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Systematic Review / Meta-analysis

Green Energy-Assisted Versus Conventional Solvent Extraction for the Recovery of Phenolic Antioxidants from Marine Macroalgae: A Meta-Analysis

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ABSTRACT

Background: Marine macroalgae are a renewable source of phenolic antioxidants. Energy-assisted extraction may replace prolonged solvent-intensive maceration, but its effect on recovery had not been quantitatively pooled.

Objective: To estimate the pooled effect of energy-assisted versus conventional solvent extraction on phenolic recovery and antioxidant capacity in marine macroalgae.

Methods: PubMed and Europe PMC were searched. Of 493 de-duplicated records, 35 full texts were assessed. Eligible reports compared energy-assisted and conventional extraction using paired arms from one homogenized macroalgal biomass. Hedges' g was pooled using random-effects models with cluster-robust inference; the ratio of means was a secondary measure. Risk of bias used five adapted Cochrane domains.

Results: Thirteen studies yielded 35 comparisons across 22 species and 93 estimates; ultrasound contributed 56 estimates, brown seaweeds 73, red seaweeds 20, and green seaweeds none. Energy-assisted extraction increased phenolic antioxidant recovery (cluster-robust Hedges' g = 8.62, 95% CI 2.98 to 14.26, p = 0.0063; ratio of means 1.385, 95% CI 1.149 to 1.671, a 38.5% gain) in a median of 10 versus 960 minutes (median per-comparison reduction, 20.6-fold). The advantage persisted in 12 duration-matched comparisons. Heterogeneity was high (I^2 = 87.8% in the DerSimonian-Laird model, 97.1% in the three-level model); the prediction interval −2.26 to 16.16 included zero. No moderator survived robust testing. Supercritical carbon dioxide recovered 51.8% less than conventional extraction.

Conclusion: Energy-assisted extraction recovered about 39% more phenolic antioxidant activity about 21 times faster. Direction was robust, but magnitude and certainty remained uncertain; a green label did not guarantee superior recovery.

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1. Introduction

Marine macroalgae accumulate a distinctive family of phenolic secondary metabolites. Industries in pharmaceuticals, food and cosmetics want to recover them, and that interest has kept growing as they search for alternatives to synthetic antioxidants.[1,2] Brown seaweeds produce phlorotannins, oligomers of phloroglucinol with no terrestrial counterpart. Red and green seaweeds accumulate bromophenols, mycosporine-like amino acids and simpler phenolic acids instead.[3,4] Laboratory models have shown that extracts of these organisms display antioxidant, photoprotective, anti-inflammatory, cholinesterase-inhibitory and antiproliferative activity,[5-8] and bench-scale studies have demonstrated their incorporation into food and cosmetic matrices.[9-11] Commercially, the presence of useful molecules has rarely been the obstacle. The difficulty lies in liberating them efficiently, cleanly and quickly from a tough, highly hydrated and polysaccharide-rich cell wall.[12]

Conventional recovery depends on prolonged solid-liquid contact. Biomass is macerated, stirred or refluxed in an organic solvent for hours or days. Passive diffusion across an intact cell wall sets the pace, since phenolics there are extensively bound to alginate, fucoidan and cellulose.[12,13] Such protocols need large solvent volumes and tie up equipment for long periods. They also expose thermolabile phenolics to extended heating. An alternative is to stop waiting for diffusion and apply energy that breaks the cell wall directly. Throughout this article that alternative is called energy-assisted extraction, a single term covering the whole family of techniques. The word green is reserved for discussion of environmental credentials, because one finding reported below is that the two are not synonymous. In ultrasound-assisted extraction, acoustic cavitation generates microjets that perforate cell walls. Microwave irradiation heats intracellular water volumetrically until the cell ruptures. Enzyme-assisted extraction uses carbohydrases to hydrolyze the wall matrix under mild aqueous conditions. Pressurized liquid, subcritical water and supercritical fluid systems act differently, altering solvent polarity and diffusivity under elevated temperature and pressure.[14-16]

Adjacent fields already hold evidence that these technologies outperform maceration. In terrestrial matrices, energy-assisted extraction has repeatedly raised polyphenol recovery from fruit pomace, leaves, seeds and agro-industrial residues,[17-21] and comparative work on distillery stillage and peach by-products has placed ultrasound, microwave and conventional extraction side by side within a single design.[22,23] The same logic has reached solvent selection through the combination of deep eutectic solvents with ultrasound,[24,25] and response-surface optimization of energy-assisted protocols is now routine.[26-28] Macroalgal biomass is different. Its wall chemistry, water content and mineral load do not match those of terrestrial biomass, so results cannot simply be transferred.

The primary literature within phycology is large but fragmented. Individual laboratories report single-species comparisons in units that do not match. Some express phenolic content per gram of dry biomass, others per gram of recovered extract, and antioxidant capacity appears as percentage inhibition, half-maximal inhibitory concentration or Trolox equivalents.[29] Meta-analyses involving algae and antioxidants exist. They address crop biostimulation, methane mitigation in ruminants, blood pressure and anthropometric outcomes in humans.[30-32] None has pooled the effect of the extraction process itself. The field's working belief that energy-assisted extraction is superior has therefore rested on narrative synthesis, with no quantitative estimate behind it. The magnitude of the advantage has not been tested. Neither has its consistency across algal lineages, nor the possibility that it is an artifact of mismatched process conditions.

The gap matters beyond process engineering. Which phenolics are liberated, and in what proportion, depends on the extraction platform. It therefore also determines the material that any later pharmacological assay actually receives. The process question comes before the pharmacological one, and some of the inconsistency in the reported potency of macroalgal extracts may be inconsistency of extraction.[6,33] In tropical archipelagic economies the effect is sharpest. Red seaweeds are cultivated there at scale, and the choice of extraction platform sets both capital outlay and solvent cost.[34-36] A process engineer deciding whether to install an ultrasonic reactor needs to know how much additional phenolic material is recovered. Learning that a difference has been reported somewhere does not help.

This study is the first quantitative synthesis to pool the effect of the extraction process itself, rather than the effect of algal extracts, on the recovery of phenolic antioxidants from marine macroalgal biomass. The evidence base is restricted to paired arms drawn from a single homogenized biomass within a single laboratory. That removes between-species and between-laboratory confounding at source. The standardized mean difference is reported alongside the ratio of means, so a measure inflated by analytical-replicate dispersions is accompanied by one that is not. Every moderator claim was also subjected to cluster-robust inference. The aim was to estimate the pooled effect of energy-assisted extraction relative to conventional solvent extraction on total phenolic content, phlorotannin content and antioxidant capacity in marine macroalgae. A second aim was to quantify the accompanying reduction in processing time. A third was to determine whether the advantage depended on algal lineage, on extraction technology, or on how closely the two arms were matched for solvent, temperature and duration.

2. Methods

2.1. Reporting and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guided the reporting of this review.[37]

2.2. Search strategy

The search covered two bibliographic databases: PubMed, accessed through the National Center for Biotechnology Information E-utilities interface, and Europe PMC. It ran in three arms. The initial arm queried PubMed and returned 84 records. A verification arm queried PubMed again with a broadened technology vocabulary and returned 60 unique records. A third arm was added against Europe PMC after the PubMed-only strategy was found to under-retrieve, and returned 396 records; that arm recovered two of the 13 included reports.

The Boolean string below uses the syntax of the final Europe PMC arm:

("ultrasound-assisted extraction" OR "ultrasonic extraction" OR "microwave-assisted extraction" OR "enzyme-assisted extraction" OR "supercritical" OR "subcritical water" OR "pressurised liquid extraction" OR "pressurized liquid extraction" OR "deep eutectic solvent" OR "green extraction") AND (seaweed OR macroalga OR macroalgae OR Rhodophyta OR Phaeophyceae OR Chlorophyta OR "marine alga") AND ("total phenolic" OR "phenolic content" OR polyphenol OR phlorotannin OR antioxidant OR DPPH OR ABTS OR FRAP) AND (conventional OR maceration OR Soxhlet OR "solid-liquid extraction" OR stirring OR reflux OR comparison OR compared) NOT (review[Publication Type])

The reference lists of retrieved reports were inspected for further eligible studies, and no language restriction was applied. One reviewer performed the search (see Section 4.4).

2.3. Eligibility criteria

Reports were eligible when all of the following held. The biomass was a marine macroalga of the Rhodophyta, Phaeophyceae or Chlorophyta, and all microalgae and all freshwater and terrestrial biomass were excluded. At least one energy-assisted extraction technique had to be applied. A comparator arm had to be run on the same homogenized biomass within the same report, so the contrast was internal and did not rely on comparison across laboratories. The report had to give at least one of total phenolic content, phlorotannin content, DPPH radical-scavenging, ABTS radical-scavenging, ferric-reducing antioxidant power or gravimetric extract yield. Both arms had to be reported as a mean with a dispersion measure, so that a standardized mean difference could be computed. Reviews, meta-analyses, conference abstracts, theses and book chapters were excluded.

The protocol specification for randomized controlled trials or cohort studies could not be applied. Neither design exists in extraction science, since there are no participants to randomize and no cohort to follow. The design in the equivalent evidential position is the controlled comparative laboratory experiment. A single homogenized biomass is divided between two or more extraction methods under otherwise identical conditions, and replicate determinations are reported as mean and standard deviation. Because biomass, laboratory, analyst, instrument and assay are held constant across arms, this design constrains confounding more tightly than a cohort does.

2.4. Data extraction

From each report, the following items were transcribed exactly as printed, with no rounding, recomputation or unit conversion: bibliographic identifiers; species and algal phylum; the geographic origin of the biomass; the energy-assisted technique together with its process conditions (power, frequency, duration, temperature, solvent identity and concentration, and solid-to-solvent ratio); the comparator method and its matching conditions; and the number of analytical replicates. For each outcome we also took the mean and dispersion in each arm, the unit as printed and the source table. A value missing from a report was recorded as not reported. A value that was present but ambiguous, internally inconsistent or of uncertain unit was flagged for adjudication, and the way it was handled was logged. When a report named an optimal energy-assisted

condition, that condition was extracted. When a study had several arms, each one was kept as a separate comparison.

Two data-handling conventions were fixed in advance. Five estimates were given as half-maximal inhibitory concentrations, where a lower value means greater activity. Their sign was reversed before pooling, so a positive effect always favored energy-assisted extraction; the Figure 3 caption restates this rule. One comparator concentration was censored and not missing: the macerated extract reached only 38.02% scavenging at the highest concentration tested. We excluded it and did not impute a value. The direction of this censoring is not neutral. The comparator failed to reach the threshold, so the excluded observation would have favored the energy-assisted arm, and dropping it pulls the pooled estimate downward, not upward. One study never stated a replicate count anywhere in its text. We assumed three replicates for its three estimates, record that assumption here, and report a sensitivity analysis that leaves the study out entirely. Finally, a script cross-checked all numeric values against the source reports.

2.5. Risk of bias assessment

The protocol named the Cochrane risk-of-bias tool for randomized trials. That instrument appraises randomized trials of interventions in human participants. Its domains cover randomization, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result, and they have no referent in a setting with no allocation sequence, no participant and no attrition. We therefore mapped the five domains one-to-one onto structural analogues for the controlled comparative laboratory experiment: allocation of biomass to arms; matching of process conditions between arms; completeness of replicate and dispersion data; measurement of the outcome; and selection of the reported result. Each domain was rated low, some concerns or high. The overall judgment followed the standard algorithm, in which the least favorable domain governs.

2.6. Statistical analysis

Effect sizes were expressed as Hedges' g, which is the standardized mean difference with the small-sample correction. A standardized form was needed because laboratories report phenolic content on incompatible denominators. Estimates were pooled in a random-effects model, using the DerSimonian-Laird estimator for between-study variance, as the protocol specified.

Most reports contributed several estimates measured on the same extracts. This breaks the independence assumed by that model, and the resulting confidence interval is anti-conservative. We therefore based inference on cluster-robust variance estimation, with the study as the clustering unit. A three-level random-effects model, fitted by restricted maximum likelihood, partitioned heterogeneity between studies and between comparisons within studies. The ratio of means was computed as a secondary measure. In this literature the dispersions are analytical replicate standard deviations, which describe the repeatability of a spectrophotometric assay and not biological variability. Dividing by such dispersions inflates the standardized mean difference to values that have no counterpart in clinical research. Both measures are reported throughout.

Heterogeneity was quantified with the I^2 statistic, the between-study variance and a 95% prediction interval. Subgroup analyses were pre-specified for outcome domain, algal phylum, energy-assisted technique, and the degree to which arms were matched for solvent, temperature and duration; cluster-robust moderator tests assessed them. A meta-regression asked whether the logarithm of the ratio of arm durations predicted effect size. Sensitivity was examined in 28 scenarios. These covered leave-one-study-out removal, alternative variance estimators, alternative treatment of unlabeled dispersions, restriction to single outcome domains, restriction to independent estimates, and exclusion of extreme values. Small-study effects were assessed with regression-based and rank-correlation tests and with trim-and-fill. The sampling variance of the standardized mean difference is itself a function of the effect size, so we added a regression test on the ratio of means, which carries no such artifact. Certainty of evidence was appraised across five domains (risk of bias, inconsistency, indirectness, imprecision and reporting bias), which correspond to the GRADE framework.[38] Analyses ran in R with the metafor and clubSandwich packages and in Python 3.

Two features of the inferential strategy need to be stated explicitly. First, five outcome domains were analyzed, and no adjustment for multiplicity was applied. These domains are strongly correlated measurements made on the same extracts, not independent hypotheses, so a Bonferroni-type correction would be unduly conservative. The consequence is that the domain-level analyses are exploratory, and their nominal p values should not be read as confirmatory. Only the composite estimate, a single pre-specified comparison, is treated as inferential. Second, cluster-robust standard errors come from the empirical dispersion of the within-cluster residuals. They do not depend on the between-study variance estimator. The cluster-robust interval therefore stays the same when that estimator is varied, which explains why it is identical across those sensitivity scenarios.

3. Results

3.1. Study selection

The three search arms returned 540 records. Once 47 duplicates were removed, 493 records remained and were screened on title and abstract; 455 of these were excluded. The usual grounds were that the biomass was not a macroalga, that the report was a review or narrative account, that the extraction target was a polysaccharide, protein or pigment rather than a phenolic fraction, or that no head-to-head extraction contrast existed. Thirty-eight reports were sought for retrieval. Three could not be obtained, since they had no PubMed Central deposit and the publisher full texts were paywalled. Thirty-five reports were assessed at full text, and 22 of them were excluded. Figure 1 sets out the selection process.

The main reason for exclusion at full text is a finding in its own right. Eighteen of the 22 excluded reports optimized an energy-assisted technique against itself, typically by response-surface methodology, and never ran a conventional comparator. Laboratories in this field have largely treated the superiority of energy-assisted extraction as settled background, not as a proposition to be tested. Three further reports were excluded because the head-to-head values carried no dispersion measure. One was excluded because the phenolic outcome was reported only as a pooled range across all arms. Thirteen studies were included. The ceiling of 13 reflects the literature, not the search.

The three reports that could not be retrieved would have addressed the very gaps that limit this synthesis most. One concerns a red seaweed compared by ultrasound against infusion, a lineage represented here by only two studies. Another covers four brown seaweeds compared by microwave against conventional extraction, and would have roughly doubled the microwave evidence. The third concerns a species already represented and would have given an

independent second estimate for it. Anyone extending this work should obtain them first.

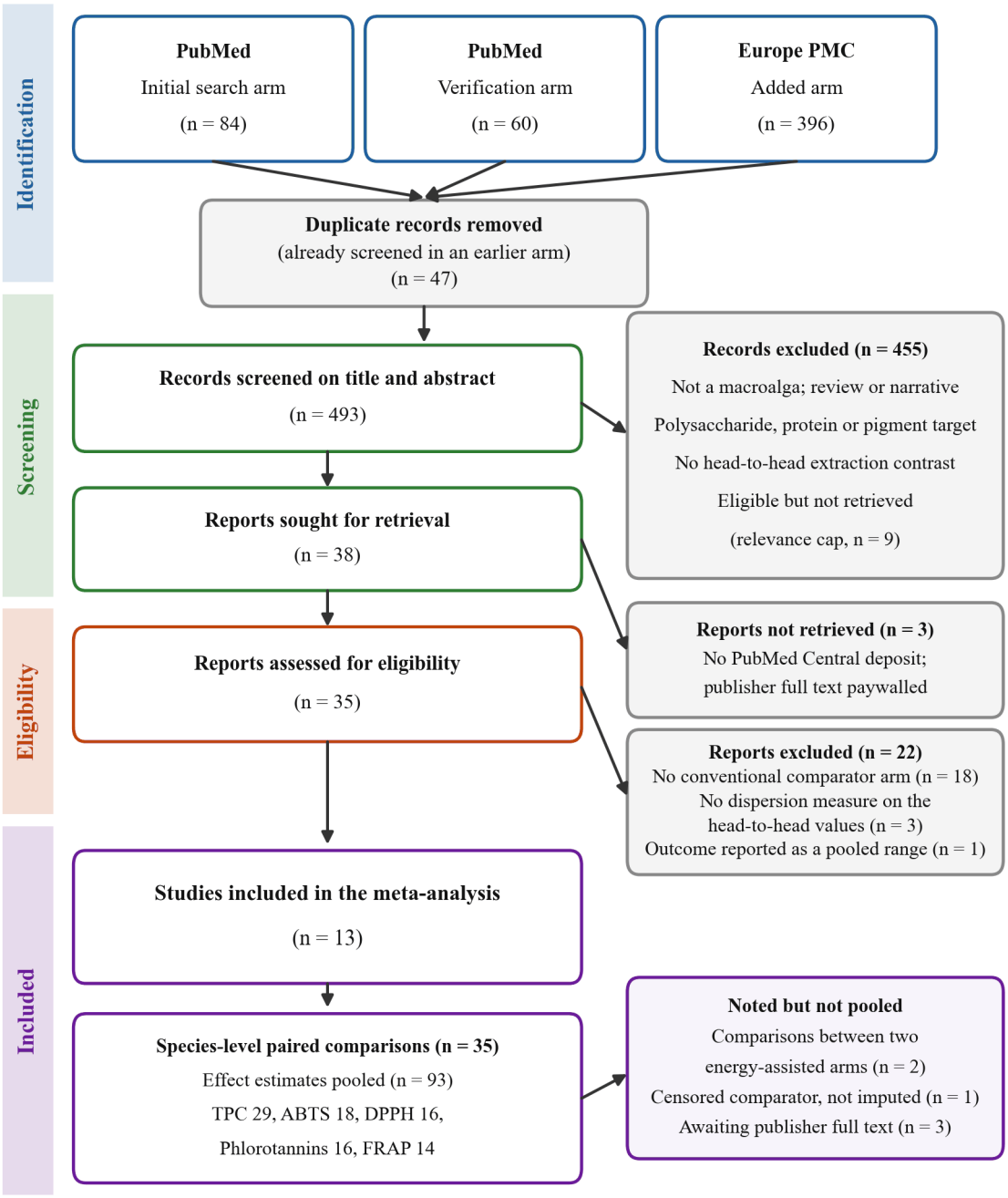


Figure 1. Study selection across the three search arms. The Europe PMC arm was added after the initial database-specific strategy was found to under-retrieve, and recovered two of the included reports.

3.2. Characteristics of the included studies

The 13 included studies contributed 35 species-level paired comparisons across 22 macroalgal species and yielded 93 effect estimates; Table 1 summarizes their characteristics. Brown seaweeds dominated the evidence base. They supplied 73 of the 93 estimates across 11 studies, whereas red seaweeds supplied 20 estimates from only two studies.[39,40] No study of a green seaweed met the eligibility criteria. Biomass came from Ireland, Portugal, Spain, Australia, Turkey, Iran, China, Vietnam, the Republic of Korea and Indonesia. The pool was therefore broad geographically, though narrow taxonomically.

Ultrasound-assisted extraction was by far the most frequently studied technology. It contributed 56 estimates from nine studies, as detailed in the energy-assisted-arm column of Table 1. Microwave-assisted and pressurized-liquid extraction contributed eight estimates each. Hydrothermal-assisted, high-pressure-assisted, combined ultrasound-microwave, supercritical-fluid and mechanical homogenization arms contributed four estimates each, and enzyme-assisted extraction a single estimate. Coverage of outcomes was uneven too, as the outcomes column of Table 1 shows. Total phenolic content was reported in 29 estimates, ABTS in 18, DPPH and phlorotannins in 16 each, and ferric-reducing antioxidant power in 14.

Table 1. Characteristics of the 13 included controlled comparative laboratory experiments.

Study	Species (phylum)	Origin	Energy-assisted arm	Conventional comparator	Outcomes	Estimates	Risk of bias
Goksen 2023[39]	*Laurencia papillosa* (R)	Turkey	UAE, probe, 15 min	Stirring, 50 °C, 24 h	TPC, DPPH, ABTS, FRAP	4	Some concerns
Lee 2024[41]	*Cystophora* sp., *Durvillaea potatorum*, *Sargassum fallax*, *Ecklonia radiata*, *Phyllospora comosa* (P)	Australia	UAE, 8 min	Shaking, 4 °C, 16 h	TPC, DPPH, ABTS, FRAP	20	High
Sonno 2026[40]	*Asparagopsis armata*, *A. taxiformis* (R)	Australia	UAE, 3 min	Shaking, 210 rpm, 24 h	TPC, DPPH, ABTS, FRAP	16	Some concerns
He 2026[42]	*Sargassum fusiforme* (P)	China	UAE, 28 kHz, 320 W, 75 min	Water bath, identical solvent, temperature and time	TPC, phlorotannins	2	Some concerns
Taherkhani 2024[43]	*Nizimuddinia zanardini* (P)	Iran	MAE 300 W, 15 min; UAE 37 kHz, 120 min	Maceration, 30 °C, 24 h	TPC, phlorotannins	4	High
Paulo 2025[44]	*Rugulopteryx okamurae* (P)	Portugal	UAE 40 kHz; mechanical homogenization	Overnight agitation, 20 °C	TPC, DPPH, ABTS, FRAP	5	High
Ummat 2020[45]	*Fucus vesiculosus*, *Laminaria digitata* (P)	Ireland	UAE, 35 kHz, 30 min	No-ultrasound control (F. vesiculosus); 50% ethanol, shaking water bath, 20 °C, 4 h (L. digitata)	TPC, phlorotannins, DPPH, FRAP	4	Some concerns
da Silva 2025[46]	*Saccharina latissima* (P)	Spain	PLE 80 °C, 30 min (MAE 80 °C, 8 min also run; no dispersion printed, not pooled)	Conventional reflux, 6 h	TPC, phlorotannins, DPPH, ABTS	4	High
Amarante 2020[47]	*Fucus vesiculosus* (P)	Portugal	MAE, 400 W, 75 °C, 5 min, 57% ethanol	Solid-liquid, 70% acetone, 3 h	Phlorotannins, ABTS	2	High
Sunarwidhi 2022[48]	*Sargassum polycystum*, *S. cristaefolium*, *Turbinaria ornata* (P)	Indonesia	UAE, 30 kHz, 90 min	Cold maceration, 72 h	ABTS	3	High
Nguyen 2024[49]	*Padina gymnospora* (P)	Vietnam	EAE, Alcalase, 60.5 °C, 1.95 h	70% ethanol, 10 °C, 16 h	DPPH	1	High
Garcia-Vaquero 2021[50]	*Fucus vesiculosus*, *Pelvetia canaliculata* (P)	Ireland	UAE, MAE, UMAE, HAE, HPAE; all 10 min	Magnetic-stirring maceration, 10 min	TPC, phlorotannins	20	Low
Baek 2025[51]	*Sargassum serratifolium* (P)	Republic of Korea	PLE 100 °C, 70 min; SFE (CO2 + ethanol co-solvent) 45 °C, 90 min	Methanol maceration, 24 h, plus 30-min sonication	TPC, DPPH, ABTS, FRAP	8	High

Note. *R, Rhodophyta; P, Phaeophyceae. UAE, ultrasound-assisted extraction; MAE, microwave-assisted extraction; UMAE, combined ultrasound-microwave-assisted extraction; HAE, hydrothermal-assisted extraction; HPAE, high-pressure-assisted extraction; PLE, pressurized liquid extraction; SFE, supercritical fluid extraction; EAE, enzyme-assisted extraction; TPC, total phenolic content.*

3.3. Risk of bias

One of the 13 studies was judged at low risk of bias on every domain,[50] four raised some concerns, and eight were judged at high overall risk. Figure 2 displays the domain-level judgments. Allocation of biomass to arms was rated low in every study, since a single homogenized biomass was invariably divided between arms.

The dominant defect lay in the matching of process conditions, shown as domain D2 in Figure 2. Energy-assisted arms were routinely tuned by response-surface or algorithmic optimization. The conventional arm, by contrast, was run as a single fixed protocol taken from earlier work. The contrast therefore confounded the technology with the effort invested in optimizing it. In several studies the two arms used different solvent systems altogether. One compared a 57% ethanolic microwave arm against a 70% acetone conventional arm,[47] and another compared an aqueous enzymatic arm against a 70% ethanolic comparator.[49] A further study applied a 30-minute sonication assist to its own conventional arm.[51] Completeness of dispersion data, domain D3 in the same figure, was the second recurrent problem. Two studies never labeled their dispersions as standard deviations or standard errors,[43,46] one never stated a replicate count,[48] and one reported its optimized microwave arm with no dispersion at all.[46] Figure 2 holds the per-study judgments behind these statements, and the study-by-study risk ratings are also listed in the final column of Table 1. This pattern of optimization asymmetry

inflates the apparent advantage and is the single most important limitation of the synthesis.

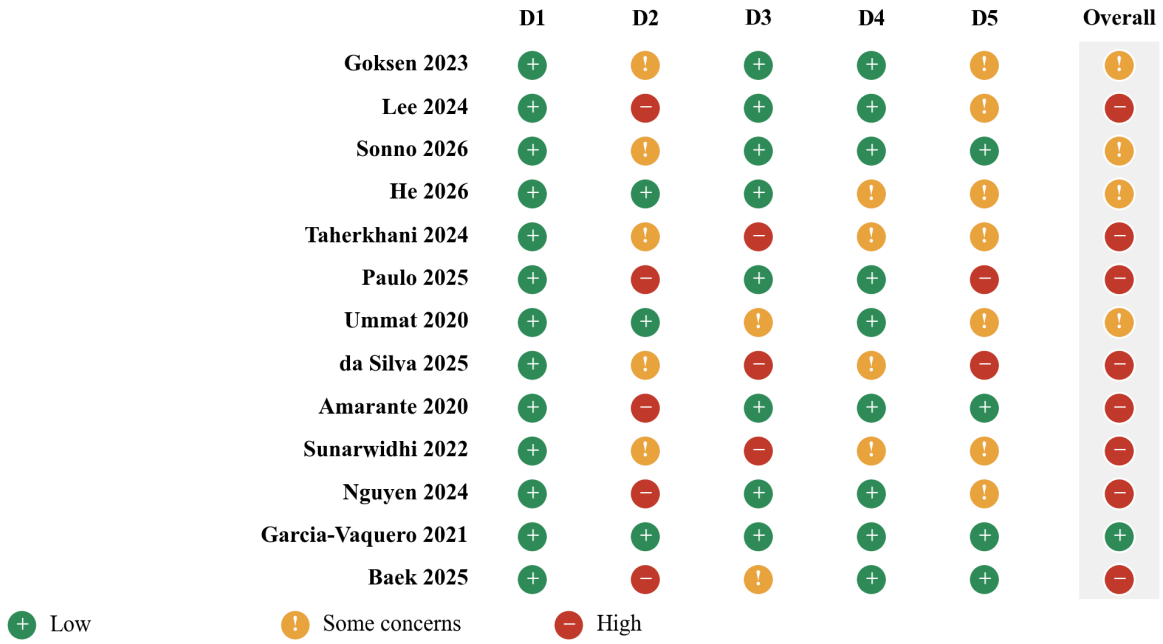


Figure 2. Risk of bias across the five Cochrane domains mapped onto their structural analogues for controlled comparative laboratory experiments. D1, allocation of biomass to arms; D2, matching of process conditions; D3, completeness of replicate and dispersion data; D4, measurement of the outcome; D5, selection of the reported result.

3.4. Pooled effect of energy-assisted extraction

Across all 93 estimates, the random-effects pooled standardized mean difference was 6.95 (95% CI 5.73 to 8.17) with the protocol-specified DerSimonian-Laird estimator. That interval assumes independence between estimates and is anti-conservative. It is retained for transparency and is not the basis of any claim made here. The primary inferential result is the cluster-robust estimate, with the study as the clustering unit: Hedges' g = 8.62 (95% CI 2.98 to 14.26, p = 0.0063). The three-level model returned the same point estimate and a closely comparable interval (95% CI 3.55 to 13.69, p = 0.0009). On the interpretable scale, energy-assisted extraction recovered 38.5% more than conventional extraction (ratio of means 1.385, 95% CI 1.149 to 1.671, p = 0.0027). Table 2 presents these results with the corresponding estimates for each outcome domain, and Figure 3 displays the individual estimates.

The three-level decomposition, reported in the third row of Table 2, attributed 50.3% of the variance to differences between studies and 46.8% to differences between species-level comparisons within studies. Roughly half of the variability was thus biological and species-specific, and not a matter of some laboratories being systematically more favorable than others.

The domain-level results need careful reading. They are exploratory, not confirmatory. Five correlated domains were analyzed and no multiplicity adjustment was applied, so a nominal p value of 0.0144 would not survive even a permissive correction across five tests. When the correlation between outcomes measured on the same extract was taken into account, only DPPH radical-scavenging reached nominal significance (g = 16.84, 95% CI 4.58 to 29.11, p = 0.0144). Total phenolic content sat at the margin (g = 5.74, 95% CI 0.13 to 11.34, p = 0.0459), and the corresponding DerSimonian-Laird estimate for this domain was 5.61 with an interval of 3.75 to 7.47. For the phlorotannin, ABTS and ferric-reducing pools, the cluster-robust intervals included the null. The composite stayed significant because pooling across domains draws on all 13 studies, whereas any single domain rests on only six to ten of them. On the ratio-of-means scale, every domain favored energy-assisted extraction, with gains running from 23.0% for ABTS to 54.9% for DPPH.

Table 2. Pooled effect of energy-assisted extraction relative to conventional solvent extraction on phenolic and antioxidant outcomes. The cluster-robust row is the inferential basis of this article.

Analysis	Estimates	Studies	Hedges' g (95% CI)	p	Ratio of means (95% CI)	Gain, % (95% CI)	I^2 (%)
Protocol-specified estimate, DerSimonian-Laird (retained for transparency; interval anti-conservative)	93	13	6.95 (5.73 to 8.17)	<0.0001	—	—	87.8
Primary inferential result: cluster-robust variance estimation	93	13	**8.62 (2.98 to 14.26)**	**0.0063**	**1.385 (1.149 to 1.671)**	**38.5 (14.9 to 67.1)**	—
Three-level random-effects model, restricted maximum likelihood	93	13	8.62 (3.55 to 13.69)	0.0009	—	—	97.1
Total phenolic content (exploratory)	29	10	5.74 (0.13 to 11.34)	0.0459	1.313	31.3	86.6

Analysis	Estimates	Studies	Hedges' g (95% CI)	p	Ratio of means (95% CI)	Gain, % (95% CI)	I^2 (%)
Phlorotannins (exploratory)	16	6	11.70 (−0.37 to 23.77)	0.0528	1.511	51.1	86.5
DPPH radical-scavenging (exploratory)	16	8	16.84 (4.58 to 29.11)	0.0144	1.549	54.9	90.2
ABTS radical-scavenging (exploratory)	18	8	13.00 (−0.62 to 26.62)	0.0585	1.230	23.0	89.7
Ferric-reducing antioxidant power (exploratory)	14	6	6.84 (−1.33 to 15.00)	0.0797	1.479	47.9	86.4

Note. *All intervals are cluster-robust except the DerSimonian-Laird row. The 95% prediction interval for the pooled effect ran from −2.26 to 16.16.*

3.5. Subgroup analyses and process meta-regression

Under cluster-robust testing, no moderator reached significance. Algal phylum had looked like a strong moderator while estimates were treated as independent. Once clustering was respected, its between-group test gave Q = 1.19 (p = 0.425). Brown seaweeds returned a pooled g of 10.08 against 1.24 for red seaweeds, yet the red-seaweed stratum rested on two studies and its interval carried no usable information. Matching between arms did not reach significance either (Q = 0.48, p = 0.775), and neither did solvent matching (Q = 1.63, p = 0.292). Table 3 presents the subgroup results.

The red-seaweed stratum needs to be described study by study. Its pooled interval of −63.18 to 72.32 is not simply imprecise; it carries no information, and it should not be read as a weak estimate of a real quantity. The stratum holds exactly two studies, and they disagree in kind rather than in degree. One reported a large and internally coherent advantage across all four outcomes in a single species, with total phenolic content rising from 169.21 to 212.03 mg gallic acid equivalents per 100 g and ferric-reducing capacity from 20.50 to 72.47 µmol Trolox equivalents per 100 g.[39] The other examined two species at two developmental stages. It reported 16 estimates that were close to null throughout, several of which favored the conventional arm, and its authors stated explicitly that they observed no universal advantage.[40] The width of the Rhodophyta interval thus reflects a real disagreement between two reports and not only a small number of observations.

These null moderator tests reflect limited power and do not demonstrate equivalence. The descriptive pattern in Table 3 still repays attention. The stratum in which energy input was the only difference between arms, with all other conditions identical, produced the largest effect (g = 12.74). It also had by far the lowest heterogeneity (I^2 = 64.6% against 87.8% overall) and a 90.2% gain on the ratio-of-means scale. That stratum held only three studies, though, and three clusters cannot support a significant robust test. At the other end, the stratum in which the comparator itself received a sonication assist showed no advantage at all (g = −0.06; ratio of means 0.886). That stratum is a single study (Baek 2025). Its methanol comparator was sonicated for 30 minutes, and its energy-assisted arms were pressurized-liquid and supercritical extraction, not ultrasound. The near-zero pooled value reflects a positive pressurized-liquid contrast (g = 8.96) offset by a negative supercritical one (g = −9.19), so it says little about acoustic energy.[51] Table 3 gives both strata in its comparator-matching block.

One technology went the opposite way. The final row of Table 3 records that supercritical carbon dioxide with ethanol as a co-solvent recovered significantly less phenolic material than conventional extraction (g = −9.19, 95% CI −14.59 to −3.79; ratio of means 0.482, a 51.8% reduction). The label green did not guarantee superior recovery. We report this counter-example in full.

Meta-regression addressed the most obvious skeptical explanation for the pooled result: energy-assisted arms might look superior only because the two arms were run for different lengths of time. Across the pool, the conventional arm ran between 1 and 480 times longer than the energy-assisted arm. The logarithm of that duration ratio did not predict effect size for the standardized mean difference (β = −1.09, 95% CI −5.00 to 2.81, p = 0.4805) or for the ratio of means (β = −0.02, 95% CI −0.16 to 0.12, p = 0.7170). It stayed non-significant in a multivariable model that also contained solvent matching and phylum (p = 0.9385). In 12 of the 35 comparisons, the two arms ran for exactly the same duration. The advantage was still present among them.

Table 3. Subgroup analyses by algal phylum, degree of matching between arms and energy-assisted extraction technology.

Moderator	Level	Estimates	Studies	Hedges' g (95% CI)	Ratio of means	I^2 (%)	Q between (p)
Algal phylum	Phaeophyceae	73	11	10.08 (3.90 to 16.73)	1.412	87.3	1.19 (0.425)
	Rhodophyta	20	2	1.24 (−63.18 to 72.32)	1.279	79.7	
Comparator matching	Isolated variable	20	3	12.74 (−5.16 to 40.16)	1.902	64.6	0.48 (0.775)
	Same solvent	62	9	6.12 (1.34 to 17.02)	1.409	87.1	
	Different solvent	3	2	1.25 (−8.41 to 10.90)	1.028	91.3	
	Partially sonicated comparator	8	1	−0.06 (−5.75 to 5.63)	0.886	91.4	
Solvent matching	Same	82	10	7.95 (3.23 to 16.86)	1.518	87.3	1.63 (0.292)
	Different	11	3	0.09 (−15.09 to 20.15)	0.976	90.4	

Moderator	Level	Estimates	Studies	Hedges' g (95% CI)	Ratio of means	I² (%)	Q between (p)
Energy-assisted technology	Ultrasound-assisted	56	9	6.36 (−2.46 to 19.64)	1.431	87.5	—
	Pressurized liquid	8	2	9.07 (5.09 to 13.05)	1.598	81.5	
	Microwave-assisted	8	3	6.27 (−59.45 to 103.24)	1.194	88.8	
	Ultrasound-microwave	4	1	14.36 (9.27 to 19.45)	1.364	26.9	
	Hydrothermal-assisted	4	1	13.77 (9.72 to 17.83)	1.366	0.0	
	High-pressure-assisted	4	1	9.57 (5.88 to 13.26)	1.250	35.1	
	Mechanical homogenization	4	1	5.89 (1.19 to 10.60)	1.583	80.4	
	Supercritical carbon dioxide	4	1	**−9.19 (−14.59 to −3.79)**	**0.482**	73.7	

Note. *Intervals are cluster-robust. Between-group tests were not computed for green technology because several levels were represented by a single study. Isolated variable denotes comparisons in which solvent, temperature, duration and solid-to-solvent ratio were identical and the energy input was the only difference.*

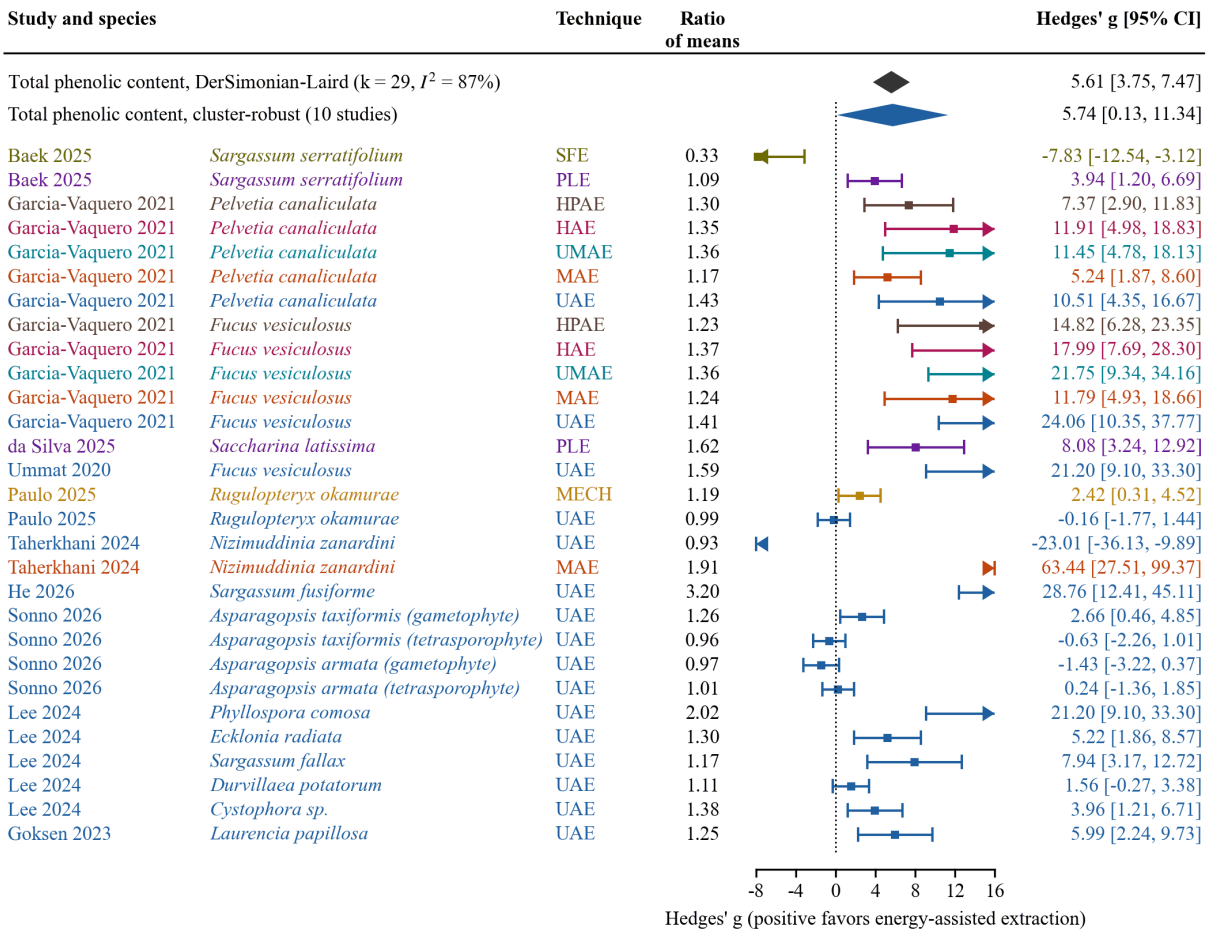


Figure 3 (part 1 of 5). Forest plot of all 93 effect estimates grouped by outcome domain and color-coded by extraction technology. Individual estimates are not intended to be read one by one; the diamonds carry the message. Gray diamonds are inverse-variance summaries and blue diamonds are cluster-robust, the latter forming the basis of inference. Positive values favor energy-assisted extraction. Five estimates expressed as half-maximal inhibitory concentrations have had their signs reversed, so that a positive value denotes greater antioxidant activity in every panel.

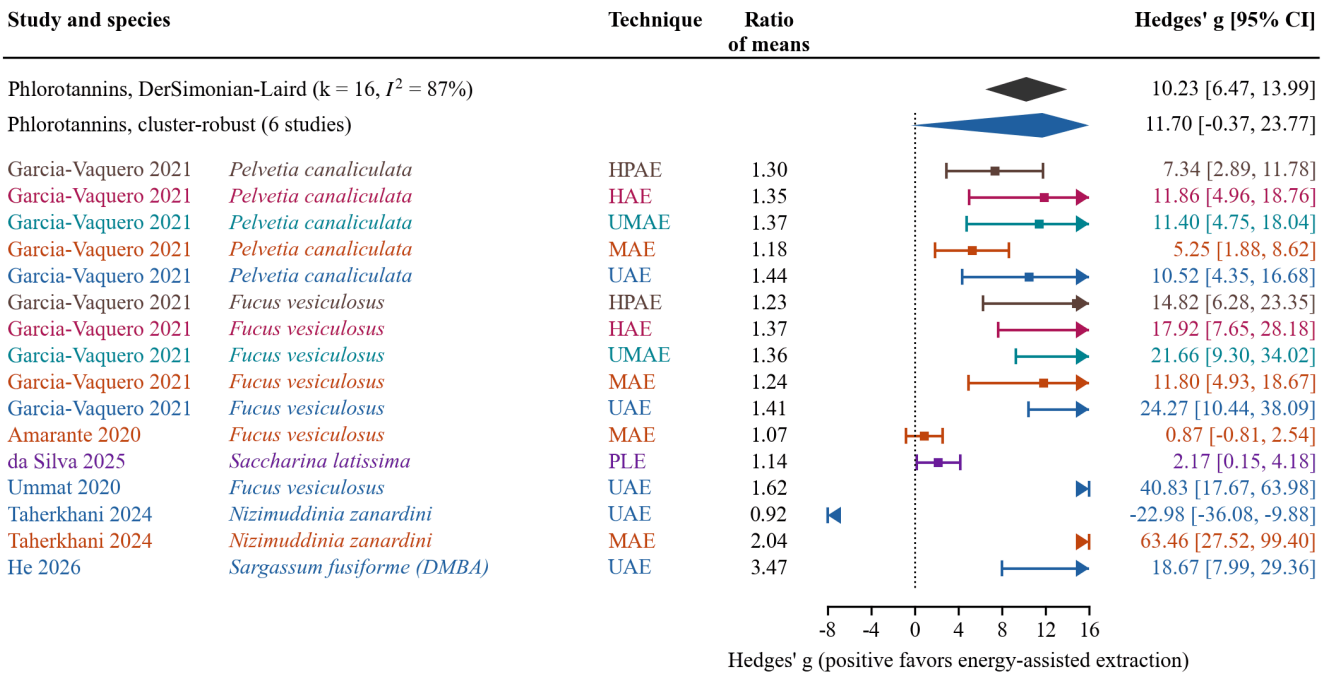


Figure 3 (continued, part 2 of 5). Phlorotannins.

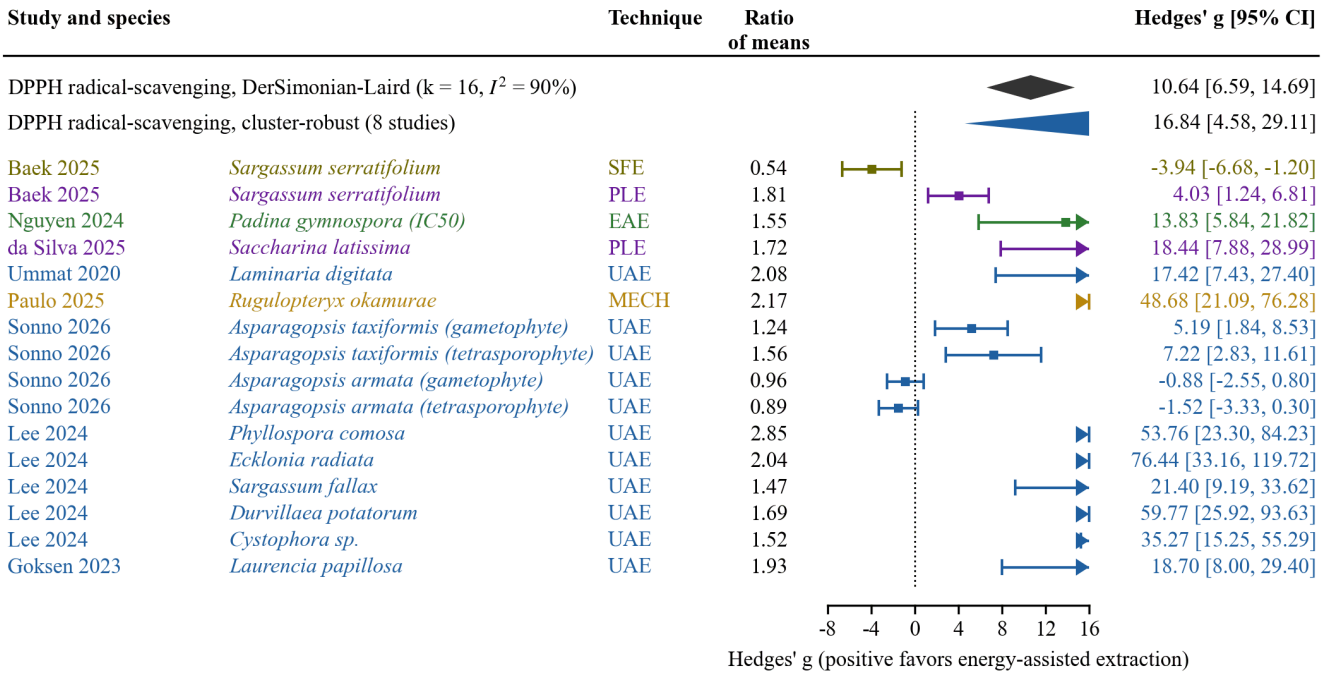


Figure 3 (continued, part 3 of 5). DPPH.

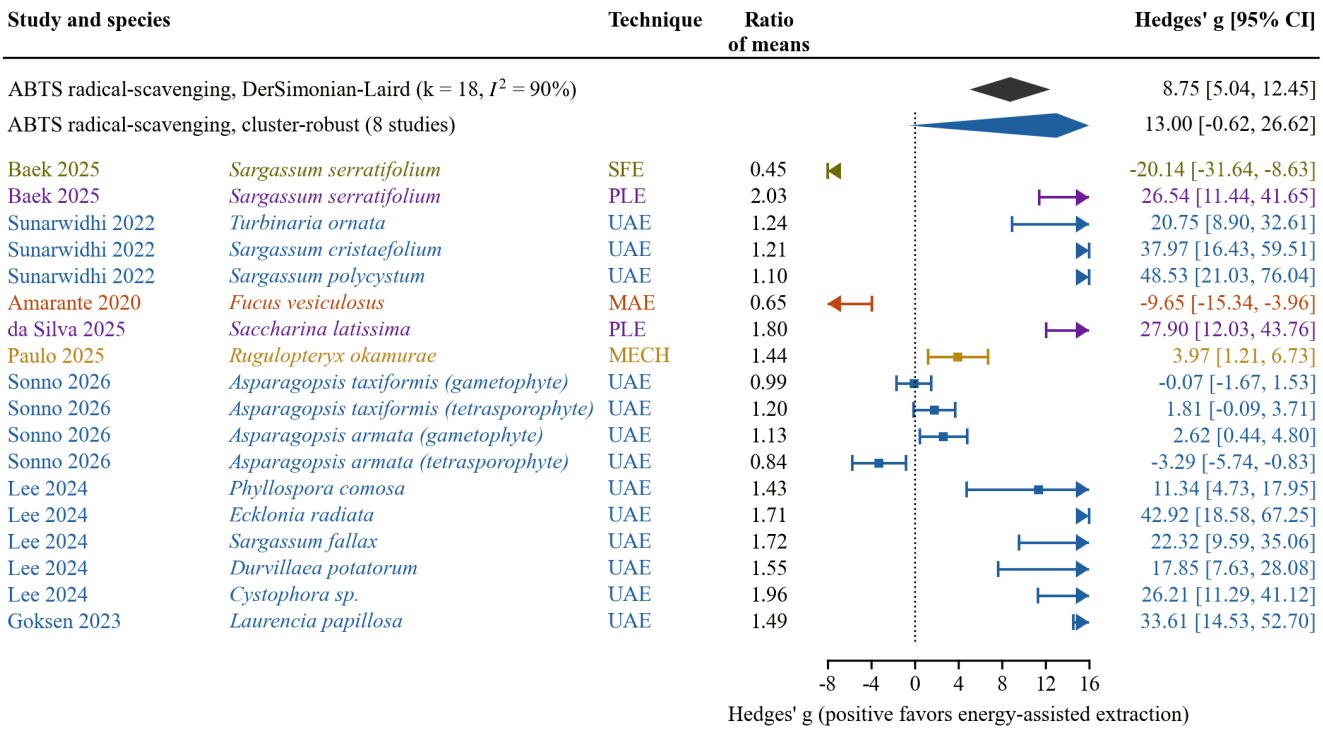
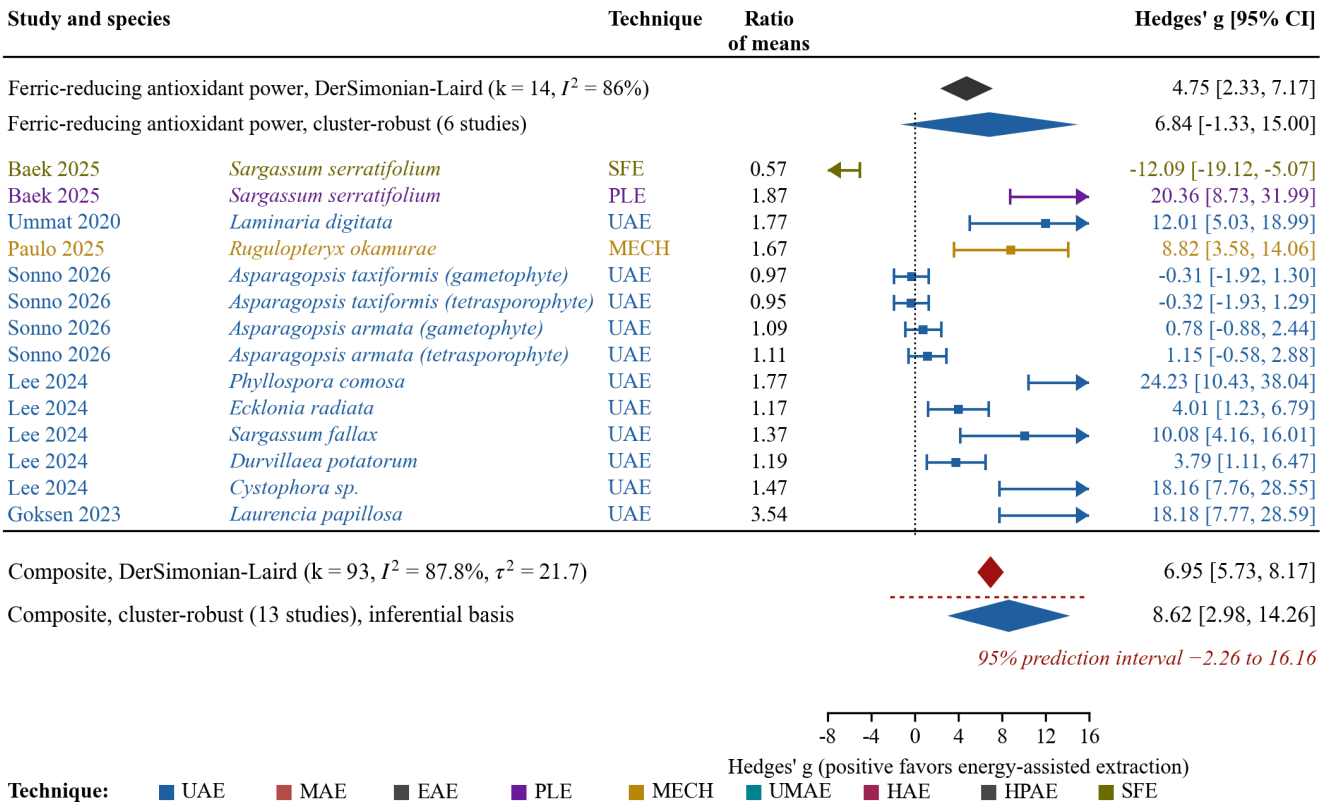


Figure 3 (continued, part 4 of 5). ABTS.



UAE, ultrasound-assisted; MAE, microwave-assisted; EAE, enzyme-assisted; PLE, pressurized liquid; MECH, mechanical homogenization; UMAE, ultrasound-microwave; HAE, hydrothermal-assisted; HPAE, high-pressure-assisted; SFE, supercritical fluid.

Figure 3 (continued, part 5 of 5). FRAP and composite pooled effect estimate.

3.6. Sensitivity analysis

We examined twenty-eight sensitivity scenarios, summarized in Table 4. The pooled estimate ranged from g = 1.87 to g = 12.74 and never reversed direction. Removing any one of the 13 studies left the cluster-robust interval entirely above zero, so no single study drove the result. Replacing the between-study variance estimator with restricted maximum likelihood or Paule-Mandel raised the point estimate instead of lowering it. Two dispersions were unlabeled. Treating

them as standard errors rather than standard deviations changed the pooled estimate only slightly, from 6.95 to 6.75.

One scenario deserves the closest attention, and Table 4 shows it in bold. It excluded every estimate with an absolute standardized mean difference above 10, which guards against inflation by very small analytical replicate dispersions. The pooled effect fell to g = 1.87 (95% CI 0.20 to 4.63) and the ratio of means to 1.085, an 8.5% gain. The direction held and the interval still excluded the null. The magnitude, however, collapsed. This is the clearest available demonstration that the standardized mean difference is inflated in this literature, and that the ratio of means is the more trustworthy expression of magnitude.

Restricting the analysis to one estimate per comparison, which enforces full independence, gave g = 9.02 (95% CI 3.39 to 17.50). Excluding the two studies retrieved only by the Europe PMC arm reproduced the evidence base of the PubMed searches and gave g = 5.86 (95% CI 2.46 to 17.07), so those additions strengthened rather than created the finding. Only two scenarios produced an interval crossing the null, and both did so because too few clusters remained for robust inference.

Table 4. Selected sensitivity analyses. Twenty-eight scenarios were examined in total.

Scenario	Estimates	Studies	Hedges' g (95% CI)	Ratio of means	Direction preserved
Base case	93	13	6.95 (2.98 to 14.26)	1.385	—
Most influential single-study removal (Sonno 2026)	77	12	10.36 (4.31 to 16.07)	1.420	Yes
Least favorable single-study removal (Garcia-Vaquero 2021)	73	12	5.26 (1.98 to 15.36)	1.383	Yes
Unlabelled dispersions treated as standard errors	93	13	6.75 (3.35 to 14.21)	1.385	Yes
Excluding the study with no stated replicate count	90	12	6.63 (2.19 to 11.90)	1.407	Yes
Excluding mechanical homogenization arms	89	13	7.03 (2.98 to 14.56)	1.357	Yes
Excluding the partially sonicated comparator	85	12	7.60 (3.57 to 15.40)	1.448	Yes
Total phenolic content only (DerSimonian-Laird point estimate)	29	10	5.61 (0.13 to 11.34)	1.313	Yes
Isolated-variable comparators only	20	3	12.74 (−5.16 to 40.16)	1.902	Yes
Excluding inverse-scaled concentration outcomes	88	11	6.72 (1.64 to 11.83)	1.432	Yes
Excluding estimates with |g| > 10	39	8	**1.87 (0.20 to 4.63)**	**1.085**	Yes
Excluding the two studies retrieved only by the Europe PMC arm	65	11	5.86 (2.46 to 17.07)	1.453	Yes
One estimate per comparison	35	13	9.02 (3.39 to 17.50)	1.418	Yes
Restricted maximum likelihood estimator	93	13	10.12 (2.98 to 14.26)	1.385	Yes
Paule-Mandel estimator	93	13	10.87 (2.98 to 14.26)	1.385	Yes

Note. *Point estimates are the random-effects estimates for each scenario and intervals are cluster-robust. Because cluster-robust standard errors are computed from the empirical dispersion of within-cluster residuals, they do not depend on the between-study variance estimator; the final three rows therefore share the base-case interval by construction rather than by coincidence, while their point estimates differ. The row restricted to total phenolic content carries the DerSimonian-Laird point estimate of 5.61 against the cluster-robust interval; the cluster-robust point estimate for that domain, 5.74, is given in Table 2. In the base-case row the point estimate is the DerSimonian-Laird estimate (6.95), whereas the interval is the cluster-robust interval around the cluster-robust estimate (8.62), so it is not centered on the printed value.*

3.7. Gravimetric extract yield

Gravimetric extract yield was pooled separately throughout. It measures the mass of material recovered and not the concentration of phenolics within it, and a process that recovers more mineral matter and polysaccharide will register a higher yield without delivering more antioxidant activity. Fifteen estimates from four studies were available. The inverse-variance estimate was large (g = 26.68). Once clustering was respected, the effect was not significant (g = 16.99, 95% CI −14.67 to 48.66, p = 0.1816). The ratio of means gave a 41.3% gain, but its interval crossed unity (1.413, 95% CI 0.877 to 2.276, p = 0.1023). Yield should therefore be treated as suggestive only. Table 5 sets it out separately.

Table 5. Gravimetric extract yield, pooled separately from the phenolic and antioxidant outcomes.

Analysis	Estimates	Studies	Estimate (95% CI)	p	I^2 (%)	Status
Hedges' g, inverse-variance	15	4	26.68 (17.21 to 36.15)	<0.0001	90.6	Anti-conservative
Hedges' g, cluster-robust	15	4	**16.99 (−14.67 to 48.66)**	**0.1816**	—	**Inferential; not significant**
Ratio of means, cluster-robust	15	4	1.413 (0.877 to 2.276)	0.1023	99.9	41.3% gain; interval crosses unity

Note. *Yield does not contribute to the pooled phenolic estimate reported in Table 2 and should not be averaged with it.*

3.8. Processing time

Processing time was the most dependable practical finding, and it rested on no modeling assumption. Across the 35 comparisons, the energy-assisted arm had a median duration of 10 minutes against 960 minutes for the conventional arm. That is a median 20.6-fold reduction, with an interquartile range from 1-fold to 108-fold. Energy-assisted arms ran for between 3 and 120 minutes, and

conventional arms for between 10 and 4320 minutes. In 12 of the 35 comparisons the two arms ran for exactly the same length of time, and the advantage was still present among them. Because this check needs no model at all, it is the most direct evidence in the article that the benefit comes from the energy input and not from contact time.

Processing time is only one axis on which a process may be judged green. The solvent and matching characteristics of the two arms were therefore tabulated descriptively as well, and Table 6 presents them. Solvent identity and concentration were identical between arms in 31 of the 35 comparisons, so the pooled estimate is mainly a comparison of energy input and not of solvent chemistry. Ten comparisons were fully isolated-variable contrasts, with solvent, temperature, duration and phase ratio all matched. Two energy-assisted arms used water alone, against 70% ethanol in one study and water at reflux in the other. Thirty energy-assisted arms and 32 conventional arms used an organic or hydro-organic solvent, one energy-assisted arm used supercritical carbon dioxide with ethanol as co-solvent, and for the two comparisons of Paulo 2025 the solvent pairing could not be verified from the source. These are descriptive counts from the extracted dataset, and no effect estimate is attached to them.

Table 6. Process and solvent characteristics of the 35 paired comparisons, reported descriptively.

Characteristic	Value
Duration of the energy-assisted arm	3 to 120 minutes (median 10)
Duration of the conventional arm	10 to 4320 minutes (median 960)
Median fold reduction in processing time	20.6-fold (interquartile range 1 to 108)
Comparisons in which both arms ran for identical durations	12 of 35
Comparisons with identical solvent identity and concentration in both arms	31 of 35
Comparisons in which solvent differed between arms	4 of 35
Fully isolated-variable comparisons (solvent, temperature, duration and phase ratio all matched)	10 of 35
Comparisons with a conventional arm that itself received a sonication assist	2 of 35
Energy-assisted arms using water or an aqueous system alone	2 of 35
Energy-assisted arms using an organic or hydro-organic solvent	30 of 35 (2 comparisons not verified)
Energy-assisted arms using supercritical carbon dioxide with ethanol as co-solvent	1 of 35
Conventional arms using an organic or hydro-organic solvent	32 of 35 (2 comparisons not verified)
Comparisons in which arm temperatures were matched	10 of 35 (9 differed, 16 not reported)

Note. *Counts describe the extracted dataset and carry no pooled estimate. Solvent volume per unit of biomass could not be tabulated for every comparison because solid-to-solvent ratio was not reported in all reports, which is itself a reporting deficiency of the primary literature.*

3.9. Small-study effects and publication bias

Small-study effects were present. Table 7 sets out the tests that establish this. The regression test applied to all 93 estimates was highly significant ($t = 11.14$, $p < 0.0001$), but it cannot be interpreted on its own. The sampling variance of a standardized mean difference depends on the effect size, so a pool containing large effects is forced into an asymmetric funnel, and panel A of Figure 4 shows this artifact as a distortion. Two artifact-free tests were therefore applied. The regression test on the 13 study-level means was significant ($t = 2.80$, $p = 0.0172$). So was the regression test on the ratio of means, which carries no such artifact ($t = 4.42$, $p < 0.0001$); these correspond to panels B and C of Figure 4 respectively. Trim-and-fill imputed 27 estimates, 29% of the 93 observed estimates, and reduced the effect from 6.95 to 4.42 (95% CI 3.17 to 5.68). That method performs poorly under heterogeneity of the size observed here. The adjusted value is therefore offered as an illustrative lower bound and not as a corrected estimate, as noted beneath Table 7.

A genuine reporting bias is highly likely on mechanistic grounds. Of the 22 reports excluded at full text, 18 never ran a conventional comparator. Laboratories that find no advantage may simply not frame their work as a comparison. Null contrasts would then be missing from the literature by design and not through suppression.

Table 7. Tests for small-study effects and publication bias.

Test	Units entering the test	Statistic	p or interval	Interpretation
Regression test, all estimates	93 estimates	t = 11.14	<0.0001	Confounded by the dependence of the sampling variance on the effect size
Regression test, study-level means	13 studies	t = 2.80	0.0172	Aggregated to one estimate per study; artifact removed
Regression test, ratio of means	**93 estimates**	**t = 4.42**	**<0.0001**	**Free of the variance artifact; the decisive test**
Rank-correlation test	93 estimates	0.822	<0.0001	Subject to the same mechanical caveat as the first row
Trim-and-fill, estimates imputed	93 estimates	27	—	29% of the pool imputed; a very large adjustment
Trim-and-fill, adjusted effect	93 estimates	g = 4.42	3.17 to 5.68	Illustrative bound, not a corrected value

Note. *Regression and rank-correlation tests are conventionally regarded as uninformative with fewer than ten units; the study-level test sits only marginally above that threshold and should be read with corresponding caution. Trim-and-fill imputed 27 estimates, or 29% of the 93 observed*

estimates, and the method is known to perform poorly when heterogeneity is as high as it is here; its adjusted value is therefore presented as an illustrative lower bound rather than as a corrected estimate.

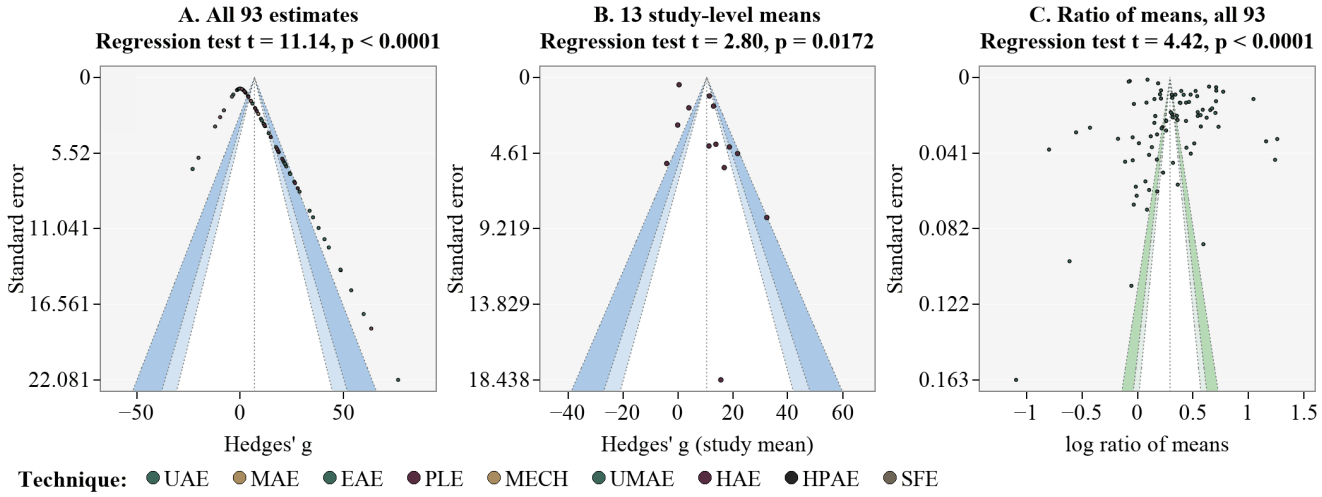


Figure 4. Contour-enhanced funnel plots. A, all estimates, distorted by the dependence of the sampling variance on the effect size; B, study-level means; C, the ratio of means, which is free of that artifact and provides the cleanest test of asymmetry.

3.10. Certainty of evidence

No outcome exceeded low certainty, as Table 8 details. The phlorotannin outcome was rated very low, because its cluster-robust interval included the null on top of the concerns that applied to every outcome. All outcomes were downgraded for risk of bias, driven by the optimization asymmetry visible in Figure 2, and for inconsistency, driven by the I^2 values above 80% reported in Table 2. Reporting bias was suspected throughout, on the evidence set out in Table 7. The direction of effect can therefore be regarded as well supported, and the magnitude as uncertain. Gravimetric extract yield was rated very low on the same reasoning as the phlorotannin outcome, since its cluster-robust interval crossed the null and its I^2 exceeded 90% (Table 5).

Table 8. Certainty of evidence across five appraisal domains.

Outcome	Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Reporting bias	Certainty
Total phenolic content	10	Serious	Serious	Not serious	Not serious	Suspected	Low
Phlorotannins	6	Serious	Serious	Not serious	Serious	Suspected	**Very low**
DPPH radical-scavenging	8	Serious	Serious	Not serious	Not serious	Suspected	Low
ABTS radical-scavenging	8	Serious	Serious	Not serious	Not serious	Suspected	Low
Ferric-reducing antioxidant power	6	Serious	Serious	Not serious	Not serious	Suspected	Low
Gravimetric extract yield	4	Serious	Serious	Not serious	Serious	Suspected	**Very low**

4. Discussion

4.1. Principal findings

This synthesis found that energy-assisted extraction recovered more phenolic antioxidant activity from marine macroalgal biomass than conventional solvent extraction, and it did so far faster. On the ratio-of-means scale the pooled advantage was 38.5%. The cluster-robust confidence interval on the ratio of means ran from 1.149 to 1.671, that is a gain of between 14.9% and 67.1%. The median energy-assisted protocol reached that advantage in 10 minutes, against 16 hours for the conventional one. The direction of effect held up under every check applied to it: all 28 sensitivity scenarios, the removal of any single study, three different between-study variance estimators, the enforcement of full independence between estimates, and the exclusion of the extreme estimates most likely to be inflated by small analytical dispersions.

The magnitude was a different matter, and the fair reading of this work is that direction and magnitude carry very different evidential weight. When estimates with an absolute standardized mean difference above 10 were excluded, the pooled gain fell from 38.5% to 8.5%. Trim-and-fill adjustment cut the standardized effect from 6.95 to 4.42. Both operations kept the sign and shrank the size. A reader should take away that energy-assisted extraction helps and helps quickly, while the precise size of the benefit for any given species and technology remains an open question.

A second finding was negative. Once the dependence between estimates measured on the same extract was handled correctly, no moderator survived testing. The apparent superiority of brown seaweeds over red, and the apparent role of matching between arms, both disappeared when clustering was respected. Neither result reflected a weak signal that grew weaker. Each was an artifact of treating 93 correlated estimates as 93 independent observations. The point carries a methodological implication for the wider field, where multiple outcomes measured on a single extract are routinely analyzed as though they were independent replicates.

4.2. Comparison with previous syntheses

No earlier meta-analysis has pooled the effect of extraction technology on phenolic recovery from macroalgae, so a direct comparison cannot be made. The published quantitative syntheses that involve algae and antioxidant outcomes asked entirely different questions. They examined seaweed-extract biostimulants and crop yield, salinity tolerance in cereals, methane mitigation and performance in ruminants, and blood pressure, anthropometric indices and metabolic status in humans.[30-32,52] The present work therefore covers ground that was genuinely unoccupied. Its pooled estimate gives the first quantitative benchmark against which future process studies can be positioned.

Primary work in adjacent matrices still offers a useful indirect comparison. Head-to-head studies in terrestrial biomass have reported that ultrasound- and microwave-assisted extraction outperformed conventional methods for polyphenol recovery from distillery stillage and peach by-products,[22,23] and head-to-head comparisons of ultrasound-assisted extraction with maceration in leaves, peel and seeds have recorded gains of roughly 14% to 70% in the recovery of phenolic or other bioactive compounds, a range that brackets the pooled 38.5%.[53-56] Two literatures with different wall chemistries agree, which strengthens the mechanistic case that the advantage comes from cell-wall disruption and not from the peculiarities of any single matrix. Studies that combined green solvents with ultrasound have reported further gains again,[24,25] in line with the good performance of the pressurized-liquid arms in the present pool.[46,51]

The most instructive discordant result came from inside the pool itself. The supercritical carbon dioxide arm recovered roughly half as much as its conventional comparator.[51] The mechanism is easy to see. Supercritical carbon dioxide is a non-polar solvent and suits polar phenolics poorly unless it is heavily modified.[57] Ethanol was used as a co-solvent in the arm concerned, and it recovered less all the same. The result also corrects the assumption that any technology carrying the green label will improve recovery. The platform should be chosen according to the polarity of the target compounds, and the environmental credentials of the solvent should not drive that choice.

4.3. Heterogeneity

Heterogeneity was very high by any conventional standard, and the prediction interval included zero. Three sources could be identified. The first was biological. The three-level decomposition attributed 46.8% of the variance to differences between species-level comparisons within the same study. In practice, two species processed in the same laboratory on the same day by the same operator responded differently. That fits the known variation in cell-wall architecture and phenolic composition between macroalgal taxa, and the reported seasonal and developmental variation within a single species.[40,58-60]

For a producer the practical consequence is direct. Half the variance arises between species processed within the same laboratory. An optimized protocol therefore cannot be moved from one species to another with any expectation of reproducing the same gain, and species-specific process development remains necessary even after a technology has been selected. The prediction interval of −2.26 to 16.16 makes the same point in inferential terms. The pooled estimate describes an average across heterogeneous pairings, and it gives no guarantee of a benefit for any particular new one.

The second source was methodological and arose from the optimization asymmetry documented in the risk-of-bias appraisal. Where an energy-assisted arm had been tuned across dozens of design points and the conventional arm had not, the measured contrast reflected optimization effort as well as technology. The stratum in which energy input was the only difference between arms showed much lower heterogeneity, at 64.6% against 87.8% overall. That supports this interpretation.

The third source was analytical. Antioxidant capacity was expressed in several different ways across the pool (percentage inhibition, half-maximal inhibitory concentration, and Trolox or ascorbic-acid equivalents), and phenolic content on several denominators (per 100 g, per gram of dry biomass and per gram of extract). Standardization absorbs the unit differences. It does not absorb the fact that DPPH, ABTS and ferric-reducing assays probe different chemistry, a difference visible in their pooled gains and in reports that assay choice materially affects the apparent antioxidant ranking of seaweed extracts.[13,61]

4.4. Limitations

Six limitations need explicit statement, and they are listed here in order of the weight we give them. The first and most serious is optimization asymmetry between the arms. In eight of the 13 studies the energy-assisted arm was optimized, often across dozens of response-surface design points. The conventional arm was run as a single fixed protocol inherited from earlier work, and in three studies the two arms used different solvent systems altogether. The pooled estimate therefore reflects the combined effect of the technology and of the effort invested in tuning it. It is biased upward by an amount that cannot be recovered from the published record. The second limitation concerns the primary effect measure itself. The dispersions reported in this literature are analytical replicate standard deviations that describe the repeatability of a spectrophotometric assay, not biological variability. Dividing by them produced individual estimates exceeding 70, values with no counterpart in the clinical framework from which the standardized mean difference is borrowed. Reporting the ratio of means throughout mitigates this, and the sensitivity analysis excluding extreme estimates quantifies it, yet the measure specified in the protocol remains inflated.

The third limitation is that small-study effects appear to be real and not artifactual. The regression test on the ratio of means carries none of the mechanical asymmetry that afflicts the same test applied to standardized mean differences, and it was clearly significant. Of the 22 reports excluded at full text, 18 had never run a conventional comparator at all. Trim-and-fill adjustment reduced the pooled estimate by roughly a third. Fourth, the evidence base is severely imbalanced taxonomically. Red seaweeds contributed 20 estimates from two studies that disagree with one another, and green seaweeds contributed none. The practical interest motivating this work concerns red algae of tropical waters, so the near-absence of Rhodophyta is a serious constraint, and no confident statement about red seaweeds can be supported. Fifth, heterogeneity was very high and the prediction interval spanned zero. The pooled estimate describes an average across a heterogeneous set of species and technology pairings, and it must not be read as a forecast for any particular new one.

The sixth limitation is procedural and concerns the conduct of the review itself. A single reviewer performed screening and data extraction, rather than two working independently in duplicate. Three eligible reports could not be obtained because their publisher full texts were inaccessible. The evidence base was capped at 13 studies by the scarcity of conventional comparator arms in the primary

literature, and the search was not narrow. Each of these constraints is stated here, so the work is not presented as a fully executed dual-reviewer systematic review.

4.5. Implications for biotechnology and green chemistry

For process biotechnology the practical case rests less on the effect size than on the time. Equal or better recovery in 10 minutes rather than 16 hours changes the economics of a macroalgal biorefinery. Reactor occupancy would be expected to fall by an order of magnitude, throughput per unit of capital to rise correspondingly, and the solvent inventory held at temperature for long periods to shrink. These quantities determine whether a valorization route is viable, and the time saving holds under every modeling assumption examined here.

For green chemistry the substantive result is that shorter processes did not sacrifice recovery. The conventional expectation of a trade-off between environmental performance and yield was not observed. In the isolated-variable stratum, where energy input was the only difference between arms, recovery rose by 90.2%. The corollary is that solvent-reduction strategies and enzyme-assisted aqueous routes deserve closer examination,[49,62] although the one study that used an aqueous enzymatic arm against a 70% ethanolic comparator contributed a single estimate.[49] In that study phenolic recovery of the enzymatic arm reached 98.9% of the ethanol comparator, and the advantage lay in the DPPH half-maximal inhibitory concentration of the phenolic fractions (48.17 versus 74.69 µg/mL).[49]

For pharmaceutical and nutraceutical development the implication is that the extraction protocol must be reported and controlled as rigorously as species identity. Two laboratories working on the same alga with different platforms may recover quite different phenolic profiles. That complicates any comparison of bioactivity results across studies, and it may partly explain inconsistencies in the reported potency of macroalgal extracts.[4,6,33,63]

For tropical archipelagic producers, this synthesis points to the generation of Rhodophyta evidence as the priority. Red seaweeds are cultivated at very large scale in Indonesian waters and are already used in food, pharmaceutical and wound-care applications,[8,34-36,64] yet the extraction literature is dominated by cold-water brown seaweeds. Well-matched comparative experiments on cultivated red species would address the largest single gap this review identified. In such experiments the energy-assisted and conventional arms should share solvent, temperature, duration and solid-to-solvent ratio.

4.6. What the evidence does and does not support

The analyses above yield a mixture of firm and fragile conclusions, so Table 9 states compactly which claims the evidence supports and which it does not. The distinction matters for anyone using this synthesis as a basis for a process decision. The unsupported column deserves as much attention as the supported one.

Table 9. Claims supported and not supported by this synthesis.

Supported by the evidence	Not supported, and should not be claimed
Energy-assisted extraction recovers more phenolic antioxidant activity than conventional solvent extraction; the direction survived all 28 sensitivity scenarios and the removal of any single study.	That the advantage holds for every outcome. Only the composite reached inferential significance; the domain analyses were exploratory and three of five intervals included the null.
The advantage is obtained with a median 20.6-fold reduction in processing time, and persists in the 12 comparisons in which both arms ran for identical durations.	That any one technology outperforms another. No between-technology comparison survived cluster-robust testing.
The advantage is present where energy input is the only difference between arms, so it is not merely an artifact of protocol mismatch.	That brown seaweeds benefit more than red. The phylum test was not significant and the red-seaweed interval is uninformative.
Solvent identity was matched between arms in 31 of 35 comparisons, so the estimate reflects energy input rather than solvent chemistry.	That every green technology helps. Supercritical carbon dioxide recovered 51.8% less than its conventional comparator.
The direction is stable across three between-study variance estimators and under full enforcement of independence.	The exact magnitude. Small-study effects are real, the standardized measure is inflated by analytical dispersions, and optimization asymmetry biases upward.
Extraction platform should be reported and controlled as rigorously as species identity in any bioactivity study.	Anything confident about red or green seaweeds. Rhodophyta rest on two disagreeing studies and Chlorophyta on none.

4.7. Recommendations for future comparative studies

Four design changes would improve the evidence base. First, arms should be matched for solvent, temperature, duration and solid-to-solvent ratio so that energy input is the only variable, as in the one study judged at low risk of bias throughout.[50] Second, both arms should receive equivalent optimization effort, or the conventional arm should be optimized and the energy-assisted arm run at a single condition, so that the direction of any residual asymmetry is at least conservative. Third, dispersions should be labeled explicitly as standard deviations or standard errors, and the number of independent extractions should be distinguished from the number of analytical replicates. Finally, absolute values should be reported for both arms in a table and not only in a figure, in a stated unit with an unambiguous denominator. Four otherwise eligible reports were lost from this synthesis for want of a printed dispersion or a numeric table.

5. Conclusion

This meta-analysis pooled 93 effect estimates from 35 paired comparisons across 22 macroalgal species, drawn from 13 controlled comparative laboratory experiments. Energy-assisted extraction recovered more phenolic antioxidant activity than conventional solvent extraction did. The cluster-robust Hedges' g was 8.62 (95% CI 2.98 to 14.26, p = 0.0063), equal to a 38.5% gain on the ratio-of-means scale (95% CI 1.149 to 1.671). It took a median of 10 minutes, against 960 for the conventional methods. The advantage persisted in the 12 comparisons whose arms ran for identical durations. Contact time did not explain it.

The direction of the effect held up. It survived all 28 sensitivity scenarios, the removal of any single study, three

variance estimators and the enforcement of full independence. The magnitude was less stable. Excluding estimates with an absolute standardized mean difference above 10 cut the gain to 8.5%. Adjusting for demonstrated small-study effects reduced the standardized effect to 4.42. For no outcome did certainty exceed low, and the domain analyses were exploratory. The 95% prediction interval of −2.26 to 16.16 included zero. No individual new pairing of species and technology is therefore assured of benefit.

Three caveats apply. No moderator survived cluster-robust testing. The green label did not guarantee better recovery, since supercritical carbon dioxide recovered 51.8% less than its comparator. And the evidence was skewed taxonomically: 73 of 93 estimates came from brown seaweeds, 20 from two red-seaweed studies that disagreed, and none from green seaweeds. What the data support is that energy-assisted extraction cuts processing time sharply without loss of phenolic recovery, and probably with a gain. Well-matched experiments on cultivated red seaweeds should come first.

6. Declarations

Statement on the Use of Artificial Intelligence

The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

Author Contribution Statement

Z.V.N.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. H.C.: Supervision, Validation, Writing – review & editing. Both authors approved the final manuscript.

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Conflict of Interest / Competing Interests

The authors declare that they have no competing interests.

Data Availability Statement

The de-identified dataset and the analysis scripts supporting the findings are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Not applicable. This study is a meta-analysis of previously published data and did not involve new human participants, animals, or identifiable personal information.

Consent for Publication

Not applicable.

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