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Review

Seaweeds-derived compounds modulating effects on signal transduction pathways: A systematic review

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Abbreviations: 184B5, normal human breast cell line; 3T3-L1, mouse adipose embryonic fibroblast cell line; 5637, human bladder cancer cell line; 5-HT, 5-hydroxytryptamine; 5HHMF, 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone; A498, human renal cell carcinoma; A549, human lung cancer cell line; ABTS, 2,2′- azinobis[3-ethylbenzothiazoline-6-sulphonic acid]; ACC, acetyl-CoA carboxylase; Ace, acetone; ACh, acetylcholine; AChE, acetylcholinesterase; AIF, apoptosis-inducing factor; AKT, protein kinase B; AML-12, normal mouse hepatocyte cells; AMPK, AMP-activated protein kinase; AOM, azoxymethane; AP-1, activator protein-1; apo E-/-, apolipoprotein E knockout; ARE, antioxidant-responsive element; B16F10, murine melanoma cell line from a C57BL/6J mouse; BALB/3T3, mouse embryonic fibroblast cell line; Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma 2; BMDC, bone marrow derived cells; BMDM, bone marrow derived macrophages; BMM, bone marrow macrophage; BuChE, butyrylcholinesterase; BV-2, murine microglial cells; BXPC-3, human pancreatic cell line; cdc, cell division cycle protein; CDK, cyclin-dependent kinase; C/EBPα, CCATT/enhancer-binding protein alpha; CLP, cecal ligation and puncture; c-myc, protooncogen; COX-2, cyclooxygenase 2; CXCL-1, C-X-C motif chemokine ligand 1; CXCL-2, C-X-C motif chemokine ligand 2; CXCL-10, interferon gamma-induced protein 10; DDSD, spatane diterpenoid, 5(R), 19-diacetoxy-15,18(R and S), dihydro spata-13, 16(E)-diene; DHA, docosahexaenoic acid; DMARDs, disease-modifying anti-rheumatic drugs; DMBA, 7,12-dimethylbenz [a]anthracene; DNMT, DNA methyltransferase; DU145, human prostate cancer cell line; EB1, 6-6 bieckol; EB5, pholorofucofuroeckol- A; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ELT-3, Eker rat leiomyoma tumor-derived cells; eNOS, endothelial nitric-oxide synthase; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; EtOAc, ethyl acetate; EtOH, Ethanol; FAK, focal adhesion kinase; FAS, fatty acid synthase; GADDI53, growth arrest and DNA-damage-inducible human gene; GRP78, glucose-regulated protein; GSH, glutathione; GSK-3β, glycogen synthase kinase 3 beta; GST, glutathione S-transferase; H_2O_2, hydrogen peroxide; HaCaT, human skin keratinocytes; HbA1C, glycosylated haemoglobin; HCAEC, human coronary artery endothelial cell; HCC, hepatocellular carcinoma; HDPC, human dental pulp cells; Hek-293, human embryonic kidney cell line; HeLa, human epithelial cervix cancer cell line; HepG2, human liver cancer cell line; HepG2-C8, human liver cancer cell line transfected with the pARE-TI-luciferase construct; HIF, hypoxia-inducible factor; HL60, acute myeloid leukemia cell line; HL-7702, human normal liver cell line; HO-1, heme oxygenase-1; HPBMCs, human peripheral blood mononuclear cells; HS-Sultan, human lymphoma cell line; HSC-T6, immortalized rat hepatic stellate cells; HT22, hippocampal neuronal cells line; HTC-116, human colorectal carcinoma cell line initiated from an adult male; hTERT, human telomerase reverse transcriptase; HTLV-1, human T-cell leukemia virus type 1; HuCCA-1, human cholangiocarcinoma cell line; HUtSMC, human uterine smooth muscle cells; HUVECs, human umbilical vein endothelial cells; HUVECtert, telomerase reverse transcriptase immortalized human umbilical vein endothelial cells; HWBC, human white blood cells; Hx, hexane; ICAM-1, intercellular adhesion molecule 1; IEC-6, rat small intestine epithelial cells; IFN-γ, interferon gamma; IGF-IR, insulin like growth factor-I receptor; IKK-IκB, IκB kinase; IL, interleukin; IL-10, interleukin 10; IL-1β, interleukin 1beta; IL-6, interleukin 6; IMP, human myeloma cell line; iNOS, inducible nitric oxide synthase; IRF3, interferon regulatory factor 3; JB6 Cl 41, mouse epidermal cell line; JB6 P+, mouse epidermal cell line; JNK, c Jun NH2-terminal kinase; K562, lymphoblast from acute myeloid leukemia cell line; KG1a, macrophage from acute myeloid leukemia cell line; L929, murine fibroblast cell line; LPS, lipopolysaccharide; LX-2, human hepatic stellate cells; MAO, monoamine oxidase; MAO-B, monoamine oxidase B; MAPK, mitogen-activated protein kinase; MCF-7, Human breast adenocarcinoma cell line; MCP-1, monocyte chemoattractant protein-1; MDA-MB-231, human breast cancer cell line; MDC/CCL22, macrophage-derived chemokine; MeCl, dichloromethane; MEK1, MAPK kinase 1; MEKK1, MAPK kinase kinase 1; MeOH, methanol; MiaPaCa-2, human pancreatic cancer cell line; MMP, mitochondrial membrane potential; MMP-1, matrix metalloproteinase 1; MMP-9, matrix metalloproteinase-9; MOLT4, human T-cell lymphoma cell line; MPO, myeloperoxidase; mTOR, mammalian target of rapamycin; NB-4, human acute promyelocytic leukemia cell line; NF-κB, nuclear factor kappa B; NIH/3T3, mouse embryonic fibroblast cell line; NO, nitric oxide; NQO1, NADPH quinone oxidoreductase 1; Nrf2 or NFE2L2, nuclear factor erythroid-2-related factor-2; NASAIDs, non-steroidal anti-inflammatory drugs; p53, tumor protein p53; PAD, peripheral arterial disease; PAI-1, plasminogen activator inhibitor-1; Panc-1, human pancreatic cell line; Panc-3.27, human pancreatic cell line; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; PPY1, peptide from *P. Yezoensis*; RAW264.7, murine macrophage cells; ROS, reactive oxygen species; SH-SY5Y, human neuroblastoma cell line; SIRT, sirtuin 1; SKBR-3, breast cancer cells; SKH-1, hairless mouse skin model; α-SMA, alpha-smooth muscle actin; SMMC-7721, human hepatocellular carcinoma cell line; SREBP-1c, sterol regulatory element binding protein-1c; Sp1, specificity protein 1; STAT1, signal transducer and activator of transcription 1; T24, human urinary bladder cancer cell line; TBK1, serine/threonine-protein kinase; TGF-β, transforming growth factor beta; TLR4, toll-like receptor 4; TMJ, temporomandibular joint; TNBS, trinitrobenzenesulfonic acid; TNF-α, tumor necrosis factor alpha; TPA, 12-otetradecanoylphorbol-13-acetate; TPH-1, human monocytic cell line derived from an acute monocytic leukemia; U251, human glioblastoma cell line; U87, human glioblastoma cell line; U937, human promonocytic cell line; UCP-1, uncoupling protein 1; UVB, ultraviolet B; V79-4, chinese hamster lung fibroblast cell line; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; WEHI-3, BALB/c mouse with transplanted myelomonocytic leukemia.

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ABSTRACT

Background: Recently, the study of marine natural products has gained interest due to their relevant biological activities. Specially, seaweeds produce bioactive compounds that could act as modulators of cell signaling pathways involved in a plethora of diseases. Thereby, the description of the molecular mechanisms by which seaweeds elicit its biological functions will certainly pave the way to the pharmacological development of drugs.
Aim: This review describes the molecular mechanisms by which seaweeds act and its possible utilization in the design of new drugs.
Methods: This review was conducted according to the PRISMA-P guidelines for systematic reviews. Two independent authors searched into four different databases using combinations of keywords. Two more authors selected the articles following the eligibility criteria. Information extraction was conducted by two separated authors and entered into spreadsheets. Methodological quality and risk of bias were determined applying a 12-question Risk of Bias criteria tool.
Results and discussion: We found 2360 articles (SCOPUS: 998; PubMed: 678; Wiley: 645 and EBSCO: 39) using the established keywords, of which 113 articles fit the inclusion criteria and were included in the review. This work comprises studies in cell lines, and animal models, any clinical trial was excluded. The articles were published from 2005 up to March 31st 2018. The biggest amount of articles was published in 2017. Furthermore, the seaweeds tested in the studies were collected in 15 countries, mainly in Eastern countries. We found that the main modulated signaling pathways by seaweeds-derivate extracts and compounds were: L-Arginine/NO, TNF-α, MAPKs, PI3K/AKT/GSK, mTOR, NF-κB, extrinsic and intrinsic apoptosis, cell cycle, MMPs and Nrf2. Finally, the articles we analyzed showed moderate risk of bias in almost all the parameters evaluated. However, the studies fail to describe the place and characteristics of sample collection, the sample size, and the blindness of the experimental design.
Conclusion: In this review we identified and summarized relevant information related to seaweed-isolated compounds and extracts having biological activity; their role in different signal pathways to better understand their potential to further development of cures for cancer, diabetes, and inflammation-related diseases.

Introduction

According to the World Health Organization reports (WHO, 2018), cancer and diabetes are two of the main health problems affecting an important number of people worldwide. It has been estimated that cancer was responsible for 9.6 million deaths in 2018; while population with diabetes increased from 108 million in 1980 to 422 million in 2014. Recently, it has been proposed that continuous oxidative stress can lead to chronic inflammation, this, in turn, could mediate chronic diseases such as cancer, diabetes, and many others (Reuter et al., 2010). For instance, cancer initiation and progression has been related to oxidative stress by mechanisms including augmentation of DNA mutations and/or DNA damage, and cell proliferation (Visconti and Grieco, 2009). On the other hand, inflammation leads to the arrival of mast cells and leukocytes at the damaged site, increasing the oxygen uptake, and consequently an increased release and accumulation of reactive oxygen species (ROS). In addition, inflammatory cells also produce mediators, such as the metabolites of arachidonic acid, cytokines, and chemokines, which act by recruiting more inflammatory cells to the site of damage and enhance ROS production (Coussens and Werb, 2002; Hussain et al., 2003).

Currently, no effective treatments for cancer and diabetes are available although the use of natural products with anti-cancer and anti-diabetes activities has been proposed. Seaweeds have important medicinal applications due to their relevant biological activities. Worldwide, traditional medicine systems have utilized numerous seaweed species for the treatment of certain diseases, *e.g., Sargassum genus* contains around 400 species and has been used for more than 2000 years in Traditional Chinese Medicine (Xiao et al., 2012) and Japanese folk medicine (Kodama et al., 1991). Other eastern societies have also applied algae species in the treatment of diseases (Yende et al., 2014). It is noteworthy that Asian communities include the consumption of seaweeds, which represents an important dietary component.

In general, seaweeds are plants that live in marine or brackish water (Dhargalkar and Kavlekar, 2004). They represent an extensive group of multicellular photoautotrophic organisms that contain chlorophyll for oxygenic photosynthesis. Marine algae have developed adaptive osmoregulation mechanisms to maintain their internal osmotic pressure avoiding turgidity effects from fluctuations in the salinity of their habitats (Bocanegra et al., 2009). Macroalgae have been classified into three categories: Chlorophyta (green algae), Rhodophyta (red algae) and Ochrophyta-Phaeophyceae (brown algae) (Gutierrez-Rodriguez et al., 2018) and it has been demonstrated their involvement in the structuring and maintenance of the marine ecosystems, introducing important nursery spots for a variety of marine species, and also for humans.

In recent years, the study of the cellular activity of compounds and extracts obtained from algae has gained interest, as they produce complex metabolites (Carvalho and Pereira, 2014). Although some of these compounds (*e.g.,* carragenans and alginates) have been used for decades within the food and pharmaceutical industries (Kilinç et al.,

2013; Laurienzo, 2010), little is known about their clinical use. Metabolites from seaweeds could be useful for the development of new drugs, since they target several intracellular molecules that modify signaling pathways. Despite the wide use of seaweeds in traditional medicine and their well-known biological actions, the molecular mechanisms triggered by algae are starting to be elucidated. Herein we show some signal pathways including the role of seaweed-isolated compounds and extracts play in these. Our aim is that this review can contribute to a better understanding of the molecular mechanisms, providing future keys to develop new drugs to alleviate cancer, diabetes, and inflammation-related diseases that affect to an important amount of people.

Methods

This systematic review protocol was design according to the PRISMA-P guidelines for reporting systematic reviews (Moher et al., 2015) (Fig. 1).

Eligibility criteria (inclusion and exclusion criteria)

All articles with full-text available that describe the signaling pathway or molecules that participate in cellular signaling were included in the review. Articles written in English, Spanish, Portuguese, and French were considered, as well as using animal models and cell lines. Also, we selected articles that describe the activity of extracts as well as compounds isolated from green, red and brown seaweeds. The articles were discarded with the following criteria: fail to describe at least one molecule of the signaling pathway, lack of a biological activity, no evidence of the mechanisms that mediate the described activity, and the absence of biological model to characterize the biological activity. When unclear or unreported data were detected in the studies, efforts were made to contact the authors.

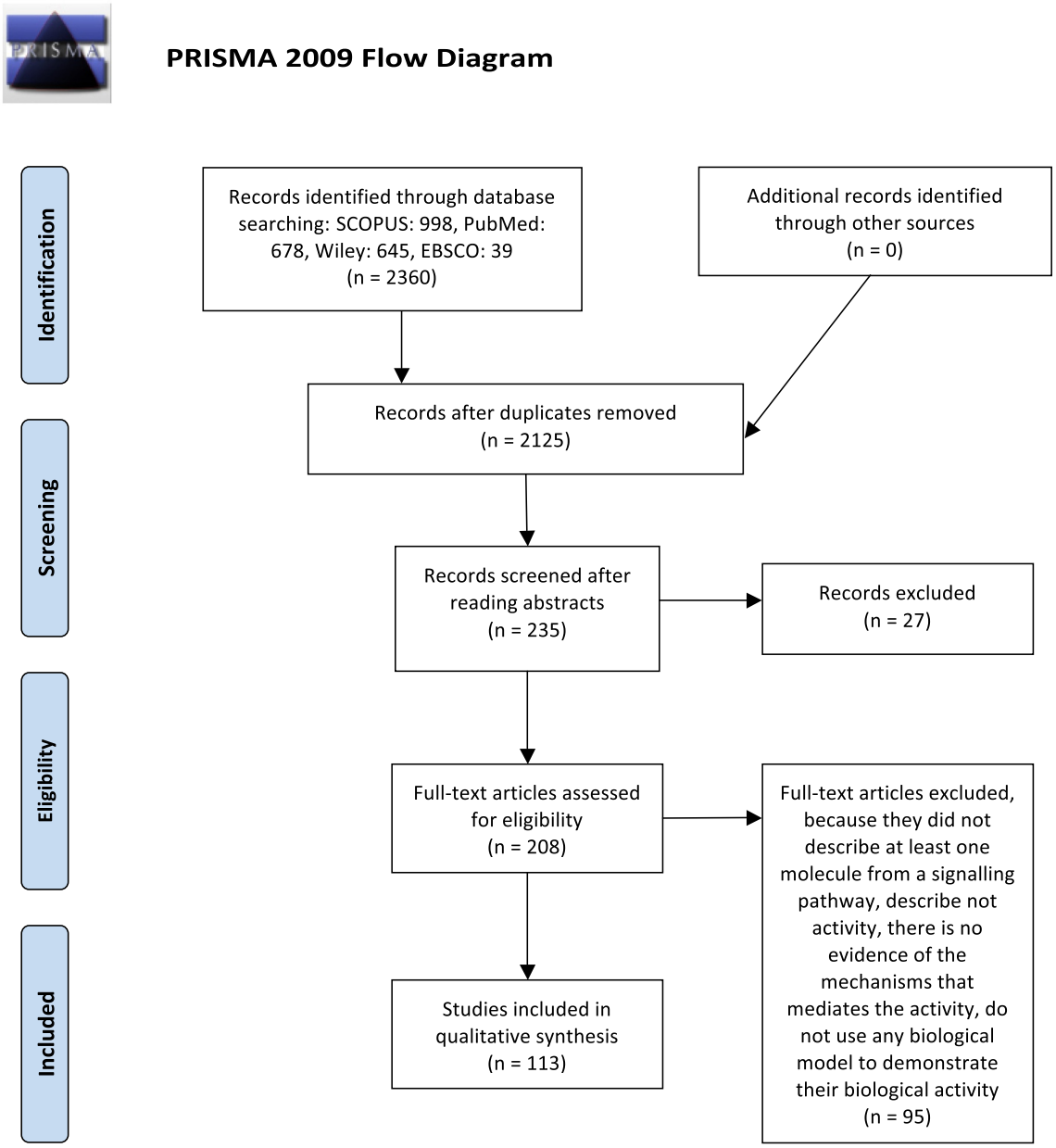

Fig. 1. PRISMA 2009 Flow Diagram of the structured literature review.

Information sources, search strategies and data extraction

Literature was searched since inception up to March 31st, 2018; in the following databases: PubMed, Wiley, SCOPUS and EBSCO; using the keywords and search terms (individually or combined): seaweeds, algae, anti-cancer, cancer, diabetes, anti-diabetic, hypoglycemic, anti-hyperglycemic, anti-oxidant, anti-inflammatory, inflammation, mechanisms, molecular, signaling, oxidant stress. Efforts were made to include grey literature. For each topic (anti-cancer, anti-diabetes, anti-inflammation and anti-oxidant) two authors searched the articles independently by reading the titles and abstracts of the studies identified in the electronic searches. They removed those studies that definitely did not accomplish the inclusion criteria.

Then, two more authors independently reviewed the full-texts and made the selection of articles to be included in the systematic review according to the eligibility criteria. In case of disagreements, they were resolved by discussion of the item, or if necessary a third review author was consulted to help in the final decision. The EndNote reference manager was used to eliminate the duplicated articles. Extraction of the information was conducted independently by two authors, and entered into spreadsheets, containing the following data items: first author's name, year of publication, seaweed's species, compound(s)/extract(s) tested, country of collection; biological activity, animal/cell model used, mechanism(s) reported.

Methodological quality and assessment of the risk of bias

The risk of bias, design and methodological quality were assessed using a 12 check point list adapted from Hooijmans et al. (2014), Siqueira-Lima et al. (2017) and OHAT risk of bias tool (OHAT, 2015) (Fig. 4). Based on these criteria, a tool to assess the main aspects contributing to the quality of the study was developed. Different parameters, such as source of seaweeds/compounds, authentication of species, appropriated design and methods to assess the hypothesis, among others were critically revised. When pre-clinical studies (using animal models) were reported we also evaluated the allocation and random assignment, blinded outcome, administration route and baseline characteristics (Fig. 4). For each question of the RoB tool, we rank the articles into fourth categories: Yes, No, Not clear and Not applicable, and reported the percentage of each category. Two authors analyzed each category independently.

Quantitative analysis of the signaling pathways

We quantitative analyzed the signaling pathways described by counting the number of times that each molecular pathway was described/mentioned in the articles. When multiples proteins were reported in the articles, we use the following criteria to name each pathway: cell cycle: cyclins, cdks, and proto-oncogenes; MAPK: ERK1/2, p38, JNK, p90RSK, c-Jun, AP-1; Apoptosis Int/Ext: Bcl-xl, Bcl-2, Bak, Caspases; NF-κB: p65, RelA, IκB; L-Arginine: iNOS, NO, ROS, COX-2, MPO, PGs. Also, we quantified the number of pathways described per article and grouped in 1, 2, 3 or >3 pathways per article.

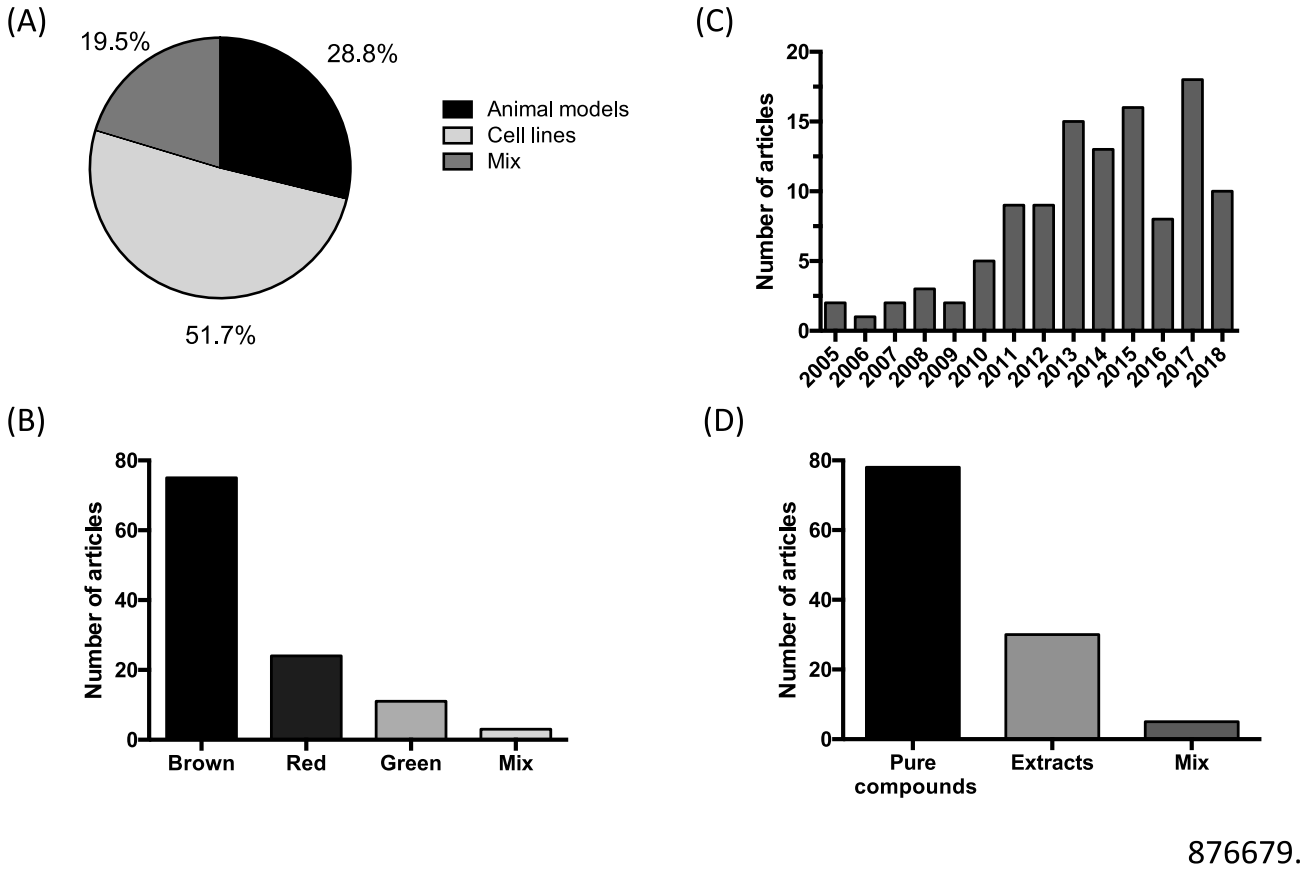

Fig. 2. Graphical distribution of qualitative aspects of the reviewed literature. The studies were classified according to the follow characteristics: (A) the model used: cell lines, animal models or both (Mix); (B) the type of seaweed analyzed: brown, red, green or using more than one seaweed (Mix); (C) the year of publication of the study; and (D) whether the authors tested pure compounds, extracts isolated from seaweeds or both (Mix). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Results and discussion

Studies description

Using the methodology described above, 2360 articles were found, 998 were identified from SCOPUS, 678 from PubMed, 645 from Wiley, and 39 from EBSCO. After the removal of duplicates and reviews, we screened 235 abstracts, 208 full-texts were read, and 113 articles fitted the eligibility criteria and were included in this review. In Fig. 1, we schematize the protocol of the searches and selection of articles using the PRISMA flow chart. In the final list of articles included in this review, 61 articles (51,7%) were *in vitro* studies in which cell lines were used, 35 articles (28,8%) used animal models, whereas in 17 articles (19.5%) the authors used cell lines and animal models (Mix, Fig. 2a). We did not find any clinical trial to be included in this work. Even when the searches were made since inception, the oldest articles included in this review were published in 2005 (Aisa et al., 2005; Kang et al., 2005), clearly pointing out that the description of molecules and signaling pathways modulated by seaweeds-isolated compounds and extracts is still a new area of research (Fig. 2b). Moreover, around one hundred articles were published in the last decade and the year with the highest number of publications was 2017 (18), followed by 2015 and 2013 (16 and 15 articles, respectively).

It is estimated that there are around 1800 species of brown, 6200 of red, and 1800 green macroalgae (Mouritsen, 2013). Although the red class is the most abundant, in the majority of the studies brown algae were used (Fig. 2b). This is not an unexpected result, in fact, in a review previously published by our group about the anti-cancer activity of macroalgae we reported similar data, *i.e.*, most of the research about biological activity were performed using brown seaweeds (Gutierrez-Rodriguez et al., 2018).

Moreover, we identified that in 78 studies pure compounds were used, and in 30 studies extracts from seaweeds were obtained and assessed. While other authors used both, pure compounds and crude extracts obtained from seaweeds (Fig. 2d). Even though the preference for the identification of the pure compounds that activate the molecular pathways, we decided to include the studies in which extracts from seaweeds were evaluated, as they represent the first attempt to show their biological activity. Nevertheless, the characterization of the extracts will provide information about the specific molecular targets and possible interactions among the secondary metabolites of the extracts.

We also describe the worldwide localization of the seaweeds collection, and the tendencies of distribution can be observed in the map of Fig. 3. We found that South Korea had highest number of seaweeds studies (30), followed by Brazil (15), China (8), India (6) and Japan (4). Other collection countries were: Portugal (3), Taiwan (3), Egypt (2), Ireland (2), Malaysia (2), Greece (1), Morocco (1), Thailand (1), Tunisia (1) and United States (1). Nevertheless, 31 authors reported the use of commercial seaweeds-derived compounds, and only two articles did not mention where the algae material was obtained. It is important to emphasize that, although most of the authors refer the country of collection, just few of them precise the geolocation. Moreover, they do not mention the season of the year when the algae were obtained.

Molecular pathways modulated by seaweeds

Anti-inflammatory activity

Inflammation is the cellular response produced after an injury or the invasion of pathogens to protect the organism through the activation of cellular pathways in immune cells and the production of pro-inflammation molecules, thereafter mediators must be released to defend the body. The inflammatory response is usually promoted by the

Fig. 3. Geolocation and distribution of seaweeds' collection. The illustration shows the source countries of the algae material for the studies. The gray scale designates the quantity of marine algae, that is, black indicates the highest amount of seaweed collected, conversely, light gray represents the lowest number of marine species. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Molecular targets of seaweeds that mediate the anti-inflammatory activity.

Species	Compund/Extract	Collection country	Mechanism	Model	Reference
Bryothamnion triquetrum	Lectin	Brazil	↓ MPO activity, TNF-α and IL-1β	Mouse carrageenan-induced paw edema and peritonitis	(Fontenelle et al., 2018)
Caulerpa cupressoides	Lectin	Brazil	↓ IL-1β, TNF-α, IL-6 and COX-2	Rat paw edema	(de Queiroz et al., 2015)
			↓ TNF-α and IL-1β	Rat zymosan-induced TMJ arthritis.	(da Conceicao Rivanor et al., 2014)
Caulerpa mexicana	Aqueous and MeOH extracts	Brazil	↓ IL-6, IL-12, and TNF-α	Peritoneal macrophagues	(Bitencourt et al., 2011)
Chnoospora minima	Fucoidan	Commercial*	↓ TNF-α, IL1-β, IL-6, NO, ROS, iNOS, and COX-2	RAW264.7	(Fernando et al., 2017)
Codium fragile	EtOAc, n-butanol, aqueous and MeOH extracts	South Korea	↓ COX-2, iNOS, TNF-α, PGE2, and NO	HaCaT and mouse UVB irradiation	(Lee et al., 2013)
	Aqueous extract	South Korea	↓ NF-κB, ERK1/2, p38 and JNK MAPK pathways	RAW264.7, rat paw edema	(Lee et al., 2017b)
Dictyopteris undulata	Zonarol	Japan	↓ IL-6 and TNF-α	Mouse ulcerative colitis and RAW264.7	(Yamada et al., 2014)
Digenea simplex	Polysaccharides	Brazil	↓ IL1-β and TNF-α	Mouse paw edema and peritonitis	(Pereira et al., 2014)
Ecklonia cava	Diekol	South Korea	↓iNOS, NF-κB and p38 MAPK Pathway	RAW264.7	(Choi et al., 2014)
	Polyphenol extract	South Korea	↑ AMPK and SIRT1	Mouse high fat-induced obesity	(Eo et al., 2015)
	Crude flakes extracts (residue product after polyphenol extraction)	Commercial	↓ TNF-α, IL-1, IL-6, and IL-10 expression and TLR4 signaling. ↓ TBK1, IRF3, NF-κB, ERK1/2 MAPK	RAW264.7	(Hwang et al., 2017)
	Eckol and dieckol	South Korea	↓ MDC/CCL22 production by down regulation of STAT1	HaCaT	(Kang et al., 2015b)
	Dieckol	South Korea	↓ α -SMA and TGF-β, AKT, NF-κB. ↑ caspase-3 and microRNA(miR)134 levels. ERK1/2, p38, JNK MAPK modulation	HepG2, AML-12, LX-2, and HSC-T6	(Lee et al., 2016)
	Dieckol	Commercial	↓ NF-κB and COX-2	Rat HCC	(Sadeeshkumar et al., 2017)
Ecklonia stolonifera	EtOH extract	South Korea	↓ COX-2, PGE2 TNF-α, IL-1β, IL-6, iNOS, NO, and NF-κB transcriptional activity. ↓ AKT, ERK1/2, p38 and JNK MAPKs pathways	RAW264.7	(Lee et al., 2012b)
Eisenia bicyclis	N-butanol, EtOAc, MeCl, MeOH extracts, fucosterol, phloroglucinol, and eckol derivatives	South Korea	↓ NF-κB, NO, iNOS, and COX-2	RAW264.7	(Jung et al., 2013)
	Dieckol	South Korea	↓ NO, ↑ HO-1	RAW264.7 and BV-2	(Yayeh et al., 2014)
	EB1 and EB5	Commercial	↓ NF-κB nuclear translocation, ERK1/2 and JNK phosphorylation	HDPC	(Paudel et al., 2014)
	Eckol and EtOAc-soluble extract	South Korea	↑ AKT and NF-κB	HaCaT	(Eom et al., 2017)
Fucus vesiculosus	Fucoidan	Commercial*	↓ TNF-α, IL-1β, and iNOS mRNA and protein expression, Bcl-2 expression. ↑ Bax and caspase-3	Acetaminophen-liver damage in male Sprague-Dawley rat and HL-7702	(Hong et al., 2012)
			↓ NO and COX-2. ↑ HO-1	Mouse alcohol-mediated liver damage and HepG2	(Lim et al., 2015)
Gracilaria birdiae	Sulphated polysaccharide fraction	Brazil	↓ MPO, MDA, IL-1β, TNF-α. ↑ GSH	Rat TNBS-colitis	(Brito et al., 2014)
Gracilaria caudata	Sulfated polysaccharide fraction	Brazil	↓ MPO activity, TNF-α, and IL-1β	Mouse paw edema	(Chaves et al., 2013)
Gracilaria changii	MeOH extract	Malaysia	↓ TNF-α and IL-6	U937 and rat gastric lesions	(Shu et al., 2013)
Gracilaria cornea	Sulfated polysaccharides	Brazil	↓ IL-1β, TNF-α, COX-2. ↑ HO-1	Rat paw edema	(Coura et al., 2015)
Hizikia fusiforme	5HHMF	South Korea	↓ NO and PGE2, TNF-α, IL-1β, NF-κB	RAW264.7	(Kim et al., 2014a)
	Fucosterol	South Korea	↓ HIF through PI3K/AKT pathway, ↓ IL-6, IL-1β, and TNF-α	HaCaT	(Sun et al., 2015)
Hypnea musciformis	Sulphated polysaccharide fraction	Brazil	↓l-arginine/NO pathway, MPO, IL-1β	Mouse paw edema and peritonitis	(de Brito et al., 2013)
Ishige foliacea	Octaphlorethol A (phenol compound)	South Korea	↓ MAPK and NF-κB pathways	Mouse BMDM and BMDC	(Manzoor et al., 2013)
Ishige okamurae	EtOH extract	South Korea	↓ NF-κB	RAW264.7	(Kim et al., 2009)
Laminaria japonica	Fucoidan	China	↑ IL-6 and IL-10 ↓ TNF-α, Iκβ-α, NF-κB, HMGB1	Rat myocardial injury	(Li et al., 2011)
			↓ TNF-α, IL-1β, IL-1β, CXCL-10, VCAM-1 and ICAM-1 levels. ↓ ERK1/2, p38 and JNK MAPK pathways	Rat hepatic ischemia-reperfusion injury	(Li and Ye, 2015)
Laurencia glandulifera	Neorogioltriol, diterpene and tricyclic brominated diterpenoid	Greece	↓ NF-κB, NO, COX-2, and TNF-α	Rat paw edema and RAW264.7	(Chatter et al., 2011)
Laurencia obtusa	MeOH and MeCl extracts	Tunisia	↓ TNF-α	THP-1, rat paw edema, and gastric lesions	(Lajili et al., 2016)

(*continued on next page*)

Table 1 (*continued*)

Species	Compund/Extract	Collection country	Mechanism	Model	Reference
Lithothamnion corallioides	Multimineral supplement Aquamin	Ireland	↓ TNF-α and IL-1β	Rat glial-enriched cultures from cortex	(Ryan et al., 2011)
Lithothamnion muelleri	Crude extract and polysaccharide-rich fractions	Commercial	↓ CXCL-1 and CXCL-2	Mouse arthritis	(Costa et al., 2015)
Lobophora variegata	Sulfated polysaccharides and fucans	Brazil	↓ NO and TNF-α	Rat arthritis	(Paiva et al., 2011)
	Sulfated polysaccharides	Brazil	↓ iNOS and COX-2 activities	Rat paw edema and peritonitis	(Siqueira et al., 2011)
Myagropsis myagroides	EtOH extract and sargachromenol	South Korea	↓ iNOS, COX-2, NO, PGE2, ↓ NF-κB, ERKs and JNKs MAPK pathways	BV-2	(Kim et al., 2014b)
	Fucoxanthin	South Korea	↓ NO, PGE2, iNOS, COX-2, TNF-α, IL-1β, and IL-6	RAW264.7	(Heo et al., 2010)
	EtOH extract	South Korea	↓ NO, COX-2, and PGE2	BV-2	(Kim et al., 2013)
Padina boergesenii	Triterpene	India	↓ IL-1β	A498	(Rajamani et al., 2018)
Padina tetrastromatica	Ascophyllan	India	↓ TNF-α, IL-6, PGE2	Rat paw edema	(Mohsin et al., 2013)
Palmaria palmata	Phycobiliproteins and chlorophyll	Japan	↓ NO, IL-6 and TNF-α	RAW264.7 and mouse paw edema	(Lee et al., 2017a)
Polysiphonia morrowii	3-Bromo-4,5-dihydroxybenzaldehyde	Commercial	↓ IL-6 and NF-κB	Mouse atopic dermatitis and RAW 264.7	(Kang et al., 2017)
Porphyra dioica, Palmaria palmata and Chondrus crispus	Lipid extracts	Ireland	↓ TLR, NF-κB, IL-6, IL-8	THP-1	(Robertson et al., 2015)
Porphyra haitanensis	R-phycocyanin	China	↓ IL-4 and TNF-α	Mouse immunization	(Liu et al., 2015)
Porphyridium sp.	Polysaccharides	United States of America	↓ TNF-α and VCAM-1	HCAEC	(Levy-Ontman et al., 2017)
Pyropia yezoensis	PPY1 peptide	Commercial	↓ NO, COX-2, TNF-α, and IL-1β	RAW264.7	(Lee et al., 2015)
Sargassum cristaefolium	Polysaccharide	Taiwan	↓ NO, NF-κB, ERK1/2, p38 and JNK MAPK pathways	RAW264.7	(Wu et al., 2016)
Sargassum horneri	EtOH extract	South Korea	↓ NO, iNOS, COX-2, and IL-1β	RAW264.7	(Kim et al., 2015)
	Sulfated polysaccharides	China	↓ TNF-α and NO	RAW264.7	(Wen et al., 2016)
Sargassum muticum	Apo-9-fucoxanthinone	Not mentioned	↓ NO, iNOS, COX-2, PGE2, IL-6, IL-1β, and TNF-α. NF-κB and MAPK pathways	Zebrafish larvae and RAW264.7	(Kim et al., 2018)
		South Korea	↓ NO, PGE2, and NF-κB	RAW264.7	(Yang et al., 2013a)
Sargassum siliquastrum	Isonahocol E2	South Korea	↓ IL-6, IL-8, TNF-α, MMPs, and VEGF-α ↓ ET-1 receptors and ERK1/2 phosphorylation	HaCaT	(Sah et al., 2013)
	MeOH and MeCl extracts	South Korea	↓ NF-κB, IκB-α, MAPK	RAW264.7	(Yoon et al., 2012)
Solieria filiformis	Polysaccharides	Brazil	↓ TNF-α and IL-1β	Rat TMJ	(Araújo et al., 2017)
Sphaerococcus coronopifolius	Diterpenes	Morocco	↓ IL-8 and TNF-α	HeLa, SKBR-3, MIA PaCa-2 and HUVECtert	(Salhi et al., 2018)
Turbinaria ornata	Aqueous extract	India	↓ COX-2 and MPO	Rat cotton pellet granuloma	(Subash et al., 2016)
Ulva latuca	Sulfated polysaccharides	Brazil	↓TNF-α, and IL-1β ↑ HO-1	Rat paw edema	(de Araujo et al., 2016)

Abbrv. 3T3-L1: mouse adipose embryonic fibroblast cell line; 5-HT: 5-hydroxytryptamine; 5HHMF: 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone; A498: human renal cell carcinoma; AKT: protein kinase B; AML-12: normal mouse hepatocyte cells; AMPK: AMP-activated protein kinase; BMDC: bone marrow derived cells; BMDM: bone marrow derived macrophages; BMM: bone marrow macrophage; BV-2: murine microglial cells: CLP: cecal ligation and puncture; COX-2: cyclooxygenase 2; CXCL-1: C-X-C motif chemokine ligand 1; CXCL-2: C-X-C motif chemokine ligand 2; CXCL-10: interferon gamma-induced protein 10; EB1: 6–6 bieckol; EB5: pholorofucofuroeckol-A; ERK: extracellular signal-regulated kinase; ET-1: endothelin-1; EtOAc: ethyl acetate; EtOH: ethanol; HaCaT: human skin keratinocytes; HCAEC: human coronary artery endothelial cell; HCC: hepatocellular carcinoma; HDPC: human dental pulp cells; HeLa: human epithelial cervix cancer cell line; HepG2: human liver cancer cell line; HO-1: heme oxygenase-1; HPBMCs: human peripheral blood mononuclear cells; HSC-T6: immortalized rat hepatic stellate cells; HUVECtert: telomerase reverse transcriptase immortalized human umbilical vein endothelial cells; HWBC: human white blood cells; ICAM-1: intercellular adhesion molecule 1; IKK-IκB: IκB kinase; IL-1β: interleukin 1 beta; IL-6: interleukin 6; IL-8: interleukin 8; IL-10: interleukin 10; iNOS: inducible nitric oxide synthase; IRF3: interferon regulatory factor 3; JNK: c Jun NH2-terminal kinase; LX-2: human hepatic stellate cells; MAPK: mitogen-activated protein kinase; MDC/CCL22: macrophage-derived chemokine; MeCl: dichloromethane; MeOH: methanol; MIA PaCa-2: human pancreatic cancer cell line; MPO: myeloperoxidase; NF-κB: nuclear factor-kappa B; NO: nitric oxide; PI3K: phosphatidylinositol 3-kinase; PPY1: peptide from *P. Yezoensis*; RAW264.7: murine macrophage cells; ROS: reactive oxygen species; SIRT: sirtuin 1; SKBR-3: breast cancer cells; α-SMA: alpha-smooth muscle actin; STAT1: signal transducer and activator of transcription 1; TBK1: serine/threonine-protein kinase; TGF-β: transforming growth factor beta; TLR4: Toll-like receptor 4; TMJ: temporomandibular joint; TNBS: trinitrobenzenesulfonic acid; TNF-α: tumor necrosis factor alpha; TPH-1: human monocytic cell line derived from an acute monocytic leukemia; U937: human promonocytic cell line; UVB: ultraviolet B; VCAM-1: vascular cell adhesion molecule 1; VEGF-A: vascular endothelial growth factor A.

activation of several intracellular pathways, such as the arachidonic acid pathway, that includes the production of prostanoids, prostaglandins (E_2, I_2, D_2 and $F_{2\alpha}$) and thromboxane A_2 (TXA_2), through the action of the cyclooxygenase (COX) enzyme isoforms: COX-1, which is responsible of the basal production of prostaglandins (PG), whereas COX-2 promotes the production of high PGs' levels during the inflammatory response. PGs may function in both the promotion and resolution of inflammation (Ricciotti and FitzGerald, 2011). Moreover, nitride oxide (NO) has been considered as the main mediator of the inflammatory response. The increase in the expression of NO synthase (NOS) by the activation of pro-inflammatory cytokines produces large amounts of NO in innate immune cells (Sharma et al., 2007). Since NO is a small free-radical gas molecule, it can easily enter across cell membranes and diffuse to adjacent cells, participating in the activation of several intracellular targets, through the interaction with soluble guanylyl cyclase and the increase of cGMP levels (Bellamy et al., 2002).

Seaweeds-derived compounds suppress the expression of inflammatory mediators including PGE2, NO, tumor necrosis factor-*α* (TNF-*α*), and several inflammatory cytokines such as interleukin-(IL) 1*β*, IL-6, among others (Table 1) (Fig. 7). The seaweed *E. cava* has been widely studied (Choi et al., 2014; Eo et al., 2015; Heo et al., 2010; Hwang et al., 2017, 2015; Kang et al., 2015a, 2015b; Lee et al., 2016; Mohsin et al., 2013; Sadeeshkumar et al., 2017). For instance, the treatment of cancer cell lines with polyphenols or polyphenol-enriched extracts isolated from *E. cava* attenuate the inflammatory response. Treatment of RAW264.7 cells with diekol (50 μM) diminishes iNOS expression and NO production in response to lipopolysaccharide (LPS, 1 μg/ml). In addition, dieckol decreases iNOS transcriptional activity by blocking nuclear factor κB (NF-κB) activation and p38 MAPK phosphorylation (Choi et al., 2014) (Fig. 7). NF-κB is a transcriptional factor critical for innate and adaptive responses. Its activation (through the liberation from its inhibitory units IκBs) and nuclear translocation binding to DNA-response element κB, located in numerous genes promoters, modulate transcription of pro and anti-inflammation mediators, such as ILs, TNF-α among others (Hoesel and Schmid, 2013). Furthermore, dieckol from *E. cava* blocks MDC/CCL22 chemokine production by down regulating STAT1 signaling pathway in human keratinocytes HaCaT cell line stimulated with IFN-γ (10 μg/ml) (Kang et al., 2015b).

Moreover, several studies using different cell types and animal models of inflammation have reported the down-regulation of NF-κB signaling pathway (Chatter et al., 2011; Eom et al., 2017; Hwang et al., 2017; Jung et al., 2013; Kang et al., 2017; Kim et al., 2018, 2014a, 2009; Kim et al., 2014b; Lee et al., 2012b, 2017b, 2016; Li et al., 2011; Manzoor et al., 2013; Yang et al., 2013a; Yoon et al., 2012). For example, the crude flakes extracts from *E. cava* inhibit NF-κB activation in LPS-induced RAW264.7 cells. Moreover, these algae's fractions inhibit the phosphorylation of ERK1/2 and the expression of pro-inflammatory cytokines TNF-α, IL-1, IL-6 and IL-10. *E. cava*-derived compounds inhibit the Toll-like receptor 4 (TLR4) signaling that is activated by LPS (Hwang et al., 2017) (Fig. 7). It is well known that TLR family receptors play an important role in innate immunity, since they detect pathogens and stimulate host defenses (Kuzmich et al., 2017). Similarly, lipid extracts from red seaweeds *Porphyra dioica, Palmaria palmata* and *Chondrus crispus* down regulate TLR signaling and inhibit pro-inflammation molecules through regulation of NF-κB in LPS-induced inflammation in human THP-1 macrophages (Robertson et al., 2015). On the other hand, the eckols 6–6 bieckol (EB1) and pholorofucofuroeckol-A (EB5) prevent nuclear translocation of NF-κB and down regulation of ERK1/2 pathway of LPS-induced inflammation in human dental pulp cells (Paudel et al., 2014).

Lectins obtained from red *Bryothamnion triquetrum* and green *Caulerpa cupressoides* seaweeds inhibit inflammation, blocking the release of pro-inflammatory cytokines by regulating several signaling pathways (da Conceicao Rivanor et al., 2014; de Queiroz et al., 2015; Fontenelle et al., 2018). For instance, the administration of lectin (10 mg/kg *i.v.*) from *C. cupressoides* reduces carrageenan-induced paw edema and peritonitis in mice, mimicking the effect of Indomethacin (10 mg/kg). Carrageenan promotes the release of PGs, NO, *etc.*, and infiltration of neutrophils, rising the activity of myeloperoxidase (MPO). The treatment with the leptin reduces the activity of MPO and the levels of TNF-α and IL-1β and the infiltration of neutrophils and leukocytes (Fontenelle et al., 2018). Also, the aqueous extract of *Turbinaria ornata* decreases COX-2 and MPO expression in rat cotton pellet granuloma model (Subash et al., 2016) (Fig. 7).

The injection of zymosan in the rat temporomandibular joint induces an acute arthritis model, characterized by mechanical hypernociception, and increases in the number of polymorphonuclear cells, and MPO activity. The treatment with lectin isolated from *C. cupressoides* prevents this effect by inhibiting the expression of IL-1β, TNF-α (da Conceicao Rivanor et al., 2014), while the aqueous and methanol extracts from *Caulerpa mexicana* also inhibit the production of IL-6, IL-12 and in TNF-α by peritoneal macrophagues stimulated with LPS (Bitencourt et al., 2011). This effect could be mediated by the inhibition of TLR receptors, since they respond to LPS stimulation. Also, fucoidan isolated from *Chnoospora minima* inhibits NO production and PGE2 expression by down-regulation of iNOS and COX-2 expression in RAW264.7 cells stimulated with LPS (Fernando et al., 2017). Moreover, fucoidan inhibits TNF-α, IL-1*β*, and IL-6 expression in this cell line, while in LPS-stimulated zebrafish suppressed NO and ROS production (Fernando et al., 2017). Similarly, the polysaccharide isolated from *Sargassum cristaefolium* inhibits NO production and NF-κB activation by down regulation of ERK1/2, p38 and JNK MAPK pathways in LPS-stimulated RAW264.7 cells (Wu et al., 2016).

Several extracts from *Codium fragile* suppress the inflammatory response to UVB, LPS and carrageenan in HaCaT and RAW264.7 cells, mouse and rat models. These reports reveal that *C. fragile* extracts halt PGE2, NO, TNF-α, IL-1β, and IL-6 expression by inhibiting COX-2, iNOS, NF-κB, and MAPK pathways (Lee et al., 2013, 2017b).

Sulphated polysaccharide fractions from *Gracilaria birdiae, Gracilaria caudata, Hypnea musciformis, Lobophora variegate, Sargassum horneri*, and *Sargassum hemiphyllum*, show anti-inflammatory activity in animal models, such as mouse and rat paw edema, peritonitis, rat arthritis, and mouse ear inflammation; or cellular lines, as RAW264.7 (Brito et al., 2014; Chaves et al., 2013; de Brito et al., 2013; Hwang et al., 2015; Paiva et al., 2011; Siqueira et al., 2011; Wen et al., 2016). Evidence suggests that the inflammatory response *via* TNF-α is repressed with these seaweeds compounds, where down regulation of inflammatory response molecules as MPO, MDA, and IL-1β inhibit the synthesis and release of pro-inflammatory mediators. An increase in the endogenous anti-oxidant GSH (Brito et al., 2014), which helps decreasing free radicals production, has been observed with these algae polysaccharides. The L-arginine/NO pathway is inhibited in mouse paw edema and peritonitis due the NOS inhibitors on neutrophil migration (de Brito et al., 2013). The activity of the potent pro-inflammatory cytokines TNF-α and IL-1β is regulated by sulphated polysaccharides; which decrease the expression of inflammatory molecules as IL-6 (Hwang et al., 2015).

Inhibition of TNF-α and IL-1β has also been observed in inflammatory cells treated with alcohol extracts of diverse seaweeds (Araújo et al., 2017; Eo et al., 2015; Kim et al., 2015, 2009, 2013; Kim et al., 2014b; Lajili et al., 2016; Lee et al., 2012b; Shu et al., 2013; Yang et al., 2013a; Yoon et al., 2012). Seaweed extracts exert significant anti-inflammatory effects on gene expression in U937 and THP-1 cells, along with rat gastric lesions and paw edema (Lajili et al., 2016; Shu et al., 2013). The pleiotropic regulator NF-κB, and pro-inflammatory mediators IκB-α and MAPK are also significantly inhibited in RAW264.7 cells. The NF-κB transcription factor is down regulated in the same cell line by methanol extracts of *Ishige okamurae* (Kim et al., 2009), apparently by regulating the expression of inflammatory mediators. *Sargassum horneri* ethanol extract treatment reduces IL-1β mRNA levels and the pro-inflammatory genes of iNOS and COX-2 (Kim et al., 2015). This extract not only regulates anti-inflammatory processes at the

Table 2
Molecular targets of seaweeds that mediate the anti-cancer activity.

Species	Extract/Compound	Collection Country	Mechanism	Model	Reference
Capsosiphon fulvescens	Polysaccharides	South Korea	↑ Caspase-3 and ↓Bcl-2. ↓ IGF-IR phosphorylation and PI3K/AkKT pathway	AGS	(Kwon and Nam, 2007)
Caulerpa microphysa	Pepsin-digested extract	Taiwan	↓ Cyclin D, cyclin E, CDK6, CDK2 and Bcl-2, ↑ p21, p27, p53, Bax, Bid, GRP78, GADD153, AIF, caspase-3 and -9	WEHI-3 mouse	(Chou et al., 2014)
Caulerpa racemosa, Padina tetrastromatica, Turbinaria ornata	Hx, MeCl, EtOAc, Ace, and MeOH extracts	Malaysia	↑ Extrinsec and intrinsec apoptosis pathways, modulation of caspase-8, -9 and -3	MCF-7	(Chia et al., 2015)
Cladosiphon novae-caledoniae	Power fucoidan	Commercial	↓Bcl-2, ↑Bax, JNK, p38 and ERK1/2 phosphorylation; ROS-mediated pathway	MCF-7	(Zhang et al., 2015)
Dictyota dichotoma, Hormophysa triquerta, Spatoglossum asperum, Stoechospermum marginatum and *Padina tetrastromatica*	Polyphenol fractions	India	↓NF-κB luciferase activity. Cell specific regulation of *Bcl2, EGFR, PDGFA, VEGF, Akt, TERT, kRas,* and *FGF*; EGFR, and AurKb; EGFR, KRAS, STAT3 protein levels	MiaPaCa-2, Panc-1, BXPC-3, and Panc-3.27	(Aravindan et al., 2013)
Ecklonia cava	Polyphenols	Commercial	↓ COX-2 and PGE2 expression	UVB radiation-induced carcinogenesis in female SKH-1 mouse	(Hwang et al., 2006)
Fucus vesiculosus	Fucoidan	Commercial*	↑ Caspase-3. ↓ ERK and GSK phosphorylation	HS-Sultan	(Aisa et al., 2005)
			↑ Caspase-3 activation and p21/WAF1/CPI1 protein levels. ↓ ERK1/2 and AkKT pathways	NB-4, HL-60, and NB-4 inoculated nude mouse	(Atashrazm et al., 2016)
			↓ hTERT, Sp1, c-myc gene expression and telomerase activity, PI3K/AkKT pathway	5637	(Han et al., 2017)
			↑ Caspases-3, -8, and -9 activation, and ERK1/2, JNK phosphorylation, and NO production	NB-4, HL-60, and THP-1	(Jin et al., 2010)
			↓ ERK1/2, AKT, mTOR and NF-κB	A549	(Lee et al., 2012a)
Gloiopeltis furcata	MeOH extract	Commercial*	↓ COX-2 mRNA and protein expression; cdcs and cdks regulation	HepG2	(Bae and Choi, 2007)
Gracilaria fisheri	Sulfated galactans	Thailand	↓ EGFR, ERK1/2 and FAK phosphorylation	HuCCA-1	(Sae-Lao et al., 2017)
Hydroclathrus clathratus	MeOH extract	South Korea	↓ TNF-α-induced MMP-9 expression; NF-κB and MAPK pathways	T24	(Jayasooriya et al., 2012)
Laminaria cichorioides	Fucoidan	Japan	↓ EGF-induced EGFR, MEK, ERK1/2, p90RSK, JNK, and c-Jun phosphorylation	JB6 Cl 41	(Lee et al., 2008)
Laurencia microcladia	Elatol	Brazil	↓ cyclin D1, cyclin-E, cdk2, cdk4, and bcl-xl expression. ↑ Bak, caspase-9 and p53	Male C57BL6 mouse, and B16F10	(Campos et al., 2012)
Monostroma nitidum	Sulfated polysaccharides	South Korea	↑ NO activity, TNF-α, and PGE2	RAW264.7	(Karnjanapratum and You, 2011)
Not mentioned	Fucoidan	Commercial*	↓ Bid, Bcl-2 and Bcl-xl, ↑ Bax and caspases 3 and 9 activation. ↓ PI3K/AKT/GSK3β pathway	MDA-MB-231 and female Sprague-Dawley rat	(Xue et al., 2017)
	Fucoxanthin	Commercial*	↓ AKT, p53, p70S6K, and mTOR phosphorylation	HeLa	(Hou et al., 2013)
			↓ AKT, mTOR and p38	U87 and U251	(Liu et al., 2016)
	Phloroglucinol	Commercial*	↓ UVB-induced MMP-1 activity. ↑ intracellular calcium, MAPKs phosphorylation, c-Fos/c-Jun expression and AP-1 binding to MMP-1 promoter	HaCaT	(Piao et al., 2012)
	Fucoxanthin	Commercial*	↓ DNMT activity, ↑ mRNA and protein levels of Nrf2	JB6 *p*+	(Yang et al., 2018)
Porphyra yezoensis	EtOH extract	South Korea	↑ IL-1β, 10, and 12, IFN-γ, and TNF-α	C57BL/6 mouse splenocytes	(Herath et al., 2018)

(*continued on next page*)

Table 2 (*continued*)

Species	Extract/Compound	Collection Country	Mechanism	Model	Reference
Sargassum filipendula	Heterofucan	Brazil	↑ GSK-3β, Bax and ↓Bcl-2	HeLa	(Costa et al., 2011)
Stoechospermum marginatum	Spatane diterpinoid DDSD	India	↑ Caspases-3 and -9; Bax. ↓Bcl-2 and PI3K/AKT pathway	C57BL/6 mouse, B16F10	(Velatooru et al., 2016)
Turbinaria ornata and *Padina pavonia*	EtOH extract	Egypt	↓NF- κB. ↑ PPARγ and p53	HCT-116 and AOM-induced colon carcinogenesis in mouse	(Mahmoud et al., 2015)
Undaria pinnatifida	Fucoxanthin, and fucoxanthinol	Commercial	↑ Cell cycle arrest, and GADD45α. ↓ cyclins D1, D2, CDK4, CDK6, Bcl-2, XIAP, cIAP2 and survivin	HTLV-1-infected T-cells	(Ishikawa et al., 2008)
	Fucoidan	China	↓Bcl-2 and ↑ Bax; ROS-mediated mitochondrial pathway	SMMC-7721	(Yang et al., 2013)

Abbrv: 5637: human bladder cancer cell line; A549: human lung cancer cell line; ABTS: 2,2′-azino-bis[3-*ethylbenzothiazoline*-6-*sulphonic acid*]; Ace: acetone; AGS: human gastric ademocarcinoma cell line; AIF: apoptosis-inducing factor; AKT: protein kinase B; AMPKα: AMP-activated protein kinase alpha; AP-1: activator protein-1; B16F10: murine melanoma cell line; BALB/3T3: mouse embryonic fibroblast cell line; BXPC-3: human pancreatic cell line; c-myc: protooncogen; cdc: cell division cycle; CDK: cyclin dependent kinase; COX-2: cyclooxygenase-2; DDSD: spatane diterpenoid, 5(R), 19-diacetoxy-15,18(*R* and *S*), dihydro spata-13, 16(E)-diene; DNMT: DNA methyltransferase; DU145: human prostate cancer cell line; EGFR: epidermal growth factor receptor; ELT-3: Eker rat leiomyoma tumor-derived cells; ERK: extracellular signal-regulated kinase; EtOAc: ethyl acetate; EtOH: ethanol; FAK: focal adhesion kinase; GADDI53: growth arrest and DNA-damage-inducible human gene; GRP78: glucose-regulated protein; GSH: glutathione; GSK-3β: glycogen synthase kinase 3 beta; HaCaT: human skin keratinocytes; HbA1C: glycosylated haemoglobin; HeLa: human epithelial cervix cancer cell line; HepG2: human liver cancer cell line; HepG2-C8: human liver cancer cell line transfected with the pARE-TI-luciferase construct; HL60: acute myeloid leukemia cell line; HL-7702: human normal liver cell line; HS-Sultan: human lymphoma cell line; HTC-116: human colorectal carcinoma cell line initiated from an adult male; hTERT: human telomerase reverse transcriptase; HTLV-1: human T-cell leukemia virus type 1; HuCCA-1: human cholangiocarcinoma cell line; HUtSMC: human uterine smooth muscle cells; HX: hexane; IFN-γ: interferon gamma; IEC-6: rat small intestine epithelial cells; IGF-IR: insulin like growth factor-I receptor; IL: interleukin; IMP: human myeloma cell line; iNOS: inducible nitric oxide synthase; JB6 Cl 41: mouse epidermal cell line; JB6 *p*+: mouse epidermal cell line; JNK: c-Jun NH2-terminal kinase; K562: acute myeloid leukemia cell line; KG1a: acute myeloid leukemia cell line; L929: murine fibroblast cell line; MAPK: mitogen-activated protein kinase; MDA-MB-231: human breast cancer cell line; MeCl: dichloromethane; MEK1: MAPK kinase 1; MEKK1: MAPK kinase 1; MeOH: methanol; MiaPaCa-2: human pancreatic cancer cell line; MMP: mitochondrial membrane potential; MMP-1: matrix metalloproteinase-1; MMP-9: matrix metalloproteinase-9; MOLT4: human T-cell lymphoma cell line; mTOR: mammalian target of rapamycin; NB-4: human acute promyelocytic leukemia cell line; NF-κB: nuclear factor-kappa B; NIH/3T3: mouse embryonic fibroblast cell line; NO: nitric oxide; Nrf2 or NFE2L2: nuclear factor erythroid-2-related factor-2; Panc-1: human pancreatic cell line; Panc-3.27: human pancreatic cell line; PGE2: prostaglandin E2; PI3K: phosphatidylinositol 3-kinase; RAW 264.7: murine macrophage cells; ROS: reactive oxygen species; SKH-1: hairless mouse skin model; SMMC-7721: human hepatocellular carcinoma cell line; Stat: signal transducer and activator of transcription; Sp1: specificity protein 1; T24: human urinary bladder cancer cell line; THP-1: human monocytic cell line derived from an acute monocytic leukemia; TNF-α: tumor necrosis factor alpha; WEHI-3: BALB/c mouse with transplanted myelomonocytic leukemia; TPA: 12-otetradecanoylphorbol-13-acetate; U251: human glioblastoma cell line; U87: human glioblastoma astrocytoma cell line; UVB: ultraviolet B; V79-4: chinese hamster lung fibroblast cell line. *Purchased from SIGMA.

transcriptional level, but also at the level of protein activation by inhibiting the phosphorylation of ERK, p38, JNKs, and NF-κB, besides PGE2 in BV-2 cells (Kang et al., 2013; Kim et al., 2014a). Likewise, ethanolic extract from *Ecklonia stolonifera* inhibits AKT, ERK1/2, p38 and JNK MAPK pathways in LPS-stimulated RAW264.7 cells (Lee et al., 2012a). Fucosterol from *Hizikia fusiforme* reduces the expression of IL-6, IL-1β and TNF-α in $CoCl_2$-stimulated HaCaT cells, by diminished the accumulation of HIF1-α through down regulation of PI3K/AKT pathway (Sun et al., 2015). Other reports also have demonstrated that seaweeds down regulate TNF-α and/or ILs (Lee et al., 2017a, 2015; Levy-Ontman et al., 2017; Liu et al., 2015; Pereira et al., 2014; Rajamani et al., 2018; Ryan et al., 2011; Sah et al., 2013; Salhi et al., 2018; Shu et al., 2013; Yamada et al., 2014).

Heme oxygenase (HO) is a protein usually located within the endoplasmic reticulum where it catabolizes heme to carbon monoxide (CO), iron, and biliverdin. In mammals, at least two isoenzymes are expressed: the inducible heme oxygenase-1 (HO-1) and the constitutive heme oxygenase-2. HO-1 is induced by a wide array of pro-oxidant and inflammatory stimuli. Low levels of HO-1 are present in mostly all cell lineages. However, after cell/tissue injury this protein expression is raised, playing an important role in cell protection by regulating anti-inflammatory, anti-oxidant, anti-apoptotic, among other pathways (Morse and Choi, 2002). Thereby, HO-1 has been open as a possible therapeutic target (Naito et al., 2011). Dieckol from *Eisenia bicyclis*, fucoidan from *Fucus vesiculosus*, sulfated polysaccharides from *Gracilaria cornea* and *Ulva latuca* have shown to increase HO-1 expression while decrease the levels of pro-inflammatory mediators in RAW264.7, BV-2 and HepG2 cells; as well as in rat paw edema inflammation and mouse alcohol-mediated liver damage models (Coura et al., 2015; de Araujo et al., 2016; Lim et al., 2015; Yayeh et al., 2014). It has been observed that commercial fucoidan from *F. vesiculosus* decreases mitochondria-mediated apoptosis in the acetaminophen-induced liver injury in rat model and inhibits pro-inflammation mediators as TNF-α, IL-1β and iNOS (Hong et al., 2012).

Liver fibrosis represents a disease produced by chronic inflammation in which extracellular matrix (ECM) is accumulated in this organ (Kershenobich-Stalnikowitz and AB., 2003). It is known that hepatic stellate cells (HSCs) activation widely contributes to development of liver fibrosis, because HSCs are fibrogenic mediators. Therefore, these cells have been targets of interest to improve the treatment of this disease (Bataller and Brenner, 2005). Dieckol causes cell arrests and apoptosis of immortalized rat hepatic stellate (HSC-T6), mouse normal liver LX-2 and human hepatocarcinoma HepG2 cells. Dieckol also decreases ERK, p38, AKT, NF-κB, and IκB phosphorylation and activates the microRNA(miR)134 levels and JNK phosphorylation in HSCs, participating in liver fibrosis suppression (Lee et al., 2016). This is interesting since microRNAs have been postulated as molecular targets in liver fibrosis, due to their notorious proliferation inhibition in other cancer cell types (Szabo and Bala, 2013). Moreover, fucoidan from *Laminaria japonica* attenuates the inflammatory response by decreasing pro-inflammatory molecules as TNF-α, IL-6, IL-1β, CXCL-10, VCAM-1, and ICAM-1 by down regulating ERK1/2, p38 and JNK MAPK pathways in rat hepatic ischemia reperfusion injury (Li and Ye, 2015).

Rheumatoid arthritis is a systemic autoimmune disease, characterized by synovial inflammation and destruction of cartilages and bones with extra-articular manifestations (Kim et al., 2017b). The treatment of this multifactorial disease has two approaches: 1) ameliorate the symptoms with non-steroidal anti-inflammatory drugs (NSAIDs) and, 2) modifying the disease progress with disease-modifying anti-rheumatic drugs (DMARDs). These DMARDs are under extensive research, and usually target inflammation pathways molecules using antibodies and cytokines inhibitors (Smolen et al., 2007). However, several natural products have been tested pre-clinical trials with animal models of arthritis (Gutierrez-Rebolledo et al., 2015). Hence, polysaccharides from *Lithothamnion muelleri* and l. *Variegata* reduce the expression of pro-inflammation cytokines CXCL-1, CXCL-2, TNF-α and the production of NO in rodent arthritis models (Costa et al., 2015; Paiva et al., 2011).

Anti-cancer activity

The term Cancer is used to describe a catalogue of diseases in which uncontrolled abnormal cells divide and can invade nearby tissues (cancer.gov, 2018). Cancer represents a therapeutic challenge since it is mediated by a number of different molecular and cellular mechanisms. Therefore, there are several intracellular pathways that could be targeted, since cell proliferation, apoptosis and extracellular matrix interactions are regulated by signaling cascades triggered by multiple stimuli that include growth factors and proto-oncogenes, among others (Patterson et al., 2018).

An important number of algae species and algae-derivate compounds have been tested as cancer alternative therapy, and it has been demonstrated that seaweeds have the capacity to produce compounds that, in turn, promote cell arrest and apoptosis, diminish angiogenesis and cell migration (Gutierrez-Rodriguez et al., 2018).

The molecular pathways that mediate the anti-cancer activity of seaweeds are shown in Table 2 Seaweeds-derived compounds modulate intrinsic as well as extrinsic apoptosis pathways. Polysaccharides isolated from *Capsosiphon fulvencens* have been shown to increase caspase-3 cleavage and activity; as well to Bad expression and decrease Bcl-2 expression in human gastric adenocarcinoma cell line (AGS) (Kwon and Nam, 2007). Since insulin like growth factor-I receptor (IGF-IR) overexpression is common in several cancer cells, its inhibition results interesting as a chemotherapeutic target (Weroha and Haluska, 2012). It has been demonstrated that these polysaccharides constrain the phosphorylation of IGF-IR in response to IGF-I stimulation. As a consequence, AKT pathway is also suppressed. Thereby, *C. fulvencens* polysaccharides diminish proliferation and promote apoptosis and DNA fragmentation by inhibiting IGF-R phosphorylation and, accordingly, AKT signaling pathway (Kwon and Nam, 2007) (Fig. 8). Likewise, two species of *Caulerpa* genus: *C. microphysa* and *C. racemosa* activate apoptosis. The pepsin digested extract obtained from *C. microphysa* causes G0/G1 cell cycle arrest in myelomonocytic leukemia cells (WEHI-3). The authors demonstrated that *C. microphysa* extracts induce the protein expression of p21, p27, p53, Bax, Bid, GRP78, GADD153, apoptosis-inducing factor (AIF), and caspase-3 and -9; whereas, the levels of cyclin D, cyclin E, CDK6, CDK2 and Bcl-2 are diminished (Fig. 9). Additionally, the extract stimulated ROS production and DNA fragmentation (Chou et al., 2014). While, *C. racemosa* also induced DNA fragmentation and the activation of caspase-3, -8 and -9 in MCF-7 cell line (Chia et al., 2015). In this cell line, Zhang and colleagues (Zhang et al., 2011) showed that the commercial fucoidan obtained from *Cladosiphon novae-caledoniae* induced caspase-independent apoptosis thought MAPK's pathway activation. Fucoidan increased the expression of Bad and Bax, while diminishing Bcl-2 and Bcl-xl expression. Fucoidan also promoted the phosphorylation of ERK1/2, p38 and JNK MAPKs (Fig. 10). Interestingly, pre-treatment of MCF-7 cells with specific MAPK inhibitors: SB203580 for p38, or PD98059 for ERK1/2 followed by fucoidan treatment failed to inhibit apoptosis. However, inhibition of JNK with SP600125 prevented fucoidan-dependent apoptosis (Zhang et al., 2011). The fucoidan isolated from *Fucus vesiculosus* promoted caspase-3 dependent apoptosis thought the inhibition of ERK1/2 and GSK pathway in HS-Sultan cells (Aisa et al., 2005). Similarly, fucoidan from *F. vesiculosus* inhibited ERK1/2 phosphorylation and promoted AKT Thr (308) phosphorylation causing apoptosis and promoting p21/WAF1/CIP1 protein levels augmentation and cell arrest in human leukemia cell lines NB-4 and HL-60. Moreover, after a 14 day consumption of fucoidan, a reduction of the tumor size of NB-4 inoculated nude mice was present (Atashrazm et al., 2016). However, other study reported that *F. vesiculosus* fucoidan promoted apoptosis by increasing ERK1/2 and JNK phosphorylation and activation of caspase-3, -8, and -9 in NB-4, HL-60 and THP-1 leukemia cell lines (Jin et al., 2010).

Fucoidan treatment of MDA-MB-231 breast cancer cell line

Table 3
Molecular targets of seaweeds that mediate the anti-diabetes activity.

Species	Extract/Compound	Collection country	Mechanism	Model	Reference
Caulerpa okamurae	EtOH extract	South Korea	↓ PPAR-γ, C/EBP-α and SREBP	Male C57BL/6 J mouse, 3T3-L1	(Sharma et al., 2017)
Ecklonia cava	Dieckol	Not mentioned	↑ AMPK and AKT phosphorylation	Male C57BL/KsJ-*db/db* diabetes mouse model	(Kang et al., 2013)
Eisenia bicyclis	8, 8′ bieckol, dieckol, phlorofucofuroeckol A	South Korea	↓ PPARγ, C/EBPα, SREBP-1c, FAS and ACC mRNA	3T3-L1	(Kwon et al., 2015)
Laminaria japonica	Fucoidan	China	↑ eNOS phosphorylation, NO and VEGF	PAD model in *db/db* C57BL mouse	(Liu et al., 2018)
	Kelp powder	Commercial	↓ NO and iNOS	Alloxan-induced diabetes model in male Wistar rat	(Long et al., 2012)
Lessonia nigrescens	EtOH extract	China	↑ PI3K and ↓ JNK1 activity	Male ICR mouse	(Zhao et al., 2018)
Undaria pinnatifida	Fucoxanthin	Commercial	↑ DHA, stearic and arachidonic acid, UCP-1 mRNA and ↓ UCP-2 mRNA ↑ UCP-1 expression and ↓ leptin, TNF-α mRNA in white adipose tissue ↓ MCP-1 and TNF-α mRNA, IL-6, PAI-1 mRNA, NO, PGE2, iNOS and COX-2 mRNA	Male Wistar rat and female KK-Ay mouse Female KK-Ay mouse Female KK-Ay and C57BL/6 J mice, 3T3-F442A, RAW264.7	(Maeda et al., 2008) (Maeda et al., 2007) (Hosokawa et al., 2010)

Abbrv. 3T3-L1: mouse adipose embryonic fibroblast cell line; ACC: acetyl-CoA carboxylase; AKT: protein kinase B; AMPK: AMP-activated protein kinase; C/EBPα: CCATT/enhancer-binding protein α; COX-2: cyclooxygenase 2; DHA: docosahexaenoic acid; eNOS: endothelial nitric-oxide synthase; EtOH: ethanol; FAS: fatty acid synthase; IL-6: interleukine 6; iNOS: inducible nitric-oxide synthase; JNK1: c-Jun N-terminal protein kinase 1; MCP-1: monocyte chemoattractant protein-1; NO: nitric oxide; PAD: peripheral arterial disease; PAI-1: plasminogen activator inhibitor-1; PGE2: prostaglandin E2; PI3K: phosphatidylinositol 3-kinase; PPARγ: peroxisome proliferator-activated receptor gamma; SREBP-1c: sterol regulatory element binding protein-1c; TNFα: tumor necrosis factor alpha; UCP1: uncoupling protein 1; VEGF: vascular endothelial growth factor.

inhibited proliferation and induced apoptosis through down regulation of PI3K/AKT/GSK3β pathway, reduction of Bid, Bcl-2 and Bcl-xl, rise of Bax expression and caspase-3 and -9 activation. Fucoidan regulation of this signaling pathway was also observed in DMBA-induced tumors in female rat, causing tumor volume reduction (Xue et al., 2017). Interestingly, MDA-MB-231 cells are a triple-negative breast cancer cell line that lack estrogen, progesterone, and HER2 receptors. This type of breast cancer has poor prognosis, and cannot be reduced with hormonal or anti-HER2R therapies, standard treatments, and represents around 20% of all breast cancers. Thereby, fucoidan constitutes a good therapeutic alternative to explore, as its action has been suggested to be downstream of the receptor level by down-regulating the PI3K/AKT pathway (Gutierrez-Rodriguez et al., 2018).

Fucoidan isolated from *Undaria pinnatifida* promotes apoptosis by the ROS-mediated mitochondrial pathway that involves the inactivation of Bcl-2 and decreased expression of Bax in human hepatocellular carcinoma SMMC-7721 cell line (Yang et al., 2013b). Besides, fucoidan from *F. vesiculosus* induced apoptosis and decreased the expression of human telomerase reverse transcriptase (hTERT) and the transcription factor c-myc and sp-1 of human bladder cancer 5637 cell line. In these cells, fucoidan increased the Bax/Bcl-2 ratio, inhibiting the PI3K/AKT pathway and increasing intracellular ROS production (Han et al., 2017).

It has been demonstrated that EGFR is over-expressed in several cancer cells types, contributing to cell transformation (Normanno et al., 2006). Interestingly, fucoidan from *Laminaria cichorioides* inhibited EGFR signaling on JBC6 CI 41 mouse epidermal cell line. Apparently, fucoidan prevents EGF binding to its receptor, as a consequence, ERK1/2, JNK, and p90RSK phosphorylation diminishes, blocking the activation of Fos and Jun transcriptional activity, and thereby inhibiting the associated activator protein-1 (AP-1) transactivation activity (Lee et al., 2008) (Fig. 10). Since EGFR signaling plays an important role in the development and progression of epidermal cancer (Normanno et al., 2006), EGFR represents an attractive therapeutic target (Seshacharyulu et al., 2012).

The diversity -and sometimes *opposing*- actions of fucoidans could be explained, in part at least, by the fact that fucoidan refers to a large class of sulfated, fucose-rich polysaccharides that can also contain galactose, mannose, xylose, glucose and glucuronic acid (Xue et al., 2012). Fucoidans are located in the ECM of brown seaweeds' cell walls where participate in the mechanical support of cell walls (Chollet et al., 2016).

Seaweed-derived polyphenols have shown to possess important anti-cancer potential (Gutierrez-Rodriguez et al., 2018). The dietary daily and topical administration of *E. cava*-derived polyphenols mix for 23 weeks, importantly reduced tumor volume in the UVB radiation-induced carcinogenesis model in female SKH-1 mouse. Also, *E. cava* reduced the UVB-induced PCNA-positive cells in the epidermis of mice, as an indicative that polyphenols prevented proliferation in these cells. Moreover, polyphenols exert an inhibitory effect on COX-2 activity, decreasing PGE2 levels (Hwang et al., 2006). PGE2 is known to play a main role in the development of tumors (Soh and Weinstein, 2003). Likewise, the methanol extract of *Gloiopeltis furcata* exhibits the same anti-proliferative effect on HepG2 cells, by inhibition of COX-2/PGE2 (Bae and Choi, 2007).

On the other hand, since pancreatic cancers have a five-year survival rate of 5,4%, with mortality rates that remained almost unchanged since the 1970s, Aravindan and colleagues (Aravindan et al., 2013) studied the anti-cancer activity of the polyphenol fractions obtained from five species of brown seaweeds: *Dictyota dichotoma, Hormophysa triquerta, Spatoglossum asperum, Stoechospermum marginatum*, and *Padina tetrastromatica* on MiaPaCa-2, Panc-1, BXPC-3 and Panc-3.27 pancreatic cancer cell lines. They demonstrated that the fractions inhibit cell viability and induced DNA fragmentation, except for the $MeCl_2$ fraction from *D. dichotoma*. Additionally, the authors evaluated several key molecules that regulate tumor progression of pancreatic

Table 4
Molecular targets of seaweeds that mediate the anti-oxidant activity.

Species	Extract/Compound	Collection country	Mechanism	Model	Reference
Codium tomentosum, Padina pavonica, Sargassum muticum, Saccorhiza polyschides, Ulva compressa	MeCl and MeOH extracts	Portugal	↓ Protection of mitochondrial membrane's potential, caspase-3 activity	SH-SY5Y	(Silva et al., 2018)
Dictyopteris undulata	Sesquiterpene zonarol	Japan	↓ Nrf2/ARE pathway	HT22	(Shimizu et al., 2015)
Ecklonia cava	Eckol	South Korea	↑ ERK and NF-κB pathways	V79-4	(Kang et al., 2005)
	Enzymatic digestion	South Korea	↓ iNOS, COX-2 and NF-κB	HUVECs	(Lee et al., 2010)
Fucus spiralis	MeOH extract	Portugal	↓ Depolarization induced by H_2O_2 and caspase-9 activity	MCF-7	(Pinteus et al., 2017b)
Fucus vesiculosus	Fucoidan	Commercial*	↑ Smad7, Nrf2, NQO1, HO-1, and GST ↓ TGF-β1 and Smad3. TGF-β1/Smad pathway	Rat liver fibrogenesis	(Hong et al., 2011)
	Fucoidan	Commercial*	↓ Bax, iNOS, TNF-α, lL-1β ↑ Bcl-2, caspase-3	Acetaminophen-liver damage in male Sprague Dawley rat and HL-7702	(Hong et al., 2012)
	Fucoxanthin	Commercial	↑ AKT, Nrf2 pathway	HaCaT	(Zheng et al., 2014)
	3-bromo-4,5-dihydroxybenzaldehyde	Commercial	↑ Nrf2 pathway	HaCaT	(Kim et., al 2017a)
Gelidiella acerosa	Petroleum ether, benzene extracts	India	↓ AChE and BuChE, β-secretase, and MAO-B activities, caspase-3 activity and Bax expression	Rat Aβ 25–35-treated	(Nisha and Devi, 2017)
Gracilaria birdiae	EtOH and aqueous extracts	Brazil	↑ GSR and CAT levels	3T3-L1 and mouse with supplemented food	(Barros-Gomes et al., 2018)
Hizikia fusiformis	Polysaccharides	South Korea	↓ JNK phosphorylation	Rat ethanol-induced peptic injury	(Choi et al., 2009)
Laminaria japonica	Fucoidan	China	↑ Bcl-2 ↓ Bax and caspase 3 and improves ACh neurotransmission	Rat Aβ 25–35-treated	(Gao et al., 2012)
Padina pavonia and Turbinaria ornata	EtOH extract	Egypt	↓ NF-κB	HTC-116 and AOM-induced colon carcinogenesis in mice	(Mahmoud et al., 2015)
Sargassum muticum	Phenolic compounds/MeOH:MeCl extracts	Portugal	↓ Caspase-9 activity	MCF-7	(Pinteus et al., 2017a)
Ulva lactuca	Crude polysaccharide extract	Egypt	↓ TNF-α and NO, Bcl-2, and p53	DMBA-induced mammary gland tumor in Wistar female rat	(Abd-Ellatef et al., 2017)

Abbrv. 184B5: normal human breast cell line; Aβ: amyloid beta peptide; ACh: acetylcholine; AChE: acetylcholinesterase; AOM: azoxymethane; AKT: protein kinase B; Bax: Bcl-2 associated X protein; Bcl-2: B-cell lymphoma 2; BuChE: butyrylcholinesterase; CAT: catalase; COX-2: cyclooxygenase-2; DMBA: 7,12-dimethylbenz[α]anthracene; ERK1/2: extracellular signal-regulated protein kinase; EtOH: ethanol; GST: glutathione S-transferase; H_2O_2: hydrogen peroxide; HaCat: human keratinocyte cell; Hek-293: human embryonic kidney cell line; HO-1: heme oxygenase-1; HT22: hippocampal neuronal cells line; HUVECs: human umbilical vein endothelial cells; iNOS: inducible nitric oxide synthase; GSH: intracellular glutathione; GSR: glutathione reductase; JNK: jun N-terminal kinase; MAO: monoamine oxidase; MAO-B: monoamine oxidase B; MCF-7: human breast adenocarcinoma cell line; MeCl: dichloromethane; p53: tumor protein p53; SH-SY5Y: human neuroblastoma cell line; TGF-β1: transforming growth factor-beta1

**Purchased from Santa Cruz Biotechnology.

* Purchased from SIGMA.

1. Were the main findings of the study clearly described?
2. Was the hypothesis/aim/objective of the study clearly defined?
3. Did the authors mention the sample size?
4. Were experimental conditions identical across study groups?
5. Were the caregivers/investigators blinded to knowledge of experimental group?
6. Were the obtaining conditions of the seaweeds/compounds (collection data) clearly described?
7. Were the agents used reported?
8. Was the route of administration defined?
9. Were the animals selected at random outcome assessment?
10. Was the distribution of relevant baseline characteristics balanced for the experimental and control groups?
11. Were protocols related to animal experiments followed the standard norms recommended by "Animal Care Committee"?
12. Was the study apparently free of other problems that could result in high-risk bias?!

Fig. 4. Methodological quality and assessment of the risk of bias tool.

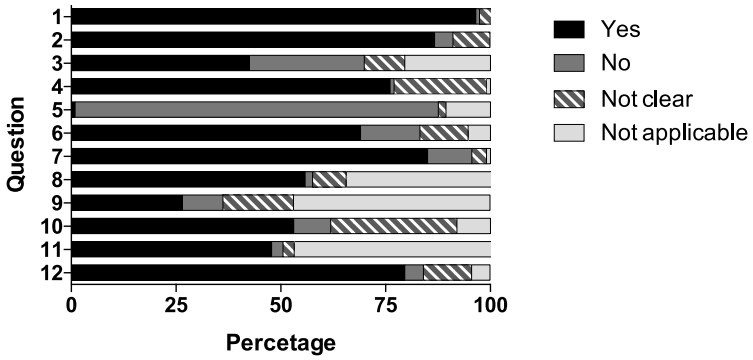

Fig. 5. Evaluation of the methodological quality and assessment of the risk of bias using the RoB tool. The bars represent the percentage of articles found in each category.

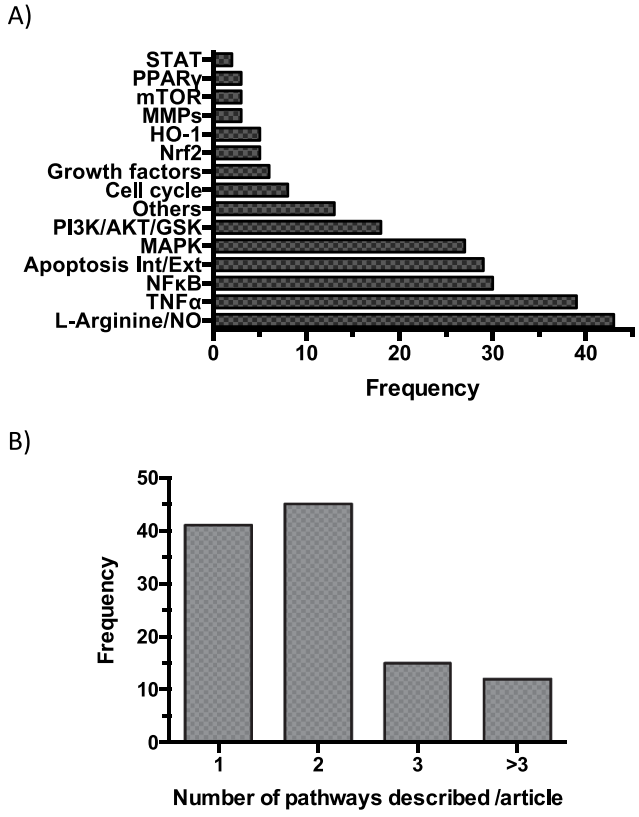

Fig. 6. Quantitative analysis of the signaling pathways reviewed. (A) Number of times that one molecular pathway was described in the articles. When multiple proteins were reported we followed the criteria describe above to name each pathway. (B) Number of pathways described per article reviewed.

cells. Thus, they reported that polyphenols selectively regulate *Bcl2, EGFR, PDGFA, VEGF, AKT, TERT, kRas* and *FGF* mRNA levels the phosphorylation of EGFR and AurKb and the protein levels of EGFR, KRAS, and STAT3. Moreover, polyphenols inhibited the transcription of NF-κB. The molecular effect of polyphenols seems to be dependent of the polarity fraction from which it is obtained. Besides, this effect was also correlated with the anti-oxidant activity of the tested polyphenols (Aravindan et al., 2013).

Sulfated polysaccharides from green alga *Monostroma nitidum* display anti-proliferative activity against a human gastric carcinoma and cervical cancer cell lines. Apparently, this effect was mediated by an immunomodulatory mechanism that activated iNOS and COX-2 expression and the production of NO and PGE2 in murine macrophage RAW264.7 cells (Karnjanapratum and You, 2011). Furthermore, the pepsin enzymatic extract from *Porphyra yezoensis* also showed an immumodulatory effect on murine splenocytes, activating CD45 + CD11b + macrophage and dendritic cell populations and Ly-6C + Ly-6G + macrophages/monocytes and the secretion of cytokines like IL-1β, IL-10, and IL-12, IFN-γ, and TNF-α (Herath et al., 2018).

Metastasis is a complex process in which cancer cells disseminate to distant organs, and involves activation of epithelial-mesenchymal transition, local invasion, intra and extravasation, among other cellular mechanisms. Several cell types participate in this process through the activation of several signaling pathways (Arvelo et al., 2016). Some of these events are achievable by the action of matrix metalloproteinases (MMPs) that degrade the ECM (Fig. 10). In this context, commercial fucoidan from *F. vesiculosus* inhibited cell invasion and migration of A549 cells through the decrease in the activity of MMP-2. This effect was due to the inhibition of the ERK1/2 MAPK and PI3K/AKT/mTOR pathways. Additionally, it has been demonstrated that fucoidan inhibits the activation and nuclear translocation of NF-κB, which plays a central role in MMP-2 gene expression (Lee et al., 2012b). Furthermore, the brown seaweed polyphenol phloroglucinol inhibited the UVB-induced expression and activation of MMP-1 through the regulation of MAPK pathway in HaCaT cells. UVB induces intracellular calcium release; consequently, MAPK family members ERK1/2 and JNK are

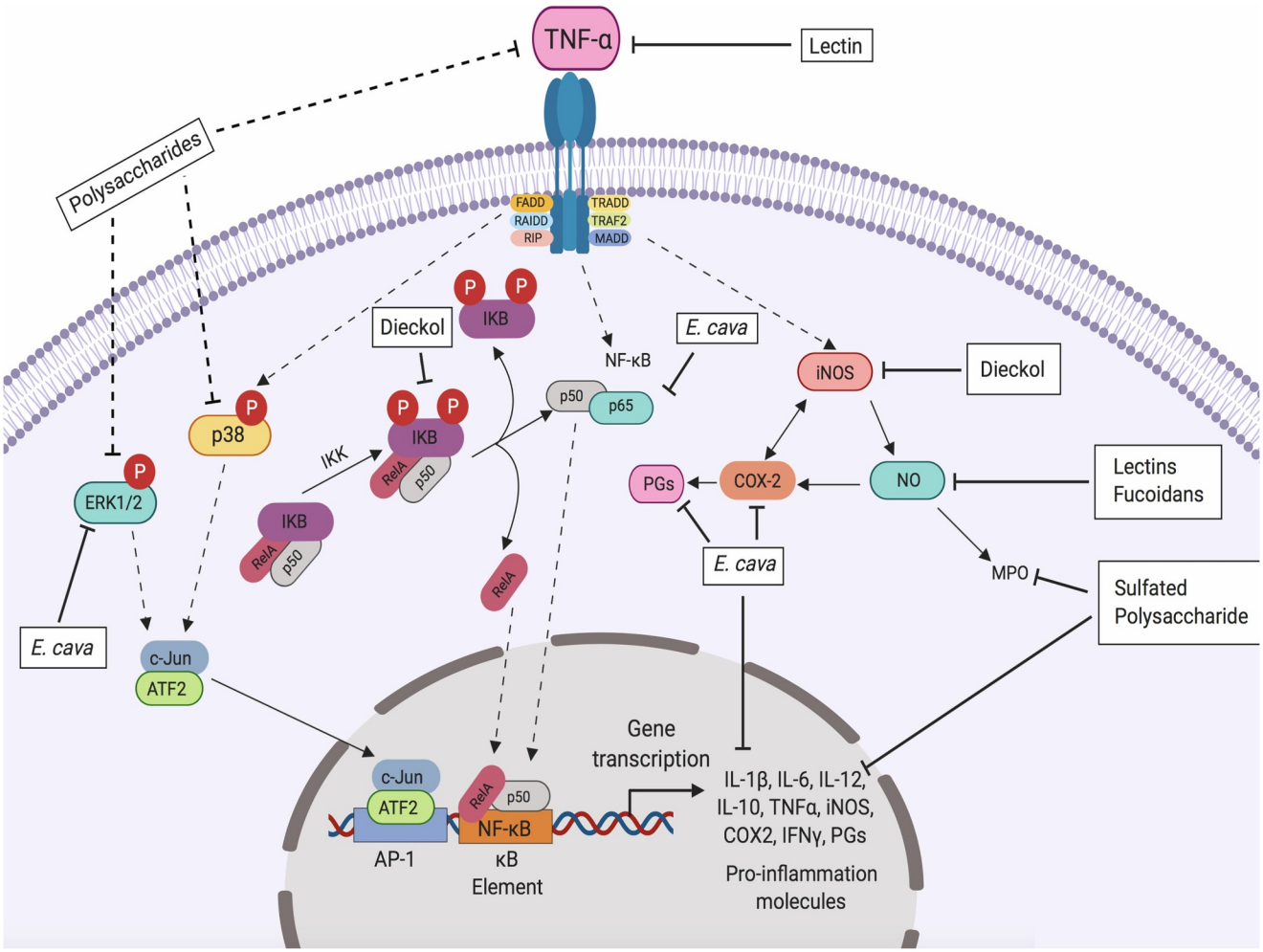

Fig. 7. Schematic representation of the TNF-α signaling pathway modulated by seaweeds. The illustration shows that polysaccharides, lectins, fucoidans and polyphenols obtained from algae block the action TNF-α signaling (see text for details).

phosphorylated and activated, following by the phosphorylation of its targets like AP-1 transcription factor that eventually binds MMP-1 promoter activating its transcription (Fig. 10). Phoroglucinol blocked this pathway and the production of ROS that also contributes to the UVB effects in HaCaT keratinocytes (Piao et al., 2012). Similarly, methanol extract from brown seaweed *Hydroclathrus clathratus* inhibited TNF-α-induced mRNA and protein expression of MMP-9 in T24 human bladder carcinoma cells, reducing cell invasion tested in a matrigel assay. *H. clathratus* extract down regulated the MAPK, PI3K/AKT and NF-κB signaling pathways (Jayasooriya et al., 2012).

Similar to fucoidans and polyphenols, fucoxanthins have also been shown to regulate intracellular pathways (Zhang et al., 2015). In mouse epidermal JB6 P+ cells fucoxanthin blocked the TPA-induced transformation through Nrf2/ARE signaling activation, which in turn, induces the demethylation of CpG sites in tNrF2 gene (Yang et al., 2018).

Commercial fucoxanthin exerts cytotoxic effects against the HeLa cell line. Fucoxanthin mediated autophagy by down-regulation of the AKT/mTOR signaling pathway (Hou et al., 2013). Likewise, fucoxanthin promoted apoptosis in U87 and U251 human glioblastoma cell lines, through the inhibition of the PI3K/AKT/mTOR signaling pathway. Furthermore, fucoxanthin attenuates invasion and migration by inhibiting the p38MAPK/MMP-2 and −9 activation (Liu et al., 2016) (Fig. 10). Fucoxanthin and fucoxanthinol from *U. pinnatifida* induced cell cycle arrest by blocking cyclin D1, cyclin D2, CDK4 and CDK6 expression, as well as GADD45a expression on HTLV-1-infected T cells. Moreover, these molecules stimulate apoptosis by reducing the expression of Bcl-2, XIAP, cIAP2 and surviving, and the activation of caspase-3, -8 and -9 (Ishikawa et al., 2008).

Heterofucan from *Sargassum filipendula* induced caspase-independent apoptosis in HeLa cells. Heterofuncan promoted apoptosis-inducing factor release from the mitochondrion and expression pro-apoptotic of Bax, while the expression of anti-apoptotic protein Bcl-2 decreased (Costa et al., 2011).

Spatane diterpinoid 5(R),19-diacetoxy-15,18(R and S),dihydrospata-13,16(E)-diene (DDSD) from *Stoechospermum marginatum* alga promoted ROS-mediated mitochondrion apoptosis in murine B16F10 melanoma cells by inactivating of PI3K/AKT signaling pathway (Velatooru et al., 2016). The sesquiterpene elatol isolated from the red alga *L. microcladia* induced apoptosis by reduction of Bcl-xl, cyclins D1 and E, cdk2 and 4, as well as the increment of Bak, caspase-9, and tumor suppressor p53 expression in murine melanoma B16F10 cell line. Moreover, elatol reduced tumor volume of C57C16 mice inoculated with B16F10 cells (Campos et al., 2012).

Ethanol extracts from brown seaweeds *Turbinaria ornata* and *Padina pavonia* possess anti-proliferative effects through up-regulation of PPARγ and p53 expression in azoxymethane (AOM)-induced colon carcinogenesis in mouse. Moreover, the extracts down-regulated NF-κB expression, thereby diminishing colon inflammation (Mahmoud et al., 2015).

Anti-diabetic activity

Diabetes mellitus (DM) is a chronic disease characterized by high

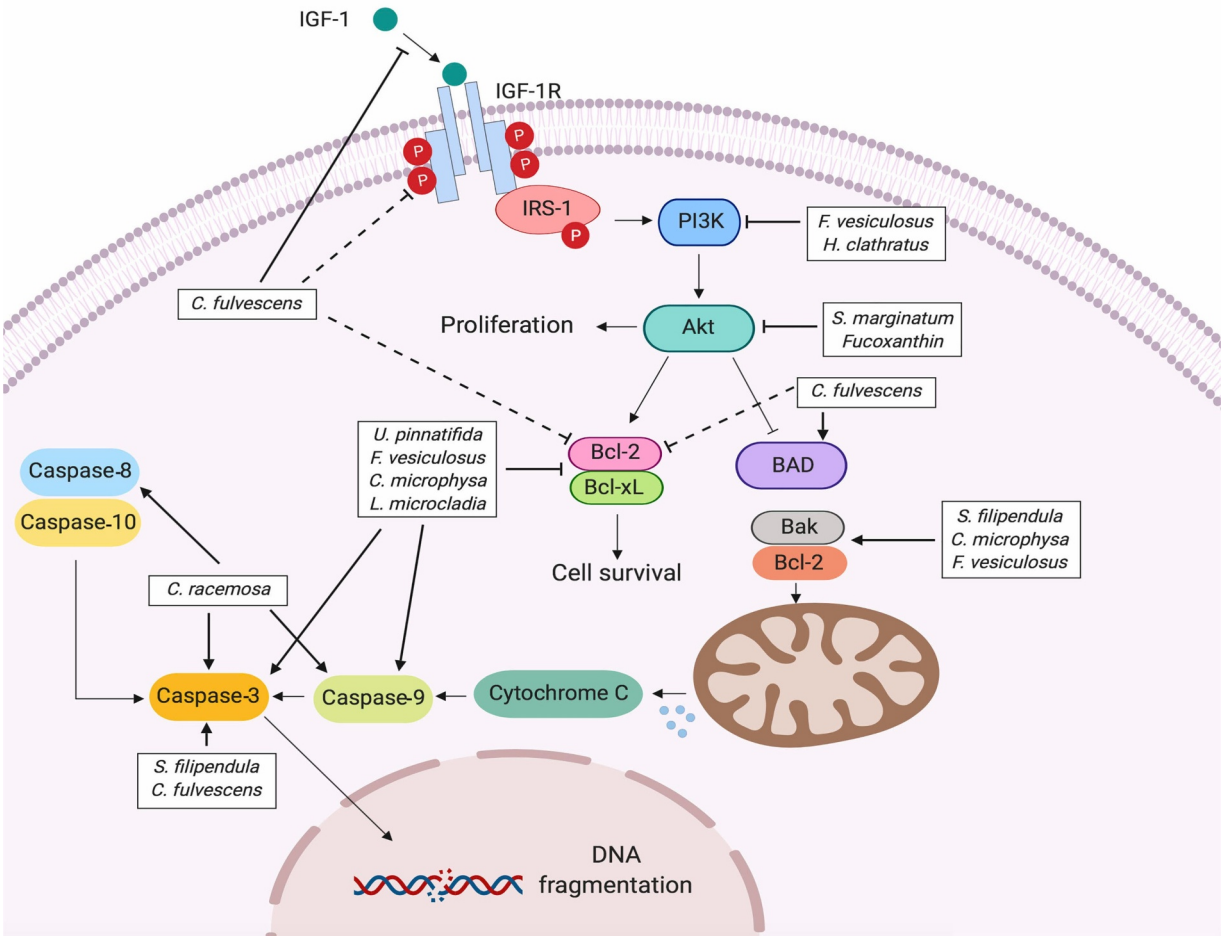

Fig. 8. Schematic representation of IGF-1R signaling modulation by seaweeds. The scheme illustrates that several seaweeds modulate targets from IGF-1R signaling that regulate apoptosis and cell survival (see text for details).

blood glucose levels caused by reduction or complete lack of insulin in the body. Insulin is produced in the pancreas and its function is to transport bloodstream glucose inside the cell. When the body does not secrete enough insulin or when the target cells do not respond to it, hyperglycemia occurs. Long-term hyperglycemia induces chronic health complications such as neuropathy, nephropathy, retinopathy and cardiopathies (stroke, myocardial infarction and peripheral vascular disease). According to the International Diabetes Federation, there are 46 millions of diabetic individuals in North America, and the increase of 35% is predicted for the year 2045 (IDF, 2017). Since DM is one of the major public health problems, efforts have been focused in the development of new drugs to control its complications. In this regard, natural products seem to have therapeutic potential.

Recently, there is a great interest in biological active compounds found in seaweeds, which appear to have anti-diabetic activity through activation of specific signaling pathways (Table 3). For instance, *Caulerpa okamurae* metabolites target transcription factors involved in adipogenesis. Indeed, ethanol extract treatment reduces free fatty acids, triglycerides, total cholesterol, glucose, and insulin in plasma and lipids in the liver in mice under a 60% of energy content fat diet. Moreover, the ethanolic extract reduced the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ), CCAAT/enhancer-binding protein-α (C/EBPα) and the sterol regulatory element binding protein-1c (SREBP) in 3T3-L1 adipocytes (Sharma et al., 2017). Likewise, *Eisenia bicyclis,* a brown alga of the Laminariaceae family, contains several bioactive compounds with biological effects such as 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, dieckol and phlorofucofuroeckol A, which have influence on transcription factors of adipocyte differentiation. These phlorotannins especially 6,6′-bieckol reduced adipocyte differentiation through the inhibition of mRNA expression of transcription factors such as PPARγ, C/EBPα and SREBP-1c in 3T3-L1 adipocytes (Kwon et al., 2015) (Fig. 11). These latter played an important role in the maintenance of size and number of fat cells during adipogenesis. Therefore, *Caulerpa okamurae and Eisenia bicyclis* could be useful in preventing metabolic disorders associated with obesity.

In addition, some reports indicate that fucoxanthin, a carotenoid found in *U. pinnatifida*, reduces the abdominal WAT in diabetic/obese KK-Ay mice and Wistar rats subjected to dietary fat. Likewise, it has been demonstrated that dietary fucoxanthin increased mitochondrial uncoupling protein 1 (UCP-1) (Fig. 11), which is involved in the control of energy expenditure and energy balance. This suggests that the reduction in weight gain by the dietary fucoxanthin may be through the induction of the protein and the gene expression of UCP-1 in WAT (Maeda et al., 2007, 2008). Furthermore, fucoxanthin increases the hepatic docosahexaenoic acid (DHA) in KK-Ay mice; which could be correlated with its anti-obesity effect (Maeda et al., 2008). Also, fucoxanthin decreases blood glucose and plasma insulin through out down-regulating TNF-α mRNA expression in WAT (Maeda et al., 2007). Moreover, fucoxanthin not only attenuated the over expression of MCP-1 and TNF-α mRNA in the perigonadal and mesenteric WATs, but also reduced the IL-6 and PAI-1 mRNA levels of KK-Ay mice, an effect that is not observed in lean C57BL/6J mice. In a similar way, fucoxanthinol reduced MCP-1 and IL-6 mRNA expression in differentiating 3T3-F442A cells stimulated with TNF-α. Moreover, fucoxanthinol decreased TNF-α mRNA expression, protein production and iNOS and COX-2 mRNA expression in RAW264.7 macrophage-like cells treated with palmitic

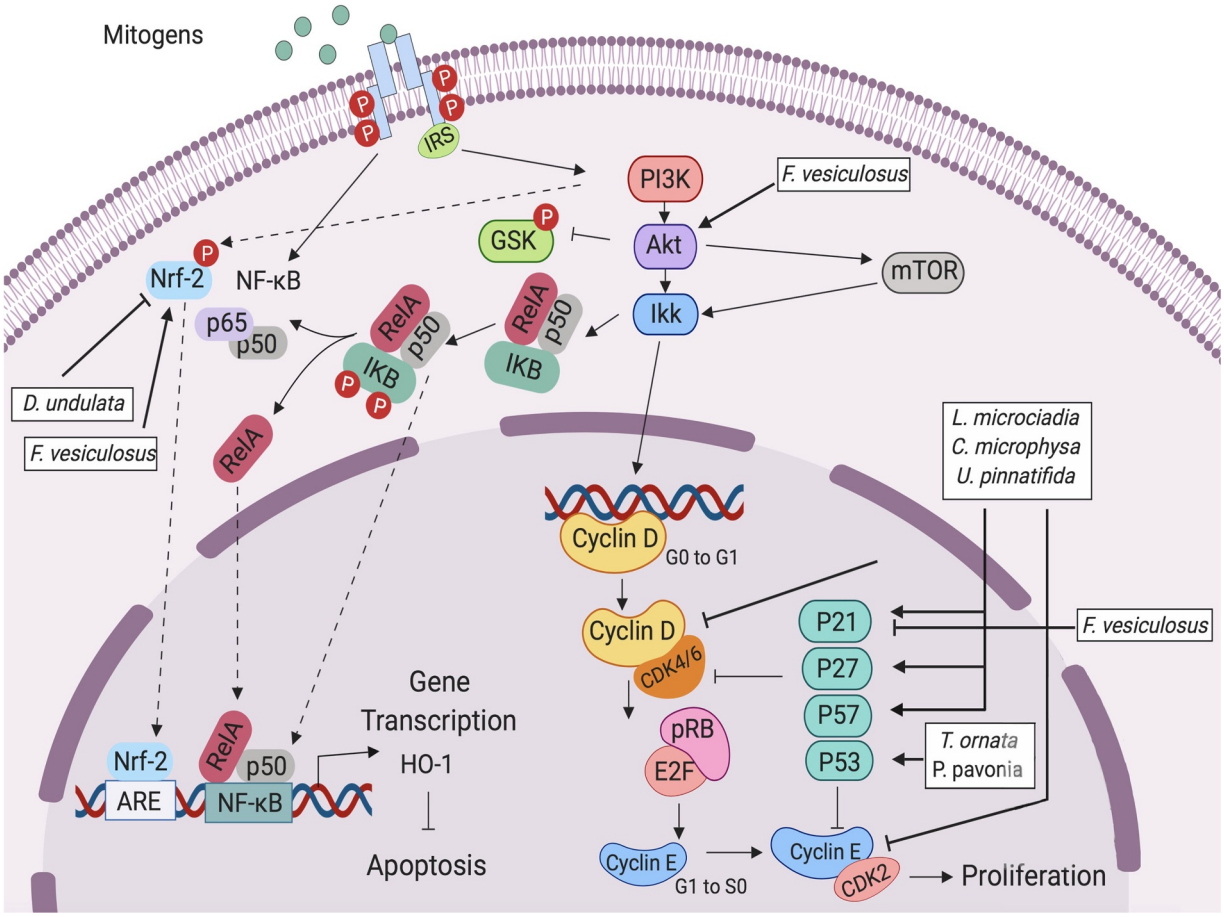

Fig. 9. Schematic representation of mitogens-activated signaling regulated by seaweeds. The illustration shows that marine algae could modulate mitogens-activated canonical signaling and therefore induce and/or block apoptosis and proliferation (see text for details).

acid (Hosokawa et al., 2010). Since, MCP-1 promotes the increase of proinflammatory cytokines such as TNF-α and IL-6 in obesity, inducing insulin resistance, and iNOS, NO and COX are related to inflammation, fucoxanthin and its metabolite fucoxanthinol could be a potential therapeutic option to reduce obesity and hyperglycemia.

In the same vein, kelp powder of *Laminaria japonica* decreased NO and iNOS expression in islet cells in a DM model induced by alloxan in rat. This result suggests a recovery of the islet cell secreting function as well as a hypoglycemic activity (Long et al., 2012). Furthermore, fucoidan, a metabolite extracted from *L. japonica* showed a protective effect on diabetic hindlimb ischemic injury by decreasing inflammatory factors and promoting endothelium-dependent vasodilation and revascularization. In human umbilical vein endothelial cells (HUVECs), the treatment with fucoidan promotes eNOS phosphorylation, NO production and the vascular endothelial growth factor (VEGF) expression (Liu et al., 2018). These results suggest a possible molecular mechanism of fucoidan in promoting vasodilatation and angiogenesis in DM.

As mentioned above dieckol isolated from *E. cava* is an important bioactive compound. Dieckol showed anti-diabetic-like effects by the activation of both AMPK and AKT signaling pathways, which regulate many cellular functions such as glucose metabolism (Kang et al., 2013). Therefore, this is one of the molecules of interest to be used for preventing DM-related health complications. Recently, it has been shown that ethanol extract of *Lessonia nigrescens* reduces blood glucose levels by inducing PI3K and inhibiting JNK signaling pathways (Fig. 11) in streptozotocin-induced diabetic mice fed with high-sucrose/high-fat diet. Therefore, ethanol extract of *L. nigrescens* might be beneficial as a treatment for type 2 DM (Zhao et al., 2018).

Anti-oxidant activity

All aerobic organisms produce reactive oxygen species (ROS) as a consequence of substrate oxidation and aerobic respiration. The anti-oxidant system is a defense mechanism that deals with small amounts of ROS like hydrogen peroxide (H_2O_2), hydroxyl radicals (-OH), and superoxide anions (O_2^-) (Mates et al., 1999; Vendemiale et al., 1999). Free oxygen radicals are unstable and toxic compounds that produce oxidized molecules, which exert their effects on lipids, proteins, and nucleotides compounds. In human cells, high levels of free oxygen species generate both morphological and functional disturbances that can lead to different diseases (Martinez-Cayuela, 1995), such as diabetes, inflammatory joint disease, atherosclerosis, asthma, cancer, senile dementia, schizophrenia, Alzheimer and other neurodegenerative diseases, among others (Atwood et al., 2018; Florence, 1995; Losada-Barreiro and Bravo-Diaz, 2017; Mitra et al., 2017). Due to these metabolic complications, there is a great interest in finding anti-oxidant compounds, mainly from natural sources, that prevent and/or reduce the effects of aforementioned pathologies. An anti-oxidant acts through various general mechanisms that include: 1) scavenging the biologically important reactive oxygen species, 2) preventing the formation of reactive oxygen species, or 3) repairing the damage that reactive oxygen species do (Halliwell, 1991; Mitra et al., 2017).

To minimize oxidative damage in living cells, the search for new and safe anti-oxidant compounds of natural origin has focused on plants and seaweeds. Several marine algae have shown anti-oxidant effects, especially those from the brown seaweed family (Fujimoto and Kaneda, 1980; Matsukawa et al., 1997; Palanisamy et al., 2017). The mechanisms by which the anti-oxidant compounds of marine algae act are diverse and involve different signaling pathways (Table 4). Cellular anti-

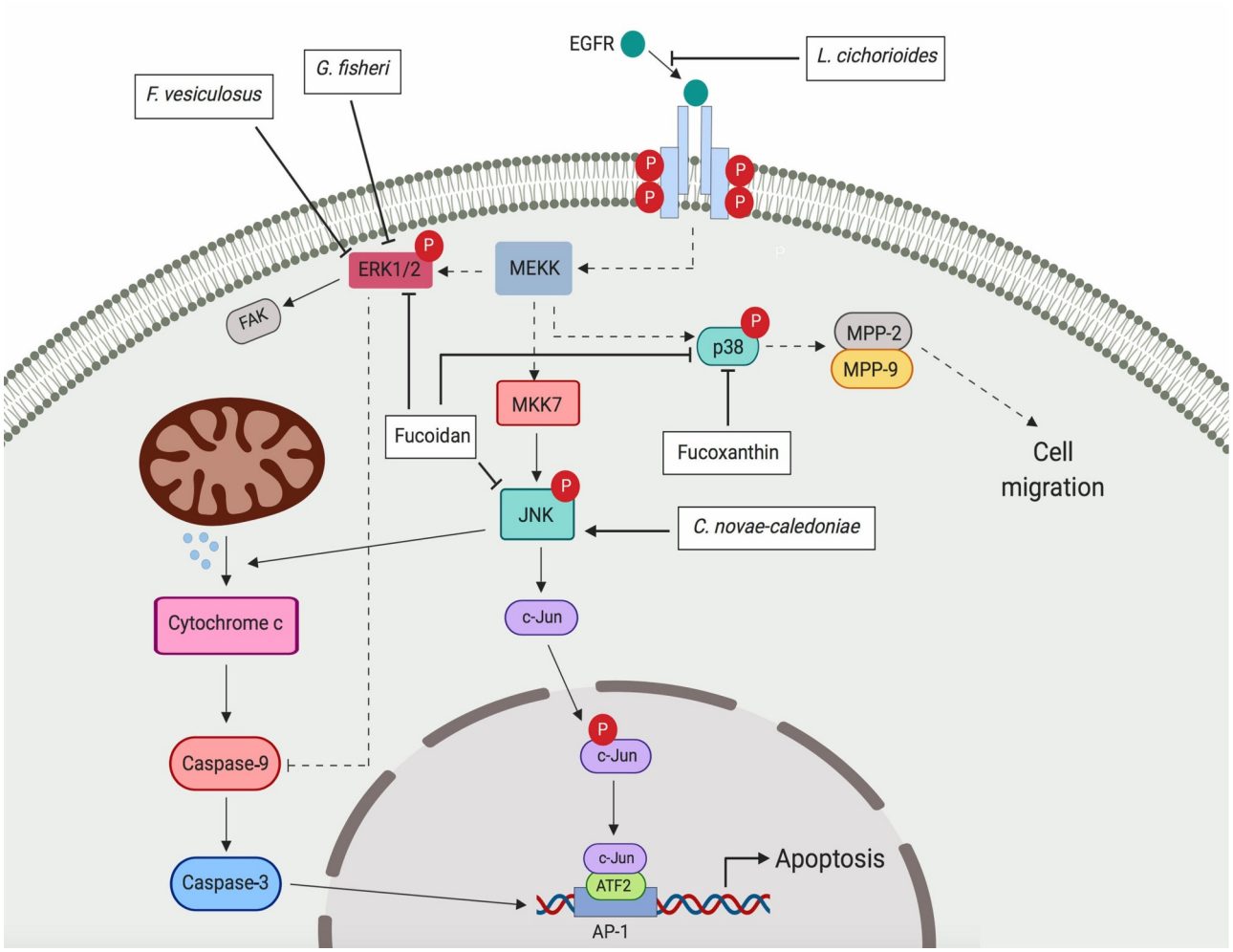

Fig. 10. Schematic representation of regulation of cell migration and apoptosis signaling pathways by seaweeds. The draw shows that several algae species modulate apoptosis and cell migration through MAPK signaling regulation (see text for details).

oxidant mechanisms of seaweeds, like *Gracilaria birdiae,* involve a decrease in the enzymatic activity of oxidative stress biomarkers like SOD, CAT and GRS, proved in mice tissues (Barros-Gomes et al., 2018).

It is proposed that seaweeds as *Codium tomentosum, Padina pavonica, Sargassum muticum, Saccorhiza polyschides, Ulva compressa, Fucus spiralis, Gelidiella acerosa*, and *Laminaria japonica* (Gao et al., 2012; Hong et al., 2012; Nisha and Devi, 2017; Pinteus et al., 2017a, b; Silva et al., 2018) have the capability to inhibit cellular apoptosis promoted by ROS (Fig. 11). These algae prevent changes in mitochondrial membrane potential, thus allowing the cells to maintain their respiratory chain physiological functions in order to produce ATP. If there are not changes in mitochondrial membrane potential, neither cytochrome c oxidase nor pro-caspase-9, are activated. When caspase-9 is not activated by the apoptosome, then do not appear cleaves or activation of other downstream caspases such as caspase-3. It has been reported that *F. vesiculosus, L. japonica*, and *G. acerosa* down-regulate the expression of pro-apoptotic genes like *Bax* (Gao et al., 2012; Hong et al., 2012; Nisha and Devi, 2017), which is an inducer of the mitochondrial outer membrane permeabilization. *Bax* regulation is related to the *Bcl* pro-survival genes (mainly with *Bcl-XL*), which are also involved in the regulation of mitochondrial membrane permeability, and experiments with fucoidan from *F. vesiculosus, U. lactuca*, and *L. japonica* showed a down-regulation of *Bcl-2* gene (Abd-Ellatef et al., 2017; Gao et al., 2012; Lee et al., 2010), indicating that these two genes are involved in the anti-oxidant response mechanism. *Bcl* expression is regulated by phosphorylated protein JNK which also mediates the phosphorylation of Fos and Jun, and their action on DNA to regulate the expression of the pro-apoptotic gene *p53*, like is reported with the crude polysaccharide extract of *U. lactuca* (Abd-Ellatef et al., 2017). In rat cells, polysaccharides of *Hizikia fusiformis* decrease the phosphorylation of JNK (Choi et al., 2009), and therefore the expression of *p53* gene. JNK phosphorylation depends of ASK1, AIP, and TRAF2, which in turn depends on the union of TNFR1 to TNF-α. Fucoidan from *F. vesiculosus* and crude polysaccharide extract of *U. lactuca* decrease activity of TNF-α (Abd-Ellatef et al., 2017; Hong et al., 2012), and therefore phosphorylation of JNK is also reduced. Besides, it seems that *E. cava* (Lee et al., 2010), and *Padina pavonia* and *Turbinaria ornata* (Mahmoud et al., 2015) extracts interfere with the formation of the TNF-TNFRI complex, which down-regulates the NF-κβ signaling pathway decreasing the synthesis of inflammatory mediators like COX-2 and iNOS, and inflammatory cytokines like IL-1 (Fig. 7). TNF-α has an indirect interaction with Smad7 who inhibit Smad3, as has been reported in *F. vesiculosus* (Hong et al., 2011). Also the down-regulation of *TGFβ* via TGFβRI phosphorylation represses Smad3, as reported in *F. vesiculosus* (Hong et al., 2011). Besides the above apoptotic pathways, it has been proved that anti-oxidative seaweeds compounds are regulating Nrf2, probably via KEAP1. Once Nrf2 is activated, it is possible the expression of HO-1, NQO1, and GST, as has been proved with 3-bromo-4,5-dihydroxybenzaldehyde (Kim et al., 2017a), fucoxanthin (Zheng et al., 2014), fucoidan (Hong et al., 2011), and sesquiterpene zonarol (Shimizu et al., 2015). The anti-oxidant effect of seaweeds has also been observed in the nervous system, where fucoidan from *L.*

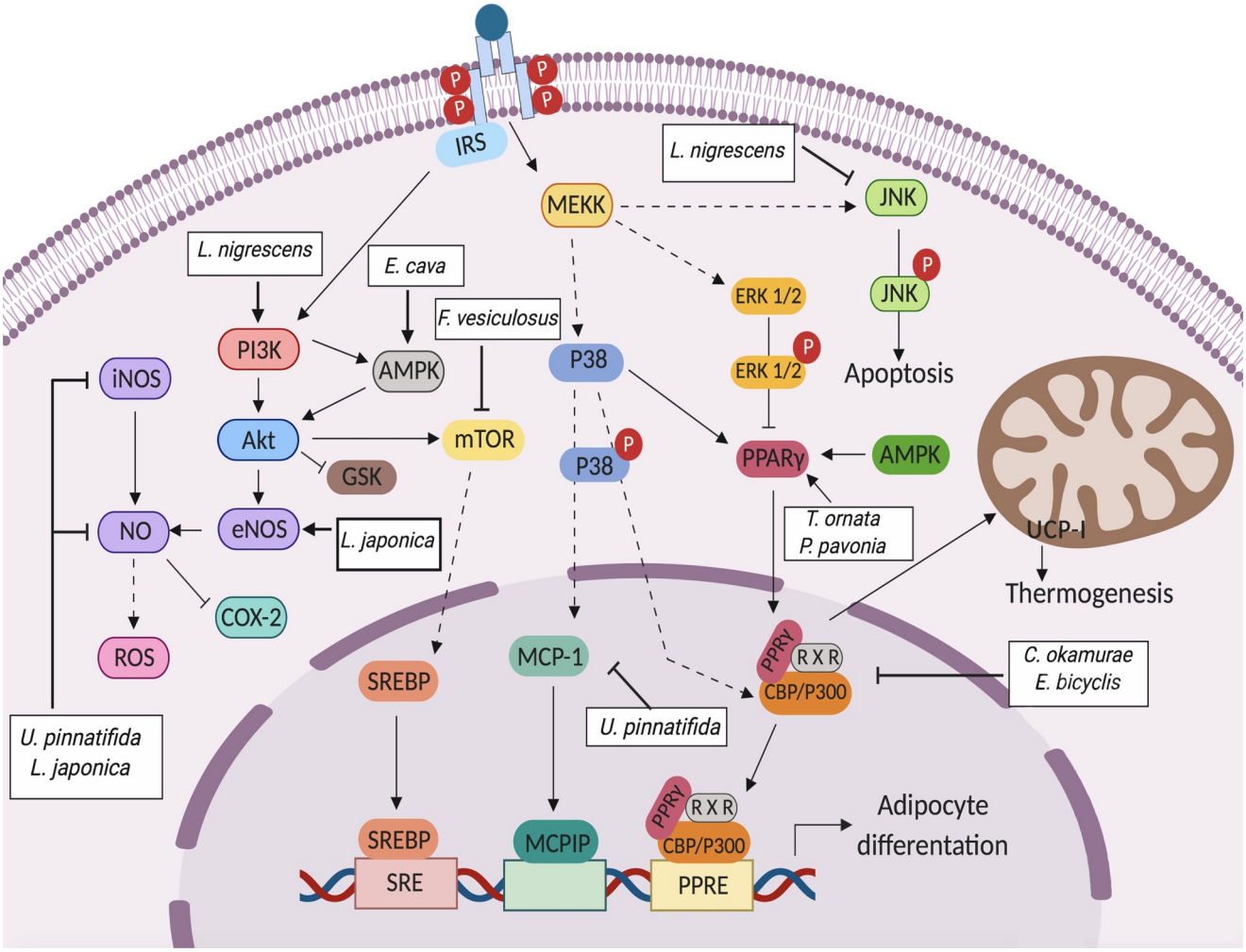

Fig. 11. Schematic representation of regulation of adipocyte differentiation by marine algae. The scheme illustrates that seaweeds modulate PI3K/AKT, l-arginine /NO and MAPK pathways regulating adipocyte differentiation and thermogenesis (see text for details).

japonica (Gao et al., 2012), and petroleum ether and benzene extracts from *G. acerosa* (Nisha and Devi, 2017) improves acetylcholine neurotransmission via AChE and BChE, enzymes that can degrade some neurotoxic compounds.

Quality and risk of bias assessment

To assess the quality and the risk of bias of the articles that fitted the inclusion criteria we design a tool made of 12 questions, in which we assessed the main quality criteria for *in vitro* and *in vivo* preclinical studies (Fig. 4). As mentioned above, we built the RoB tool in three documents. The highest risk we found was blindness of the studies: 86,7% of the articles did not mentioned if the caregivers/investigators were blinded to knowledge of experimental group. We found that less than 1% described blindness in the design of the study. The other bias of risk we detected was to the question: Did the authors mention the sample size? To answer this question we decided to asses the studies in accordance with the type of model used: when animal models were used we search for the number of animals in which the compound/extract were tested. However, when cell lines were used we search the number of replicates in which the compound/extract were tested. Using these criteria, 27,4% did not mention the sample size, whereas in 9,7% of the studies was not clear.

We detected moderate risk of bias when describing the collection data. As mention above, although the authors mentioned the country where the collection was performed (Fig. 3), they did not provide the geolocation, the season of the year and specific conditions of algae material collection. The effect that the different collection sites may have on the composition of algae must be added, due to the diverse nutrients and the dissimilar temperatures of their habitats. The authors also made no mention which controls they used when prepared the extracts, *e.g.*, microbiological (data not show), but the authors did describe in detail the methods of preparation and storage conditions. There is only one article in which a commercial dietary supplement was tested (Costa et al., 2015). Thereby, 24,4% of the studies does not mention the sample sized (Fig. 5). Moreover, 30,1% of the studies was not clear if the distribution of relevant baseline characteristics was balanced for the control and the experimental group. In the same manner, in 22,1% of the studies the conditions between experimental and control groups were not clear. All other criteria were considered low risk of bias. Despite these variables, the effects that marine algae have on a diversity of mammalian cellular pathways are clear.

Quantitative and qualitative description of the signaling pathways

After describing all the pathways activated by seaweeds, we performed the analysis of them and the quantitative results are shown in Fig. 6. As we can observe, the pathway that was more frequently mentioned in the articles was L-Arginine/NO (43), followed by TNF-α (39), NF-κB (30), apoptosis (29), MAPK (27), PI3K/AKT (18), cell cycle (8), growth factors (6), Nrf2 (5), HO-1 (5), MMPs (3), mTOR (3), PPARγ (3), STAT (2), others (13) (Fig. 6a). It is noteworthy that some articles

just mentioned one molecule from the signaling pathway, *e.g.,* ERK1/2 or NF-κB, but some other articles showed the modulation of more than one pathway. Therefore, we quantify the number of pathways mentioned in each article. We found that 41 articles reported the modulation of one pathway, while 45 described two, 12 articles mentioned three and 15 works showed more than three pathways, being five the largest number of pathways mentioned. This latter is not unexpected since most of the pathways are related with each other. It means, that there is cross talk between molecular pathways, in which two, or even more, signaling pathways reinforce between each other. This has been described in several tissues, and also by algae-derivate compounds, as caulerpenyne, caulerpin, caulersin, and racemosin C, in which targets include microtubule dynamics, unfolded protein response, mitochondrial health, cell cycle, metabolic and stress pathways by the modulation of AMPK, GRP78, GADD153, Bid, Bax, AIF, Bcl2, P21, cyclin D, cyclin E, caspase-9, and PTP1B (Mehra et al., 2019). Moreover, MAPK, PI3K, among others signaling families are considering to converge pathways because many intracellular signals pass through their activation, and this has been observed in several cell types and activation molecules (Jacob et al., 2002; Müller et al., 1998). The concomitant activation is also relevant since numerous target genes and effector molecules required more than one signal to be activated. Therefore, some diseases as well as biological functions share molecular mechanisms, and sometimes the activation or blocking of one molecular pathway could drive to the modulation of an alternative and/or completely different cellular function (Abd-Ellatef et al., 2017). In this sense, the molecular mechanisms herein described should also share signaling pathways. For instance, TNF-α could activate apoptosis pathway by the action of molecules as FADD, RIP. On the other hand, TNF-α-mediated NF-κB activation modulates proliferation or inflammation through MAAD, TRADD molecules. However, NF-κB activation also could mediate ROS production that participates in the development of cancer (Sethi et al., 2008).

Another important aspect is the characterization of the molecules that are targeted by seaweeds. For this, molecular docking studies are needed. Ogunwa and colleagues (2018) performed *in silico* analysis of the interactions of brown seaweeds-derived compounds: phlorofucofuroeckol-A, eckol, dieckol, 7-phloroeckol, dioxinodehydroeckol, phloroglucinol and glucose metabolism regulators protein tyrosine phosphatase (PTP) 1B and α-glucosidase. The authors demonstrated that the phlorotannins are able to bind to allosteric pocket of PTP1B and to the putative substrate-binding site of α-glucosidase. Therefore, these compounds are promising drugs in the management of DM (Ogunwa et al., 2018).

The complexity of seaweeds-derived compounds over the terrestrial plants-derived compounds should be noticed (Carvalho and Pereira, 2014). Besides proteins, polysaccharides and lipids components, another macroalgal secondary metabolites can be found, for example terpenoids, acetogenins, and polyphenols. The degree of complexity within seaweeds-derived compounds could be explained, at least in part, by differences on growth and interactions that they have. Marine algae habitats included characteristics such as light exposure, temperature, shore features, depth, tides, and intertidal species, etc., that determine the compounds that individual alga produces. Another important aspect of seaweeds is that they have faster growth rate than higher terrestrial plants, and a higher mean photosynthetic efficiency (Gutierrez-Rodriguez et al., 2018). Also, the metabolites are produced as defense source (Paul et al., 2014). Therefore, seaweeds metabolites included large amounts of halogenated compounds that help to the algae functioning, and all these characteristics make seaweeds-metabolites irreplaceable to drug development. Besides the importance of secondary metabolites (*e.g.* polyphenols, terpenoids, etc.,) in the modulation of signal transduction, a wide type of polysaccharides also targets intracellular pathways. We found that 29 articles reported the modulation of molecular targets by fucoidans and sulfated polysaccharides (see above). This is important because polysaccharides are free-radical scavengers and possess antioxidant activity (Ahmed et al., 2014). Additionally, they usually are produced in high amounts.

Finally, it is important to mention that there is other important bioactivities modulated by algae, *e.g.* anti-viral, bactericide, anti-fungal, anti-microalgae, anti-leishmanial, etc., (Li et al., 2017; Saito and Tamrin, 2019; Tchokouaha Yamthe et al., 2017; Zerrifi et al., 2018), however, in this review were not included.

Conclusion

The development of molecular biology techniques has allowed the discovery of the molecular mechanisms that mediate diseases, in this sense, signaling molecules have gained importance as therapeutic targets. In this systematic review we gathered plenty information distributed in four databases from studies on the seaweed-isolated compounds and extracts biological activity. Since seaweeds represent a group of organisms with wide biological actions and pharmaceutical potential, several efforts have been made to use algae in therapeutics of cancer, diabetes, inflammation, and asthma, among other diseases. So far, studies have used *in vitro* and *in vivo* models to understand how seaweeds-derived compounds modulate effects on signal transduction pathways. However, clinical trials are needed to understand the efficacy of seaweeds to treat diseases such as cancer, diabetes, and inflammation, among others. We believe this review might facilitate the discovery and design of new drugs from seaweeds to treat diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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