhibition (quercetin as control), and antioxidant activity by ABTS radical scavenging assay (gallic acid as reference). In silico analyses encompassed screening of identified metabolites, prediction of biological activities, assessment of drug-likeness (Lipinski's Rule of Five), molecular docking and dynamics to evaluate ligand–receptor stability, and ADMET profiling to determine pharmacokinetic and toxicity properties.

Results and Discussion

The methanolic extract of Eucheuma spinosum was obtained by maceration for 3 × 24h with daily solvent replacement. Maceration was selected to avoid thermal degradation of thermolabile secondary metabolites [6]. Antioxidant activity was evaluated using the ABTS radical scavenging assay, which measures the ability of compounds to reduce the $ABTS^{+}$ radical, indicated by a decrease in absorbance at 743 nm [15]. Gallic acid, a well-known phenolic antioxidant, was used as a positive control [16].

The extract exhibited concentration-dependent antioxidant activity at 50, 100, and 150 ppm, yielding an IC_{50} value of 97.72 ppm. Based on established criteria, this value categorizes

the extract as having strong antioxidant activity (IC_{50} = 50–100 ppm) [17]. Lower IC_{50} values indicate higher antioxidant capacity, suggesting that E. spinosum extract possesses a substantial ability to neutralize free radicals. The ABTS assay results are summarized in Table 1.

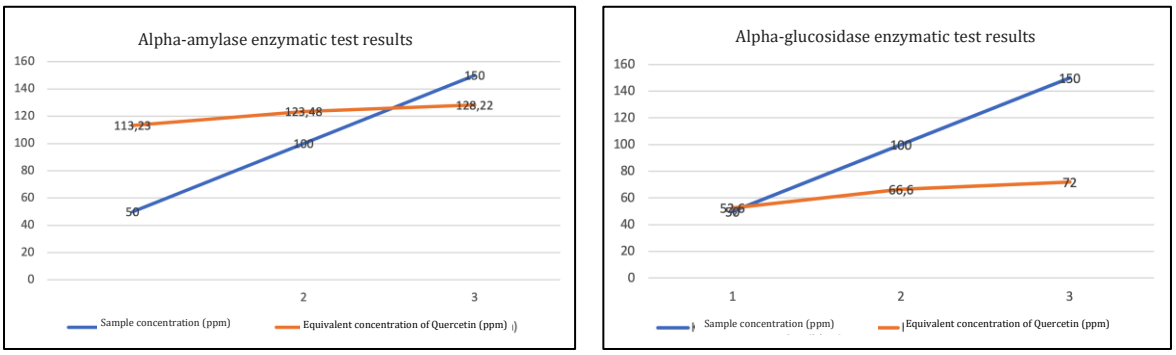
Table 1. ABTS Radical Scavenging Activity of the E. spinosum Methanolic Extract

Consentration (ppm)	Absorbance	% Inhibition	IC_{50} Value
50	0.0833	20.83	
100	0.1951	48.78	97.72
150	0.3391	84.78	

The antidiabetic potential of the E. spinosum extract was assessed through inhibition assays against α-amylase and α-glucosidase enzymes. α-Amylase catalyzes the hydrolysis of polysaccharides into oligosaccharides, while α-glucosidase further converts oligosaccharides and disaccharides into absorbable monosaccharides in the small intestine [18],[19]. Inhibition of these enzymes is a widely accepted strategy for controlling postprandial hyperglycemia. Quercetin, a flavonoid with well-documented antidiabetic activity, was used as a positive control [20].

The extract demonstrated dose-dependent inhibition of both α-amylase and α-glucosidase at concentrations of 50, 100, and 150 ppm. As shown in Fig. 1, increasing extract concentration resulted in higher quercetin-equivalent inhibitory activity, indicating a positive correlation between dose and enzyme inhibition. These findings suggest that the E. spinosum extract effectively suppresses carbohydrate-hydrolyzing enzymes and are consistent with previous reports describing the antidiabetic potential of E. spinosum extracts [18]. Notably, the observed bioactivities are likely attributable not only to individual active compounds but also to synergistic interactions among multiple constituents present in the crude extract. Such synergistic effects are commonly reported in complex plant and algal matrices, particularly involving polyphenolic and flavonoid compounds, and may enhance enzyme inhibition beyond the activity of isolated compounds [21].

Metabolite profiling of the methanolic extract was performed using liquid chromatography–high resolution mass spectrometry (LC–HRMS), which enables untargeted detection of molecular features in complex biological samples with high mass accuracy and chromatographic resolution [22],[23]. The LC–HRMS analysis resulted in the detection of 2,373 molecular features across the chromatographic run. These features were tentatively annotated based on accurate mass matching against reference databases and subsequently grouped into major metabolite classes, including alkaloids, flavonoids, terpenoids, carbohydrates, proteins, and mineral-associated compounds. Fig. 2 illustrates the mass spectrogram obtained from *E. spinosum* extract analysis.



(a) (b)

Fig. 1. Dose-dependent antidiabetic activity of Eucheuma spinosum extract. (a) α-Amylase inhibition expressed as quercetin-equivalent activity across increasing extract concentrations. (b) α-Glucosidase inhibition expressed as quercetin-equivalent activity across increasing extract concentrations.

Given the well-established role of phenolic and flavonoid compounds in antioxidant and antidiabetic activities, subsequent analyses focused on these metabolite classes. Strong positive correlations between total phenolic and flavonoid contents and in vitro bioactivities have been widely reported [24]. Polyphenols confer protection against diabetes through reactive oxygen species scavenging, attenuation of oxidative stress, and modulation of inflammatory signaling, including suppression of tumor necrosis factor-α (TNF-α) [25]. Consistent with this profile, the methanolic extract of E. spinosum exhibited strong antioxidant activity in the ABTS assay (IC_{50} = 97.72 ppm). Given the extract's chemical complexity, this activity likely arises from additive or synergistic interactions among phenolic and flavonoid constituents rather than a single dominant compound. The results of the screening of the most abundant phenolic and flavonoid compounds are summarized in Supplementary 1.

From the LC–HRMS dataset, 18 phenolic and flavonoid compounds were selected for downstream in silico analysis. The selection was based on a combination of criteria, including relatively high signal intensity (as an indicator of higher relative abundance), consistent chromatographic behavior, and the availability of reliable structural information in public chemical databases. Molecular features with low abundance, ambiguous annotations, or insufficient structural data were excluded. This targeted selection approach was applied to prioritize compounds most likely contributing to the observed in vitro bioactivities while ensuring robustness and feasibility of subsequent computational analyses.

PASS prediction suggested moderate antidiabetic and high antioxidant probabilities for several phenolic and flavonoid compounds, particularly Eu18, Eu9, and Eu8. While Pa values below 0.7 indicate modest predicted activity, such values are commonly observed for natural products and may still be biologically relevant, especially when compounds act cooperatively in a crude extract. PASS analysis, using Pa (Potential Activity) and Pi (Potential

Inactivity) parameters via the Way2Drug PASS webserver [26]. Detailed results are provided in Supplementary 2.

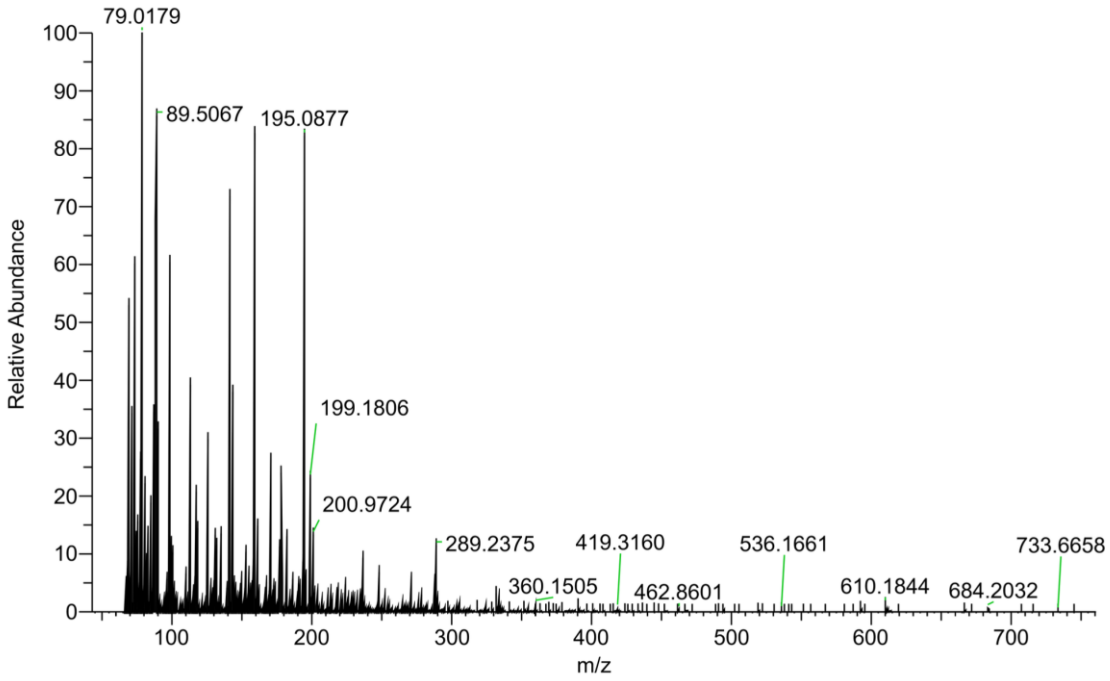


Fig. 2. Representative LC–HRMS mass spectrum of the methanolic extract of *E spinosum*

Following the prediction of compound potential, drug-likeness was evaluated using Lipinski's Rule of Five, with results provided in Supplementary 3. This rule assesses oral bioavailability based on five criteria: hydrogen bond donors ≤5, hydrogen bond acceptors <10, molecular weight <500 g/mol, molar refractivity (MR) between 40–130, and logP <5 [27]. Among the 18 selected compounds, only Eu7 slightly violated the MR criterion (34.11) but remains a viable oral drug candidate. Molecular weight influences membrane permeability, while logP reflects lipophilicity and absorption potential. Hydrogen bond donors and acceptors further affect the energy required for cellular uptake, collectively informing the compounds' pharmacokinetic suitability [28].

Molecular docking is a computational approach to predict ligand binding affinity to protein receptors, an essential tool in in silico drug discovery [29]. In this study, all test compounds were docked to three receptors: 1B2Y (human pancreatic α-amylase), 5NN8 (human lysosomal acid α-glucosidase), and 1CB4 (bovine Cu-Zn superoxide dismutase). Receptor structures were obtained from the PDB, while ligands and reference compounds (quercetin for antidiabetics, gallic acid for antioxidants) were drawn and geometry-optimized using the Hartree-Fock method [30]. Docking was performed in Dock6 after preparation in Chimera, with grid scores quantifying interaction strength through van der Waals and electrostatic potentials [31]. Validation via redocking of native ligands yielded RMSD <2 Å, confirming protocol reliability [32]. Eu9 and Eu8 showed the highest binding affinities toward

1B2Y (-54.70) and 5NN8 (-47.95), respectively, surpassing quercetin, indicating strong antidiabetic potential. Detailed grid scores are provided in Supplementary.

Table 2. Total Binding Free Energy (ΔG) of Ligand–Receptor Complexes

No	Reseptor	Ligan	H	TS	Total Free Energy Binding (kcal/mol)
1	1B2Y	Eu9	-31,91	3,59	-35,3
		Kuersetin	-42,1	5,11	-47,21
2	5NN8	Eu8	-23,91	2,74	-26,65
		Kuersetin	-24,63	18,41	-43,04
3	1CB4	Eu8	-19,51	5,87	-25,38
		Asam galat	-21,19	4,01	-25,2

Docking scores alone are limited by rigid receptor assumptions, necessitating molecular dynamics (MD) simulations to evaluate complex stability under physiological conditions. MD is a computational technique that simulates the dynamic behavior of atoms in a molecular system over time using Newtonian mechanics [33,34]. In this study, MD simulations were performed using Ambertools25, with outputs including RMSD, RMSF, protein-ligand contacts, and total binding free energy calculated via the MM-GBSA method (Table 2). The ΔG binding reflects ligand-receptor interaction strength, with more negative values indicating stronger affinity. While quercetin showed more negative ΔG values than the test ligands for 1B2Y and 5NN8, gallic acid's binding energy was comparable to Eu8, suggesting the ligands remain viable candidates. Differences between docking and MD binding energies arise from methodological distinctions: docking treats receptors as rigid and uses simplified implicit solvent models with statistical scoring functions, whereas MD accounts for receptor-ligand flexibility, explicit solvation, and enthalpy/entropy contributions, providing a more realistic estimation of binding stability [35].

Molecular dynamics (MD) results were visualized in 2D and 3D formats. 2D RMSD and DCCM plots for 5NN8 bound to Eu8 and gallic acid are shown in Fig. 4. RMSD reflects the average atomic displacement between receptor and ligand [36]. The 5NN8–gallic acid complex exhibited light purple-orange patterns, indicating a relatively stable conformation but higher internal fluctuations. In contrast, 5NN8–Eu8 displayed a more homogeneous RMSD, suggesting faster convergence and greater dynamic stability. DCCM analysis revealed that gallic acid induced distributed positive and negative correlations across residues, reflecting dynamic internal movements [37]. Conversely, Eu8 showed a dominant red pattern with fewer anticorrelated regions, indicating stronger residue synchronization and more stable interactions. These findings suggest that Eu8 maintains consistent binding and exhibits higher conformational stability with 5NN8 than the control ligand.

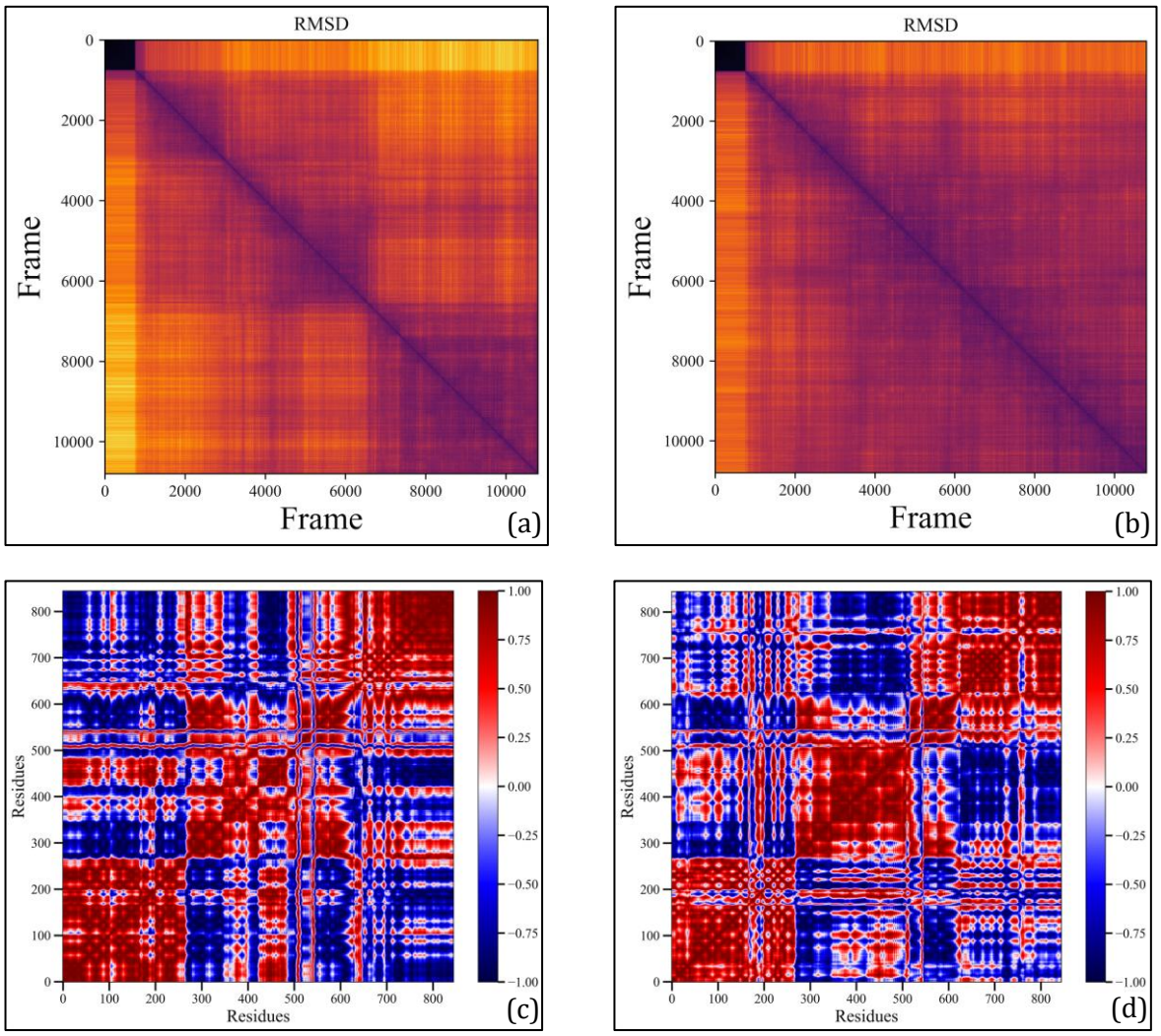


Fig. 3. MD analysis of 5NN8 with test and control ligands: (a) RMSD of 5NN8–gallic acid; (b) RMSD of 5NN8–Eu8; (c) DCCM of 5NN8–gallic acid; (d) DCCM of 5NN8–Eu8.

ADMET prediction was performed to evaluate the pharmacokinetic and toxicity profiles of Eu8 and Eu9 [38],[39]. Using preADMET and Toxtree, parameters including Caco-2 permeability, human intestinal absorption (HIA), plasma protein binding (PPB), blood-brain barrier (BBB) permeability, P-glycoprotein interactions, Kroes TTC, mutagenicity, and carcinogenicity were assessed (Suppl. 5). Both ligands exhibited moderate Caco-2 permeability (4–50 nm/sec) and high HIA (>70%), while Eu8 showed high PPB (>90%) and BBB penetration (>2), in contrast to Eu9 (<90% PPB, BBB <0.1). Both compounds were predicted to be non-mutagenic and non-carcinogenic. These results indicate favorable absorption, distribution, and safety profiles, highlighting that compound-specific pharmacokinetics, alongside enzymatic affinity, determine therapeutic potential. Furthermore, these findings support the potential of Eu8 and Eu9 as promising candidates for further preclinical investigation in antidiabetic drug development.

Conclusion

The methanolic extract of Eucheuma spinosum showed notable antidiabetic and antioxidant activities. Among the identified metabolites, nobiletin and Undecyl 3,4,5-trihydroxybenzoate exhibited strong receptor interactions and favorable ADMET properties, highlighting their potential as lead compounds for the development of antidiabetic and antioxidant therapeutics.

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Conflict of Interest

The authors should declare that there is no conflict of interest.

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