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Mechanistic pathways underlying the antidiabetic potential of sea grapes (*Caulerpa spp.*): A systematic review across experimental and human evidence

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A R T I C L E I N F O

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A B S T R A C T

Sea grapes (*Caulerpa lentillifera* and *Caulerpa racemosa*) are edible green seaweeds of interest for glycaemic control, but the evidence is dispersed across heterogeneous assays and primarily in preclinical models. We conducted a PRISMA 2020 systematic review (PROSPERO CRD420251121741), searching PubMed, Scopus, and Web of Science from inception to 1 August 2025, with citation chasing. Studies evaluating sea-grape foods/processed products, extracts/fractions for glycaemic outcomes or diabetes-relevant mechanisms were synthesised using a tier-aware hierarchy (enzyme/cell/animal/human) reflecting their proximity to glycaemic regulation. Forty-nine studies were included, dominated by animal and enzyme-tier evidence with three human studies. Findings were most consistent for proximal mechanisms—α-glucosidase and α-amylase inhibition and attenuation of postprandial glycaemic excursions—whereas insulin sensitivity and glucose uptake pathways were

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supportive but preclinical-only. Antioxidant and anti-inflammatory outcomes were common but less diabetes-specific and rarely confirmed in humans. Sea grapes show promise for postprandial glycaemic control, but translation into functional-food applications requires food-grade standardised preparations, compositional characterisation, harmonised outcomes, and adequately powered meal-challenge trials.

1. Introduction

Metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension and non-alcoholic fatty liver disease, are leading contributors to global morbidity and premature mortality (Chew et al., 2023; Danpanichkul et al., 2025; Quitério et al., 2022). Together, these conditions account for substantial disability-adjusted life years (DALYs) and deaths worldwide. In GBD 2021 estimates, hypertension contributed 226 million (95% UI 190–259 million) and T2DM contributed 75 million (95% UI 63–90 million) DALYs in 2021, with the burden of common metabolic diseases rising over the past three decades (Zhang et al., 2024). These conditions drive downstream morbidity largely through cardiovascular disease, stroke, chronic kidney disease, and certain cancers (Dina et al., 2025; Roth et al., 2020). Their prevalence has risen across high-income and low- and middle-income settings, driven by urbanisation, physical inactivity, population ageing, and energy-dense diets (Ruze et al., 2023). Because these disorders frequently cluster as metabolic syndrome, cardiometabolic risk is compounded over the life course (Kim & Hwang, 2018; Zhang & Lerman, 2017).

Despite effective pharmacological and lifestyle-based interventions, sustained metabolic control remains difficult for many individuals due to barriers to access, late diagnosis, treatment burden, and challenges in maintaining recommended targets for glycaemia, lipids, blood pressure, and body weight (Saleem et al., 2025). These challenges are often unequally distributed, with greater constraints among people experiencing lower socioeconomic status, food insecurity, limited access to preventive care and healthy food environments, and higher competing demands, contributing to persistent inequities in metabolic outcomes (Brown et al., 2019; Militao et al., 2024; Reeder & Reneker, 2024). These constraints have intensified interest in complementary, scalable approaches that can be integrated into daily life, including food-based strategies and functional foods with plausible metabolic benefits (Fekete et al., 2025).

Edible seaweeds have emerged as candidates within this broader strategy. Sea grapes, such as *Caulerpa lentillifera* and *C. racemosa,* are edible green seaweeds traditionally consumed across East and Southeast Asia and Pacific Island nations (Choudhary et al., 2021; Pangestuti et al., 2025). Sea grapes are typically low in energy and provide fibre, minerals, and bioactive compounds, including sulphated polysaccharides, phenolics, and carotenoids, which may plausibly modulate glycaemic response, lipid handling, oxidative stress, and inflammation (Kahwa et al., 2025). Sea grapes contain soluble polysaccharides, particularly glucans and sulphated polysaccharides, whose biological activity is influenced by monosaccharide composition, sulphation pattern, glycosidic linkage, and molecular weight; phenolic compounds with antioxidant and enzyme-inhibitory potential; carotenoids such as β-carotene, lutein, and related pigments; and alkaloids such as caulerpin, a bis-indole metabolite reported in edible *Caulerpa* species (Syakilla et al., 2022). This structural diversity and different fractions may contribute differentially to digestive enzyme inhibition, redox modulation, gut-mediated effects, and downstream metabolic signalling. They are culturally acceptable in several Asia–Pacific settings and can be cultivated in controlled aquaculture systems, which can support more reliable and standardised supply where appropriate (Duarte et al., 2022; García-Poza et al., 2020). Collectively, these features support sea grapes as a scalable, lower-impact functional food option, particularly where long-term access to pharmacotherapy is constrained (Dalle Grave et al., 2010; Wells et al., 2017).

Mechanistic studies suggest sea grapes may act through complementary pathways relevant to diabetes and metabolic regulation, including inhibition of carbohydrate-digesting enzymes (α-glucosidase and α-amylase), attenuation of postprandial hyperglycaemia, modulation of insulin signalling and metabolic regulators (e.g., AMPK and PPAR pathways), and antioxidant and anti-inflammatory effects implicated in insulin resistance and cardiometabolic dysfunction (du Preez et al., 2020; Joel et al., 2018; Magwaza & Islam, 2025; Shannon & Abu-Ghannam, 2019). Previous reviews have generally considered sea grapes within broader syntheses of seaweeds, *Caulerpa* phytochemistry, or general health-promoting properties, rather than systematically evaluating species-specific antidiabetic mechanisms across mechanistic, preclinical, and human evidence tiers (Ganesan et al., 2019; Garcia-Perez et al., 2023; Zubia et al., 2020). Interpretation is further limited by heterogeneity in species identification, processing, extraction, dosing, and outcome measurement (Flórez et al., 2017; Quitério et al., 2022).

Importantly, while previous reviews have summarised the bioactive properties of seaweed in relation to metabolic health, they have generally treated mechanistic findings descriptively, without explicitly distinguishing between biological plausibility and translational relevance. There has been limited effort to systematically integrate evidence across mechanistic, preclinical, and human tiers to prioritise pathways based on their proximity to clinically meaningful glycaemic outcomes. This limits the utility of existing syntheses for informing clinical research, functional food development, and policy decision-making. To address this gap, this review introduces a tier-aware mechanistic synthesis framework that explicitly links mechanistic pathways to evidential directness and clinical interpretability.

Definition of mechanistic hierarchy

Primary antidiabetic (glycaemic) mechanisms: Primary evidence refers to mechanisms that directly influence glycaemic control through inhibition of carbohydrate digestion, attenuation of postprandial glucose excursions, or enhancement of glucose uptake and insulin sensitivity.

Secondary metabolic modifiers related to diabetes: Secondary evidence comprises metabolic mechanisms that indirectly affect glycaemic regulation through lipid digestion, lipid storage, and body composition.

Supportive and background biological pathways: Supportive evidence includes biological pathways that do not directly lower blood glucose but may modify disease progression through oxidative stress reduction and inflammation control

Research question and objectives

Research question: What is the nature, strength, and distribution of evidence linking sea grapes (*C. lentillifera* and *C. racemosa*) to antidiabetic and metabolic outcomes across mechanistic, preclinical, and human evidence tiers?

Objectives:

1. To identify and synthesise in silico, in vitro (enzyme and cell), in vivo (animal), and clinical (human) studies evaluating sea grapes against glycaemic and diabetes-relevant metabolic outcomes.
2. To classify reported effects within a hierarchical framework comprising (i) primary antidiabetic mechanisms, (ii) secondary metabolic modifiers, and (iii) supportive background mechanisms.
3. To summarise evidence consistency and strength across mechanisms and tiers using structured semi-quantitative summaries.
4. To map evidence density and gaps to inform future mechanistic research, standardise preparation, and design clinical trials.

Conceptual framework

This review is anchored in a hierarchical conceptual framework (the 'Diabetes Mechanism Spine'; Fig. 1) that organises sea-grape effects by (i) mechanistic proximity to glycaemic control and (ii) evidential directness to clinically relevant outcomes. At the proximal level, inhibition of intestinal carbohydrate-digesting enzymes (α-glucosidase and α-amylase) is a well-established route to attenuate postprandial glucose excursions, a recognised therapeutic target in type 2 diabetes (Alssema et al., 2021; Hossain et al., 2020; Ogunyemi et al., 2022; Peter et al., 2009). Sea-grape constituents (notably polyphenols and sulphated polysaccharides) have been reported to inhibit these enzymes in vitro and in studies focused on *Caulerpa*, supporting this primary pathway (Dissanayake et al., 2022; Fajriah et al., 2021; Sharma & Rhyu, 2014). Because sea grapes are also a fibre-containing food, food-matrix effects may additionally dampen postprandial glycaemic responses by slowing digestion and absorption (Giuntini et al., 2022; Mao et al., 2021). Secondary modifiers include improvements in insulin sensitivity and glucose uptake, as well as modulation of lipid handling and adiposity, mechanistically consistent with AMPK signalling and PPAR-γ–linked pathways that regulate insulin action and lipid–glucose crosstalk (Choi et al., 2014; Entezari et al., 2022; Leonardini et al., 2009; O'Neill, 2013). Surrounding these are supportive background mechanisms, particularly antioxidant and anti-inflammatory effects, which are biologically plausible contributors to improved metabolic milieu but are less specific to glycaemic control (Oguntibeju, 2019). Finally, the framework is tier-aware: evidence closer to clinical decision-making is typically more 'direct' than mechanistic models, aligning with established evidence hierarchy and indirectness concepts used in evidence appraisal (Howick et al., 2026). To our knowledge, this is among the first sea-grape-focused syntheses in the seaweed or functional food literature to explicitly integrate mechanistic proximity with evidential directness across translational tiers, allowing mechanisms to be prioritised not only by frequency of reporting but also by their relevance to clinically interpretable outcomes. Abbreviations and acronyms used in this manuscript are listed in Supplementary Table S1

2. Methods

2.1. Protocol, registration and reporting standards

This systematic review was conducted according to a pre-specified protocol and reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). The protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews; registration number: CRD420251121741) (Adhikary et al., 2025). Ethical approval was not required because the review synthesised only published data.

2.2. Eligibility criteria

We included primary research spanning five evidence tiers: in silico studies; in vitro enzyme assays; cell-based experiments; animal models; and human observational or interventional studies. Eligible studies evaluated sea grapes defined as *Caulerpa lentillifera* and/or *C. racemosa*, administered as whole foods, processed products, extracts, fractions, or explicitly derived compounds. We included full-text journal articles and conference proceedings/abstracts only when they provided sufficient methodological detail and extractable outcome data to support synthesis; otherwise, they were excluded. We excluded non-primary research (e.g., reviews, editorials), studies of non-*Caulerpa* seaweeds, multicomponent or co-interventions where the independent effect of sea grapes could not be isolated, and reports lacking extractable methodological or outcome information relevant to diabetes-related endpoints.

2.3. Information sources and search strategy

The evidence base was identified through systematic searches of PubMed, Scopus and Web of Science from inception to 01 August 2025 (Suppl. Table S2). Searches were supplemented by backward and forward citation tracking of included studies and relevant reviews, using species- and mechanism-related terms. No language restrictions were applied at the search stage.

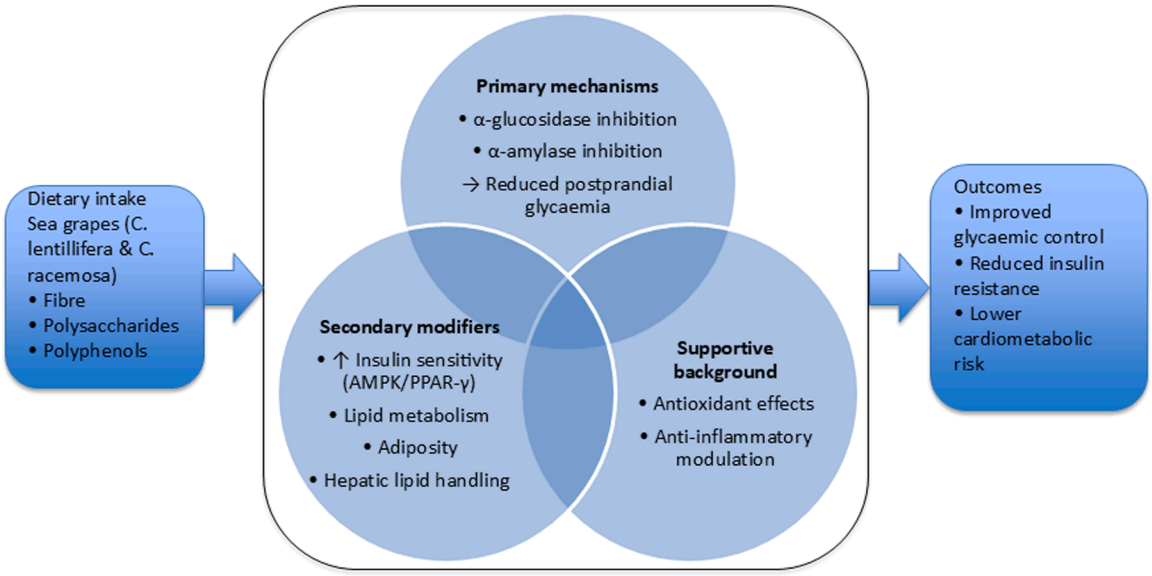

Fig. 1. Diabetes Mechanism Spine: hierarchical conceptual framework for sea-grape effects on diabetes-related pathways. Sea-grape constituents (e.g., polysaccharides, polyphenols, fibre) are mapped to (i) primary proximal mechanisms (α-glucosidase/α-amylase inhibition and postprandial glycaemia), (ii) secondary metabolic modifiers (insulin sensitivity/glucose uptake; lipid handling; adiposity; hepatic lipid metabolism; AMPK/PPAR-γ–linked pathways), and (iii) supportive background mechanisms (oxidative stress and inflammatory modulation). The framework also reflects evidential directness across tiers (mechanistic → animal → human)(Howick et al., 2026; Leonardini et al., 2009; O'Neill, 2013).

2.4. Study selection

Screening proceeded in two stages: title/abstract screening followed by full-text assessment.Prior to manual title/abstract screening, we used Rayyan's automation feature to flag records likely to be irrelevant. These flagged records were verified by reviewers and removed before screening, and are reported in the PRISMA flow diagram as 'records marked as ineligible by automation tools'. Two reviewers (RKA and SM) screened independently, resolving disagreements by consensus and, where needed, consultation with a third reviewer (HS). Study selection is summarised in the PRISMA 2020 flow diagram (Fig. 2).

2.5. Data extraction and synthesis

Data were extracted using a structured template that captured bibliographic characteristics, evidence tier, study design, country of the corresponding author, sea-grape species and preparation (including processing state), exposure/intervention characteristics (e.g., formulation, dose/concentration, duration), comparators, and diabetes-related outcomes. Evidence was synthesised using a tier-aware mechanistic hierarchy comprising primary antidiabetic mechanisms, secondary metabolic modifiers, and supportive background mechanisms. Given heterogeneity in study designs, preparations, dosing metrics, and outcome reporting, we prioritised structured narrative synthesis supported by semi-quantitative summaries and evidence mapping, rather than performing meta-analysis. For enzyme-based outcomes, we applied pragmatic potency categories to reported IC_{50}/EC_{50} values (high: $\leq$100 μg/mL; moderate: 100–500 μg/mL and low: >500 μg/mL) to support structured cross-study comparison of crude extracts and fractions. These thresholds were used as interpretive categories for narrative synthesis rather than as formal regulatory or pharmacological benchmarks and were considered alongside assay conditions based on reported data.

Where multiple reports appeared to originate from the same underlying experiment, study population, or dataset, they were identified and treated as a single study during synthesis to avoid double-counting, and in such cases, data were extracted primarily from the most comprehensive report, with supplementary methodological or outcome details taken from companion reports where relevant (Higgins et al., 2024).

2.6. Risk-of-bias and quality assessment

Risk of bias was assessed using tier-appropriate tools: Risk of Bias (RoB) 2 for randomised human trials; ROBINS-I for non-randomised human studies; SYRCLE-informed appraisal for animal studies; and domain-based checklists for in vitro and in silico studies focusing on reporting transparency, assay validity, controls and replication (in vitro) and model preparation/validation (in silico). Two reviewers assessed independently, resolving disagreements by consensus. Domain-level judgments were used descriptively to contextualise the findings.

3. Results

3.1. Study selection

Database searching identified 3193 records from PubMed (n = 1330), Scopus (n = 993), and Web of Science (n = 870). Before screening, 1137 records were removed, comprising duplicates (n = 637), records marked as ineligible by automation tools (Rayyan) (n = 497), and other removals (n = 3). The remaining 2056 records were screened at the title/abstract level, and 1728 were excluded (Fig. 2). Full-text assessment included 328 database-sourced reports, of which 282 were excluded because they did not evaluate sea-grape species (n = 42), did not include diabetes-related outcomes within scope (n = 234), or were review articles (n = 3) or conference abstracts/proceedings without sufficient extractable data (n = 3). This yielded 44

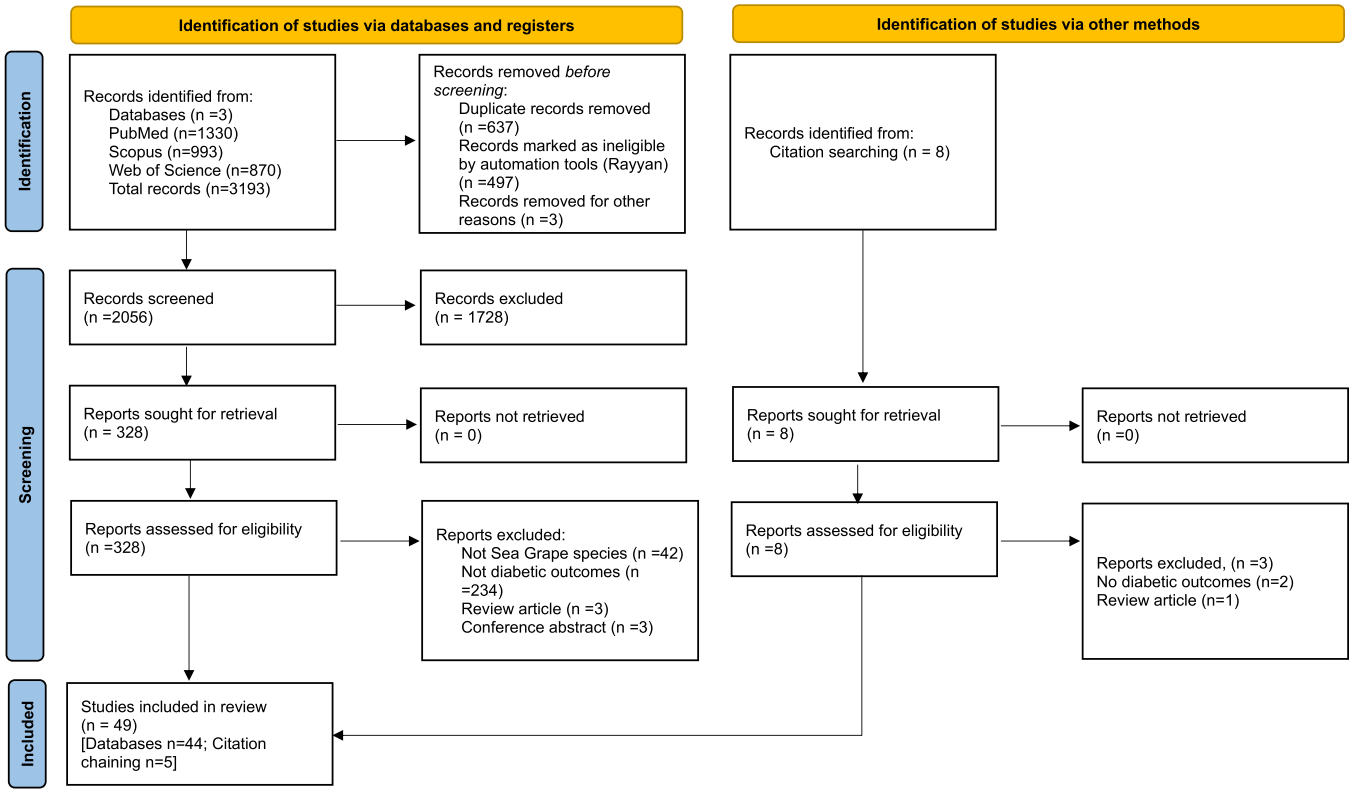

Fig. 2. PRISMA 2020 flow diagram for study selection. Flow of records identified, screened, assessed for eligibility and included, with reasons for exclusion at full-text assessment. Diagram adapted from Page et al., 2021 (Page et al., 2021) PRISMA 2020 statement.

studies from database searching. Citation searching identified 8 additional reports, of which 5 met the inclusion criteria, resulting in a total of 49 studies (Fig. 2, Suppl. Table S3).

3.2. Study characteristics

Included studies (N = 49) were predominantly full-text journal articles, with one conference proceeding retained because it provided sufficient methodological detail and extractable diabetes-related outcomes for synthesis. The evidence base was largely recent: publication volume was low and intermittent prior to 2020 (≤2 studies/year, including no included studies in 2016–2017), then increased sharply from 2020 onwards, peaking in 2023 (10 studies) and remaining high in 2024–2025 (8 and 6 studies, respectively); overall, 38/49 (77.6%) studies were published during 2021–2025 (Suppl. Fig. S1). Corresponding authors' institutional affiliations were most frequently based in Indonesia (18/49, 36.7%) and Thailand (7/49, 14.3%), followed by China (6/49, 12.2%) (Table 1); these data reflect author affiliation and should not be interpreted as study setting or material origin. Harvest/sourcing location of sea-grape material was reported for 23/49 (46.9%) studies; where clearly identifiable, material was most commonly sourced from Thailand (7/49, 14.3%) and Indonesia (3/49, 6.1%), with smaller contributions from Malaysia, Vietnam, Pakistan, China, Egypt, and Brazil, while 26/49 (53.1%) studies did not report harvest/sourcing location (Table 1).

Sea-grape species were split between *C. lentillifera* (25/49, 51.0%) and *C. racemosa* (22/49, 44.9%), with mixed-species studies comprising 2/49 (4.1%) (Table 1). The evidence base was therefore distributed almost evenly across the two species, and the available studies did not indicate a clear species-specific difference in antidiabetic efficacy; instead, observed variation appeared more likely to reflect differences in preparation, extract composition, and study design than species alone.

In terms of processing state, powder was the most common form (28/49, 57.1%), followed by dried materials (10/49, 20.4%), other or processed forms (8/49, 16.3%), and fermented products (2/49, 4.1%), whereas fresh preparations were rare (1/49, 2.0%). In terms of preparation type, most studies evaluated fractionated or isolated compounds (31/49, 63.3%), with fewer investigating crude extracts (11/49, 22.4%), whole food/material interventions (5/49, 10.2%), or fermented products (2/49, 4.1%) (Table 1). These patterns indicate that the literature is weighted towards processed and laboratory-derived preparations rather than minimally processed consumer-relevant food forms.

Extraction approaches were heterogeneous. Organic solvent-only extraction was the most common solvent category (27/49, 55.1%), followed by water-only extraction (6/49, 12.2%) and water plus organic solvent systems (4/49, 8.2%), while 9/49 studies (18.4%) involved whole foods, formulated products, or other contexts in which a conventional extraction solvent was not applicable. The most common extraction method was maceration or soaking (16/49, 32.7%), whereas hot-water or aqueous extraction, ultrasound-assisted extraction, enzymatic extraction, organic solvent extraction or partitioning, and other multi-step workflows were each less frequent. Across evidence tiers, the literature remained dominated by preclinical studies, with animal (25/49, 51.0%) and enzyme-tier (22/49, 44.9%) evidence most common, alongside more limited cell-based (11/49, 22.4%) and human (3/49, 6.1%) evidence, in silico evidence was present in six studies (12.2%), typically as docking or modelling undertaken alongside wet-lab experiments, highlighting a clear translational gap (Table 1).

3.3. Risk of bias and study quality

Overall, the overall risk-of-bias judgement was low risk for 18/49 (36.7%) studies, some concerns for 14/49 (28.6%), and unclear for 17/49 (34.7%); no studies were judged high risk of bias. Animal studies were most commonly rated unclear (15/25, 60.0%), whereas enzyme-tier and cell-based studies were more frequently judged low risk of

Table 1
Characteristics of included studies (N = 49).

Section	Characteristic	Category	n	%
A. Evidence base profile				
	Evidence tier	In silico	6	12.2
		Enzyme (cell-free)	22	44.9
		Cell-based	11	22.4
		Animal	25	51.0
		Human	3	6.1
	Year of publication	≤ 2015	5	10.2
		2016–2020	6	12.2
		2021–2025	38	77.6
	Country (Corr. author)	Indonesia	18	36.7
		Thailand	7	14.3
		China	6	12.2
		Pakistan	3	6.1
		Malaysia	3	6.1
		Republic of Korea	3	6.1
		Taiwan	2	4.1
		Indonesia/Republic of Korea	2	4.1
		Australia	1	2.0
		Brazil	1	2.0
		Egypt	1	2.0
		Sri Lanka	1	2.0
		Indonesia/Republic of Korea (collaboration)	1	2.0
B. Sea-grape material and preparation				
	Caulerpa species	*Caulerpa lentillifera*	25	51.0
		Caulerpa racemosa	22	44.9
		Mixed (*lentillifera* + *racemosa*)	2	4.1
	Harvest/sourcing location	Thailand	7	14.3
		Indonesia	3	6.1
		Malaysia	2	4.1
		Vietnam	2	4.1
		Pakistan	2	4.1
		China	1	2.0
		Egypt	1	2.0
		Brazil	1	2.0
		Reported but unclear	4	8.2
		Not reported	26	53.1
	Processing state	Fresh	1	2.0
		Dried	10	20.4
		Powder	28	57.1
		Fermented	2	4.1
		Other/processed	8	16.3
	Preparation type	Whole food/material	5	10.2
		Crude extract	11	22.4
		Fraction/isolated compound	31	63.3
		Fermented product	2	4.1
	Extraction solvent	Organic solvent(s) only	27	55.1
		Water + organic solvent(s)	4	8.2
		Water only	6	12.2
		Mixed/sequential solvents	1	2.0
		Not applicable	9	18.4
		Not reported/unclear	2	4.1
	Extraction method	Maceration/soaking	16	32.7
		Hot-water / aqueous extraction	5	10.2
		Ultrasound-assisted extraction	3	6.1
		Enzymatic extraction	3	6.1
		Organic solvent extraction / partitioning	5	10.2
		Fermentation / food-product preparation	2	4.1
		Other / complex multi-step extraction	5	10.2
		Not applicable	7	14.3
		Not reported/unclear	3	6.1

Notes: Evidence-tier counts are not mutually exclusive; a single study may contribute to more than one tier (e.g., in silico plus enzyme assay or animal experimentation). Country (Corr. author) indicates corresponding author affiliation, whereas Harvest/sourcing location indicates the reported origin of sea-grape material (when available).

bias. In silico studies were consistently judged as some concerns, and human studies were largely assessed as some concerns using RoB 2. Full study-level judgements and tier summaries are provided in Suppl. Tables S4a–S4d. The prevalence of 'unclear risk' ratings indicated inadequate reporting rather than explicit evidence of flawed conduct, particularly in animal studies where key methodological domains such as sequence generation, allocation concealment, blinding and handling of incomplete outcome data were insufficiently described, with similar limitations also evident in some in vitro and in silico studies regarding replication, comparator clarity and model validation.

3.4. Processing, characterisation, and implications for food application

To better assess the translational relevance of the evidence base for food use, we further examined plant part, source type, processing profile, fractionation, analytical characterisation, standardisation, extract yield, and storage-related reporting across the included studies (Table 2). Most studies used whole thallus or edible biomass (39/49, 79.6%), whereas waste or by-product biomass was less common (3/49, 6.1%), and only one study focused exclusively on an isolated peptide or compound. Source reporting was limited: 15/49 studies (30.6%) explicitly used farmed or aquaculture-derived material, 5/49 (10.2%) used wild-harvested material, and 1/49 (2.0%) evaluated a commercial product, while the source remained unclear in 28/49 (57.1%). This restricted the ability to assess how cultivation context, harvesting environment, or product provenance may have influenced composition and observed metabolic effects.

The processing profile was dominated by dried or laboratory-processed preparations. Dried whole biomass or powder accounted for 20/49 studies (40.8%), while a further 9/49 (18.4%) used dried biomass as the starting material for extract preparation. Formulated foods, beverages, or supplements were evaluated in 10/49 studies (20.4%), and purified extracts or fibre-rich fractions in 9/49 (18.4%). Although the presence of formulated products increases the practical relevance of the evidence base, much of the literature still relied on preparations that were more representative of mechanistic or laboratory workflows than of standardised consumer-ready food products.

Characterisation and standardisation were often limited. Nineteen studies (38.8%) used crude extracts, whole products, or unfractionated preparations, whereas more detailed fractionation methods such as chromatographic purification, polysaccharide precipitation/deproteinisation, and liquid–liquid partitioning were each used in smaller subsets of studies. Only 8/49 studies (16.3%) clearly reported chromatography- or mass spectrometry-based profiling, and explicit standardisation markers were reported in just 5/49 (10.2%). Reporting of extract yield and storage conditions was also sparse, appearing in only 4/49 (8.2%) and 6/49 (12.2%) studies, respectively. Overall, these patterns indicate that although some studies incorporated more advanced preparation and characterisation procedures, the majority of sea-grape interventions remained incompletely characterised and weakly standardised from a food-application perspective.

3.5. Evidence synthesis by mechanistic hierarchy

3.5.1. Primary antidiabetic mechanisms

Across the mechanistic hierarchy, the most consistent and translation-ready evidence clustered around pathways proximal to glycaemic control, particularly digestive enzyme inhibition and postprandial glycaemic attenuation (Tables 3, 6 and 7). Quantification metrics included IC_{50}/EC_{50} values (μg/mL) or percentage inhibition in enzyme assays, and fasting glucose, OGTT/iAUC, insulin, and HbA1c in animal and human studies. Enzyme inhibition dominated as the primary mechanism, with evidence from the base. α-Glucosidase inhibition was reported in 16 studies and was represented across tiers (enzyme n = 16; cell n = 5; animal n = 4; human n = 1), with 100% of studies demonstrating a positive direction of effect. α-Amylase inhibition was reported

Table 2
Processing, characterisation, and food-application considerations of sea-grape preparations across included studies (N = 49).

Domain	Category/level	n (%)	Food-application relevance
Plant part used			
	Whole thallus / edible biomass	39 (79.6)	Supports food relevance because most studies used edible biomass, but this does not necessarily reflect consumer-ready or standardised products.
	Waste / by-product biomass	3 (6.1)	Relevant to value-add utilisation, circular-economy approaches, and development of secondary food ingredients.
	Isolated peptide / compound only	1 (2.0)	Useful for mechanistic clarification, but less directly representative of food use.
	Not reported / unclear	6 (12.2)	Reduces reproducibility and limits interpretation of whether the tested material reflects edible biomass.
Source type			
	Farmed / aquaculture	15 (30.6)	Favourable for future food application because aquaculture can support supply reliability, traceability, and batch standardisation.
	Wild / natural beds	5 (10.2)	Potentially relevant to traditional food use, but may introduce greater compositional and contaminant variability.
	Commercial product	1 (2.0)	Most directly relevant to consumer-facing application, although too infrequent to support firm conclusions.
	Not reported / unclear	28 (57.1)	A major limitation for food translation because provenance, traceability, and source-related quality variation cannot be assessed.
Processing profile			
	Dried whole biomass / powder	20 (40.8)	Most compatible with shelf-stable ingredients and practical incorporation into noodles, drinks, bakery products, and supplements.
	Dried biomass + extract preparation	9 (18.4)	Common in mechanistic studies, but less directly comparable with customary food intake.
	Purified extract / fibre fraction	9 (18.4)	Potentially useful for ingredient development, but may overstate applicability to whole-food use.
	Formulated food / beverage / supplement	10 (20.4)	Most directly relevant to real-world food application because these studies approximate consumer-facing delivery formats.
	Synthetic / isolated compound preparation	1 (2.0)	Lowest direct food relevance; mainly informative for mechanistic interpretation rather than product translation.
Fractionation approach			
	None / crude extract or whole product	19 (38.8)	Simpler preparations may be easier to translate to foods, although compositional precision is lower.
	Chromatographic purification / fractionation	8 (16.3)	Improves chemical precision, but reduces direct comparability with minimally processed food products.
	Polysaccharide precipitation / deproteinisation	6 (12.2)	Relevant to development of fibre- or polysaccharide-rich ingredients with possible functional-food applications.
	Liquid–liquid partitioning / solvent fractionation	7 (14.3)	Useful for identifying active fractions, but less reflective of

(*continued on next page*)

Table 2 (*continued*)

Domain	Category/level	n (%)	Food-application relevance
			typical food-processing workflows.
	Not reported / unclear	9 (18.4)	Limits reproducibility and weakens confidence in the comparability of preparations across studies.
Analytical characterisation			
	Chromatography / MS-based profiling reported	8 (16.3)	Supports compositional confidence, ingredient traceability, and future product standardisation.
	Basic composition assays only	10 (20.4)	Provides only limited characterisation and is often insufficient for robust product development or cross-study comparison.
	Not reported / unclear	31 (63.3)	A major barrier to reproducibility, standardisation, and regulatory translation of food applications.
Standardisation markers			
	Explicit standardisation marker reported	5 (10.2)	Important for batch consistency and future functional-food development, but currently uncommon.
	No explicit marker / unclear	44 (89.8)	Indicates that most preparations remain insufficiently standardised for confident product translation.
Extract yield reporting			
	Reported	4 (8.2)	Helpful for process comparability, scalability, and manufacturing interpretation.
	Not reported / unclear	45 (91.8)	Strongly limits evaluation of processing efficiency and feasibility for larger-scale food applications.
Storage conditions reporting			
	Reported	6 (12.2)	Relevant to ingredient stability, shelf life, and preservation of bioactive quality.
	Not reported / unclear	43 (87.8)	Limits interpretation of product stability, reproducibility, and practical food-quality control.

in 11 studies overall (enzyme n = 11; animal n = 4; human n = 1), again with 100% positive findings across all tiers (Table 3).

Potency categorisation based on IC_{50}/EC_{50} thresholds showed substantial variability and frequent limitations in extractability and comparability. For α-glucosidase, 15 studies contributed IC_{50}/EC_{50} information, of which 12 had extractable values enabling potency classification (high: n = 5; moderate: n = 3; low: n = 4), while 3 were not classifiable due to non-extractable or non-comparable reporting (Table 4a). For α-amylase, IC_{50}/EC_{50} values were available in 10 studies, with 7 classifiable (high: n = 4; moderate: n = 1; low: n = 2) and 3 not classifiable (Table 4a).

Evidence for postprandial glycaemic attenuation, the most clinically interpretable primary outcome, was reported in 15 studies (animal n = 12; human n = 3) (Table 3). Among studies with extractable relative reductions suitable for effect-size binning, animal studies clustered into strong (n = 4; ≥30% reduction) and moderate (n = 4; 15–29% reduction) categories, with no weak effects observed in the extractable subset. Only one human study had extractable data suitable for binning and was rated as strong (Table 5a). Consistent with the tier-aware emphasis on clinical proximity, tier-weighted scoring ranked postprandial glycaemic attenuation as the strongest translation-ready primary signal (weighted score 34), followed by α-glucosidase inhibition (Table 6).

Beyond digestive mechanisms, insulin sensitivity and glucose uptake outcomes (AMPK/PPAR-γ–related pathways) were evaluated in 10 studies, with 100% positive direction of effect (Table 3) and evidence arising predominantly from cell-based studies (n = 7) and animal models (n = 3), noting that at least one study contributed to both tiers and there was no direct human evidence for this mechanism category (Tables 3 and 7). Collectively, these findings support a plausible mechanistic contribution to glycaemic regulation via insulin-resistance pathways, but with lower translational certainty than the digestive enzyme and postprandial mechanisms. Study-level qualitative mapping of these primary mechanisms, including the sea-grape materials studied and their relevance to diabetes-related outcomes, is provided in Table S1. Tier-weighted evidence scores (Table 6) were highest for postprandial glycaemic attenuation (score = 34) and α-glucosidase inhibition (score = 31). Overall strength-of-evidence ratings were High for α-glucosidase inhibition, α-amylase inhibition, and postprandial glycaemic attenuation, and Moderate for insulin sensitivity/glucose uptake (Table 7). Importantly, when interpreted through a tier-aware lens, the strength of evidence is not determined solely by study volume but by the alignment of mechanisms with clinically interpretable outcomes and their representation across higher evidence tiers, particularly human studies.

3.5.2. *Secondary metabolic modifiers*

Secondary metabolic modifiers were reported frequently but were generally less proximal to glycaemic regulation and more heterogeneous in outcome measurement than primary pathways (Tables 3 and 7). Digestive lipid enzyme (pancreatic lipase) inhibition was reported in six studies overall, predominantly in enzyme-tier assays (n = 6), with smaller contributions from cell-based (n = 2), animal (n = 2), and human (n = 1) evidence, and 100% positive direction of effect across all tiers (Table 3). Hepatic lipid handling outcomes were reported in 13 studies, dominated by animal evidence (n = 12) with limited cell-based representation (n = 2) and no direct human evidence (Tables 3 and 7). Potency categorisation (Table 4b) identified 2 high-potency studies (≤100 μg/mL), 1 moderate-potency study, and 1 low-potency study. The tier-weighted evidence score for lipase inhibition was 15 (Table 6), and the overall strength of evidence was rated High (Table 7).

Hepatic lipid handling was assessed in two cell-based studies and 12 animal studies, with 10 of 12 animal studies reporting beneficial effects (Table 3). Outcomes included hepatic lipid accumulation, serum lipid profiles, and related metabolic markers. No human studies were identified. The tier-weighted evidence score was 26, with an overall Moderate strength-of-evidence rating (Tables 6 and 7). Adiposity reduction was assessed in 10 studies, again largely in animal models; among the subset with extractable relative changes suitable for binning, most showed strong reductions (5 studies; ≥20%), with one moderate (10–19%) and one weak (<10%) effect (Table 5b). Collectively, these modifiers are most plausibly linked to glycaemic outcomes indirectly, through reduced lipotoxicity, improved hepatic metabolic handling, and reduced adiposity-related insulin resistance—rather than acting as primary glucose-lowering mechanisms.

3.5.3. *Supportive background mechanisms*

Supportive background mechanisms accounted for the largest volume of evidence but were generally less diabetes-specific than primary pathways (Tables 3 and 7). Antioxidant/oxidative-stress modulation was the most frequently reported supportive mechanism, spanning predominantly cell-based experiments (n = 9), animal models (n = 12), and limited human evidence (n = 2) (Table 3). Anti-inflammatory modulation was reported in cell-based (n = 5) and animal studies (n = 6), with additional evidence arising from other tiers. (Table 3). Effect-size categorisation (Table 5c) indicated strong reductions (≥40%) in 1 cell and 1 animal study, and moderate reductions (20–39%) in 2 animal studies. No human studies were available. The tier-weighted evidence score was 19, with an overall Moderate strength-of-evidence rating (Tables 6 and 7).

A full study-level qualitative mapping of supportive mechanisms,

Table 3
Primary, secondary and supportive antidiabetic mechanisms of sea grapes across evidence tiers (enzyme, cell-based, animal, human), including study counts, direction of effect (n beneficial/total), typical quantification metrics, and key references.

Antidiabetic mechanism	Evidence tier	Number of studies (n)	Direction of effect (n positive / total)	Quantification metric used	References
Primary antidiabetic mechanism					
α-Glucosidase inhibition	Enzyme	16	16 / 16	IC_{50}/EC_{50} (μg/mL) or % inhibition	(Aroyehun et al., 2020; Chaiklahan et al., 2020; Dissanayake et al., 2022; Fajriah et al., 2021; Koodkaew et al., 2024a, 2024b; Kurniawan et al., 2023, 2024; Montolalu et al., 2024; Ngadiarti et al., 2022; Nurkolis et al., 2023d, 2023a; Permatasari et al., 2021, 2022b; Sharma & Rhyu, 2014; Srinorasing et al., 2021)
	Cell	5	5 / 5	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Dissanayake et al., 2022; Kurniawan et al., 2023, 2024; Nurkolis et al., 2023a; Sharma & Rhyu, 2014)
	Animal	4	4 / 4	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Aroyehun et al., 2020; Ngadiarti et al., 2022; Nurkolis et al., 2023d; Permatasari et al., 2021)
	Human	1	1 / 1	Clinical endpoints (e.g., fasting/ postprandial glucose; OGTT/IAUC; HbA1c; insulin; % change vs baseline/ control)	(Permatasari et al., 2022b)
α-Amylase inhibition	Enzyme	11	11 / 11	IC_{50}/EC_{50} (μg/mL) or % inhibition	(Aroyehun et al., 2020; Dissanayake et al., 2022; Koodkaew et al., 2024b; Kurniawan et al., 2023, 2024; Ngadiarti et al., 2022; Nurkolis et al., 2023d, 2023a; Permatasari et al., 2021, 2022b; Teixeira et al., 2007)
	Animal	4	4 / 4	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Aroyehun et al., 2020; Ngadiarti et al., 2022; Nurkolis et al., 2023d; Permatasari et al., 2021)
	Human	1	1 / 1	Clinical endpoints (e.g., fasting/ postprandial glucose; OGTT/IAUC; HbA1c; insulin; % change vs baseline/ control)	(Permatasari et al., 2022b)
Postprandial glycaemic attenuation	Animal	12	12 / 12	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(AbouZid et al., 2014; Akhtar et al., 2019; Aroyehun et al., 2020; Khairuddin et al., 2020; Kuswari et al., 2021; Manoppo et al., 2022; Mayulu et al., 2023; Ngadiarti et al., 2022; Nurkolis et al., 2023d; Permatasari et al., 2021; Sharma et al., 2015; Wahjuningsih et al., 2025)
	Human	3	3 / 3	Clinical endpoints (e.g., fasting/ postprandial glucose; OGTT/IAUC; HbA1c; insulin; % change vs baseline/ control)	(Nurkolis et al., 2022; Permatasari et al., 2022b; Syakilla et al., 2025)
Insulin sensitivity & glucose uptake (AMPK / PPAR-γ)	Cell	7	7 / 7	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Kurniawan et al., 2025a, 2023, 2024; Nurkolis et al., 2023b; Sangpairoj et al., 2024; Sharma et al., 2015; Sharma & Rhyu, 2014)
	Animal	3	3 / 3	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Khairuddin et al., 2020; Mayulu et al., 2023; Sharma et al., 2015)
Secondary metabolic modifier					
Lipase inhibition	Enzyme	6	6 / 6	IC_{50}/EC_{50} (μg/mL) or % inhibition (pancreatic lipase)	(Montolalu et al., 2024; Nurkolis et al., 2023d, 2023c, 2023a; Permatasari et al., 2022a, 2022b)
	Cell	2	2 / 2	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Nurkolis et al., 2023c, 2023a)
	Animal	2	2 / 2	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Nurkolis et al., 2023d; Permatasari et al., 2022a)
	Human	1	1 / 1	Clinical endpoints (e.g., fasting/ postprandial glucose; OGTT/IAUC; HbA1c; insulin; % change vs baseline/ control)	(Permatasari et al., 2022b)
Hepatic lipid handling	Cell	2	2 / 2	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Sangpairoj et al., 2024; Sharma et al., 2015)
	Animal	12	10 / 12	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Akhtar et al., 2019; Ara et al., 2002; Aroyehun et al., 2020; Azam et al., 2022; du Preez et al., 2020; Long et al., 2025; Nurkolis et al., 2023d; Nursidika et al., 2025; Permatasari et al., 2022a; Sharma et al., 2015; You et al., 2022, 2023)
Adiposity reduction	Animal	10	10 / 10	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Aroyehun et al., 2020; Chumphoochai et al., 2023; Damayati et al., 2024; du Preez et al., 2020; Manoppo et al., 2022; Ngadiarti et al., 2022; Nursidika et al., 2025; Permatasari et al., 2022a; You et al., 2022, 2023)
Supportive mechanism					

(*continued on next page*)

Table 3 (*continued*)

Antidiabetic mechanism	Evidence tier	Number of studies (n)	Direction of effect (n positive / total)	Quantification metric used	References
Antioxidant stress reduction	Cell	9	9 / 9	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Chia et al., 2015; Dissanayake et al., 2022; Kurniawan et al., 2025a, 2023, 2024; Nurkolis et al., 2023c, 2023a, 2023b; Sharma & Rhyu, 2014)
	Animal	12	12 / 12	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Aroyehun et al., 2020; Azam et al., 2022; Cao et al., 2021; Khairuddin et al., 2020; Kuswari et al., 2021; Manoppo et al., 2022; Mayulu et al., 2023; Ngadiarti et al., 2022; Nurkolis et al., 2023d; Permatasari et al., 2022a, 2021; Wahjuningsih et al., 2025)
	Human	2	2 / 2	Clinical endpoints (e.g., fasting/ postprandial glucose; OGTT/IAUC; HbA1c; insulin; % change vs baseline/ control)	(Nurkolis et al., 2022; Permatasari et al., 2022b)
Anti-inflammatory modulation	Cell	5	5 / 5	Cell assay endpoints (e.g., glucose uptake; signalling/protein expression; % change vs control)	(Kurniawan et al., 2025a, 2023, 2024; Nurkolis et al., 2023b; Sharma et al., 2015)
	Animal	6	6 / 6	In vivo endpoints (e.g., fasting glucose; OGTT/IAUC; insulin; HbA1c; % change vs control)	(Cao et al., 2021; du Preez et al., 2020; Khairuddin et al., 2020; Mayulu et al., 2023; Nurkolis et al., 2023d; Sharma et al., 2015)

Footnotes: Tier counts are not mutually exclusive; studies may contribute to more than one evidence tier. IC_{50}/EC_{50}, concentration producing 50% inhibition/effect; iAUC, incremental area under the curve; PPG, postprandial glucose; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; LDL-C/HDL-C, low-/high-density lipoprotein cholesterol; ROS, reactive oxygen species; SOD/CAT/GPx, superoxide dismutase/catalase/glutathione peroxidase; GSH, reduced glutathione; MDA, malondialdehyde; TNF-α/IL/NF-κB, tumour necrosis factor-alpha/interleukin/nuclear factor kappa-B. Potency categories are based on IC_{50}/EC_{50} expressed in μg/mL (where available). Not classifiable indicates IC_{50}/EC_{50} was not reported/extractable or not in comparable units. "n" denotes the number of included studies contributing to each cell. Evidence tiers: Enzyme (in vitro enzyme assays), Cell (cell-based), Animal (in vivo non-human), Human (clinical/participant studies).

Table 4a
Potency category of α-glucosidase and α-amylase inhibition by sea-grape-derived materials.

Potency category*	IC_{50} / EC_{50} range	α-Glucosidase studies (n)		α-Amylase studies (n)	
		Number of studies (n)	References	Number of studies (n)	References
High potency	≤ 100 μg/mL	5	(Kurniawan et al., 2023; Nurkolis et al., 2023d, 2023a; Permatasari et al., 2022b; Sharma & Rhyu, 2014)	4	(Kurniawan et al., 2023; Nurkolis et al., 2023d, 2023a; Permatasari et al., 2022b)
Moderate potency	100–500 μg/mL	3	(Dissanayake et al., 2022; Fajriah et al., 2021; Montolalu et al., 2024)	1	(Dissanayake et al., 2022)
Low potency	> 500 μg/mL	4	(Chaiklahan et al., 2020; Koodkaew et al., 2024a, 2024b; Srinorasing et al., 2021)	2	(Koodkaew et al., 2024b; Teixeira et al., 2007)
Not classifiable†	IC_{50}/EC_{50} not extractable / not reported	3	(Aroyehun et al., 2020; Ngadiarti et al., 2022; Permatasari et al., 2021)	3	(Aroyehun et al., 2020; Ngadiarti et al., 2022; Permatasari et al., 2021)
Total		**15**		**10**	

including evidence-tier distribution and relevance to diabetes-related outcomes, is provided in Suppl. Table S5.

4. Discussion

4.1. Principal findings

This systematic review synthesised 49 primary studies evaluating sea grapes (*Caulerpa lentillifera* and/or *C. racemosa*) in relation to antidiabetic and diabetes-relevant metabolic mechanisms, drawing on mechanistic, preclinical, and limited human evidence. Three overarching patterns were apparent when evidence was mapped using the tier-aware mechanistic hierarchy and the processing/application-oriented synthesis presented in Tables 2–7 and Supplementary Table S1. Accordingly, this systematic review contributes to the integration of sea-grape-specific evidence across translational tiers, particularly by prioritising mechanisms according to their clinical interpretability. This review provides a more decision-oriented synthesis than existing narrative reviews, which have generally summarised composition and broad bioactivities without clearly differentiating mechanistic relevance to glycaemic regulation or the directness of evidence for human outcomes (Syakilla et al., 2022). Additionally, this review is not only a synthesis of existing evidence but also a demonstration that mechanistic consistency alone does not equate to translational readiness, particularly in fields dominated by preclinical research.

First, the most translation-ready evidence clustered around proximal mechanisms directly linked to glycaemic exposure, namely inhibition of intestinal carbohydrate-digesting enzymes and attenuation of postprandial glycaemia, pathways that are well-established targets for managing postprandial hyperglycaemia in type 2 diabetes (Kashtoh & Baek, 2023). Overall, the findings indicate that sea grapes exert their antidiabetic effects most convincingly through mechanisms that are directly linked to glycaemic regulation. Evidence was strongest for inhibition of digestive enzymes, particularly α-glucosidase, and for attenuation of postprandial glucose excursions. These pathways were supported across multiple evidence tiers, including limited human studies, and were prioritised when evidential directness and translational relevance were considered (Burns et al., 2011). Together, these findings suggest that sea grapes may primarily influence glucose homeostasis by slowing carbohydrate digestion and reducing post-meal glucose peaks, mechanisms that are both biologically plausible and clinically interpretable.

These findings are broadly consistent with a prior study, particularly studies of brown seaweeds and fucoidan-rich fractions in which the most

Table 4b
Potency category of secondary enzyme inhibition outcomes reported for sea grapes.

Potency category	IC_{50} / EC_{50} range	Number of studies (n)	References	Example comparison
High potency	≤ 100 μg/mL	2	(Montolalu et al., 2024; Nurkolis et al., 2023c)	Lipase inhibition EC_{50} (μg/mL): GACL-FS 118.7; GACL-AFD 144.5; GACL-MD 97.17; orlistat 96.27
Moderate potency	100–500 μg/mL	1	(Permatasari et al., 2022b)	Lipase inhibition IC_{50} for sea grape extract: 128.30 μg/mL (orlistat IC_{50}: 98.41 μg/mL).
Low potency	> 500 μg/mL	1	(Permatasari et al., 2022a)	Pancreatic lipase inhibition IC_{50} (mg/mL): Sea grapes kombucha drink 129.9; orlistat 104.6.
Total		**4**		

Table 4c
Potency category of antioxidant capacity outcomes reported for sea grapes.

Potency category*	IC_{50} / EC_{50} range	Number of studies (n)	References
High antioxidant capacity	≤ 100 μg/mL	5	(Kurniawan et al., 2023; Montolalu et al., 2024; Nurkolis et al., 2023d, 2023a; Sharma & Rhyu, 2014)
Moderate antioxidant capacity	100–500 μg/mL	1	(Nurkolis et al., 2023c)
Low antioxidant capacity	> 500 μg/mL	5	(Chaiklahan et al., 2020; Chia et al., 2015; Koodkaew et al., 2024a, 2024b; Srinorasing et al., 2021)
Total		**12**	

consistent human-relevant effect also appears to be attenuation of postprandial glycaemia rather than marked improvement in long-term glycaemic markers (Vaughan et al., 2022). However, unlike the brown-seaweed study, which has largely focused on fucoidan, alginate and laminarin, sea grapes represent green macroalgae in which multiple constituents (sulphated polysaccharides, glucans, carotenoids and peptides) and food-matrix effects may contribute. Thus, the present findings position sea grapes within a broader marine-bioactive context while also highlighting the need for species-specific and matrix-specific evaluation rather than assuming interchangeability across seaweed classes.

Secondary metabolic effects, including modulation of lipid digestion, hepatic lipid handling, and reductions in adiposity, were also frequently reported. However, these outcomes were more heterogeneous and were less consistently linked to validated glycaemic endpoints. The evidence suggests that improvements in lipid metabolism and body composition may contribute indirectly to glycaemic control by reducing lipotoxicity and improving insulin sensitivity, rather than acting as primary mechanisms for glucose lowering (Mohiuddin et al., 2025). As such, these pathways appear to play a supportive but secondary role within the broader mechanistic cascade.

Supportive background mechanisms, particularly antioxidant and anti-inflammatory effects, were common and directionally consistent across preclinical studies, although human evidence remained limited. These pathways are biologically plausible given the well-established links between oxidative stress, chronic inflammation, and insulin resistance in type 2 diabetes. Nevertheless, they are more distal to glycaemic outcomes and less translation-ready in the absence of consistent human study confirmation (Caturano et al., 2023). Taken together, the key findings support a hierarchical model in which sea grapes most plausibly influence glycaemic outcomes through direct effects on carbohydrate digestion and postprandial glucose regulation, with secondary improvements in lipid metabolism and adiposity, and broader antioxidant and anti-inflammatory effects that contribute indirectly by improving the overall metabolic milieu.

4.2. *Interpretation in the context of the "Diabetes Mechanism Spine"*

The primary contribution of the Diabetes Mechanism Spine is not the identification of novel biological pathways, but the reorganisation of existing mechanistic evidence into a translationally meaningful structure. By explicitly linking mechanistic proximity to glycaemic control with evidential directness across study tiers, the framework enables prioritisation of pathways based on their clinical interpretability rather than frequency of reporting. The Diabetes Mechanism Spine conceptual

Table 5b
Effect-size categories for adiposity-related outcomes.

Effect size category†	Definition (relative to control)	Number of studies (n)	References	Typical outcome measure
Strong	≥ 20% reduction	5	(Aroyehun et al., 2020; Chumphoochai et al., 2023; Damayati et al., 2024; du Preez et al., 2020; Ngadiarti et al., 2022)	Body weight, fat mass / Lee index / visceral fat
Moderate	10–19% reduction	1	(Manoppo et al., 2022)	Body weight, fat mass / Lee index / visceral fat
Weak	< 10% reduction	1	(Permatasari et al., 2022a)	Body weight, fat mass / Lee index / visceral fat
Total		**7**		

Table 5a
Effect-size categories for postprandial glycaemic attenuation outcomes.

Effect size category†	Definition (vs control or baseline)	Animal studies		Human studies	
		Number of studies (n)	References	Number of studies (n)	References
Strong	≥ 30% reduction in IAUC or peak glucose	4	(AbouZid et al., 2014; Aroyehun et al., 2020; Khairuddin et al., 2020; Wahjuningsih et al., 2025)	1	(Syakilla et al., 2025)
Moderate	15–29% reduction	4	(Ngadiarti et al., 2022; Nurkolis et al., 2023b; Permatasari et al., 2021; Sharma et al., 2015)	0	
Weak	< 15% reduction	0		0	
Total		**8**		**1**	

Table 5c
Effect-size categories for anti-inflammatory marker reduction outcomes.

Effect size category†	Definition (vs control)	Cell studies		Animal studies	
		Number of studies (n)	References	Number of studies (n)	References
Strong	≥ 40% reduction in inflammatory markers	1	(Kurniawan et al., 2023)	1	(Khairuddin et al., 2020)
Moderate	20–39% reduction	0		2	(du Preez et al., 2020; Sharma et al., 2015)
Weak	< 20% reduction	0		0	
Total		**1**		**3**	

Table 6
Tier-weighted evidence scores for primary, secondary and supportive antidiabetic mechanisms. Weighted evidence scores for primary mechanisms, calculated by applying tier weights to study counts (enzyme ×1; cell ×1; animal ×2; human ×3) and summing across tiers.

Mechanism	Enzyme (×1)	Cell (×1)	Animal (×2)	Human (×3)	Weighted evidence score‡
Primary antidiabetic mechanisms					
α-Glucosidase inhibition	16	5	4	1	31
α-Amylase inhibition	10	3	4	1	24
Postprandial glycaemic attenuation	0	1	12	3	34
Insulin sensitivity/ glucose uptake	2	7	3	0	15
Secondary metabolic modifiers					
Lipase inhibition	6	2	2	1	15
Hepatic lipid handling	0	2	12	0	26
Adiposity reduction	0	0	10	0	20
Supportive background mechanisms					
Antioxidant stress reduction	18	9	12	2	57
Anti-inflammatory modulation	2	5	6	0	19

Notes: Tier counts are not mutually exclusive; studies may contribute to more than one evidence tier. Tier-weighted scores reflect a prespecified weight-of-evidence scheme informed by evidence hierarchies and increasing directness (human > animal > mechanistic in vitro/in silico) (Hardy et al., 2017; Howick et al., 2026)

Table 7
Overall strength-of-evidence ratings for primary, secondary and supportive antidiabetic mechanisms. Overall strength-of-evidence classification for mechanisms integrating total study volume, presence of human evidence, and consistency across tiers.

Mechanism/ Modifier	Total studies (n)	Human evidence present	Consistency across tiers	Overall strength of evidence
Primary antidiabetic mechanisms				
α-Glucosidase inhibition	16	Yes	Very high	High
α-Amylase inhibition	11	Yes	Very high	High
Postprandial glycaemic attenuation	15	Yes	High	High
Insulin sensitivity / glucose uptake	9	No	Moderate	Moderate
Secondary metabolic modifiers				
Lipase inhibition	6	Yes	Very high	High
Hepatic lipid handling	13	No	Moderate	Moderate
Adiposity reduction	10	No	Low	Low
Supportive background mechanisms				
Antioxidant stress reduction	29	Yes	Very high	High
Anti-inflammatory modulation	10	No	High	Moderate

framework (Fig. 1) was developed to synthesise heterogeneous evidence by explicitly positioning mechanisms along a continuum defined by their proximity to glycaemic regulation and their representation across translational tiers. Interpreted through this lens, the findings show the greatest coherence and translational relevance for mechanisms that act proximally on the appearance of glucose in the circulation. Inhibition of carbohydrate-digesting enzymes and attenuation of postprandial glycaemia emerged as the most robust and interpretable pathways, aligning with established therapeutic targets for limiting postprandial glucose excursions in the management of type 2 diabetes (Baron, 1998; Davies et al., 2022). These mechanisms map directly onto clinically meaningful glycaemic domains and therefore provide a clearer bridge between experimental evidence and potential dietary or therapeutic application.

In contrast, supportive background mechanisms such as antioxidant and anti-inflammatory effects, although frequently reported, sit further downstream from direct glycaemic control within the framework. Their relevance as independent antidiabetic actions is less clear unless they are explicitly linked to improvements in validated glycaemic or insulin-resistance outcomes. This pattern is consistent with broader evidence-appraisal principles, which highlight an increase in indirectness as one moves from mechanistic or preclinical markers to patient-relevant outcomes. As such, high reporting frequency alone does not equate to greater translational importance when mechanisms are distal to the primary clinical endpoints of interest.

A key implication of applying the Diabetes Mechanism Spine is that evidence density should not be interpreted as a surrogate for translational readiness, because density captures the volume of studies rather than effect magnitude, consistency, or certainty. For example, oxidative stress and antioxidant outcomes were reported in 39 studies, yet these relied on a wide range of assays, including DPPH, ABTS, FRAP, and related methods, which vary in biological relevance, lack consistent standardisation, and are often poorly integrated with clinically interpretable endpoints. These limitations are well recognised in the literature on antioxidant measurement (Poljšak et al., 2025; Shahidi & Samarasinghe, 2025). By contrast, postprandial glycaemic attenuation was reported in fewer studies overall but represents a more clinically meaningful exposure domain for diabetes prevention and management because it directly reflects glucose handling following food intake. Although the postprandial evidence base was smaller, most studies reported attenuation of postprandial glycaemia; however, effect sizes were not directly comparable due to heterogeneity in endpoints and reporting.

Taken together, this tier-aware, mechanism-centred interpretation

helps explain why the evidence landscape is characterised by the coexistence of high-volume, indirect domains and lower-volume, translation-ready domains. It also clarifies why greater weight is placed on proximal glycaemic mechanisms than on distal supportive pathways when assessing the overall plausibility of sea grapes as anti-diabetic agents. This structured interpretation reinforces the value of prioritising mechanistic proximity and clinical interpretability over study counts alone when synthesising complex bodies of evidence on nutrition and metabolism. This distinction is critical for advancing the field, as it shifts the focus from simply documenting biological activity to identifying which mechanisms are most likely to translate into real-world glycaemic benefits, thereby providing a clearer pathway for future clinical research and application.

4.3. Potency, reporting completeness, and implications for comparability

Potency categorisation revealed important limitations for reproducibility and cross-study comparability, notably that a meaningful proportion of studies could not be classified due to non-extractable or non-comparable IC_{50} or EC_{50} reporting, and that inhibitory potency varied widely across sea grape preparations and assay approaches. For α glucosidase inhibition, only 12 of 15 studies were classifiable across high, moderate, and low potency categories, while three were not classifiable, and for α amylase inhibition, seven out of 10 studies were classifiable with three not classifiable, largely reflecting incomplete or inconsistent reporting of assay conditions, concentration definitions, response curves, and controls, long recognised challenges in bioassay based natural product research (Tipton et al., 2014). This variability was further compounded by substantial heterogeneity in sea grape material and preparation, including differences in processing state and extraction methods, which cautions against interpreting potency rankings as definitive indicators of optimal preparations in the absence of compositional profiling and standardised comparative assays (Orchard et al., 2011). Together, these findings highlight the need for future mechanistic studies to adopt harmonised reporting of concentration response parameters, clearly defined units, detailed assay conditions, and appropriate reference comparators, and, where possible, to link inhibitory potency to compositional characterisation to strengthen reproducibility, causal inference, and translational relevance (Sebaugh, 2011).

4.4. Strength of evidence and translational gaps

While the predominance of preclinical evidence may appear to limit immediate clinical applicability, it also provides a coherent mechanistic foundation that, when systematically synthesised, allows identification of the most promising targets for translation. The distribution of evidence across translational tiers reveals a clear gap between preclinical and human research, with the literature dominated by enzyme-based and animal studies and only limited human investigation. While this pattern is common in functional food research, it has particular significance for sea grapes because they are consumed as foods rather than administered as pharmacological agents, meaning that any effects in humans are likely to be modest, context dependent, and influenced by preparation, dose, dietary background, and timing relative to meals. This constrains inference regarding the durability of effects, dose-response relationships under realistic dietary conditions, interactions with background diet or concomitant therapies, and generalisability across populations with differing metabolic risk. Despite a biologically plausible and internally consistent mechanistic cascade supported by preclinical evidence, the current data are insufficient to support strong clinical recommendations. Future progress depends on well-designed and adequately powered human intervention trials using standardised preparations, clinically interpretable glycaemic endpoints, and rigorous protocol and reporting standards consistent with established trial guidance (EFSA Panel on Dietetic Products & Allergies, 2016; Schulz et al., 2010; Sebaugh, 2011).

This discrepancy may be explained by differences in bioavailability between cell-based experimental models and human studies. Numerous seaweed-derived sulfated polysaccharides are structurally complex, high-molecular-weight molecules that are not readily absorbed intact in the upper gastrointestinal tract; instead, they tend to resist host enzymatic digestion and undergo partial hydrolysis and microbial fermentation in the colon, with only smaller fragments or derived metabolites likely to enter systemic circulation (Cotas et al., 2025). Seaweed phenolics also appear to have limited direct bioavailability and may be substantially transformed during gastrointestinal digestion and colonic fermentation (Cotas et al., 2025). This has important implications for the interpretation of secondary mechanisms, such as AMPK signaling or insulin-sensitivity pathways, observed in cell systems, because these effects may depend on metabolites, low-molecular-weight fractions, or gut-mediated processes rather than on intact parent compounds reaching target tissues in vivo.

4.5. Processing, standardisation, and implications for food application

Because this review is positioned within an applied food context, the way sea grapes were processed, characterised, standardised, and delivered is central to interpretation. The evidence summarised in Tables 1 and 2 indicates that the literature is dominated by dried biomass, powders, crude extracts, and fractionated preparations, whereas comparatively fewer studies examined formulated foods, beverages, or supplement-like products that more closely reflect consumer-facing applications. This distinction is important because biological activity observed in purified extracts or laboratory-derived fractions cannot be assumed to translate directly to whole foods or realistic food ingredients, where matrix effects, serving size, palatability, processing stability, and habitual intake patterns may all modify efficacy (Garcia-Perez et al., 2023; Giuntini et al., 2022).

From a food-application perspective, the predominance of dried and powdered preparations is both a strength and a limitation. On the one hand, these formats are compatible with shelf-stable ingredients, beverage powders, bakery incorporation, noodles, snack products, and other functional-food applications. On the other hand, drying, milling, extraction, and fractionation may substantially alter the composition, stability, and bioaccessibility of polysaccharides, phenolics, carotenoids, and other putative bioactives (Flórez et al., 2017). As a result, the current evidence base is better interpreted as establishing proof-of-concept biological activity than as identifying an optimal consumer-ready preparation. This is especially relevant because the most translation-ready effects observed in this review, namely attenuation of postprandial glycaemic responses and inhibition of carbohydrate-digesting enzymes, are likely to depend not only on chemical composition but also on the food matrix, meal context, and timing of intake.

A useful way to interpret the current evidence is along a food-to-medicine continuum (Defraeye et al., 2025; Sun et al., 2026). The distribution of study types and preparation forms in Tables 1 and 2 suggests that the literature remains concentrated in the early and middle stages of this continuum, with most studies examining edible biomass, dried powders, formulated products, or partially refined extracts rather than highly standardised therapeutic preparations. At the food end, sea grapes are consumed as edible biomass and incorporated into products such as noodles, beverages, and powders. Further along the continuum, several studies have investigated fibre-rich fractions, polysaccharide preparations, and other semi-refined ingredients with potential functional-food relevance. By contrast, relatively few studies have focused on isolated compounds, purified fractions, or highly mechanistic assays that might support more medicine-oriented applications. Interpreted in this way, the present evidence supports sea grapes most strongly as functional-food or food-ingredient candidates for postprandial glycaemic moderation, while support for medicine-like applications remains limited and predominantly preclinical. Framing the

evidence in this way helps prevent over-interpretation of extract- or compound-based findings as though they were immediately applicable to whole-food or consumer-product settings.

A related major issue is the limited maturity of preparation characterisation and product standardisation. Only a small proportion of studies reported chromatography- or mass spectrometry-based profiling, explicit standardisation markers, extract yield, or storage conditions (Table 2). This weakens reproducibility and makes it difficult to compare results across studies, even when apparently similar species or mechanisms are being investigated. For functional-food development, this is a substantial barrier. Food-grade translation requires not only demonstration of efficacy, but also batch consistency, traceable raw materials, reproducible processing workflows, stability during storage, and clear specification of the components likely to drive biological effects (Duarte et al., 2022). In the absence of such information, promising findings remain difficult to translate into robust product development, health-claim substantiation, or regulatory evaluation.

The source of biomass is also relevant to application. Although some studies used aquaculture-derived sea grapes, more than half did not clearly report source type (Table 2). This matters because farming conditions, wild harvesting environments, seasonality, and water quality may all affect nutrient composition, bioactive profiles, and contaminant burden. These concerns intersect directly with food safety. As noted above, *Caulerpa* species may bioaccumulate heavy metals and contain secondary metabolites such as caulerpin, yet adverse-event reporting, contaminant screening, and product-quality characterisation were limited across the included studies (Cotas et al., 2025). Thus, future food-oriented research should integrate efficacy testing with routine safety monitoring, contaminant analysis, and compositional quality control.

Taken together, these findings suggest that the field is not yet equally mature across all stages of translation. The current literature provides moderate support for sea grapes as promising functional-food candidates, particularly for postprandial glycaemic moderation, but much of the evidence remains upstream of true product translation. Future work should therefore prioritise food-grade preparations, transparent processing descriptions, compositional profiling, standardisation markers, storage and stability data, and meal-based human intervention studies using realistic serving formats. Such improvements would substantially strengthen the evidence base for practical food application and better align future sea-grape research with the expectations of applied food science.

4.6. Methodological limitations in the primary studies

Several recurring methodological challenges limit the interpretation of the evidence base. Across studies, sea grape preparations and exposure characterisation were highly heterogeneous, with substantial variation in species identification, processing state, extraction methods, and fractionation approaches, as well as inconsistent compositional profiling of key bioactive constituents, which constrains mechanistic attribution and reproducibility. Outcome measurement also lacked standardisation, particularly for oxidative stress and antioxidant activity, where diverse assays, units, and reporting conventions were used, reducing cross-study comparability and limiting quantitative synthesis (Bibi Sadeer et al., 2020; Shahidi & Samarasinghe, 2025). Risk of bias (RoB) assessments suggest that many of these limitations stemmed from incomplete reporting rather than fundamental design flaws, especially in animal studies where key elements such as randomisation, allocation concealment, and blinding were often insufficiently described, despite clear guidance in established reporting frameworks (Hooijmans et al., 2014; Percie du Sert et al., 2020). Human studies frequently raised concerns about incomplete reporting of interventions and outcomes. Together with the very limited human evidence base, these issues limit inference about the clinical magnitude, durability, and safety under real-world dietary conditions, underscoring the need for well-powered, rigorously designed, and transparently reported human intervention studies.

Although a brief safety perspective is warranted for food products, formal reporting of adverse events or toxicity outcomes was limited, especially in human investigations across the included studies. Evidence indicates that, like other macroalgae, *Caulerpa* species can bioaccumulate heavy metals and contain secondary metabolites such as caulerpin, depending on cultivation environment and water quality, that demand compositional monitoring (Perryman et al., 2017). Therefore, future clinical studies should incorporate routine safety monitoring, including systematic adverse-event reporting, contaminant screening, and batch-level compositional characterisation.

4.7. Strengths and limitations of this review

This review has several notable strengths, including adherence to a pre-specified protocol registered in PROSPERO and reporting in accordance with PRISMA 2020, which together support transparency and reproducibility. Use of a structured data extraction template aligned with the review objectives and mechanistic hierarchy enabled consistent capture of study characteristics, sea grape preparation features, and diabetes relevant outcomes across in silico, in vitro, animal, and human evidence tiers. A further strength is the tier-aware Diabetes Mechanism Spine framework, which facilitated coherent synthesis of heterogeneous evidence by prioritising mechanisms according to their proximity to glycaemic regulation and their support across translational tiers, while structured evidence mapping enhanced auditability by allowing mechanistic summaries to be traced back to the underlying studies. Key limitations include substantial heterogeneity in species identification, processing, extraction, dosing, and outcome measurement, as well as a predominantly preclinical evidence base that limited comparability and precluded meta-analysis. The small number of human studies further constrained inference regarding clinical magnitude, durability, and generalisability, and risk of bias assessments were often hampered by incomplete reporting of methodological safeguards, particularly in animal studies, which should be considered when interpreting effect direction and overall strength of evidence.

4.8. Implications for research and practice

The distribution of evidence across translational tiers reveals a clear gap between preclinical research and human studies, with the literature dominated by animal models and enzyme-based assays and only limited direct human investigation. While this pattern is common in food bioactive research, it is relevant to sea grapes because they are consumed as foods rather than used as pharmacological agents, suggesting that any effects in humans are likely to be modest, context-dependent, and sensitive to dietary background, preparation, dose, and timing relative to meals. This elevates the importance of rigorous trial design and clinically interpretable endpoints, especially post-meal glucose responses, where proximal mechanisms are most relevant (Ceriello & Colagiuri, 2008; Hooijmans et al., 2014; Percie du Sert et al., 2020). The scarcity of human evidence further limits inference regarding the durability of effects, dose-response relationships under realistic dietary conditions, interactions with background diet or concomitant therapies, and generalisability across populations with differing metabolic risk. As a result, despite a biologically plausible and preclinically consistent mechanistic cascade, the current evidence is insufficient to support strong clinical recommendations, and future progress depends on adequately powered, well-controlled human intervention trials using standardised preparations, harmonised outcome measures, and transparent reporting aligned with established trial guidance (Ceriello & Colagiuri, 2008; Hoffmann et al., 2014; Percie du Sert et al., 2020; Schulz et al., 2010).

From a public health and policy perspective, these findings have important implications. The identification of postprandial glycaemic

attenuation as the most translation-ready mechanism aligns with growing recognition of post-meal glucose regulation as a key target in diabetes prevention strategies. As a culturally accepted and potentially scalable food source in Asia–Pacific settings, sea grapes may represent a feasible dietary intervention within broader nutrition and non-communicable disease prevention frameworks. The framework developed in this review can therefore inform not only future research prioritisation but also the integration of functional foods into population-level strategies.

5. Conclusions

In this systematic review of 49 studies, evidence for sea grapes' antidiabetic potential was strongest for proximal mechanisms directly related to glycaemic regulation, particularly inhibition of carbohydrate-digesting enzymes (α-glucosidase and α-amylase) and attenuation of postprandial glycaemic excursions. Secondary metabolic modifiers (including lipase inhibition, hepatic lipid handling, and adiposity-related outcomes) and supportive antioxidant/anti-inflammatory pathways were frequently reported and biologically plausible, but were more heterogeneous, less diabetes-specific, and rarely confirmed in human studies. The evidence base remains dominated by animal and enzyme-tier investigations, with only three human studies, indicating a substantial translational gap between mechanistic promise and practical food application. Future research should prioritise standardised, characterisable sea-grape preparations with compositional profiling, alongside rigorously designed human intervention trials using clinically interpretable glycaemic endpoints and mechanistically aligned secondary outcomes.

The current literature remains largely dominated by animal and enzyme-tier investigations, highlighting a substantial translational gap. Beyond synthesising the existing literature, this review provides a structured, tier-aware framework for interpreting mechanistic evidence in relation to translational relevance, enabling prioritisation of pathways most likely to impact clinically meaningful glycaemic outcomes. This approach offers a foundation for guiding future research, informing clinical trial design, and supporting the integration of functional foods into public health strategies.

Ethics statement

Ethics approval was not required for this study because it is a systematic review of published literature and did not involve collection of new data from human participants or animals.

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used ChatGPT (OpenAI) to assist with language editing and improving clarity and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.foohum.2026.101315.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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