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Multi-mechanistic cardiovascular potential of sea cucumber compounds: A narrative review of preclinical evidence

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ABSTRACT

Background: Cardiovascular disease is the leading cause of death worldwide, and residual risk persists despite current drugs. Objectives: To compare the strength of preclinical evidence for sea cucumber (*Holothuroidea*) compounds across four cardiovascular mechanisms and identify studies needed before clinical testing. Methods: This SANRA-guided narrative review included peer-reviewed English-language studies of sea cucumber-derived compounds with cardiovascular-relevant endpoints. After a five-database search (January 2020–April 2026), PubMed was searched on 29 September 2026 (January 2020–June 2026); 37 of 187 records and 13 articles from other sources were included. Primary studies were graded on five evidence levels, and *in vivo* studies were assessed with SYRCLE's tool. Results: The evidence base comprised 36 primary studies, none clinical, and 14 reviews. Eight had *in vivo* cardiovascular endpoints, eight *in vivo* indirect endpoints, 17 *in vitro*, *ex vivo*, or structural endpoints, and three *in silico* only. Risk of bias was unclear in most domains. Of the four mechanisms, anticoagulant activity had the strongest evidence: fucosylated chondroitin sulfate selectively inhibited the intrinsic tenase complex, prevented thrombosis in rodents with less bleeding than heparin, and remained active orally in two rat studies. An intravenous angiotensin-converting enzyme inhibitory peptide lowered blood pressure in rats with hypertension. Phospholipids and an ultrafine powder reduced aortic plaque in mice with atherosclerosis. Anti-inflammatory effects came mainly from non-vascular models. Conclusions: Sea cucumber compounds have multi-mechanistic cardiovascular potential, but the evidence is preclinical, pharmacokinetic data are limited, and no controlled clinical trial was identified. Pharmacokinetic, toxicity, and oral efficacy studies must precede randomised trials.

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INTRODUCTION

Cardiovascular disease (CVD) caused an estimated 19.8 million deaths in 2022, approximately 32% of all deaths worldwide (World Health Organization, 2025). Hypertension, dyslipidaemia, atherosclerosis, and thrombosis are its main modifiable drivers. Current drugs are effective but have dose-limiting adverse effects, and in a European study of 5888 patients receiving lipid-lowering therapy, only 33% reached the 2019 LDL-cholesterol goals (Ray et al., 2021). This residual risk motivates the search for complementary agents.

Sea cucumbers have been studied as a source of compounds acting on several of these drivers, as summarised in the next section. Previous reviews each covered one therapeutic area, such as dyslipidaemia (Lin et al., 2022), anticoagulation (Felix et al., 2025; H. Li et al., 2021), or cancer (Nurhidayati et al., 2025), and none examined blood-pressure regulation, anticoagulation, vascular inflammation, and lipid metabolism in comparable depth. A more important gap is that the evidence behind each mechanism has not been compared on the same terms: which effects rest on *in vivo* cardiovascular endpoints and which only on enzyme, cell, or docking data; whether structure–activity relationships are consistent across species; whether pharmacokinetic data support oral use; and how far each mechanism is from clinical testing. This review therefore asks three questions. First, for each mechanism, what is the highest level of evidence, and is it direct or indirect? Second, are the structure–activity and pharmacokinetic data consistent enough to guide the choice of a lead compound or fraction? Third, which studies are needed before clinical evaluation?

To answer these questions we use a conceptual framework, presented with the integration of the results. Each compound group is linked to its molecular target, the biological pathway it modulates, and the cardiovascular effect, and every link is labelled by the type of evidence that supports it. Related Work, Among sea cucumbers (class *Holothuroidea*, phylum *Echinodermata*), *Cucumaria frondosa* contains compounds with antihypertensive, anticoagulant, anti-inflammatory, and antioxidant activity (Hossain et al., 2020). Sulfated polysaccharides from many species have anticoagulant, anti-inflammatory, and metabolic activity (Hossain et al., 2023; Saeid et al., 2025), and peptides with angiotensin-converting enzyme (ACE) inhibitory activity are well documented (Lu et al., 2022).

Of the compound classes in sea cucumbers, four groups are the most relevant to cardiovascular pharmacology. ACE-inhibitory peptides act on the renin–angiotensin–aldosterone system (RAAS), and marine peptides are an established antihypertensive class (Festa et al., 2020). Sulfated polysaccharides, mainly fucosylated chondroitin sulfate (FCS) and fucan sulfate, have anticoagulant and antithrombotic activity (Dwivedi & Pomin, 2020; Hossain et al., 2023). Triterpene glycosides have anti-inflammatory and antithrombotic activity (Fagbohun et al., 2023). Lipids such as phospholipids and cerebrosides lower serum and hepatic lipids in animal models compared with untreated controls (Lin et al., 2022). Earlier reviews also covered neurological disorders (Debi et al., 2025).

RESEARCH METHOD

Review Type and Reporting Framework

This is a narrative review. It was not registered and did not follow a systematic-review protocol, so PRISMA was not applied. Reporting followed the six items of the Scale for the Assessment of Narrative Review Articles (SANRA): importance, aims, literature search, referencing, level of evidence, and endpoint data (Baethge et al., 2019).

Information Sources and Search Strategy

Two searches were conducted. The first, begun during the 2024 programme described in the Acknowledgements, covered PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and

Embase. Its final strings combined three concept blocks (sea cucumber taxa, cardiovascular mechanisms, and compound classes), The PubMed string was limited to publications dated January 2020 to April 2026; the other four databases were limited by publication year (2020–2026), and the strings differ in breadth (Supplementary Table S2); the date on which they were last run and their record counts were not saved. The second search is the reproducible search reported here: PubMed was searched on 29 September 2026 for publications dated 1 January 2020 to 30 June 2026. Reference lists of included articles were also checked (citation searching).

The PubMed string combined MeSH and title/abstract terms with Boolean operators: ("Sea Cucumbers"[MeSH] OR "sea cucumber*"[tiab] OR Holothuroidea[tiab] OR holothurian*[tiab]) AND ("Cardiovascular Diseases"[MeSH] OR cardiovascular[tiab] OR hypertension[tiab] OR antihypertensive[tiab] OR "angiotensin-converting enzyme"[tiab] OR anticoagulant*[tiab] OR antithrombotic[tiab] OR thrombosis[tiab] OR "Inflammation"[MeSH] OR anti-inflammatory[tiab] OR "NF-kappa B"[MeSH] OR hypolipid*[tiab] OR dyslipid*[tiab] OR cholesterol[tiab] OR atherosclerosis[tiab]), with the publication date limited to 2020/01/01–2026/06/30. Unlike the first search, this string did not require a compound-class term, so it also retrieves studies of lipids, sterols, and whole-body preparations.

Eligibility Criteria

Eligible primary studies were peer-reviewed, English-language reports that tested a compound, fraction, or synthetic derivative of defined sea cucumber origin and reported an *in vitro*, *ex vivo*, *in vivo*, or *in silico* endpoint relevant to at least one of the four mechanisms. Reviews were eligible only as background and as the source of findings published before 2020; they were not graded and are identified as reviews where they are cited. Conference abstracts and studies without a defined sea cucumber source were excluded. Studies designed for other indications were retained only when they measured an endpoint on a pathway in the framework (for example NF-κB, coagulation factors, or cholesterol metabolism) or a pharmacokinetic outcome. Antiviral studies that reported no coagulation endpoint were therefore excluded. Synthetic analogues of structures specific to sea cucumbers, such as FCS oligosaccharides, were eligible and are flagged in Table 1; commercially obtained compounds that also occur in other organisms were not.

Study Selection and Data Extraction

The PubMed search returned 187 records, of which 37 are in the final evidence base. Thirteen further articles came from the five-database search and citation searching: 12 are indexed in PubMed but were not retrieved by the string, and one is not indexed in PubMed. The evidence base therefore comprised 50 articles: 36 primary studies and 14 reviews. Eligibility decisions were made by the authors but were not logged record by record, so reasons for not including the other 150 PubMed records cannot be reported, and duplicate independent screening and inter-reviewer agreement were not documented. From each primary study we extracted the compound and species, model, dose, route and duration, comparator, main endpoint, main result with statistics as reported, and level of evidence (Table 1).

Grading of Evidence

Each primary study was assigned to the highest of five levels it reached: Level 1, controlled clinical study; Level 2, *in vivo* study with a direct cardiovascular endpoint (blood pressure, thrombosis, bleeding, coagulation time after dosing, or atherosclerotic plaque); Level 3, *in vivo* study with an indirect endpoint (lipids, body weight, or inflammation in a non-vascular model); Level 4, *in vitro*, *ex vivo*, enzyme, or structural study; Level 5, *in silico* only. Findings were also labelled as direct, indirect (a shared pathway in another disease model), or hypothetical (predicted but not measured). This hierarchy was built for this review and is not a validated tool. The risk of bias of the 16 *in vivo* studies was assessed from their full texts and supplementary data with SYRCLE's risk of bias tool, which rates ten domains as low, high, or unclear risk (Hooijmans et al.,

2014; Supplementary Table S1). One author rated each study, a second author checked every rating, and the two authors agreed on all ratings. Certainty grading, inter-reviewer agreement statistics, and meta-analysis were not performed, because the studies were too heterogeneous to pool. No validated risk-of-bias tool was applied to the *in vitro*, *ex vivo*, and *in silico* studies; for these, quality was not appraised and only the level and directness of evidence were assigned.

RESULTS AND DISCUSSION

Overview of the Evidence Base

None of the 36 primary studies was clinical. Eight reached Level 2, eight Level 3, 17 Level 4, and three Level 5 (Table 1). Level 2 evidence was concentrated in anticoagulation (five studies) and atherosclerosis (two); blood-pressure regulation had one Level 2 study and inflammation none.

Risk of Bias

Most SYRCLE domains were rated unclear because the 16 *in vivo* studies did not report the relevant methods (Figure 1; Supplementary Table S1 and Figure S1). No study described how the random sequence was generated or reported allocation concealment, random housing, blinding of caregivers or outcome assessors, or random outcome assessment, and one study assigned mice to groups haphazardly (H. Wang et al., 2022). Baseline characteristics were comparable between groups in four studies, and complete outcome data were reported in six. Two studies had a high risk of other bias: one applied a $P < 0.1$ threshold with three mice per group (Liu et al., 2024), and in the other the test material was supplied by a company that employed a co-author, and dose units and the statin comparator were reported inconsistently (Z. Wang et al., 2025). The Level 2 and Level 3 findings should therefore be regarded as hypothesis-generating.

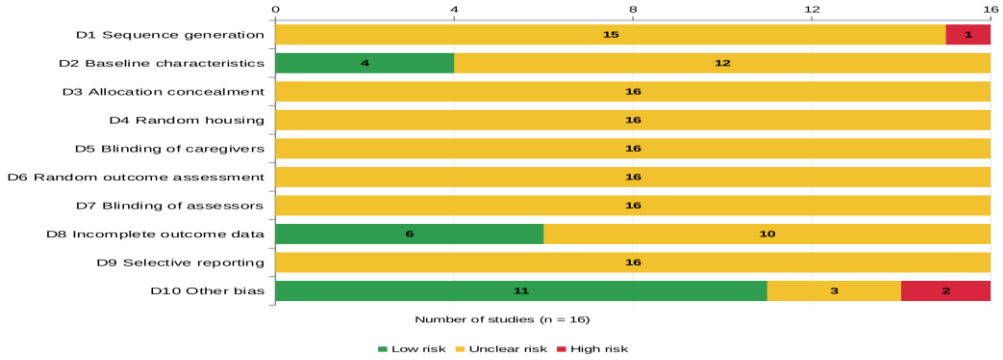


Figure 1. Risk of bias of the 16 *in vivo* studies across the ten domains of SYRCLE's tool (Hooijmans et al., 2014). Numbers are studies; ratings per study are given in Supplementary Table S1 and Figure S1

Table 1. Evidence synthesis matrix of the 36 primary studies, ordered by level of evidence; Level 4–5 studies are grouped by compound class

Study	Compound (source)	Model and design	Dose, route, duration	Main endpoint and result	Level / type
Y. Wang et al., 2024	HDWWKER peptide (*A. japonicus* gonads)	ACE enzyme assay; male SHRs (SBP > 220 mmHg) with saline and captopril (5 mg/kg) controls	12 mg/kg i.v., single dose; n = 6/group	IC_{50} 583.6 µM (noncompetitive); SBP lowered 2–8 h after dosing ($P < 0.05$), nadir 176 mmHg at ~4 h	2 / direct
Liu et al., 2024	FCS-10K, ~10 kDa (*C. frondosa*)	Clotting and FXase/FXa/FIIa assays (sheep plasma); tail-bleeding test in male KM mice	*In vitro*; bleeding test 2 mg/kg (route not stated), n = 3/group	APTT doubled at 0.352 µg/mL (FCS-10K) vs 1.01 µg/mL (LMWH); FXase IC_{50} 130.6 ng/mL; bleeding time	2 / direct (bleeding only)

Study	Compound (source)	Model and design	Dose, route, duration	Main endpoint and result	Level / type
		vs LMWH		similar to saline, whereas LMWH prolonged it	
H. Wang et al., 2022	DAHG10, ~10 kDa (*A. japonicus*)	Mice: bleeding time (i.p., n = 10/group); rats: thrombosis (i.v.), oral PK–PD	i.p. or i.v. 1–20 mg/kg; oral 50 and 250 mg/kg	Thrombus −61.7% and −65.4% at 10 and 20 mg/kg i.v. (P < 0.05); oral 250 mg/kg: APTT ×1.23, TT ×1.44 vs blank at 90 min (P < 0.05); bioavailability 1.16%	2 / direct
Yan et al., 2020	FCS 9- to 18-mers and 6-mers (*I. badionotus*, *P. graeffei*)	Male SD rats, venous thrombosis (n = 8/group); male KM mice, tail bleeding (n = 6/group); LMWH comparator	5 and 10 mg/kg s.c. (thrombosis); 120 mg/kg s.c. (bleeding)	Thrombus inhibited 92–95% at 10 mg/kg and 55–65% at 5 mg/kg (P < 0.001), regardless of size; no blood loss at 120 mg/kg, whereas LMWH 40 mg/kg caused bleeding (P < 0.01)	2 / direct
Yan et al., 2021	FCS 6–18-mer oligomers in gastro-resistant (GR) microcapsules	Male SD rats (n = 5/group); venous thrombosis and tail bleeding; rivaroxaban and native FCS-GR comparators	Oral 10 or 50 mg/kg single dose; 50 mg/kg every 12 h for 5 days	50 mg/kg: antithrombotic effect similar to rivaroxaban 10 mg/kg; 10 mg/kg: ~19% inhibition; no bleeding, whereas native FCS-GR caused bleeding (P < 0.05)	2 / direct
Xu et al., 2026	Synthetic FCS nonasaccharide derivatives A-3, B-1 (flagged: synthetic)	Carrageenan tail thrombosis in male ICR mice (enoxaparin 5 mg/kg control); APTT time course in SD rats	10 mg/kg i.v. (mice, n = 6/group); 7.2 mg/kg s.c. (rats, n = 6–7)	Thrombus length −30% (A-3) and −40% (B-1) vs untreated model (P < 0.05); APTT ×1.82 (A-3) and ×1.67 (B-1) vs baseline at Tmax 30 min, lasting ~3 h; bleeding not tested *in vivo*	2 / direct (synthetic)
Yang et al., 2023	Phospholipids PE-P and PC-O (*C. frondosa*)	Male ApoE−/− mice; chow, HFD, and HFD + simvastatin controls	0.03% in HFD, 12 weeks; n = 6/group	Aortic plaque reduced (Oil Red O); serum TC 10.40 (PE-P) vs 13.03 mmol/L (HFD); LDL-C 5.16 (PE-P) vs 9.13 mmol/L (HFD); hepatic total CE −63% (P < 0.05)	2 / direct
Z. Wang et al., 2025	Ultrafine sea cucumber powder	Male ApoE−/− mice on HFD; atorvastatin (1.8 mg/kg) and conventional-powder comparators	1 or 2 mg/g i.g. (Fig. 1 states mg/kg/d), 8 weeks; n = 8/group	High dose vs HFD: aortic lipid area −82%, wall thickness −67%, LDL-C −27%, TC −31% (P < 0.05); atorvastatin −89% and −70%	2 / direct
Zeng et al., 2020	Sulfated sea cucumber sterol	Male C57BL/6J mice, high-fat–fructose diet; phytosterol comparator	0.4% (4 g/kg) in diet, 8 weeks; n = 8/group	vs HFF: TC −14%, LDL-C −35%, hepatic TG −29% (means of authors' raw data); similar to phytosterol	3 / indirect
Z. Wang et al., 2024	Plasmalogen PlsEtn (PakCho comparator)	Male C57BL/6J mice (5 months), HFD (60% fat); normal-diet and HFD controls	0.1% (w/w) in HFD, 8 weeks; n = 8/group	Weight gain 14.22 g (PlsEtn) vs 18.74 g (HFD) (P < 0.0001); hepatic TG and TC lowered; lipophagy	3 / indirect

Study	Compound (source)	Model and design	Dose, route, duration	Main endpoint and result	Level / type
				restored	
S. Li et al., 2022	Fucoidan (*P. graeffei*)	Male C57BL/6J mice, HFD; simvastatin (20 mg/kg) positive control	20 and 80 mg/kg/day by gavage, 8 weeks; n = 8/group	Serum TG, TC, LDL-C, ApoB lowered; TLR4/NF-κB suppressed in colon and liver	3 / indirect
Wen et al., 2022	Saponins (holothurin A 23.8%, echinoside A 65.5%)	Obese male KM mice; HFD and 40% energy restriction comparators	0.06% in diet for 2 weeks; n = 16/group (8 per phase)	Weight loss smaller than with 40% energy restriction; weight regain 7.1% (saponins) vs 19.5% (restriction); serum TC unchanged; LDL-C lower on regain ($P < 0.05$)	3 / indirect
Sang et al., 2025	Polysaccharides (body wall; 519 kDa)	Healthy male C57BL/6J mice on normal diet; water control	400 mg/kg/day oral, 8 weeks; n = 9/group	No significant change in serum lipids; epididymal fat lower ($P < 0.05$); F/B ratio lowered	3 / indirect
Yin et al., 2024	FCS (*S. chloronotus*)	Female C57BL/6 mice, cyclophosphamide injury; Caco-2 monolayers	50 and 200 mg/kg i.g., 2 weeks; n = 6/group	ZO-1, claudin-1, Nrf2, SOD, NQO1 restored ($P < 0.05$); not transported across Caco-2 monolayers	3 / indirect (GI model)
Zhu et al., 2022	Peptide HEPFYGNEGALR (*A. japonicus*)	Male C57BL/6 mice, binge-ethanol liver injury; spermidine control	10 and 20 mg/kg oral every other day, 35 days; n = 5/group	Nrf2/HO-1 activated; NF-κB nuclear translocation reduced ($P < 0.05$)	3 / indirect (liver model)
Zhuo et al., 2025	Peptide EIILEAGK (*A. japonicus*)	Male C57BL/6J mice, LPS (1 mg/kg i.p.) depression model	25 and 50 mg/kg i.p., 13 days; n = 8/group	Serum and brain TNF-α, IL-6, IL-1β lowered; NF-κB nuclear translocation reduced ($P < 0.05$)	3 / indirect (CNS model)
Lee et al., 2024; Liang, Zhong, et al., 2025; Liang, Zhou, et al., 2025; Mecheta et al., 2020	ACE-inhibitory peptide fractions and peptides (NSPGDSFP, FPTY, GFPGLP and others)	ACE enzyme assays and kinetics; EA.hy926 and IR-HepG2 cells for GFPGLP	*In vitro*	IC_{50} 0.30–0.51 mg/mL (fractions), 15.92 μg/mL (NSPGDSFP), 0.03 mg/mL (FPTY); GFPGLP dual ACE/DPP-IV inhibition	4
Gao et al., 2020; Hong et al., 2026; X. Li et al., 2021; J. Sun et al., 2026; R. Yin et al., 2022	FCS, fucan sulfate, and their oligosaccharides (five species)	Clotting and iXase assays	*In vitro*	iXase or HCII-dependent thrombin inhibition; activity depends on molecular size (fucan sulfate optimum ~20 kDa; *T. anax* fractions > ~6 kDa stronger than native FCS)	4
Dwivedi et al., 2023, 2024; Farrag et al., 2023	FCS (*P. pygmaea*, *H. floridana*); marine glycans	Antiviral and anticoagulant assays; NMR structure	*In vitro*	Anticoagulant activity depends on high-molecular-weight structures; structural data without a cardiovascular endpoint	4 / indirect
H. Sun et al., 2025	HS14 tetradecasaccharide	Human platelets and whole blood	*Ex vivo*, concentration-dependent	Pam3CSK4-induced platelet activation and aggregation inhibited;	4 / direct (platelet)

Study	Compound (source)	Model and design	Dose, route, duration	Main endpoint and result	Level / type
				fewer platelet–granulocyte aggregates	
Ghelani et al., 2025; Hou et al., 2025; Jiang et al., 2021	Fucoidans (*S. chloronotus*, *A. japonicus*); Frondanol (*C. frondosa*)	RAW264.7 macrophages, with or without LPS	*In vitro* (Hou: 25–400 µg/mL, 24 h)	NF-κB/MAPK inhibition and lower cytokines (Frondanol, *A. japonicus* fucoidan); TLR2/4–NF-κB activation by *S. chloronotus* fucoidan	4 / indirect
Sales et al., 2024	Extracts of several species and tissues	Bioactivity assays	*In vitro*	Activity varied with species and tissue	4
La Paglia et al., 2026; Senadheera et al., 2022; Wargasetia et al., 2023	By-product peptides; saponins (*H. scabra*); coelomic-fluid peptides (*H. tubulosa*)	Bioinformatics, docking, molecular dynamics	*In silico*	Predicted ACE-inhibitory peptides; predicted KEAP1, iNOS, TNF-α, and NF-κB binding	5 / hypothesis

Level 1, controlled clinical study (none found); Level 2, *in vivo* with a direct cardiovascular endpoint; Level 3, *in vivo* with an indirect endpoint; Level 4, *in vitro*, *ex vivo*, enzyme, or structural; Level 5, *in silico* only. Direct, measured on a cardiovascular endpoint; indirect, measured on a shared pathway in another model; hypothesis, predicted but not measured. ApoB, apolipoprotein B; APTT, activated partial thromboplastin time; CE, cholesteryl ester; F/B, Firmicutes/Bacteroidota; HCII, heparin cofactor II; HFD, high-fat diet; i.v., intravenous; i.p., intraperitoneal; LMWH, low-molecular-weight heparin; PK–PD, pharmacokinetic–pharmacodynamic; s.c., subcutaneous; SBP, systolic blood pressure; SHRs, spontaneously hypertensive rats; TC, total cholesterol; TG, triglyceride; TT, thrombin time.

ACE Inhibition and Antihypertensive Mechanisms

ACE-inhibitory peptides are among the few sea cucumber compounds tested for an effect on blood pressure *in vivo*. Y. Wang et al., (2024) purified three noncompetitive ACE-inhibitory peptides from *Apostichopus japonicus* gonads (DDQIHIF, HDWWKER, and THDWWKER). In SHRs with a baseline systolic blood pressure above 220 mmHg, a single intravenous dose of HDWWKER (12 mg/kg; six rats per group) lowered systolic pressure to a nadir of 176 mmHg about 4 h after injection; the reduction lasted from 2 to 8 h, and pressure returned to about 220 mmHg by 12 h. This result shows an acute haemodynamic effect, not an effect after oral intake, which is how a food-derived peptide would be used; an oral peptide must survive digestion and absorption before it reaches vascular ACE. For the other sequences, the evidence comes only from enzyme assays (Level 4) or computational prediction (Level 5) (Z. Lu et al., 2022; Senadheera et al., 2022). Peptide fractions from four Algerian species had IC_{50} values of 0.30–0.51 mg/mL (Mecheta et al., 2020). The purified peptides NSPGDSFP (from sea cucumber viscera) and FPTY (from *Stichopus japonicus*) had IC_{50} values of 15.92 µg/mL (Liang, Zhong, et al., 2025) and 0.03 mg/mL (Lee et al., 2024), and DDQIHIF, HDWWKER, and THDWWKER had values of 333.5, 583.6, and 1291.8 µM, respectively (Y. Wang et al., 2024). Because substrates and assay conditions differ between studies, these values cannot be used to rank the peptides; a common assay platform is needed.

Two structural and kinetic features recur. First, several viscera-derived peptides end in proline, including NSPGDSFP (Liang, Zhong, et al., 2025) and WEPFP, GFPGLP, FPGGPP, and LPPGPFP (Liang, Zhou, et al., 2025). C-terminal proline is associated with ACE inhibition by marine peptides (Festa et al., 2020), although FPTY and the gonad peptides lack it. Second, NSPGDSFP and the gonad peptides inhibited ACE noncompetitively (Liang, Zhong, et al., 2025; Y. Wang et al., 2024). A noncompetitive inhibitor is not displaced by rising substrate concentrations, so it may be less affected by the compensatory rise in angiotensin I that limits competitive inhibitors; this is a kinetic inference, not a demonstrated clinical advantage. GFPGLP also inhibited dipeptidyl peptidase-IV (DPP-IV) and altered markers of blood-pressure and glucose regulation in

endothelial and insulin-resistant liver cells (Liang, Zhou, et al., 2025). This dual activity could benefit patients with both hypertension and type 2 diabetes, but it rests on enzyme and cell data (Level 4) and network prediction (Level 5) and has not been tested *in vivo*.

Anticoagulant and Antithrombotic Properties

Of the four mechanisms, anticoagulation has the most advanced evidence. FCS partly separates the two effects because it selectively inhibits the intrinsic tenase (iXase) complex, and low-molecular-weight FCS and its oligosaccharides have shown anticoagulant activity with negligible bleeding (Dwivedi & Pomin, 2020; H. Li et al., 2021). Liu et al., 2024) showed that a 10 kDa FCS fraction from *C. frondosa* (FCS-10K) had greater intrinsic anticoagulant activity than low-molecular-weight heparin (LMWH) *in vitro*: FCS-10K doubled APTT at 0.352 µg/mL, whereas LMWH required 1.01 µg/mL. In mice (three per group), FCS-10K did not prolong tail bleeding compared with saline, whereas LMWH did. The sulfate groups of FCS-10K bind arginine side chains on factor IXa and prevent iXase assembly. FCS from *Holothuria fuscopunctata* and *Thelenota anax* also inhibited iXase (Gao et al., 2020; Hong et al., 2026), and FCS from *T. anax* additionally inhibited heparanase and P-selectin. In these studies, anticoagulant activity (APTT and anti-iXase activity) was measured *in vitro* or *ex vivo*, whereas bleeding and thrombosis were measured in rodents (Table 1). The low bleeding risk is therefore supported by animal models only, not by human data.

Within the review period, two rat studies reported activity after oral dosing. H. Wang et al., (2022) showed that DAHG10 (~10 kDa), a depolymerised FCS from *A. japonicus*, was absorbed after oral administration and prolonged activated partial thromboplastin time (APTT) and thrombin time (TT) in proportion to its plasma concentration; its estimated oral bioavailability was only 1.16%. In the same study, DAHG10 given intraperitoneally to mice caused less bleeding than the native polysaccharide. Yan et al., (2021) delivered FCS oligomers of 6–18 saccharide units in gastro-resistant microcapsules. At 50 mg/kg, this formulation prevented venous thrombosis as effectively as rivaroxaban at 10 mg/kg and did not cause bleeding, whereas native FCS in the same microcapsules did. In contrast, native FCS from *Stichopus chloronotus* did not cross Caco-2 monolayers (H. Yin et al., 2024), which is consistent with molecular size limiting absorption. Molecular size also affects activity. Among fucan sulfate fractions of different sizes from *Stichopus herrmanni*, the ~20 kDa fraction inhibited thrombin through heparin cofactor II most strongly (X. Li et al., 2021), and depolymerised FCS fractions from *T. anax* above ~6 kDa inhibited iXase more strongly than the native polysaccharide (Hong et al., 2026). (Liu et al., (2024) noted that FCS fragments smaller than an octasaccharide lack anticoagulant activity, whereas J. Sun et al., (2026) found that hepta- and decasaccharides still inhibited iXase and attributed this activity to their oxidised reducing ends. Anticoagulant and antithrombotic potency can also diverge. After subcutaneous dosing in rats, FCS 9–18-mers at 10 mg/kg inhibited thrombosis by 92–95% regardless of size, an effect similar to that of LMWH at 4 mg/kg, and a 6-mer was antithrombotic despite weak anticoagulant activity (Yan et al., 2020). Synthetic FCS nonasaccharide derivatives that selectively inhibited iXase reduced thrombus length by 30–40% compared with untreated model mice at 10 mg/kg i.v., an effect almost comparable to that of enoxaparin at 5 mg/kg (Xu et al., 2026). The optimal size and structure must therefore be determined for each fraction rather than generalised across species.

Two antiviral screens also measured anticoagulant activity *in vitro* (Level 4). The activity of *Pentacta pygmaea* FCS depended on high-molecular-weight structures (Dwivedi et al., 2023), and that of *Holothuria floridana* FCS oligosaccharides depended on defined structural features (Farrag et al., 2023).

Anti-Inflammatory Effects Relevant to Cardiovascular Disease

Most anti-inflammatory evidence comes from non-vascular models. Chronic inflammation drives atherogenesis from endothelial activation to plaque rupture, and nuclear factor kappa B

(NF-κB) is the target most often reported for sea cucumber compounds. A review of echinoderm compounds summarises *in vivo* NF-κB suppression by FCS, fucoidan, sphingolipids, and peptides in earlier studies, the triterpene glycosides holothurin A and echinoside A reduced pro-inflammatory cytokines in vascular and peritoneal macrophages of apolipoprotein E (ApoE)-deficient mice compared with untreated ApoE-deficient mice (Ghelani et al., 2022). Within the review period, fucoidan from *Pearsonothuria graeffei* suppressed TLR4/NF-κB signalling in the colon and liver of high-fat-fed mice compared with untreated high-fat-fed mice (S. Li et al., 2022). In LPS-stimulated macrophages, Frondanol, a lipid extract of *C. frondosa*, inhibited NF-κB and MAPK activation (Ghelani et al., 2025), and fucoidan from *A. japonicus* lowered NO, TNF-α, IL-1β, and IL-6 through autophagy (Hou et al., 2025). The effect depends on the compound: fucoidan from *S. chloronotus* activated TLR2/4–NF-κB signalling and increased NO, TNF-α, IL-6, and IL-10 production compared with untreated macrophages (Jiang et al., 2021). The fucosylated glycosaminoglycan oligosaccharide HS14 links inflammation with thrombosis: in human whole blood, it inhibited platelet activation and aggregation induced by the TLR2 agonist Pam3CSK4 and reduced platelet–granulocyte aggregates compared with stimulated blood without HS14 (H. Sun et al., 2025). The saponins scabraside and holothurinoside G bound KEAP1 and inducible nitric oxide synthase (iNOS) only in docking and molecular dynamics simulations, and they were predicted to cross cell membranes poorly (Wargasetia et al., 2023).

Peptides follow the same pattern. Compared with mice given LPS alone, mice pretreated intraperitoneally with EIILEAGK from *A. japonicus* had lower NF-κB activation and lower TNF-α, IL-6, and IL-1β in the brain and serum (Zhuo et al., 2025). Compared with untreated alcohol-exposed mice, mice given oral HEPFYGNEGALR had higher Nrf2/HO-1 activity and less NF-κB nuclear translocation in the liver (Zhu et al., 2022). Both studies addressed non-cardiovascular conditions, so they support a shared mechanism rather than a vascular effect. In *Holothuria tubulosa*, computational screening of the coelomic-fluid proteome ranked 40 candidate peptides, and docking of eight of them suggested binding to TNF-α, NF-κB, KEAP1, and iNOS (La Paglia et al., 2026), these predictions have not been tested experimentally.

The anti-inflammatory evidence therefore falls into three categories. Direct evidence on a cardiovascular-relevant endpoint is limited to two findings: HS14 inhibited TLR2-mediated platelet activation in human blood *ex vivo* (H. Sun et al., 2025), and atherosclerotic mice given ultrafine powder had 62% lower aortic RAGE and 36% lower SRC protein expression than untreated high-fat-fed mice (Z. Wang et al., 2025). NF-κB suppression in colon, liver, brain, or macrophages is indirect evidence. Predicted binding of saponins and coelomic-fluid peptides to KEAP1, iNOS, TNF-α, and NF-κB is a hypothesis (La Paglia et al., 2026; Wargasetia et al., 2023). No study in the review period measured plaque inflammation directly, and the immunostimulant effect of *S. chloronotus* fucoidan (Jiang et al., 2021) shows that the direction of effect cannot be predicted from the compound class.

Hypolipidaemic Activity and Lipid Metabolism Modulation

Since 2020, lipid-related evidence has expanded more than the evidence for the other three mechanisms and now includes vascular endpoints. In ApoE-deficient mice fed a high-fat diet, the sea cucumber phospholipids plasmenyl phosphatidylethanolamine (a plasmalogen) and plasmanyl phosphatidylcholine reduced arterial plaque formation compared with untreated high-fat-fed mice and regulated hepatic cholesterol metabolism, including genes for bile acid synthesis and lysosomal activity (Yang et al., 2023). In the same mouse model, an ultrafine sea cucumber powder reduced aortic lipid area and wall thickness, lowered total and LDL cholesterol, and increased aortic PPARα and PPARγ expression compared with untreated high-fat-fed mice (Z. Wang et al., 2025). Other studies measured lipid lowering without vascular endpoints. Compared with mice fed a high-fat–fructose diet alone, mice fed sea cucumber sterol had lower serum and hepatic lipids, but the reductions were similar to those with phytosterol (Zeng et al., 2020). Compared with

untreated high-fat-fed mice, plasmalogen lowered hepatic triglyceride and cholesterol by restoring lipophagy (Z. Wang et al., 2024), and fucoidan from *P. graeffei* lowered serum triglyceride, total cholesterol, LDL cholesterol, and apolipoprotein B (S. Li et al., 2022). Dietary saponins suppressed SREBP-1c-mediated lipogenesis, and after the intervention ended, weight regain was lower with saponins than after 40% energy restriction (7.1% vs 19.5%) (Wen et al., 2022). Earlier studies, summarised by Lin et al., (2022), also reported less plaque in ApoE-deficient mice fed sea cucumber cerebrosides than in untreated ApoE-deficient mice. Gut-mediated effects have also been reported: compared with water-treated healthy mice, mice given sea cucumber polysaccharides had a lower Firmicutes/Bacteroidota ratio and altered hepatic steroid-biosynthesis gene expression, without changes in serum lipids (Sang et al., 2025).

The design of these studies limits generalisation (Table 1). Yang et al., (2023) fed male ApoE-deficient mice (six per group) a high-fat diet containing 0.03% of each phospholipid for 12 weeks; serum total cholesterol was 10.40 mmol/L with plasmenyl phosphatidylethanolamine vs 13.03 mmol/L with the high-fat diet alone, and LDL cholesterol was 5.16 vs 9.13 mmol/L ($P < 0.05$). Wang et al., (2025) gave the powder for 8 weeks (eight mice per group); the high dose reduced aortic lipid area by 82% and wall thickness by 67% compared with the high-fat group ($P < 0.05$), close to the effect of atorvastatin (89% and 70%). These are the only two atherosclerosis studies with a statin arm (simvastatin and atorvastatin, respectively). The sterol, plasmalogen, and fucoidan studies each lasted 8 weeks (S. Li et al., 2022; Z. Wang et al., 2024; Zeng et al., 2020), and the saponin study compared 0.06% dietary saponins with 40% energy restriction in 16 mice per group (Wen et al., 2022). Because doses, diets, durations, and outcome units differ, the percentage changes should not be compared across studies.

Integration Across the Four Mechanisms

Table 2 summarises the main compound groups, primary effects with the type of evidence, and target pathways. Figure 2 maps these groups onto cardiovascular endpoints.

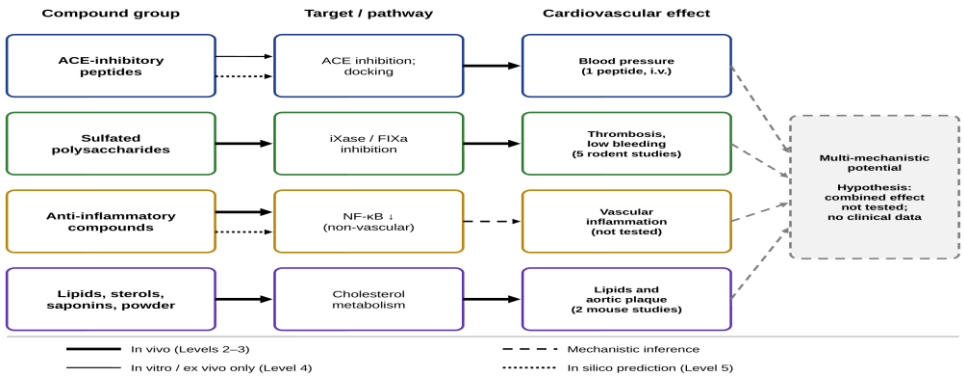


Figure 2. Conceptual framework linking four groups of sea cucumber compounds to molecular targets and cardiovascular effects. Thick solid lines, experimental *in vivo* evidence (Levels 2–3); thin solid lines, *in vitro* or *ex vivo* evidence only (Level 4); dashed lines, mechanistic inference; dotted lines, computational prediction (Level 5). The grey box is an untested hypothesis; no clinical evidence exists

Table 2. Major bioactive compound groups from sea cucumbers and their cardiovascular-relevant mechanisms

Compound group	Primary CV mechanism	Target pathway / molecule	Highest evidence level and main limitation
ACE inhibitory peptides	Competitive or noncompetitive ACE inhibition (*in vitro*); dual ACE/DPP-IV inhibition (GFPGLP, cell models); SBP reduction in SHRs (HDWWKER, i.v.)	ACE (RAAS); DPP-IV	Level 2 for one peptide (i.v.); others Level 4–5. No oral *in vivo* data; IC_{50} values from non-comparable assays.

Compound group	Primary CV mechanism	Target pathway / molecule	Highest evidence level and main limitation
Sulfated polysaccharides (FCS, fucan sulfate)	Selective intrinsic-pathway anticoagulation; antithrombotic in rodents with no or reduced bleeding; activity after oral dosing in rats (DAHG10, microencapsulated oligomers)	Factor IXa / intrinsic tenase (iXase); FXa and FIIa (antithrombin-dependent); thrombin via heparin cofactor II (fucan sulfate)	Level 2 (five rodent studies). Oral bioavailability low where measured (1.16% for DAHG10); optimal molecular size differs between fractions and species.
Anti-inflammatory compounds (several classes)	NF-κB suppression and reduced pro-inflammatory cytokines, mostly in non-vascular models; reduced cytokines in macrophages of ApoE-deficient mice (glycosides); inhibition of platelet TLR2 (HS14); predicted KEAP1/iNOS binding (saponins, *in silico*)	NF-κB, MAPK; TLR2/4; COX-2, iNOS; TNF-α, IL-6, IL-1β; Nrf2/HO-1; KEAP1 (docking)	Level 3 (non-vascular models); aortic RAGE and SRC measured in one atherosclerosis study; several targets predicted by docking only.
Lipids, sterols, saponins, and whole-body preparations	Reduced aortic plaque in atherosclerotic mice (phospholipids, powder); reduced serum and hepatic lipids; gut-microbiota modulation	Cholesterol synthesis and catabolism; lipophagy; SREBP-1c; PPARα/γ; F/B ratio	Level 2 for plaque (two mouse studies); doses and diets differ; statin arms in only two atherosclerosis studies.

CV = cardiovascular; ACE = angiotensin-converting enzyme; RAAS = renin–angiotensin–aldosterone system; DPP-IV = dipeptidyl peptidase-IV; SBP = systolic blood pressure; SHRs = spontaneously hypertensive rats; i.v. = intravenous; FCS = fucosylated chondroitin sulfate; iXase = intrinsic tenase complex; FXa = factor Xa; FIIa = thrombin; NF-κB = nuclear factor kappa B; MAPK = mitogen-activated protein kinase; TLR = Toll-like receptor; COX-2 = cyclooxygenase-2; iNOS = inducible nitric oxide synthase; TNF-a = tumour necrosis factor alpha; IL = interleukin; ApoE = apolipoprotein E; Nrf2 = nuclear factor erythroid 2-related factor 2; HO-1 = heme oxygenase-1; KEAP1 = Kelch-like ECH-associated protein 1; SREBP-1c = sterol regulatory element-binding protein 1c; PPAR = peroxisome proliferator-activated receptor; F/B = Firmicutes/Bacteroidota.

The four mechanisms therefore differ in maturity. Anticoagulation is the most advanced of the four; lipid-related activity now includes plaque reduction in two mouse models; antihypertensive activity rests on one intravenous *in vivo* result; and anti-inflammatory activity has rarely been measured in vascular tissue. One biological source thus supplies compounds that act on several mechanisms, which we call multi-mechanistic potential. This does not show that a single preparation acts on several targets at once *in vivo* (Figure 2). Combination effects remain largely untested, apart from one earlier study summarised by Lin et al. (2022). Yield and potency also vary with species and tissue (C. Lu et al., 2024; Sales et al., 2024), so any standardised product must control its biological source.

CONCLUSION

This review shows that the cardiovascular potential of sea cucumber compounds is multi-mechanistic but still preclinical. Of the four mechanisms, anticoagulation has the most mature evidence: FCS and its oligosaccharides selectively inhibit the intrinsic tenase complex, prevent thrombosis in rodents with less bleeding than low-molecular-weight heparin or native FCS, and were active after oral dosing in two rat studies. Sea cucumber phospholipids and an ultrafine powder reduced aortic plaque in ApoE-deficient mice compared with untreated high-fat-fed mice, and the effect of the powder was close to that of atorvastatin. One ACE-inhibitory peptide lowered blood pressure in hypertensive rats after a single intravenous dose, and anti-inflammatory effects were shown mainly in colon, liver, brain, and macrophage models rather than in blood vessels. This graded comparison separates established preclinical findings from hypotheses and identifies FCS-based anticoagulants as further advanced than the other compound groups and the most realistic candidates for development. The review is limited by its narrative design, the unclear risk of bias in most animal studies, and a PubMed-only update. Future work should define

standardised fractions, measure pharmacokinetics and absolute bioavailability, assess toxicity and bleeding risk alongside existing antithrombotic drugs, and test oral efficacy in validated cardiovascular models before randomised controlled trials are considered. No controlled clinical trial of sea cucumber compounds with cardiovascular endpoints was identified in the review period, so the cardiovascular benefit of a multi-mechanistic approach has not been validated in humans.

Limitations and future work, this review has several limitations. It is narrative rather than systematic, and the reproducible search was limited to PubMed. Eligibility decisions were not logged record by record, the date and record counts of the five-database search were not saved, and duplicate independent screening was not documented, so eligible studies may have been missed. Risk of bias was unclear in most SYRCLE domains for every *in vivo* study, and no certainty grading, inter-reviewer agreement assessment, or meta-analysis was performed; the evidence levels describe study design, not study quality. All evidence from the review period is preclinical, most studies used a single species, dose range, and animal model, and group sizes were small (3–16 animals per group where reported). The only clinical data come from an earlier study, summarised by Lin et al. (2022), in which a capsule containing sea cucumber acid mucopolysaccharide improved lipid profiles and blood viscosity in patients with ischaemic heart disease. Pharmacokinetic data are missing for most compounds. Several supporting studies addressed other indications, namely antiviral (Dwivedi et al., 2023; Farrag et al., 2023), antidepressant (Zhuo et al., 2025), gastrointestinal (H. Yin et al., 2024), and hepatoprotective research (Zhu et al., 2022); their cardiovascular relevance rests on shared mechanisms. One study tested synthetic FCS analogues rather than material isolated from sea cucumber (Xu et al., 2026).

Four studies follow from these gaps: re-testing ACE-inhibitory peptides after oral dosing on a common assay platform; establishing FCS structure–activity relationships and absolute oral bioavailability in thrombosis models; testing anti-inflammatory compounds against vascular endpoints such as endothelial function and plaque inflammation; and comparing lipid-lowering fractions with a statin in adequately powered atherosclerosis studies with blinded outcome assessment.

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