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Phytosterols of marine algae: Insights into the potential health benefits and molecular pharmacology

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ABSTRACT

Background: Marine algae are rich in some unique biologically active secondary metabolites having diverse pharmacological benefits. Of these, sterols comprise a group of functional lipid compounds that have attracted much attention to natural product scientists.

Purpose: This review was aimed to update information on the health effects of algae-derived phytosterols and their molecular interactions in various aspects of human health and diseases and to address some future perspectives that may open up a new dimension of pharmacological potentials of algal sterols.

Methods: A literature-based search was carried out to retrieve published research information on the potential health effects of algal phytosterols with their pharmacological mechanisms from accessible online databases, such as Pubmed, Google Scholar, Web of Science, and Scopus, using the key search terms of 'marine algae sterol' and 'health potentials such as antioxidant or anti-inflammatory or anti-Alzheimer's or anti-obesity or cholesterol homeostasis or hepatoprotective, antiproliferative, etc.'

Results: Phytosterols of marine algae, particularly fucosterol, have been investigated for a plethora of health benefits, including anti-diabetes, anti-obesity, anti-Alzheimer's, antiaging, anticancer, and hepatoprotection, among many others, which are attributed to their antioxidant, anti-inflammatory, immunomodulatory and cholesterol-lowering properties, indicating their potentiality as therapeutic leads. These sterols interact with

Abbreviations: 5-Fu, 5-fluorouracil; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ACE, Angiotensin-converting enzyme; AChE, acetylcholinesterase; AD, Alzheimer's disease; AGE, advanced glycation endproduct; ALI, acute lung injury; ALT, alanine aminotransferase; AP-1, activator protein-1; ApoE, apolipoprotein E; APP, amyloid precursor protein; AR, aldose reductase; ARIs, AR inhibitors; AST, aspartate aminotransferase; Aβ, amyloid β; BACE1, Beta-secretase 1; Bax, BCL2 Associated X; BChE, butyrylcholinesterase; Bcl-2, B-cell lymphoma 2; BDNF, brain derived neurotrophic factor; C/EBPα, CCAAT/enhancer-binding protein α; CAT, Catalase; Cdc2, cell division cycle protein 2; CKD, chronic kidney disease; CNS, central nervous system; $CoCl_2$, cobalt chloride; ConA, Concanavalin A; COX-2, Cyclooxygenase-2; CTx, carboxy-terminal collagen crosslinks; CVD, cardiovascular diseases; cyt-c, cytochrome c; ELISA, Enzyme-linked immunosorbent assay; ERK1/2, extracellular signal–regulated kinases 1/2; FasL, Fas ligand; FoxO, Forkhead box; FST, forced swim test; GPx, glutathione peroxidase; GR, glucocorticoid receptor; GRP78, glucose-regulated protein 78; GSH, Glutathione (reduced); HIF-1α, *Hypoxia-inducible factor 1*-alpha; HO-1, heme oxygenase-1; HRAR, human recombinant aldose reductase; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; Insig-2a, insulin induced gene 2a; IRS1, phosphorylation of insulin receptor substrate; JNK, c-Jun N-terminal kinases; LPS, lipopolysachharide; LXR-β, Liver X-receptor-beta; MAPK, mitogen-activated protein kinase; MD, macular degeneration; MIC, minimum inhibitory concentration; MK2, mitogen-activated protein kinase-activated protein kinase 2; MKK3/6, mitogen-activated protein kinase kinases 3/6; MMP, matrix metalloproteinase; MPO, Myeloperoxidase; mTOR, mammalian target of rapamycin; NE, norepinephrine; NF-κB, nuclear factor-κB; Ngb, neuroglobin; NHDFs, Normal Human Dermal Fibroblasts; NO, nitric oxide; NPC1L1, Niemann-Pick C1-Like 1; Nrf2, nuclear factor erythroid 2-related factor 2; OVX, ovariectomized; PfLDH, *P. falciparum* L-lactate dehydrogenase; PGE2, prostaglandin E2; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; PM, particulate matter; PPARs, Peroxisome proliferator-activated receptors; PPARγ, peroxisome proliferator-activated receptor γ; PTP1B, protein-tyrosine phosphatase 1B; RLAR, rat lens aldose reductase; ROS, reactive oxygen species; $sA\beta_{1\text{-}42}$, soluble $A\beta_{1\text{-}42}$; SIRT1, sirtuin 1; SOD, superoxide dismutase; SREBP-1, sterol regulatory element-binding protein 1; t-BHP., tert-butyl hydroperoxide; t-BHP, tert-butylhydroperoxide; T2DM, Type 2 diabetes mellitus; TGF-β1, transforming growth factor-β1; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; TrkB, tropomyosin receptor kinase B; TST, tail suspension test; UV, ultraviolet

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enzymes and various other proteins that are actively participating in different cellular pathways, including antioxidant defense system, apoptosis and cell survival, metabolism, and homeostasis.
Conclusion: In this review, we briefly overview the chemistry, pharmacokinetics, and distribution of algal sterols, and provide critical insights into their potential health effects and the underlying pharmacological mechanisms, beyond the well-known cholesterol-lowering paradigm.

Introduction

Phytosterols, including both sterols and stanols, constitute a class of sterol compounds that are similar to cholesterol in structure and function. Physiologically, they contribute to essential functions in plant cells, such as membrane fluidity and signal transduction (Piironen et al., 2000). Their contribution to human nutrition and health is also significant. The highly reputed therapeutic activity of phytosterols rests in their cholesterol-lowering potential (Gylling et al., 2014). With the structural resemblance and sharing of the same absorption route, phytosterols compete and thereby hinder the intestinal absorption of cholesterol, lowering the plasma level of low-density lipoprotein cholesterol, a causal risk factor for many chronic diseases, including cardiovascular diseases. Beyond this pharmacological effect that was always being in the limelight by the nutritionists, phytosterols possess numerous additional, albeit not less significant, health benefits (Catani et al., 2018; Derdemezis et al., 2010; Plat et al., 2019; Shahzad et al., 2017), such as anti-diabetes, anti-obesity, anti-atherosclerosis, anticancer, anti-Alzheimer's, and hepatoprotective, among many others, rendering them essential components of functional foods.

Macroalgae, popularly known as seaweed among the consumers, comprise a highly significant element of the marine ecosystem contributing a major feeding ground for marine lives as well as potentially renewable resources for human civilization. A significant number of the secondary bioactive metabolites, including carotenoids, polyphenolics, polysaccharides, and sterols that are reported in seaweeds are unique in terms of their structural and functional diversity, which are attributed largely to the extreme and hostile living environment the organisms often encountered with. Like phytosterols in plants, marine algae also contain diverse types of sterols, namely fucosterol in brown algae, cholesterol in red algae and β-sitosterol in green algae, with a similar profile of health benefits. Five years back, an excellent piece of work entitled 'health benefit of fucosterol from marine algae: a review' by Abdul and his colleagues compiled some potential pharmacological importance of fucosterol (Abdul et al., 2016). However, beyond these health benefits, some very influential research works on the various dimensions of health benefits of fucosterol have been published in the last five years. By this time, some other significant phytosterols with novel bioactivity have also appeared. It is, therefore, worth writing a comprehensive review compiling up to recent information on the health effects of algae-derived phytosterols. Also, being stable lipid compounds, sterols are often exploited as potential biomarkers in the marine biogeochemical survey (Geng et al., 2017) as well as in the taxonomic classification of marine algae (Chapman, 1946). However, in this review, we limit our discussion to the chemical diversity, pharmacokinetics, and distribution of algal sterols, and provide critical insights into their potential health benefits with the underlying pharmacological mechanisms against various human ailments.

Chemistry and pharmacokinetics of algal sterols

Phytosterols structurally and functionally resemble cholesterol, differing at C-24 in having an alkyl substitution on the side chain. The side chain of phytosterols usually contains 9 or 10 carbon atoms as opposed to 8 carbon in cholesterol (Kritchevsky and Chen, 2005). The sterol nucleus, 1, 2-cyclopentanoperhydrophenanthrene, comprising of four fused rings (A, B, C, and D), attaches a *β*-hydroxyl group (3-OH) at C-3 and a long flexible side chain at C-17 (Fig. 1). The hydrophilic 3-OH usually contributes to hydrogen bonding with other hydrophilic groups, while the conformation and length of the side chain and the stereochemistry of the C-24 alkyl group are key to intermolecular interactions (Nes, 2011). Like cholesterol, algal sterols can exist either in free form or conjugated with other molecules such as fatty acids (for example, oleate) and sugars (most often, glucose) (Moreau et al., 2002), through covalent linkage with 3-OH. The most abundant sterol in macroalgae is fucosterol, which differs from its close neighbors, stigmasterol, sitosterol, and campesterol, also at its hydrocarbon tail. Saringasterol, on the other hand, possesses two unusual features in its structure- a vinyl group (rather than conventional ethylidene group) and a 24-hydroxyl group.

Numerous studies have investigated the pharmacokinetics of terrestrial plant-derived phytosterols (Delaney et al., 2004; Ostlund et al., 2002); however, such information on sterols from macroalgae, particularly fucosterol is scarce. A very recent effort based on *in silico* approach (Hannan et al., 2019) described that fucosterol obeys the Lipinski's rule of five (mol_MW $<$ 500, donor HB $\leq$ 5, and acceptor HB $\leq$ 10) and Jorgensen's rule of three (QPlogS $>$ −5.7 and QPPCaco $>$ 22 nm/s), and thus exhibits drug-like attributes and more likely to be orally available. Moreover, the predicted brain/blood partition coefficient (QPlogBB) of fucosterol is within the recommended range (−3.0 to 1.2), indicating that this sterol might cross the blood-brain barrier.

Sterol distribution across the phyla of macroalgae

Marine algae are diverse in their sterol composition (Fig. 1). The general sterol pattern among the various algal classes is usually quite stable; however, numerous biotic and abiotic factors, including developmental stages, geographic origins, and ecological variation, largely influence the phytosterol make-up of algae (Lopes et al., 2011). Fucosterol is the major sterol of brown algae, whereas cholesterol in red algae; however, the sterol composition of green algae is relatively heterogeneous with a complex mixture of 28-isofucosterol, ergosterol, β-sitosterol, poriferasterol, cholesterol and others (Patterson, 1971). Examining the sterol contents in 18 macroalgae samples consisting of three Chlorophyta, five Rhodophyta, and ten Phaeophyta species, Andrade and colleagues reported that the contribution of phytosterols for the composition of Chlorophyta reaches 25%, which is similar to that of Rhodophyta (26%), while in Phaeophyta they represented up to 15% (Andrade et al., 2013).

Brown algae

Fucosterol has been reported to be a principal sterol of brown seaweed, and also not rare in terrestrial plants, if not frequent (Kalsait et al., 2011). It is even more dominant in brown algae than cholesterol is in red algae (Patterson, 1971). However, fucosterol was first isolated from a brown alga *Fucus vesiculosus* by Heilbron and his colleague (Heilbron and Phipers, 1935) nearly a century ago. Since then, fucosterol has been isolated from various marine algae that originated from diverse ecological zones. For example, Majik and colleagues purified fucosterol as a major metabolite from the bioactive hexane-fraction of *Sargassum tenerrimum* (Majik et al., 2015). Fucosterol is also the predominant sterol in *Himanthalia elongata, Undaria pinnatifida, Laminaria ochroleuca*, comprising 83–97% of the total sterol content (Sanchez-Machado et al., 2004). *Cystoseira barbata* contains a considerable

amount of fucosterol (21.76 ± 0.1 μg/g) (Milović et al., 2019). On the contrary, the principal sterols in *Cystoseira adriatica* Sauvageau were cholesterol and β-sitosterol, while fucosterol was in minute quantity (Kapetanovic et al., 2005).

Saringosterol, a dihydroxy steroid to be reported for the first time in the marine source, was isolated by Ikekawa and the team

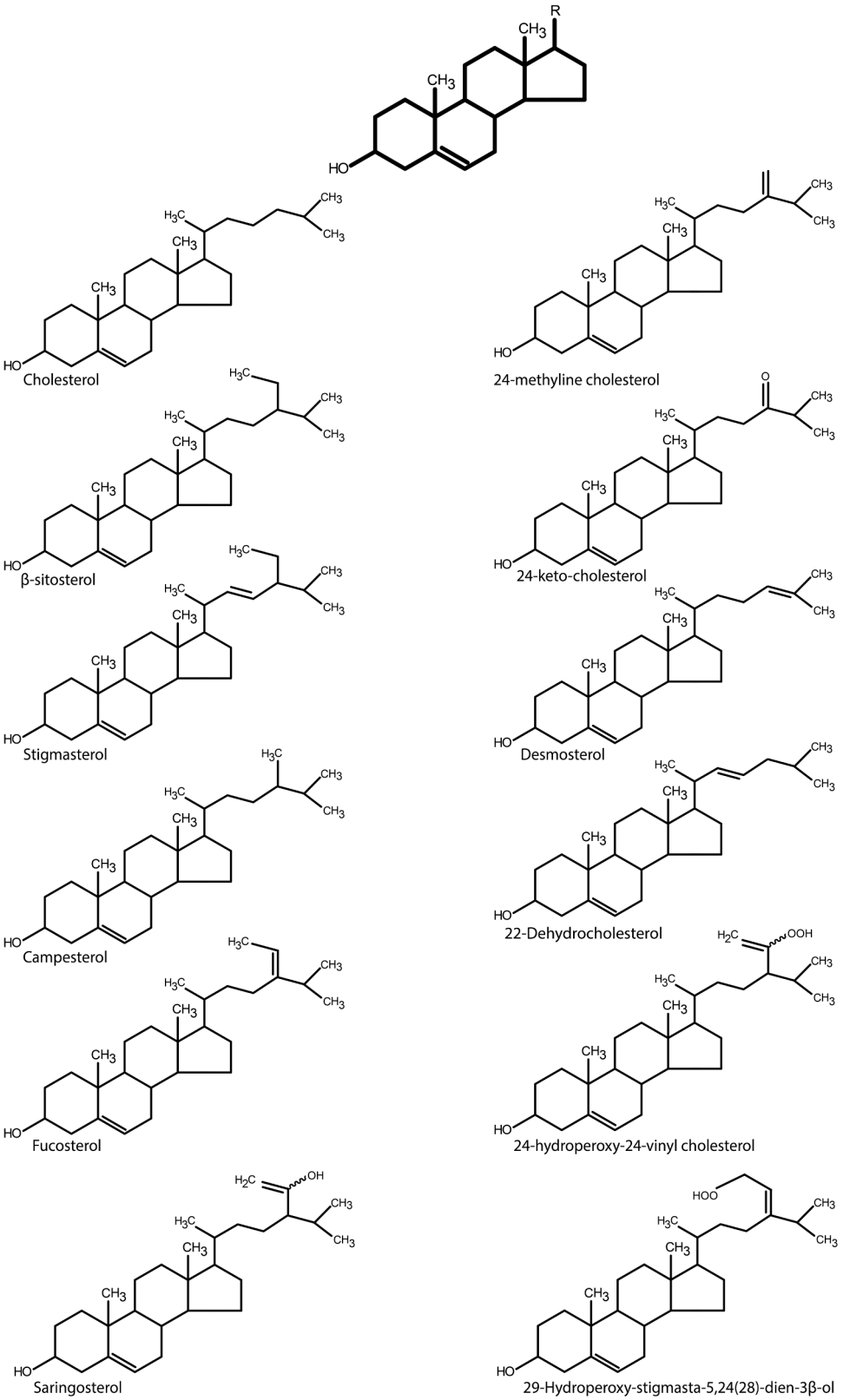

Fig. 1. Chemical structure of diverse phytosterols in the marine algae. Of these, fucosterol is primarily concentrated in brown algae and cholesterol in red algae, along with heterogeneous sterol compositions in green algae. Notably, phytosterols, namely β-sitosterol, stigmasterol, and campesterol, that are common in terrestrial plants, have also been reported in marine algae.

Table 1
Summary on health effects, occurrence, experimental model, dosage, major techniques, cellular effects, potential pharmacological mechanism of algal phytosterols.

Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
Antioxidant activity	Fucosterol, 3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene and 14,15,18,20-diepoxyturbinarin	*Pelvetia siliquosa*	-	Rat model	A seven days-dose regimen at 30 mg/kg/day before carbon tetrachloride (CCl4) administration	-	-	↑ SOD, CAT, and GPx	Lee et al., 2003
	Fucosterol	*Eisenia bicyclis,* edible brown alga	Dichloromethane fraction of methanolic extract	RAW 264.7 murine macrophages (t-BHP stimulated)	25, 50, 100, 200 and 400 μM	-	Protects against oxidative stress	↓ ROS generation	Jung et al., 2013a
	Fucosterol	*Ecklonia stolonifera and Eisenia bicyclis* Brown algae	-	Tert-butyl hydroperoxide- and tacrine-induced HepG2cell injury model	25, 50 and 100 μM	Intracellular ROS scavenging assay (DCFH-DA)		↓ ROS generation ↑ GSH level	Choi et al., 2015
	Fucosterol	*Sargassum Binderi* brown alga	-	Particulate matter-induced injury and inflammation in A549 human lung epithelial cells	3.125, 6.25, 12.5, 25, 50, 100 μg ml^{-1}	Western blot	Attenuates oxidative stress	↓ ROS level ↑ SOD, CAT, and HO-1 in the cytosol, and NRF2 in the nucleus	Fernando et al., 2019a.
Anti-inflammatory activity	Fucosterol	*Eisenia bicyclis,* edible brown alga	Dichloromethane fraction of methanolic extract	RAW 264.7 murine macrophages (t-BHP200 Mm, LPS-1μM stimulated)	5–20 μM for NO	Western blot	↓ Inflammatory response	↓ NO production ↓ iNOS and COX-2 ↓ NF-κB pathway	Jung et al., 2013a
	Fucosterol	*Undaria pinnatifida*	80% MeOH	LPS-induced RAW 264.7 macrophages and THP-1 human monocyte cell line	10, 25 or 50 μM	qRT-PCR and Western blot	↓ Inflammatory response	↓ iNOS, TNF-α, and IL-6 ↓ DNA binding ↓ phosphorylation of NF-κB, MKK3/6 and MK2	Yoo et al., 2012
	Fucosterol	*Hizikia fusiformis*	Methanol extract	$CoCl_2$ induced hypoxia in keratinocytes	1-10 μM	LC–MS, RT-PCR and MTT assay	↓ Inflammatory response	↓ IL-6, IL-1β and TNF-α ↓ pPI3K and pAkt and HIF1-α accumulation	Sun et al., 2015
	Fucosterol	*Panida. australis*	Dichloromethane extract	LPS-induced BV2 (microglial) cells	0.004,0.2 and 10 μM	RT-PCR, ELISA, and Griess test (NO content)	Protects against LPS-mediated neuroinflammation	↓ IL-6, IL-1β, TNF-α, NO, and PGE2	Wong et al., 2018
	Fucosterol	*Sargassum Binderi* brown alga	-	Particulate matter-induced injury and inflammation in A549 human lung epithelial cells	3.125, 6.25, 12.5, 25, 50, 100 μg ml^{-1}	Western blot	↓ Inflammatory response	↓ COX-2, PGE2, TNF-α and IL-6	Fernando et al., 2019a
Anti-AD effects *Anticholinesterase activity*	Fucosterol and 24-hydroperoxy 24-vinylcholesterol	*E. stolonifera*	EtOAc soluble fractions of ethanolic extract	*In vitro* enzymatic assay	IC_{50} values of 421.72 ± 1.43, 176.46 ± 2.51 μM, respectively	Bioassay-guided fractionation	↓ BChE activity	Selective inhibition of BChE	Yoon et al., 2008
	Fucosterol	*Panida. australis*	Dichloromethane extract	*In vitro* enzymatic assay	inhibition against AChE (10.99–20.71%) and BChE (4.53–17.53%) with	Bioassay-guided fractionation	↓ AChE and BChE activities	Nonselective cholinesterase inhibition	Wong et al., 2018

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Table 1 (*continued*)

Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
					concentrations ≤ 56 μM				
	Fucosterol	*Sargassum horridum*	Ethanolic extract	*In vitro* enzymatic assay	-	Docking simulation	↓ AChE activity	Non-competitive inhibition	Castro-Silva et al., 2019
β-Secretase inhibitory activity	Fucosterol	*Ecklonia stolonifera and Undaria pinnatifida.*	-	-*In vitro* enzyme assay -*In silico* analysis	10-100 μM (IC_{50} value of 64.12 ± 1.0 μM)	Spectrofluorometry	↓ β-secretase activity	Noncompetitive inhibition	Jung et al., 2016a
Neurprotective activity	Fucosterol	*Ecklonia stolonifera*	Dichloromethane (CH_2Cl_2) *fraction of methanolic extract*	-$sA\beta_{1-42}$ (10 μM) -induced ER stress model of primary neurons -$sA\beta_{1-42}$-induced memory dysfunction in aging rats	1–10 μM at 24 h before $sA\beta_{1-42}$ exposure (effective fucosterol conc. 5–10 μM)	Cell viability by Cyto X, Fluo-8 calcium assay, Western blot, Immunostaining, and Morris water maze test for learning and memory	Attenuates $A\beta_{1-42}$-induced neurotoxicity and ameliorates $A\beta_{1-42}$-induced memory impairement	↑ TrkB-mediated ERK1/2 signaling ↓ GRP78 expression ↑ BDNF expression	Oh et al., 2018
	Fucosterol	*Panida. australis*	Dichloromethane extract	Amyloid-induced BV2 (microglial) cells	0.004,0.2 and 10 μM	RT-PCR, ELISA and Griess test (NO content).	Protects against Aβ-mediated neuroinflammation	↓ IL-6, IL-1β, TNF-α, NO, and PGE2	Wong et al., 2018
	Fucosterol	-	-	Aβ-induced cytotoxicity in SH-SY5Y cells	0.0032 to 20 μM.	RT-PCR, Flowcytometry and FITC Annexin V	Reduces apoptosis in Aβ-induced SH-SY5Y cells	↑ Ngb mRNA ↓ APP mRNA and intracellular Aβ levels	Gan et al., 2019
Psychoactive function									
Antidepressent and ainticonvulsant activities	Fucosterol	*Sargassum fusiforme*	n-Hexane fraction of 95% ethanolic extract	Male Balb/e mice	10-40 mg/kg	ELISA, HPLC, Antidepression tests (forced swim test, tail suspension test and open field test), Maximal electroshock seizure test and Neurotoxicity assay (minimal motor impairment-rotorod screen)	Shortens immobility time	↑ NE, 5-HT, and the metabolite 5-HIAA	Zhen et al., 2015
Antidepressant activity	Saringosterol	*Sargassum fusiforme*	-	Mice model	10-30 mg/kg in mice	Forced swim test and tail suspension test	Shortens immobility time	↑ NE, 5-HT, and the metabolite 5-HIAA	Jin et al., 2017
	Total sterol and β-sitosterol	*Sargassum horneri*	-	Forced swimming and tail suspension in mice	Total sterols at oral doses of 50-200 mg/kg for 7 days and β-sitosterol through i.p at 10-30 mg/kg	Forced swim test and tail suspension test	Shortens immobility time	↑ NE, 5-HT, and the metabolite 5-HIAA	Zhao et al., 2016
Antiaging potential	Fucosterol	*Hizikia fusiformis*	-	Culture model of *C. elegans*	50 μg ml^{-1}	-	Extends lifespan	↑Antioxidant mechanism	Oktaviani et al., 2019
Antiadipogenic and antiobesity activity	Fucosterol	*Ecklonia stolonifera*	CH_2Cl_2 fraction of methanolic extract	3T3-L1 pre-adipocytes	12.5–50 μg ml^{-1}	Oil Red O staining and Western blot	↓ Intracellular lipid accumulation	↓ PPARc and CCAAT/C/EBPa expression	Jung et al., 2014
	Fucosterol	*Ecklonia stolonifera*	-	Murine 3T3-L1 preadipocytes	25 and 50 μM	Oil Red O staining and Western blot	↓ Intracellular lipid accumulation	↓ Insulin-triggered PI3K/Akt, and ERK	Lee et al., 2017

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Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
								signaling pathways ↓ Expression of PPARc, C/EBPa and SREBP-1 ↑ SIRT1 expression ↑ FOXO signaling pathway	
	Isofucosterol and saringosterol	*Sargassum thunbergii*	-	-	-	*In vitro* enzymatic assy	-	↓ Lipase activity	Kim et al., 2014
Cholesterol homeostasis	Fucosterol	-	-	-HEK293 cell cultures (Reporter system) -THP-1-derived macrophages Caco-2 cells - HepG2 cells	-100 and 200 μM (HEK293 cell cultures) -100 or 200 μM (macrophages and HepG2, H4IIE, and $Caco_2$ cells)	Reporter gene assay	Reverses cholesterol transport. No accumulation of triglyceride in HepG2	Dual-LXR agonist (LXR-α and LXR-β) ↑ABCA1, ABCG1, and ApoE ↑ Intestinal NPC1L1 and ABCA1 ↑ Insig-2a, that delays nuclear translocation of SREBP-1c	Hoang et al., 2012
	Saringosterol	*Sargassum fusiforme*	Dichloromethane/ methanol (1:2) extract	-Luciferase reporter assay system -HEK293T, THP-1 monocytes, HepG2, RAW264.7, THP-1 macrophages and Caco-2 cells	-30 μM	Transfection, Luciferase assay, Quantitative RT-PCR and Molecular docking		Selective LXRβ agonist. ↑ABCA1, ABCG1, and SREBP-1c	Chen et al., 2014
Cholesterol-lowering effect	Fucosterol	-	-	Adult male Wistar rat model	Intragastric administration of a single emulsified lipid meal containing 25 mg cholesterol and 25 mg fucosterol	Biochemical techniques	Hinders cholesterol absorption	Displaces cholesterol from bile salt micelles	Ikeda, 2015
Antidiabetic effects	Fucosterol	*Pelvetia siliquosa*	-	Streptozotocin-induced diabetic rats	30, 100 and 300 mg/ kg	-	↓ Serum glucose level ↓ Sorbitol accumulation in the lens	↓ Glycogenolysis	Lee et al., 2004
	Fucosterol	*Ecklonia stolonifera*	-	-HepG2 cell line *2-NBDG (40 μM) and Metformin (10 μM) were used to trigger insulin resistance	12.5, 25, and 50 μM	Western blot and MTT assay	↓ Insulin-triggered glucose uptake	↓ PTP1B expression ↓ pIRS1 ↑ pAkt, pPI3K, and pERK1 ↓ Caspase-3 and NF-κB in insulin-resistant hepatocytes ↓ NF-κB p65 expression	Jung et al., 2016b
	Fucosterol	*Eisenia bicyclis* and *Ecklonia stolonifera*	-	*In vitro* enzymatic assay	IC_{50} (μM): RLAR 18.94 HRAR 143.88 PTP1B 60.15	Enzymatic assay	Enzyme inhibition	↓ RLAR, HRAR, and PTP1B ↓ PTP1B, α-glucosidase, and AGE formation	Jung et al., 2013b

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Table 1 (*continued*)

Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
Angiotensin-converting enzyme (ACE) inhibitory activity	Fucosterol	-	-	Bovine carotid endothelial cell culture	25 μM	Enzymatic essay and Receptor assay	Regulates endothelial cell functions	↓ Glucocorticoid receptor levels	Hagiwara et al., 1986
Antiproliferative, cytoxic and anticancer properties									
Antiproliferative effects	Fucosterol	-	-	Lung cancer cell lines (HCC827, A549, SK-LU-1, A427) and noncancerous cell lines (MRC-5, IMR-90 and HEL-299)	7.5-30 μM	MTT assay, Colony formation assays, DAPI and annexin V/PI staining assay, Flow cytometery, Boyden chamber assay and Western blot	↓ Cellular growth, ↑ G2/M cell cycle arrest of the A549 and SK-LU-1 cells ↓ Invasion of A549 and SK-LU-1 cells	↑ Bax and cleaved caspase-3 expression ↓ Bcl-2 expression ↓ Cdc2, Cyclin A and Cyclin B1 expression ↑ p21Cip1, and p27Kip1 (negative regulators of cell cycle progression)	Mao et al., 2019
	Fucosterol	*Sargassum angustifolium*	Hexane extract	Breast (T47D) and Colon cancer cell lines (HT29)	27.94 ± 9.3 and 70.41 ± 7.5 μg/ ml	MTT assay			Khanavi et al., 2012
	Fucosterol	*Dictyota ciliolata*	Hexane extract	Breast cancer (MCF-7) and Cervical cancer cell lines (SiHa)	43.3 mgml for both cell lines	MTT assay			Caamal-Fuentes et al., 2014
	Fucosterol			Leukemia cell lines (HL-60)	34.4 μM	MTT assay	↑ Apoptosis and G2/M cell cycle arrest	↑ Expression of cyt-c, Fas, FasL, and Fadd ↑ Caspase-3 and -9 ↓ MMP	Ji et al., 2014; Ji et al., 2013
	Fucosterol			Cervical cancer (HeLa)	40 μM		↑ Apoptosis and G2/M cell cycle arrest, ↓ Cell migration	↑ PI3K/Akt/ mTOR signaling pathway ↑ ROS ↓ Mitochondrial membrane potential	Jiang et al., 2018
Cytotoxic effects	Fucosterol	*Sargassum carpophyllum*		Leukemia cells (P-388)	0.7 μg ml^{-1}		-	-	Tang et al., 2002
	Fucosterol	*Sargassum thunbergii*	EtOAc extract	Melanoma (B16F10) and Colon (HT-29) cancer cell lines	15.15 μgml for HT-29	MTT assay	↑ Cell shrinkage, membrane blebbing and formation of apoptotic bodies	-	Kim et al., 2009
Synergistic effects (anti-invasive and cytotoxic)	Fucosterol			Colorectal cancer cell lines (HCT116 and HT29)			↑ Cytotoxicity and anti-invasiveness		Ramos et al., 2019
Hepatoprotective effects	Fucosterol	*Pelvetia siliquosa*	-	CCl_4-intoxication in rats	-	Enzymatic essay	↓ Serum ALT and AST activites	↑ SOD, CAT and GPx activities	Lee et al., 2003
	Fucosterol	*Ecklonia stolonifera* and *Eisenia bicyclis* Brown Alge	-	-*in vitro* (tert-butyl hydroperoxide- and tacrine-induced HepG2cell injury model) -in vivo (tacrine-treated mice (hepatic injury model)	25, 50 and 100 μm	MTT assay and Intracellular ROS scavenging assay (DCFH-DA)	No cytotoxicity by fucosterol itself. ↑ Cell viability ↓ Serum ALT and AST levels in tacrine-treated mice	↑ GSH levels ↓ ROS production	Choi et al., 2015
	Fucosterol	-	-	Concanavalin A (25 mg/kg)-induced acute liver injury in Male BALB/c mice	Daily oral doses of 25, 50, and 100 mg/ kg	Western blot, qRT-PCR, Immunohistochemi-stry and Transmission Electron Microscopy	No cytotoxicity by fucosterol itself. ↓ ALT and AST levels. ↓ Aapoptosis and necrosis	↑ Bcl-2 transcription ↓ Bax expression ↓ Autophagy markers Beclin-1, LC3 ↑ P62 accumulation ↓ TNF-α, IL-6, and IL-	Mo et al., 2018

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Table 1 (*continued*)

Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
								1β. ↑ PPARγ. ↓ P38 MAPK/NF-κB signaling	
Antimicrobial effects (antibacterial, antifungal, and antiprotozoan)									
Antibacterial activity	Fuscosterol	*Sargassum longifolium*, brown alga from Gulf of Mannar	-	Human pathogen (*Vibrio parahaemolyticus*) and fish pathogens (*Vibrio vulnificus, Vibrio harveyii* and *Aeromonas hydrophila*)	20 μg/20 μl/disc (zone of inhibition: 6.3-8.3 mm)	Disc diffusion method	↓ Bacterial growth	-	Rajendran et al., 2013.
Antitubercular activity	Saringosterol and its 24*S* and 24*R* epimers	*Lessonia nigrescens*	-	*M. tuberculosis*	MIC values 0.25, 1, and 0.125 μg/ml	BACTEC 460 assay system and CellTiter 96 aqueous nonradioactive cell proliferation assay	↓ Growth of *M. tuberculosis*	-	Wachter et al., 2001
Antibacterial and antifungal activity	-Fucosterol -3,6,17-trihydroxy -stigmasta-4,7,24(28)-triene and -14,15,18,20-diepoxyturbinar	*Turbinaria conoides*, brown alga	Cyclohexane extract	*S. aureus* and *E. coli* *C. albicans* and *A. niger*	Inhibits the growth of *C. albicans* and *A. niger* with MIC of 8 and 16 μg/ml, respectively	-	↓ Microbial growth	-	Kumar et al., 2010
Antifungal properties	Fucosterol	-	-	*Fusarium culmorum* Fc37	-Inhibition at 1.0% -Shorter macroconidia growth at 0.05–0.2% (Macroconidia germination inhibition, IC_{50} 0.06)	-	↓ Macroconidia germination	Might involve modification of lipid bilayer	Tyśkiewicz et al., 2019
Antiplasmodial activity	Fucosterol	*Sargassum linearifolium*	-	*Plasmodium falciparum*	7.48 μg ml^{-1}	Erythrocyte stabilisation assay	Suppression of parasitaemia	Changes in RBC	Perumal et al., 2018
Protective effects against skin damage									
Protection aginst particulate matter-induced skin lesions	Fucosterol	*Sargassum binderi*	-	HDF and HaCaT	3.125, 6.2, 12.5, 25, 50, 100 μg ml^{-1}	Western blot	↓ Apoptotic body formation and inflammatory functionalities	↓ ROS and MMP production ↓ NF-κB-p65 nuclear translocation and phosphorylation of p38 MAPK, Erk1/2, and JNK ↓ COX-2, PGE2, TNF-α and IL-6	Fernando et al., 2019b
Anti-skin aging	Fucosterol	-	-	HaCaT cells and monkey kidney COS-7 cells	0.5, 1, or 5 μM	ELISA, RT-PCR, Western blot and -2′,7′-dichlorofluorescein diacetate assay	↓ Inflammatory response ↑ Antioxidant defence.	↓ MMP-1 production and MMPs mRNA expression ↑ Type-I procollagen and its mRNA levels ↓ ROS levels ↑ mRNA levels of	Kim et al., 2013

(*continued on next page*)

Table 1 (*continued*)

Health effects	Sterols	Algal source (if any)	Extract/ fraction (quantity in unit)	Experimental model (*in vivo/in vitro*)	Dosage (EC/IC_{50}, if calculated)	Major techniques employed	Cellular effects/ major findings	Molecular pharmacology	References
								SOD1,GPx and CAT ↑ Phosphorylation of ERK, JNK and p38 ↓ c-Jun and c-Fos	
Protect skin photodamage	Fucosterol	*Hizikia fusiformis,* brown algae	-	NHDF (UVB-induced photodamage)	0.01, 0.1, 1,10 μg ml^{-1}	ELISA, Western blot and RT-PCR.	Prevents keratinocytes against photodamage	↓ MMP-1, IL-6, p-c-Jun, and p-c-Fos expression ↑ Type I procollagen and TGF-β1 production	Hwang et al., 2014
Bone regenerative, anti-osteoarthritic and anti-osteoporotic	Fucosterol	*Hizikia fusiforme*	-	-MG63 human osteoblastic cell line -Rat model of ovariectomy-induced osteoporosis	-	MTT assay, Alkaline phosphatase assay, Western blot, CT scan, Bone densitometry and ELISA	↑ Femur bone mineral density	↑ Alkaline phosphatase activity ↑ Osteocalcin ↓ CTx	Lee et al., 2014b
Immunomodulatory activity	Fucosterol	*Hizikia fusiforme,* brown seaweed	-	*In vitro* and *ex vivo* models of murine macrophage cell line (RAW 264.7)	1, 10, 100 μg ml^{-1}	ELISA and Western blot	↑ Cell viability ↑ Phagocytic activity ↑ Splenocyte proliferation	↑ NO production ↑ TNF-α production ↑ TNF-α, IL-1β, and IL-6 expression	Park et al., 2017
Protection against pulmonary tissue damage.	Fucosterol	-		-LPS-induced ALI in male BALB/c mice -LPS-stimulated alveolar macrophages	15-60 mg/kg	ELISA and Western blot	Ameliorates the pulmonary injury. ↓ MPO activity ↓ Lung W/D ratio	↓ TNF- α, IL-1β and IL-6 in ALI in mice ↓ NF-κB activation and TNF-α, IL-6, and IL-1β production in LPS-stimulated alveolar macrophages	Li et al., 2015
	Fucosterol	*Sargassum binderi* brown alga	-	Particulate matter-induced injury and inflammation in A549 human lung epithelial cells	3.125, 6.25, 12.5, 25, 50, 100 μg ml^{-1}	Western blot	↑ Cell viability ↓ Oxidative stress and inflammatory response.	↓ DNA damage ↓ Bax, p53, and Caspases-3 and 9 as well as cleavage of Caspases-3 and 9 ↓ PARP cleavage ↑ Bcl-xL ↓ ROS level ↑ SOD, CAT, and HO-1 in the cytosol, and NRF2 levels in the nucleus. ↓ Nuclear translocation of P65 and P50 and pp38 MAPK, ERK½, and JNK. ↓COX-2, PGE2, TNF-α and IL-6.	Fernando et al., 2019a

(Ikekawa et al., 1966) as a minor sterol in *Sargassum ringoldianum*. Safe et al. has reported saringosterol and 24- ketocholesterol for the first time in *Laminaria* (Safe et al., 1974).

Ayyad and co-investigators isolated 24-vinyl cholest-4-ene-24-ol-3 one as a new steroidal derivative from a red sea alga *Sargassum asperifolium*. They also purified three known sterols, including saringosterone, 24-vinyl cholest -5-ene -3b, 24-diol and saringosterol (Ayyad et al., 2003). A brassinosteroid-related metabolite, 3-keto-22-epi-28-nor-cathasterone from *Cystoseira myrica*, is the first reported sterol in its kinds in seaweed (Hamdy et al., 2009). *Sargassum oligocystum* (Heterokontophyta), an abundant brown alga in the Persian Gulf, has been exploited for cholesterol, 22-dehydrocholesterol, fucosterol, 29-hydroperoxystigmasta-5,24(28)-dien-3-ol, 24-hydroperoxy-24-vinylcholesterol, a mixture of 24(S)-hydroxy-24-vinylcholesterol and 24(R)-hydroxy24-vinylcholesterol, and ostreasterol (Permeh et al., 2012). Fucosterol has been isolated as a dominant sterol in *Undaria pinnatifida*, of New Zealand origin, followed by 24-methylenecholesterol, among the sterols reported (Boulom et al., 2014). This study also noticed that *U. pinnatifida* accumulates a higher amount of sterol in winter, perhaps to cope with the cold shock in this season. Chen and team isolated a total of seven sterols including fucosterol, saringosterol, 24-hydroperoxy-24-vinyl-cholesterol, 29-hydroperoxy-stigmasta-5,24(28)-dien-3β-ol, 24-methylenecholesterol, 24-keto-cholesterol and 5α,8α-epidioxyergosta-6,22-dien-3β-ol from *Sargassum fusiforme* (Chen et al., 2014). An interesting investigation led by Pereira and colleagues reported for the first time all the major phytosterols including fucosterol, *β*-sitosterol, campesterol, cholesterol, stigmasterol, ergosterol, and brassicasterol in six species of brown macroalgae, such as *Adenocystis utricularis, Ascoseira mirabilis, Cystosphaera jacquinotii, Desmarestia anceps, Desmarestia antarctica*, and *Himantothallus grandifolius* from Antarctica, where fucosterol was the most abundant (6.60 to 48.13 mg/kg), followed by *β*-sitosterol (5.29 to 16.49 mg/kg), stigmasterol (2.69 to 14.84 mg/kg), with a scanty of campesterol (Pereira et al., 2017). In another investigation on the sterol composition of red sea algae, fucosterol was the major sterol in *Padina pavonica* and *Hormophysa triquetra*. On the other hand, β-sitosterol was detected only in *P. pavonica,* whereas β-sitostanol and Stigmasterol were characterized in *H. triquetra*. Campesterol was found in both species (El Shoubaky and Salem, 2014).

Very recently, Xia and colleagues purified two analog phytosterols, including fucosterol and saringosterol from *Sargassum horneri*, with a yield of 23.7 mg and 3.1 mg, respectively, from 300 mg of crude extract in one-step separation using high-speed counter-current chromatography (Xia et al., 2019).

Red algae

Unlike brown algae, red algae have not been investigated extensively for their sterol composition. In majority cases, the red algae that have been explored primarily contain cholesterol as their major sterol. For example, in the unsaponifiable fraction of *Solieria chordalis,* cholesterol comprises the principal sterol (43%) while cholest-4-en-3-one has been detected as a minor (Kendel et al., 2015). The sterols identified in *Gracilaria salicornia* (Gigartinales) include 22-dehydrocholesterol, cholesterol, and stigmasterol whereas *Hypnea flagelliformis* (Gigartinales) additionally contains cholesterol oleate, and (22*E*)-cholesta-5,22-dien-3β-ol-7-one (Nasir et al., 2011). *Gracilariopsis persica* (Rhodophyta), a highly abundant alga of the Persian Gulf, contains 22-dehydrocholesterol, cholesterol, stigmasterol,*β*-sitosterol and fucosterol with cholesterol, the main sterols *in G. Persica* and 22-dehydrocholesterol in *Gp. Persica* (Saeidnia et al., 2012). Another study led by Han and the team reported six sterols, including 6-hydroxycholest-4-ene-3-one, cholest-5-ene-3 beta-ol, beta-sitosterol, cholest-4-ene-3, 6-dione, 5-alpha-cholestane-3, 6-dione, and saringosterol from the ethanolic extract of *Acanthophora spicifera*. Of these, the first three sterols have been reported for the first in this genus (Han et al., 2009). On the contrary, desmosterol is the principal sterol in *Palmaria* sp. and *Porphyra* sp. (87–93% of total sterol content) followed by cholesterol in *Porphyra* sp. (8.6% of total sterols) (Sanchez-Machado et al., 2004).

Green algae

The sterol composition in green algae is equivalent to higher plants (Ikekawa et al., 1968). However, this algal family is relatively heterogeneous in sterol composition (Patterson, 1971). β-sitosterol is a major sterol in *Halimeda tuna* and *Codium bursa* (95.21 ± 0.16 μg/g and 73.90 ± 0.08 μg/g, respectively) (Milović et al., 2019). However, the main sterols in *Ulva lactuca* Linnaeus include cholesterol and isofucosterol (Kapetanovic et al., 2005). Investigating 12 macroalgae under three Chlorophyceae orders from the Senegalese coast, Akin and colleagues concluded that isofucosterol is a typical sterol for Ulotrichales. By contrast, clionasterol is for all species of Siphonales not belonging to *Codium* genus, which is, itself, characterized by clerosterol (Aknin et al., 1992). (24*Z*)-stigmasta-5,24-dien-3β-ol (28-isofucosterol) is a major sterol in green-tide forming alga *Ulva prolifera* (Geng et al., 2017). Kendel and co-investigators reported cholesterol (35%) as the principal sterol in *Ulva armoricana*, whereas cholest-4-en-3-one has been reported as minor (0.8%). Other minor sterols in this green alga include brassicasterol, isofucosterol and campesterol (Kendel et al., 2015).

Pharmacological potentials of algal sterols

Like many other biologically active secondary metabolites, algae-derived sterols exhibit a diverse array of health benefits with the distinct pharmacological mechanisms (Table 1 and Fig. 2). In the following sections, the up-to-date information on various health effects of algal sterols with potential pharmacological mechanisms, where possible, has been compiled.

Algal sterols as antioxidants

Cellular oxidative stress is a pathological outcome of the production of reactive oxygen species (ROS) in excess, that plays a pivotal role in the pathobiology of several acute and chronic diseases, such as neurodegenerative disorders (NDs), cardiovascular diseases (CVDs), chronic kidney disease (CKD), chronic hepatic diseases, and various forms of cancer (Liguori et al., 2018). Thanks to antioxidant defense system furnished with enzymatic tools, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and non-enzymatic antioxidants, such as glutathione, ascorbate, and tocopherol, cells in physiological condition are well-protected from the burden of excess ROS (Finkel and Holbrook, 2000). The bioactive phytochemicals that we achieve through dietary consumption further bolster intrinsic antioxidant defenses including induction of the expressions of SOD, GPx, CAT, heme oxygenase and other proteins through activating adaptive cellular stress pathways, which, in turn, prepare cells to withstand stress (Lee et al., 2014a; Mattson and Cheng, 2006). Moreover, natural products exhibit their antioxidant effects through inducing antioxidant defense-associated transcription factors, for example, nuclear factor erythroid 2-related factor 2 (Nrf2) (Tavakkoli et al., 2019).

Like other bioactive metabolites, algal phytosterols are also shown to have antioxidant activity. Lee and co-investigators have reported that fucosterol treatment increases the level of SOD, CAT, and GPx1 in CCl_4-intoxicated rats (Lee et al., 2003). In another study with tert-butyl hydroperoxide (t-BHP)-induced RAW264.7 macrophages, fucosterol inhibits the generation of ROS (Jung et al., 2013a). In addition, fucosterol attenuates oxidative stress in HepG2 cells through lowering intracellular ROS and increasing glutathione levels (Choi et al., 2015) and in A549 human lung epithelial cells through up-regulating SOD, CAT, and heme oxygenase-1 (HO-1) in the cytosol, and Nrf2 levels in the nucleus (Fernando et al., 2019a). These findings suggest a potent

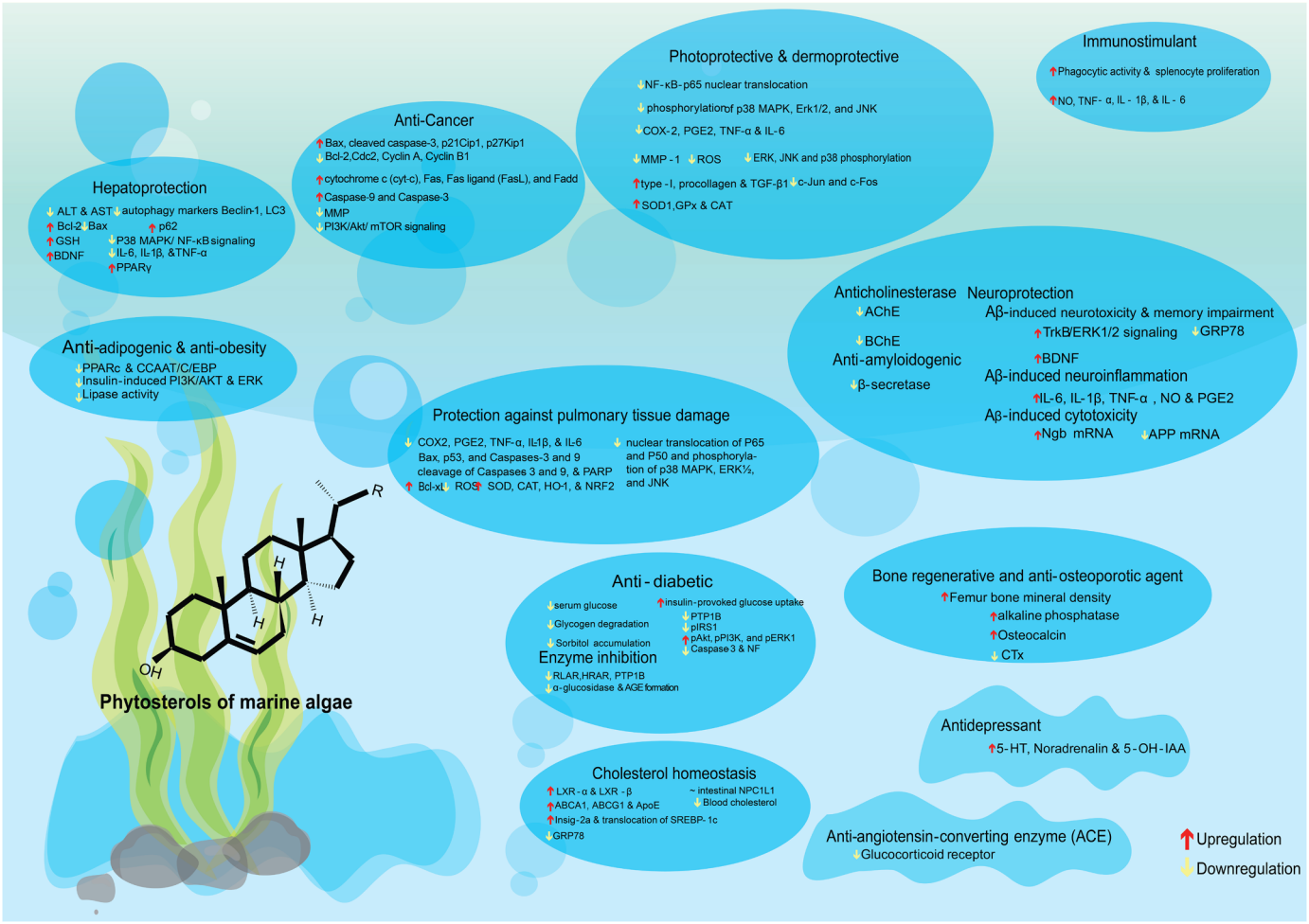

Fig. 2. Illustration showing an array of health benefits of algae-derived phytosterols with the associated molecular markers that regulate various biological processes and cellular pathways implicated in human health and diseases. Algal phytosterols generate health effects in almost every system of human physiology (see text for details).

antioxidant property of fucosterol and thus might pose a significant role against oxidative stress-related diseases.

Algal sterols as anti-inflammatory agents

Chronic and deregulated inflammation has been implicated in the pathophysiology of chronic health conditions, such as cardiovascular diseases, cancer, obesity, diabetes, metabolic syndrome, arthritis, hepatitis, stroke, and other degenerative brain disorders. The inflammatory cytokines, including inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) are the significant biomarkers in the pathobiology of these chronic diseases (Wojdasiewicz et al., 2014). The bioactive natural products having the capability to modulate inflammatory cytokines have been shown to protect several chronic diseases (Lv et al., 2017; Wang et al., 2017).

Several studies have investigated the anti-inflammatory potentials of algal sterols (Juárez-Portilla et al., 2019). For instance, fucosterol isolated from the methanolic extract of the brown alga, *Eisenia bicyclis* exhibits anti-inflammatory activity through repressing the expression of COX-2 and iNOS in lipopolysaccharide (LPS)-induced RAW 264.7 macrophages (Jung et al., 2013a). Fucosterol also attenuates LPS-induced inflammatory response through lowering the activation of nuclear factor-κB (NF-κB) and the expression of TNF-α, IL-6, and IL-1β in LPS-induced alveolar macrophages (Li et al., 2015). Sun and colleagues also reported that fucosterol shows anti-inflammatory activity through suppressing TNF-α, IL-6, and IL-1β expression (Sun et al., 2015). Fucosterol, isolated from *Sargassum binderi*, has been shown to attenuate CPM-induced inflammatory responses through lowering the nuclear translocation of P65 and P50 and phosphorylation of p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinases 1/2 (ERK1/2) and c-Jun N-terminal kinases (JNK), and the levels of COX-2, prostaglandin E2 (PGE2), TNF-α and IL-6 (Fernando et al., 2019a). A similar study also reported that fucosterol protects against amyloid β (Aβ)-mediated neuroinflammation through inhibiting the production of IL-6, IL-1β, TNF-α, nitric oxide (NO), and PGE2 in LPS- or Aβ-induced microglial cells (Wong et al., 2018). In another study conducted by Yoo and colleagues, fucosterol suppresses the expressions of iNOS, TNF-α, and IL-6 by down-regulating their transcriptions, and subsequently inhibits the synthesis of NO, TNF-α, and IL-6. Also, fucosterol attenuates LPS-mediated DNA binding and the transcriptional activity of NF-κB, thus inhibiting the nuclear translocation of NF-κB. Furthermore, fucosterol inhibits the phosphorylation of mitogen-activated protein kinase kinases 3/6 (MKK3/6) and mitogen-activated protein kinase-activated protein kinase 2 (MK2), both of which are involved in the p38 MAPK pathway, suggesting that the anti-inflammatory effects of fucosterol might be, at least in part, correlated with the suppression of NF-κB and p38 MAPK pathways (Yoo et al., 2012).

Algal sterols as anti-Alzheimer's agents

Alzheimer's disease (AD) is a highly prevalent degenerative brain

disorder with a gradual loss of memory and cognition, contributing up to 75% of the total dementia cases among the elderly citizens (Scheltens et al., 2016). The pathological hallmarks include amyloid plaques and neurofibrillary tangles. However, being a multifactorial brain disorder, the AD therapeutic strategy requires a multitarget-oriented approach. The cholinergic deficit, one of the clinical consequences of AD pathology, could pharmacologically be treated by a reversible inhibitor to acetylcholinesterase (AChE), an enzyme responsible for acetylcholine breakdown during cholinergic neurotransmission. Like other bioactive metabolites from marine algae, phytosterols also have shown inhibition against cholinesterase activity. For example, fucosterol and 24-hydroperoxy 24-vinylcholesterol, purified through bioassay-guided isolation from the ethanolic extracts of *E. stolonifera* exhibit inhibitory activity against butyrylcholinesterase (BChE) with IC_{50} values of 421.72 ± 1.43 and 176.46 ± 2.51 μM, respectively (Yoon et al., 2008). Wong and colleagues reported that fucosterol shows dose-dependent inhibition against both AChE and BChE. It has been observed that at concentrations of ≤56 μM, this inhibition was more significant against AChE (10.99–20.71%) than BChE (4.53–17.53%) (Wong et al., 2018). Enzyme kinetics and structural analysis revealed that fucosterol function as a non-competitive AChE inhibitor. Structural analysis revealed that fucosterol interacts with the peripheral "anionic" sub-site of the AChE, further validating the non-competitive nature of binding. Binding free energy analysis proved that fucosterol reaches the AChE binding site with higher affinity (Castro-Silva et al., 2019).

β-Secretase catalyzes the initial processing of amyloid precursor protein (APP) to produce Aβ, whose aggregation is one of the hallmarks in AD. Thus, β-secretase could offer a potential target for the development of an anti-AD agent (Ghosh et al., 2012). However, accumulated evidence suggests that the complete abolishment of β-secretase activity might have unintended consequences with behavioral deficits (Koelsch, 2017). Therefore, natural molecules that show reversible and non-competitive binding patterns have a therapeutic promise against the β-secretase activity. Phytosterols, particularly fucosterol, also have shown anti-amyloidogenic potentials. For example, fucosterol exhibits a significant inhibitory activity (IC_{50} value of 64.12 ± 1.0 μM) against β-secretase (Jung et al., 2016a). The mode of inhibition is of non-competitive type, indicating an effective and safer inhibitor. Also, *in silico* analysis demonstrating the interaction of fucosterol with the active site of β-secretase through hydrogen-bonding (between Lys224 of enzyme and 3-OH of fucosterol) and multiple hydrophobic interactions (among Ile118, Tyr71, Ile226, Thr231, Val332, Phe108, and Val69 residues of the enzyme and the methyl group of fucosterol), along with network pharmacology findings (Hannan et al., 2019) suggests that fucosterol could be a potent anti-amyloidogenic agent. Moreover, fucosterol shows binding energies of −10.1 kcal/mol (Jung et al., 2016a) and −19.88 kcal/mol (Hannan et al., 2019), respectively indicating that hydrogen bonding may ensure intimate association with enzyme active site, resulting in more effective β-secretase inhibition.

Aβ aggregation induces an inflammatory response mediated by microglia and astrocytes (Meraz-Rios et al., 2013). Therefore, bioactive molecules that mitigate inflammation might show therapeutic efficacy in AD. Several studies have demonstrated the inhibitory activity of algal sterols against Aβ-induced neuroinflammation. For instance, fucosterol isolated from *Panida australis* has been shown to protect against Aβ-mediated neuroinflammation in BV2 cells through inhibiting the production of pro-inflammatory cytokines, IL-6, IL-1β, TNF-α, NO, and PGE2 (Wong et al., 2018). Moreover, fucosterol attenuates soluble $Aβ_{1-42}$ ($sAβ_{1-42}$)-induced cytotoxicity and downregulates $sAβ_{1-42}$-induced expression of glucose-regulated protein 78 (GRP78) in primary hippocampal neurons through activating tropomyosin receptor kinase B (TrkB)-mediated ERK1/2 signaling (Oh et al., 2018), a TrkB-dependent neuroprotective effect, which was abrogated by a selective TrkB inhibitor, cyclotraxin B. These *in vitro* cellular effects of fucosterol have further been translated into in vivo effects, in which chronic fucosterol co-infusion ameliorates $sAβ_{1-42}$-induced cognitive impairment in aging rats via downregulation of GRP78 expression and upregulation of mature brain-derived neurotrophic factor (BDNF) expression in the dentate gyrus of the dorsal hippocampus signaling (Oh et al., 2018). In an *in vitro* experiment investigating the neuroprotective effects of fucosterol against Aβ-induced neurotoxicity in SH-SY5Y cells, Gan and colleagues reported that fucosterol pretreatment significantly attenuates apoptosis induced by Aβ through enhancing the expression of neuroglobin (Ngb) mRNA. Fucosterol preconditioning also reduces the mRNA levels of APP and results in a decrease of intracellular Aβ levels in Aβ-induced SH-SY5Y cells (Gan et al., 2019).

Moreover, a very recent system pharmacology-oriented analysis revealed that fucosterol specifically targets several proteins of TNF, MAPK, phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), neurotrophin, and toll-like receptor (TLR) signaling pathways, that are closely associated with neuronal growth and survival, inflammation, and immune response. The molecular modeling study further verified the binding of fucosterol with liver X-receptor-beta (LXR-β), glucocorticoid receptor (GR), TrkB, TLR2/4, and *β*-secretase, which are the crucial regulators of those pathways implicated in the pathophysiology of degenerative brain diseases (Hannan et al., 2019).

Algal sterols as antidepressants and anticonvulsants

Depression is a highly prevalent psychiatric disorder, causing long-term disability (Nabavi et al., 2017). Reduction in the levels of BDNF and monoamine neurotransmitters, such as serotonin (5-HT), dopamine, and norepinephrine (NE) in the brain, is known to be implicated in depression (Jeon and Kim, 2016). Also, patients with epilepsy very often experience depression (Chandrasekharan et al., 2017; Kanner, 2006). A line of evidence suggests the therapeutic importance of medicinal herbs and their bioactive natural products in mitigating depression (Muszynska et al., 2015; Nabavi et al., 2017). Marine bioactive metabolites are also shown to have antidepressant property. For instance, fucosterol isolated from *S. fusiforme* significantly shortens immobility time in the forced swim test and tail suspension test for 30 min after treatment at the doses of 10–40 mg/kg, indicating its antidepressant activity which is attributed to an increase in the level of BDNF, 5-HT, NE and the metabolite 5-hydroxyindoleacetic acid (5-HIAA) in mouse brain (Zhen et al., 2015). In addition to antidepressant activity, fucosterol (at 20, 40, 100 mg/kg) also exhibits anticonvulsant activity that lasts for 4 h following administration at a dose of 100 mg/kg. Moreover, fucosterol does not show neurotoxicity at the same dose levels in mice (Zhen et al., 2015). Saringosterol, another phytosterol of *S. fusiforme*, also exhibits a similar antidepressant-like activity (Jin et al., 2017). In both cases, there was no influence on the locomotor activity of model animals. Another study evaluating the antidepressant-like activity of total sterols and β-sitosterol isolated from *Sargassum horneri* also reported that these sterols significantly reduce the immobility time in the forced swim test and tail suspension test in mice, which is also attributed to an increase in 5-HT, NE, and the metabolite 5-HIAA in the mouse brain, suggesting an antidepressant effects of these sterols (Zhao et al., 2016). These shreds of evidence strongly recommend further investigation of these phytosterols to exploit their antidepressant and anticonvulsant activities with aiming to develop a potential therapy for patients with depression and epilepsy.

Algal sterols as anti-aging agents

The aging or senescence is an inevitable phenomenon in the organism's lifespan. Dietary manipulation or pharmacological interventions that can slow the aging process have received much attention among the health-conscious people/stakeholders as well as the scientific community who are dedicated to anti-aging research (de Cabo et al., 2014). Phytochemicals that are abundant in various food commodities, including fruits and vegetables, showing antioxidant activity,

are sought to have anti-aging potentials. Like other bioactive metabolites (de Cabo et al., 2014), algal sterols, particularly fucosterol have been shown to extend lifespan in an experimental condition. For instance, *Caenorhabditis elegans* given with fucosterol (at 50 μg ml^{-1} in nematode culture media), a significant constituent of *Hizikia fusiformis* survived longer (~14 vs. ~11 days) than those without fucosterol intervention, indicating that this algal sterol might have therapeutic promise against premature aging (Oktaviani et al., 2019). This longevity/survival-promoting effect of fucosterol might be attributed to its antioxidant, anti-inflammatory, and immunostimulatory properties.

Algal sterols as anti-adipogenic and anti-obesity agents

The obesity refers to a state of being involved to the abnormal accumulation of adipose tissue to an extent where it might cause serious health consequences associated with type 2 diabetes mellitus, fatty liver, hypertension, cardiovascular disease, stroke, specific forms of cancer and many other health complications (Flier, 2004). With metabolic roles, adipose tissue regulates insulin sensitivity and energy homeostasis. An increased mass of adipose tissue indicates the increased number and size of adipocytes (Jo et al., 2009). The suppression of adipocyte differentiation and lipogenesis, therefore, represents one of the viable approaches against obesity. Recent evidence suggests anti-adipogenic or anti-obesity activities of macroalgae-derived sterols. For instances, fucosterol isolated from *E. stolonifera* significantly reduces the accumulation of lipid in 3T3-L1 pre-adipocytes through down-regulating the expression of adipocyte marker proteins such as peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer-binding protein α (C/EBPα) (Jung et al., 2014). A similar but more precise mechanism underlying anti-adipogenic potential of fucosterol has been described by Lee and colleagues who reported that fucosterol, also from *E. stolonifera* inhibits adipogenesis in 3T3-L1 pre-adipocytes through suppressing insulin-triggered PI3K/Akt and extracellular signal-regulated kinases (ERK) pathways, downregulating the expression of PPARγ, C/EBPα and sterol regulatory element-binding protein 1 (SREBP-1), enhancing sirtuin 1 (SIRT1) expression and modulating Forkhead box (FoxO) signaling pathway (Lee et al., 2017).

The reduction in dietary fat absorption through partially inhibiting pancreatic lipase, a lipolytic enzyme, is another potential strategy against obesity (Sebban-Kreuzer et al., 2003). Phytosterols from marine algae have also been shown to reduce pancreatic lipase activity. In an *in vitro* study, Kim and co-investigators have demonstrated that isofucosterol and saringosterol isolated from *Sargassum thunbergii* inhibit lipase activity (Kim et al., 2014). These evidence strongly suggests the therapeutic significance of algal sterols, particularly fucosterol against obesity.

Algal sterols as antidiabetic agents

Type 2 diabetes mellitus (T2DM) is a non-communicable chronic metabolic disease associated with insulin resistance. The fact that more than 450 million adults are currently living with diabetes worldwide (according to IDF Diabetes Atlas 9th Edition) reflects the pandemic nature of this metabolic disease. The potentially viable therapeutic strategies to control T2DM include inhibition of carbohydrate hydrolyzing-enzymes (for example, α-glucosidase and α-amylase) in the digestive tract (Bischoff, 1995) or regulation of protein-tyrosine phosphatase 1B (PTP1B that negatively regulates insulin signaling) (Johnson et al., 2002). Pharmacological strategies including stimulation of insulin release, glucose transport activity, or inhibition of gluconeogenesis, and reduction of intestinal glucose absorption, have been investigated on diabetes treatment (Thilagam et al., 2013). However, many of these compounds have low efficacy or severe side effects. Thus, a line of research has been implemented to identify more effective and safer anti-hyperglycemic agents from natural origins. Indeed, sterols from marine algae have been increasingly exploited as viable sources with promising anti-diabetic activity as well as for α-glucosidase, α-amylase, PTP1B inhibitory effects (Zhao et al., 2018). For example, fucosterol from *Pelvetia siliquosa* at an oral dose of 30 mg/kg causes a significant reduction in serum glucose and, inhibition of sorbitol accumulations in the lenses in streptozotocin-induced diabetic rats, whereas the epinephrine-induced diabetic rats requires an oral dose of 300 mg/kg to have the similar effects (Lee et al., 2004). In addition, fucosterol promotes insulin-provoked glucose uptake and decreases PTP1B expression (Jung et al., 2016b; Seong et al., 2019). Fucosterol also reduces phosphorylation of insulin receptor substrate 1 (IRS1) and increases phosphorylation of Akt, PI3K, and ERK1, inhibits caspase-3 activation and NF-κB in insulin-resistant HepG2 cells, and thus improves insulin resistance (Jung et al., 2016b). However, long-term hyperglycaemic condition implies various complications by increasing aldose reductase (AR)-related polyol pathway, advanced glycation endproduct (AGE) formation, and oxidative load (El-Kabbani et al., 2004). Therefore, the inhibition of hyperglycemia-induced polyol pathway flux by AR inhibitors (ARIs) could be another potential therapeutic strategy in the management of diabetic complications (Kawanishi et al., 2003). Jung and colleagues reported that fucosterol exhibits enzymatic inhibition of rat lens AR (RLAR), human recombinant AR (HRAR), α-glucosidase and PTP1B activity. Further docking simulations proved that fucosterol shows a higher affinity and tighter binding capacity for the AR active site (Jung et al., 2013b). Subsequently, sterols in *Sargassum glaucescens* possess α-amylase inhibitory activity (Payghami et al., 2014) suggesting their antidiabetic effect.

Algal sterols as regulators of cholesterol homeostasis

Cholesterol as a critical constituent of cell membranes regulates cell-cell interaction and transmembrane signaling (Morinaga et al., 2018). In the central nervous system (CNS), cholesterol plays an essential role in neuronal physiology, spanning from development in early ages to maintenance in adult life. An age-dependent loss of cholesterol has been observed in the human brain and the rodent hippocampus, and A defect in cholesterol metabolism provokes alteration of synaptic functions, induces oxidative stress and inflammation, and thus, triggers the onset of major brain disorders (Martin et al., 2014). However among the type II nuclear receptor, particularly LXR-β, upon ligand activation, accelerates the expression of Apolipoprotein E (ApoE), ATP-binding cassette transporters (ABCA1, ABCG1), and SREBP1, the key genes in reverse cholesterol transport and has been implicated in protection of neurodegeneration (ND) (Ito et al., 2015; Xu et al., 2013). For example, LXR-β protects against loss of dopaminergic neurons (Dai et al., 2012) and the burden of mutant huntingtin (Futter et al., 2009) as well as enhances the clearance of Aβ (Wolf et al., 2012). Notably, fucosterol of *Sargassum fusiforme* is a selective LXR-β agonist and accelerates the expression of LXR target genes, such as ABCA1, ABCG1, and ApoE (Chen et al., 2014; Hoang et al., 2012) These findings suggest that fucosterol might produce a similar LXR-β-mediated effect to help in cholesterol homeostasis in the brain and play a significant role against NDs like AD pathology involving the Aβ clearance via ABC/SHREBP1/ApoE-dependent pathways. Moreover, saringasterol, another sterol isolated from *Sargassum fusiforme* is also a selective LXRβ agonist and induces the transcriptional activation of ABCA1, ABCG1, and SREBP-1c in multiple cell lines and thus suggested to be a potent natural cholesterol-lowering agent (Chen et al., 2014).

Algal sterols as cholesterol-lowering agents

Phytosterols are well-known for their hypocholesterolemic activity (Ikeda, 2015). In an in vivo study, Ikeda et al. reported that fucosterol inhibits cholesterol absorption (Ikeda et al., 1988). The report showed that the intragastric administration of a single emulsified lipid meal containing 25 mg [3H] cholesterol and 25 mg of fucosterol inhibits the

lymphatic absorption of cholesterol by 41% in 24 h while only less than 2% of fucosterol was absorbed in the same period. However, the inhibition of cholesterol absorption by plant sterols are likely due to the reduction in the solubility of cholesterol by plant sterols solubilized in micelles as phytosterols are solubilized in bile salt micelles and the sterol-solubilizing capacity of bile salt micelles is limited (Ikeda, 2015).

Algal sterols as angiotensin-converting enzyme (ACE) inhibitors

ACE, a zinc-containing protease plays a critical role in the regulation of blood pressure through converting angiotensin I into a potent vasoconstrictor angiotensin II and degradation of the vasodilator bradykinin (Soffer, 1976). Inhibition of ACE activity, therefore, relieves hypertension, a major contributory risk factor of chronic human diseases, including cardiovascular diseases (Paiva et al., 2017; Zhang et al., 2006). Hagiwara and colleagues reported an indirect ACE inhibitory activity of fucosterol in bovine carotid endothelial cells. There is an elevation of ACE levels in untreated cells upon addition of dexamethasone, while this effect has not been observed in fucosterol-treated culture. Receptor assays further revealed that glucocorticoid receptors are decreased to an undetectable level in fucosterol-treated cells, concluding that fucosterol decreases the ACE levels in endothelial cells by inhibiting the synthesis of glucocorticoid receptors which is implicated in the regulation of ACE levels (Hagiwara et al., 1986).

Algal sterols as cytotoxic, anti-proliferative and anti-cancer agents

Phytosterols are well known for their anticancer activity, including anti-proliferation, anti-metastasis, and induction of apoptosis (Baskar et al., 2012; Guo and Xu, 2005). A line of experimental evidence supports that dietary phytosterols can diminish the cancer risk by 20% (Ramprasath and Awad, 2015; Suttiarporn et al., 2015), in consequence of modulating immune functions, sterol biosynthesis and hormone-dependent endocrine tumor growth (Awad et al., 2004; Bouic, 2001; Bouic et al., 1996; Moreno, 2003). Like terrestrial-origin phytosterols, algal phytosterols also have anti-cancer activity. For instance, fucosterol isolated from the brown alga *Sargassum carpophyllum*, exhibits cytotoxicity against leukemia cells with IC_{50} values of 0.7 μg ml^{-1} (Tang et al., 2002). Fucosterol from *Sargassum thunbergii* also shows cytotoxicity against melanoma and colon cancer lines (Kim et al., 2009). Likewise, fucosterol purified from the hexane fraction of *Sargassum angustifolium* exhibits cytotoxic activity against breast and colon cancer cell lines with a respective IC_{50} of 27.94 ± 9.3 and 70.41 ± 7.5 μg ml^{-1} (Khanavi et al., 2012). In breast cancer cell lines, fucosterol extracted from similar species, i.e., *Sargassum* spp, also shows antitumor activities (Ayyad et al., 2011). Another study reported an antiproliferative effect on breast cancer and cervical cancer cell lines of fucosterol isolated from the hexane fraction of *D. ciliolate* (Caamal-Fuentes et al., 2014). In a combined approach, fucosterol also shows synergistic anticancer actions with 5-fluorouracil (5-Fu) in 2D and 3D colon culture cell lines, where this approach reduces the side effects in healthy cells, enhancing anti-invasive and cytotoxic actions of 5-Fu in colon cancer cell lines (Ramos et al., 2019).

A putative antiproliferative or antitumor mechanism involves fucosterol-mediated induction of apoptosis and cell cycles arrests by increasing expression of cytochrome c (cyt-c), Fas, Fas ligand (FasL), and Fadd, activating Caspase-9 and Caspase-3, and reducing matrix metalloproteinase (MMP) in leukemia cell lines (Ji et al., 2014, 2013). Furthermore, fucosterol inhibits the PI3K/Akt/ mTOR signaling pathway in the cervical cancer cell line (Jiang et al., 2018). Also, fucosterol decreases the expression of B-cell lymphoma 2 (Bcl-2), while increasing expression of Bcl-2 Associated X (Bax), cleaved caspase-3, cell division cycle protein 2 (Cdc2/Cdk1), Cyclin A, and Cyclin B1, which are the negative regulators of cell cycle progression, therefore, confirms G_2/M cell cycle arrest in the lung cancer cell lines (Mao et al., 2019). These evidence, thus, suggests that fucosterol targets Raf/MEK/ERK signaling pathway to induce apoptosis and cell cycle arrests and inhibit tumorigenesis in the Xenografted mice model.

Algal sterols as hepatoprotectant

The liver is considered as an essential organ of vertebrates that accomplishes multiple biological functions such as self-regeneration, detoxification by excreting various metabolites, digestion by producing bile, metabolism, storage of glucose, vitamins, mineral, and protection by synthesizing coagulation enzymes (Ilyas et al., 2016). Liver injury leads to acute liver failure, whose primary causal factors include viral infections, drugs, food additives, and alcohol (Liberal et al., 2013).

Oxidative stress is known to be crucially implicated in the pathobiology of several chronic liver diseases, including hepatocellular carcinoma, viral and alcoholic hepatitis, and nonalcoholic steatosis (Loguercio and Federico, 2003; Takaki and Yamamoto, 2015). Toxicant such as t-BHP- and tacrine-induced oxidative stress leads to the accumulation of ROS and deplete the glutathione (GSH) that contributes to the leakage of excessive serum transaminases such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) into blood serum, which is an indicator of liver disease (Choi et al., 2015). On the contrary, inflammation in the liver is a type of reaction where the liver tissues deliver a continuous stimulus, which can be both positive and negative, in response to extrinsic and intrinsic factors (Saha et al., 2019; Liu et al., 2017). The NF-κB signaling pathway, a classical inflammatory pathway, regulates the expression of genes inducing a plethora of biological processes, such as innate and adaptive immunity, inflammation, and stress responses (Liu et al., 2017). PPARs are nuclear receptors that function as transcription factors and regulate gene expression by binding retinoid X receptors (Tyagi et al., 2011; Liu et al., 2017). The inflammatory factors, therefore, might comprise significant markers to assess the hepatocyte status. However, as a potential hepatoprotectant, fucosterol furnishes a wide range of protective strategies against toxicants as well as chronic inflammation-induced hepatic damage.

Fucosterol has been shown to attenuate increased activities of serum transaminases (AST and ALT) in carbon tetrachloride (CCl_4)-induced hepatic damage in rats by increasing the hepatic cytosolic antioxidant enzymes such as SOD, CAT, and GPx1 (Lee et al., 2003). Choi and co-investigators reported that t-BHP- and tacrine-induced increase in intracellular ROS and decrease in glutathione levels in HepG2 cells were successfully reversed when the cultures were pretreated with fucosterol (25–100 μm) (Choi et al., 2015). Authors also suggest that fucosterol-mediated elevation of GSH level, in turn, might contribute to the decline in ROS generation. The hepatoprotective effect of fucosterol was further supported by the reduction of serum ALT and AST levels in tacrine-treated mice. These results indicate that the hepatoprotective function of fucosterol might be, in part, attributed to the antioxidant activity of fucosterol via the increase of antioxidant capacity in hepatocytes. Fucosterol may, therefore, be an effective hepatoprotective agent against toxic insult as well as oxidative stress-induced hepatic damage. Moreover, in an experimental model of concanavalin A (ConA)-induced acute liver injury, fucosterol given orally at doses of 25–100 mg/kg attenuates the elevation of serum hepatic enzyme (ALT and AST) activities by inhibiting necrosis and apoptosis in a process mediated by PPARγ activation and NF-κB inhibition, which reduces the release of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β (Mo et al., 2018). Fucosterol also suppresses apoptosis and autophagy by upregulating Bcl-2 (an anti-apoptotic protein) via PPARγ, which reduces the functional Bax and Beclin-1. Overall, fucosterol alleviates ConA-induced acute liver injury through stimulating antioxidant and anti-inflammatory mechanisms via the P38 MAPK/PPARγ/NF-κB pathway, indicating a potentiality of fucosterol as a promising hepatoprotective agent.

Algal sterols as antimicrobials (antibacterials, antifungals, and antiprotozoals)

Antimicrobial activates of fucosterol have also been reported against various pathogens such as bacteria, protozoa and fungi. Kumar and his team have isolated two new steroids 3,6,17-trihydroxy-stigmasta-4,7,24(28)-triene and 14,15,18,20-diepoxyturbinarin, along with fucosterol from the cyclohexane extract of a brown alga *Turbinaria conoides* (Kumar et al., 2010). The first two sterols showed moderate antibacterial activity against two bacteria- *S. aureus* and *E. coli*- and inhibits the growth of *C. albicans* and *Aspergillus niger*. 14,15,18,20-diepoxyturbinarin has shown the most potent inhibition against *A. niger*, suggesting that this sterol might have clinical value as a novel antifungal agent. Fuscosterol isolated from *Sargassum longifolium*, an abundant brown alga from the Gulf of Mannar region, south India has been evaluated against several pathogenic bacteria (Rajendran et al., 2013). Fucosterol exhibits antibacterial activity against the human pathogen (*Vibrio parahaemolyticus*) and fish pathogen (*V. vulnificus, V. harveyii* and *Aeromonas hydrophila*). However, there is no activity by fucosterol against *Pseudomonas fluorescens*. Overall, fucosterol could be an effective antibacterial agent. Fucosterol has also been detected as a major sterol in lipophilic fraction (dichloromethane extract) of *Bifurcaria bifurcata*, which has shown antibacterial activity against *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa* (Santos et al., 2017), indicating that this sterol could be effective against both gram positive and negative microorganisms.

Antifungal properties of fucosterol against *Fusarium culmorum* have been investigated by Tyśkiewicz and colleagues who reported that fucosterol at 1.0% concentration fully inhibits the germination of macroconidia (Tyśkiewicz et al., 2019). Moreover, macroconidia were presented with a shorter length and structural degradation when they were encountered with low doses (0.05–0.2%) of fucosterol. Authors suggest that like other sterols, fucosterol might contribute to the modification of lipid bilayer regarding both structural and thermodynamic properties, causing liquid-ordered phase separation.

Fucosterol isolated from a common brown alga on the southeast coast of India, *Sargassum linearifolium* was investigated for its antimalarial activity against the 3D7 chloroquine-sensitive *Plasmodium falciparum* strain. Fucosterol exhibits higher antiplasmodial activity (IC_{50} value 7.48 μg ml^{-1}) against the *P. falciparum* as compared to chloroquine (IC_{50} value 12.81 μg ml^{-1}), indicating that fucosterol could be a potent antimalarial against (Perumal et al., 2018). This study also suggested a similar mechanism of antiplasmodial activity of fucosterol and chloroquine, which inhibits the schizont stage of *P. falciparum* during the intra-erythrocyte asexual development. The binding of fucosterol (at the schizont stage of *P. falciparum*) inhibits *P. falciparum*L-lactate dehydrogenase (PfLDH) through particular interaction with Tyr85 & Glu122 residues by exhibiting significant binding energy resulting in an alteration of binding site/conformation change (Nabuurs et al., 2007). In another study, fucosterol isolated from Patagonia Argentina's coastal brown macroalga, *Lessonia vadosa* Searles, was evaluated for antiprotozoal activity against trypanosomatid parasites such as *Leishmania*, the causal agent of leishmaniasis (Becerra et al., 2015). Herein, fucosterol shows potent activity against the intracellular amastigote, the disease-associated form of the parasite (IC_{50} < 10 μM) compared to the extracellular promastigote (IC_{50} > 45 μM). Overall, fucosterol may represent a novel lead scaffold for antileishmanial drug development, and thus its pharmacological efficacy in a murine model of leishmaniasis deserves further evaluation.

Algal sterols as photoprotectants and dermoprotectants

Skin is the largest human organ that is engaged in many vital bodily functions, including protection of the internal organs, the first line of defense against biotic (pathogens) and abiotic (UV-irradiation) insults, and synthesis of vitamin D, among many other (Sveikata et al., 2011). However, this precious organ naturally ages with time, termed as skin aging, which is caused by extrinsic damages through the heatwave, sunlight, smoking, and environmental pollution, and intrinsic damage due to chronological aging (Zhang and Duan, 2018). Exposure to ultraviolet (UV) irradiation leads to skin photoaging through an intrinsic mechanism that involves the overexpression of MMP and depletion of the extracellular matrix. The activation of MMP is associated with the increased production of IL-6 and type I procollagen, a process that, in turn, is under the regulation of transforming growth factor-β1 (TGF-β1). Also, the activation of activator protein-1 (AP-1) further induces MMP-1 production and reduces type I procollagen secretion. On the other hand, hypoxia deserves a major consideration in intrinsic skin damage (Barcelos et al., 2009). Cobalt chloride ($CoCl_2$), as an inducer of chemical hypoxia in an experimental setup, decreases cell viability, and increased the mRNA of TNF-α, IL-6 and IL-1β and overexpression of p-Akt, p-PI3K and Hypoxia-inducible factor 1-alpha (HIF-1α), leading to cytotoxicity and skin damage (Sun et al., 2015). Therefore, natural products with antioxidant and anti-inflammatory potentials have a therapeutic promise against skin damage (Binic et al., 2013). Having antioxidant and anti-inflammatory roles, fucosterol is also a potential candidate for anti-aging and anti-damaging effects on the skin. For instance, in UV-irradiated HaCaT cells, fucosterol attenuates expression of MMP and inflammatory cytokines through suppressing ROS- induced activation of MAPKs, and increases type-I procollagen synthesis and antioxidant enzyme expression, and subsequently enhances skin protection (Kim et al., 2013). Moreover, Hwang and colleagues also reported an anti-photodamage property of fucosterol purified from the brown alga *Hizikia fusiformis*, involving similar mechanisms in which there is an increased expression of MMP-1, IL-6, p-c-Jun, and p-c-Fos, and increased production of type I procollagen and TGF-β1 in UVB-irradiated normal human dermal fibroblasts (Hwang et al., 2014). Fucosterol also protects against $CoCl_2$-induced hypoxic damage to keratinocytes (HaCaT cells) through antioxidation and anti-inflammation, which is mediated by suppressed expression of IL-6, IL-1β and TNF-α and phosphorylation of PI3K and Akt and accumulation of HIF-1α (Sun et al., 2015). These findings lead us to conclude that fucosterol might be a potential botanical candidate in protecting skin against UV irradiation and hypoxia-induced damage.

Skin is also vulnerable to direct exposure to polluted air, which contains particulate matter (PM). The effects of particulate matter are primarily due to PM-induced oxidative stress and inflammation (Kim et al., 2016). Fernando et al. reported that PM induces an imbalance in ROS generation, leaving cells at risk. Moreover, PM treatment increases the collagenases, elastases, PGE2, COX-2, TNF-α, IL-1β and IL-6, and increases the nuclear translocation of NF-κB-p65 and phosphorylation of p38 MAPK, ERK1/2, and JNK (Fernando et al., 2019a). Increased activity of proteases, such as collagenases and elastases, degrades connective tissues and results in skin wrinkling. Fucosterol also dose-dependently attenuates the detrimental effects in keratinocytes by reducing ROS production, the activity of collagenases, elastases, PGE2, COX-2 TNF-α, IL- 1β and IL-6, the nuclear translocation of NF-κB-p65 and phosphorylation of p38 MAPK, Erk1/2, and JNK, restoring the conditions near to physiological levels and suggesting its application in rejuvenating cosmeceuticals (Fernando et al., 2019b).

Algal sterols as bone regenerative and anti-osteoporotic agent

Fucosterol has shown bone regenerative potential in rat models of ovariectomy-induced osteoporosis. Lee and colleagues have reported that fucosterol promotes osteoblast proliferation, alkaline phosphatase activity, and mineralization, and decreases osteoclast differentiation in MG63 cells (Lee et al., 2014b). Moreover, in ovariectomized (OVX) rats given with fucosterol, there is a reduction in body weight and an increase in femur bone mineral density, which is characterized by increased bone volume/total volume and decreased trabecular separation. As for serum biomarkers of bone formation and resorption,

fucosterol triples osteocalcin and reduces carboxy-terminal collagen crosslinks (CTx) level. Together, fucosterol has the dual potentials to stimulate osteogenesis and suppress osteoclasts differentiation to reduce bone resorption, suggesting its application as estrogen replacement therapy in postmenopausal osteoporosis.

Algal sterol as an immunostimulant

Nitric oxide (NO) produced by iNOS regulates the adaptive immune response, linking innate and adaptive immunity (García-Ortiz and Serrador, 2018). NO also functions as a vasodilator and neurotransmitter in the cardiovascular and nervous systems, respectively (Calabrese et al., 2007). Fucosterol, an active component of enzyme-modified *H. fusiforme* extracts, elicits NO synthesis with no cytotoxicity in RAW 264.7 murine macrophages, contributing immunomodulatory action of this functional extract (Park et al., 2017). Like other plant sterols, algae-derived sterols might also influence the immune system (Plat et al., 2019).

Algal sterols against pulmonary tissue damage

Algal sterols, particularly, fucosterol have shown a protective role against inflammation-induced injury of lung tissue. For example, fucosterol attenuates acute lung injury induced by LPS stimulation in mice through suppressing generation of proinflammatory mediators, such as TNF- α, IL-6 and IL-1β. Moreover, in LPS-stimulated alveolar macrophages, fucosterol attenuates cellular injury through inhibiting NF-κB activation and TNF-α, IL-6, and IL-1β production (Li et al., 2015). Fucosterol also protects against air pollutant-induced pulmonary tissue damage. Particulate matter (PM) of pollutant air may induce inflammatory responses and oxidative stress in pulmonary tissue causing a cellular injury that could be ameliorated through fucosterol application (Fernando et al., 2019a). Fucosterol minimizes PM-induced inflammatory response by lowering the nuclear translocation of P65 and P50 and inhibiting the phosphorylation of p38 MAPK, ERK1/2, and JNK, and the levels of COX-2, PGE2, TNF-α and IL-6 and attenuates PM-induced oxidative stress by lowering intracellular ROS levels and the production of antioxidant enzymes such as SOD, CAT, and HO-1, suggesting fucosterol-based inhaler development against PM-induced pulmonary tissue inflammation.

Future perspectives

The current review highlights that the pharmacological importance of algae-based phytosterols is by no means less than other bioactive secondary metabolites, even than phytosterols of terrestrial origin (Fig. 2). Although algal sterols exhibit a plethora of health benefits, there is still a scarcity of pharmacological investigations in some systemic aspects. For example, despite the sufficient scientific evidence on anti-Alzheimer's potentials of algal sterol, no study, so far, investigates the neuroprotective function of algal sterols against toxic insults that induce other neurological disorders, including Parkinson's and Huntington's diseases as well as ischemic stroke. Moreover, algal sterols are yet to be evaluated for their efficacy against kidney aging, in which oxidative stress is known to be implicated. Having antioxidant potential, fucosterol might play a significant role in preserving kidney function. Still, in some other physiological systems such as the digestive system, sterol's effects need to be evaluated. Pharmacokinetics information is also inadequate and needs to be updated using appropriate experimental models.

Moreover, an extensive study on structure-activity relationships using derivatives from structural modification of algal sterols might offer more potent leads with novel pharmacological activity. In the regions where seaweeds are freely available, they as a dietary menu are by no means less popular than conventional plant foods rich in phytosterols, indicating that this marine source of phytosterols is safe as food and their sterols are as safe as plant sterols. However, still, the untoward consequence, if any, of algal phytosterols needs to be investigated more in detail in an appropriate animal model. Almost every data on the health benefits of algal sterols originates from *in vitro* experiments. The *in vivo* studies using animal models as well as human subjects are, therefore, crucial to further characterize the beneficial roles of sterols as well as to recommend for future clinical use. Beyond all these concerns in human health benefits, uncovering the biological mystery why a particular phytosterol is highly accumulated in specific algal class under a defined living condition while others lack or contain a very little might shed light on some of the essential health effects of algal sterols.

Conclusion

This review covering all the revealed pharmacological effects of algae-derived phytosterols with their putative molecular mechanisms helps to understand the substantial health benefits of sterols as well as sterol-based functional food formulation, particularly for chronic diseases. Additionally, future drug designing through utilizing chemical diversity and pharmacokinetics of marine algal sterols will make a new window for developing novel therapeutics. The possible advantages of phytosterols as a drug lie on their multitarget-oriented pharmacological effects that include antioxidation, anti-inflammation, cholesterol homeostasis, anti-amyloidogenic, anticholinesterase, antilipidemic, and anti-proliferative rendering these underexplored secondary metabolites highly attractive to manage chronic human diseases.

CRediT authorship contribution statement

Md. Abdul Hannan: Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Abdullah Al Mamun Sohag:** Data curation, Writing - original draft. **Raju Dash:** Visualization, Writing - original draft. **Md. Nazmul Haque:** Writing - original draft, Writing - review & editing. **Md. Mohibbullah:** Writing - original draft, Writing - review & editing. **Diyah Fatimah Oktaviani:** Writing - original draft. **Md. Tahmeed Hossain:** Writing - original draft. **Ho Jin Choi:** Writing - original draft. **Il Soo Moon:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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