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REVIEW

Marine macroalga *Caulerpa*: role of its metabolites in modulating cancer signaling

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Abstract

Cancer, the leading causes of death worldwide, causes multiple metabolic and physiological alterations, leading to an unregulated proliferation of cells. The existing anticancer therapies are usually nonspecific with side effects and or are extremely expensive, thus hunt for better therapeutics is still on, specially efforts are made to look for naturally occurring molecules. Sea harbors several organisms which are unexplored for their biological potentials. Green macroalga genus, *Caulerpa*, is one such invaluable repository of bioactive metabolites like alkaloids, terpenoids, flavonoids, steroids and tannins with reported bioactivities against many diseases including cancer. Anti-cancerous metabolites of *Caulerpa* like caulerpenyne (Cyn), caulerpin, caulersin, and racemosin C, possess unique structural moieties and are known to exhibit distinct effects on cancer cells. Theses metabolites are reported to affect microtubule dynamics, unfolded protein response, mitochondrial health, cell cycle progression, metabolic and stress pathways by their cross-talk with signalling proteins like AMPK, GRP78, GADD153, Bid, Bax, AIF, Bcl2, P21, cyclin D, cyclin E, caspase 9, and PTP1B. Targeting of multiple cancer hallmarks by *Caulerpa* metabolites, with concomitant modulations of multiple signalling cascades, displays its multifactorial approach against cancer. Evaluation of anti-cancer properties of this genus is particularly important as *Caulerpa* species are widely edible and utilized in several delicacies in the coastal countries. This is the first review article providing a consolidated information about the role of *Caulerpa* in cancer with major contributing metabolites and plausible modulations in cancer signaling and prospects.

Keywords Cancer · *Caulerpa* · Caulerpenyne · Secondary metabolites · Marine algae · Anti-cancer

Abbreviations

Cyn	Caulerpenyne
MXR	Multixenobiotic resistance
ER	Enodplasmic reticulum
UPR	Unfolded protein response
MAPs	Microtubule associated proteins

Introduction

Natural products represent a significant share in global pharmaceutical industry and include anti-cancer drugs like velban (Vinblastine), oncovin (Vincristine), etoposide and teniposide, while many more remain unexplored [1–3]. Where conventional terrestrial resources are being exploited for many decades, marine resources largely remain untapped. The earliest report of marine-derived anti-cancerous agents dates back to 1950s, wherein spongouridine was isolated from a Caribbean sponge, *Tectitethya crypta* (formerly *Cryptotethya crypta*) [4]. However, due to technical hurdles,

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fewer reports emerged thereafter. In the past two decades, a renewed interest in marine-derived products is seen, especially from algae. *Caulerpa*, a green macroalgal genus of family Caulerpaceae, is one such store-house of bioactive ingredients. This siphonous green alga derived its name from two Greek words: *caulos* denoting “stem” and *erpos* signifying “I creep”. The genus *Caulerpa* (J V Lamourox 1809) consists of 97 species, and over 100 varieties [5]. These coenocytic algae have creeping rhizome with colorless rhizoids and erect fronds. The fronds occur in variable shapes ranging from oval grapes and flat blades to feather-like structures [6]. These are salty and peppery in taste and are consumed by many around the world, where *C. lentillifera* and *C. racemosa* are most widely edible with common names viz. sea grapes, lelato, green caviar, limu-fuafua, and lai–lai [7]. These species have fetched enormous attention in the international food market due to their high nutritional value [8]. Many *Caulerpa* species were extensively utilized in aquaria, owing to their aesthetically pleasing phenotype and highly adaptable nature [9]. On the contrary, *Caulerpa* species are also listed in the ‘*world’s worst invasive algal species’* as a noxious weed and consequently termed as *killer algae* [9]. In fact, the genus gained much attention since last three decades mainly because of the invasive potential of species like *C. taxifolia* and *C. cylindracea* (previously recognised as *C. racemosa* var. *cylindracea*) [10].

Caulerpa spp. are distributed in the intertidal and intratidal tropical and semitropical marine waters. Due to inter-tidal zone habitation, these species are periodically exposed to various kinds of stresses like UV, salt, nutrient limitation, light, temperature, shear and desiccation stress etc. which leads to the production of many stress molecules [11]. In response to stress, these species produce many secondary metabolites like bisindole alkaloids and diterpenoids, of which particular interest lies in diterpenoids and sesquiterpenoids with an aldehyde or/and enol acetate. Many of these compounds exhibit a diverse range of bioactivities like insecticidal, anti-microbial, anti-fouling, feeding deterrent, ichthyotoxic, anti-inflammatory, plant growth regulatory, cytotoxic, anti-proliferative, and anti-metastatic activities [12, 13]. Since *Caulerpa* species are edible and have pharmacologically active metabolites, these may provide preventive as well as curative benefits. In this paper anti-cancer activity of *Caulerpa* metabolites and their intervention in cancer signaling cascades is discussed for the first time in this context.

Bioactive metabolites of *Caulerpa*

The uniqueness of secondary metabolites of *Caulerpa* can be attributed to distinct marine environment and physiological adaptations through evolutionary processes. These metabolites include various bioactive compounds for defense, communication, reproduction, competition and infection [14]. Initial probing of this genus was initiated because of the avoidance of *Caulerpa* species by herbivores and a peppery taste of edible species, which fascinated researchers for chemical profiling of several species [15]. *Caulerpa* spp. produce several unprecedented secondary metabolites and most of them are linear or monocyclic terpenoids possessing aldehydic and enol-acetate functional groups. A terminal bis-enol acetate group is uniquely found in this genus of marine algae. This functional group is represented by an acetylated bis-enol category of 1,4-dialdehyde group imparting biological activity to several species [16]. Several solvent-based extraction techniques and chromatographic-purification methods are available that can be utilized for the isolation of these metabolites subject to minor seasonal variations [17–19]. Our group is working on the isolation of bioactive metabolites from methanolic extracts of *C. racemosa* and *C. taxifolia*. Major metabolites documented from genus *Caulerpa* and their bioactivities are listed in Table 1 and major metabolites (Fig. 1) with anti-cancer activity are discussed in brief below.

Caulerpin

Caulerpin ($C_{24}H_{18}N_2O_4$), ‘dimethyl-6,13-dihydrodibenzo [b,i] phenazine-5,12-dicarboxylate methyl ester’, is a red bis-indole alkaloid containing two indole moieties fused to a central cyclooctatetraene diester, with a molar mass of 398.418 g/mol. Its chemical structure was first elucidated by Santos in 1970 and later revised by Maiti and Thompson in 1977 [22, 23]. A major setback for exploring biological effects of caulerpin was its lower yield, however, a recent report suggests an increased total yield from 11 to 25% achieved by Li’s group following modified Chay’s synthesis scheme [24]. Two caulerpin analogues i.e. CLP I and CLP II, have also been reported from *C. racemosa*. It was initially reported as a major constituent of *C. racemosa*, but was later obtained from several species viz. *C. sertularioides, C. serrulata, C. lamourouxii* [25], *C. racemosa var. macrophysa, C. racemosa var. laetevirens, C. ashmeadii, C. cupressoides, C. paspaloides, C. prolifera, C. sertularioides, C. peltata, C. racemosa var. clavifera, C. taxifolia, C. serrulata* [26, 27], and other green and red algae like *Halimeda incrassate* and *Laurencia majuscula*, respectively [28]. Caulerpin exhibits in-vitro anti-tumor activity [29], anti-microbial activity [30, 31], antinociceptive, anti-inflammatory [32], multixenobiotic resistance (MXR) pump inhibitor in algae [33], plant growth regulatory [34] and PTP1B inhibitory activities [35]. In comparison to taxol the activity is relatively lower, however, it is still considered a potential drug lead due to its efficacy on a range of cancer cells and low toxicity in mice model [24].

Table 1 Bioactivity of semi-purified extracts and pure compounds obtained from various species of *Caulerpa*

S. no.	Compound	Activity	References
1	Caulerpenyne	Anti-bacterial; anti-neoplastic; neurotoxic; allelotoxic; anti-mitotic; phytotoxic; and anti-proliferative activity	[44, 45, 56, 58]
2	Caulerpin	Anti-tumor; anti-inflammatory; anti-mitotic, anti-microbial; AMPKα modulatory; and antinociceptive activity	[32, 74, 91]
3	Racemosin C	PTP1B inhibitory activity	[21]
4	Caulersin	PTP1B inhibitory activity	[21]
5	10,11-epoxycaulerpenyne	Cytotoxic	[93]
6	Flexilin	anti-bacterial, anti-fungal	[94]
7	(23E)-3β-hydroxy-stigmasta-5,23-dien-28-one	PTP1B inhibitory; and neuroprotective activity	[47]
8	40,50 -dehydrodiodictyonema A	PTP1B inhibitory activity	[47]
9	Trans-phytol	PTP1B inhibitory activity, MAPK inhibitory activity	[47, 96]
10	Trans-phytyl acetate	PTP1B inhibitory activity	[47]
11	α-tocopherol quinone	PTP1B inhibitory activity	[47]
12	α-tocospirone	PTP1B inhibitory; and neuroprotective activity	[47]
13	(3β,24R)-stigmasta-5,28-diene-3,24- diol	PTP1B inhibitory activity	[47]
14	(3β,24S)-stigmasta-5,28-diene-3,24-diol	PTP1B inhibitory activity	[47]
15	(22E)- 3β-hydroxy-cholesta-5,22-dien-24-one	PTP1B inhibitory; and neuroprotective activity	[47]
16	Taraxerol	Anti-viral; phosphatase inhibitory; anti-nephretic; phospholipase-C (PLC) inhibitory activity, anti-cancer	[95, 97]
17	β-sitosterol	PLC inhibitory; nephrotoxic, Transcription factor inhibitory; acylglycerol lipase inhibitory; hepatoprotectant; phosphatase inhibitory activity	[95]
18	Palmitic acid	Superoxide dismutase (SOD) inhibitory; Catalase inhibitory; NADPH inhibitory; NADH inhibitor; Succinate-CoA ligase inhibitory; apoptosis agonistic activity	[95]
19	Sulfoquinovosyldiacylglycerol (SQDG)	anti-viral activity, DNA pol inhibitory activity	[98, 99]
20	Two unnamed compounds isolated from *C. prolifera* and *C. bikinensis*, respectively	Phospholipase-A_2 inhibitory activity	[100]
21	Sulphated polysaccharide fractions	Antinociceptive; anti-inflammatory; anti-coagulant activity; anti-herpetic activity	[101–103]

Caulersin

Caulersin is another bis-indole alkaloid, first isolated from *C. serrulata* in 1997 and is the only natural product known so far to have a central troponoid bridging bis-indole framework [36]. It has three isomers named caulersin-A, B, and C. Caulersin was, synthetically synthesised and characterized by many researchers [37, 38] and is reported to inhibit activity of Protein Tyrosine Phosphatase 1B (PTP1B), a known negative regulator of insulin signaling [21]. Considering the essential role of PTP1B inhibitors in cancer, it is assumed that caulersin is a potential candidate in cancer therapy [39].

Caulerpenyne

Caulerpenyne (Cyn) ($C_{21}H_{26}O_6$) is a sesquiterpene with molar mass 374.433 g/mol and was first isolated from *C. prolifera* in 1978 [40]. It is the most studied metabolite of this genus and its maximum yield is reported from *C. taxifolia*. Variations in Cyn yield may appear with different climate and habitat. Cyn production is reported maximum during fall (September–October) and minimum during spring (March–May). In addition, *C. taxifolia* facing competition from *Posidonia oceanica* has been observed to yield lower Cyn as compared to non-competitive habitat, which can possibly be an adaptive strategy to win the competition [41]. A *queueing theory* is also proposed to estimate the increase or decrease in Cyn yield, before reaching a critical level [42]. Cyn has well documented biological activities viz. anti-bacterial, anti-neoplastic, neurotoxic, allelotoxic, anti-mitotic, phytotoxic, and anti-proliferative activity [43–45]. It modulates organelles' Ca^{2+} storage, DNA synthesis, protein phosphorylation and is cytotoxic to eight different tumor cells of human origin. It also blocks the cell cycle of sea urchin embryos at a metaphase-like stage and inhibits the activation of MAPK (mitogen activated protein kinases) proteins [46]. On the contrary, there are reports of neurological disorders in the patients who consumed *C. taxifolia*, accidently, and Cyn mediated modulation of the activity of Na^+ induced Na^+/K^+ ATPase in leech neurons [45].

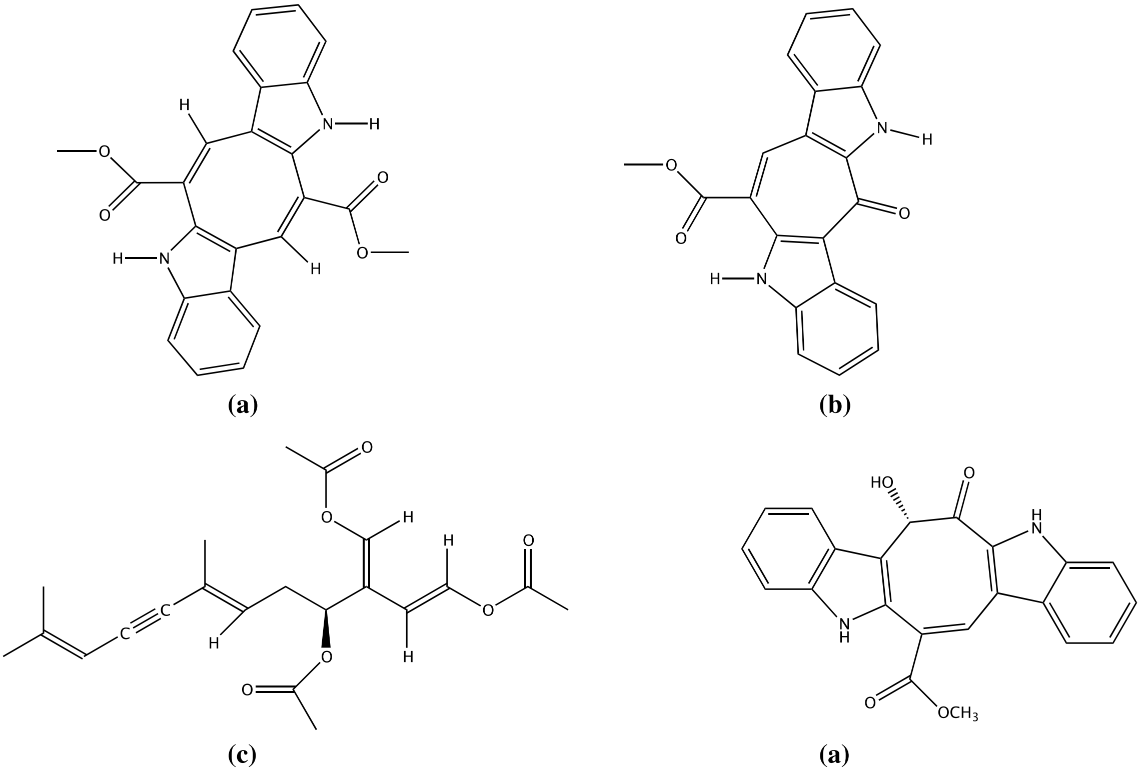

Fig. 1 Chemical Structures of secondary metabolites from genus *Caulerpa* : **a** Caulerpin; **b** Caulersin; **c** Caulerpenyne; and **d** Racemosin C [20, 21]

Racemosin C

Three novel bisindole alkaloids, named racemosin A-C, were isolated from *C. racemosa* by and its two isomers by Liu et al., in 2013 and Yang et al., in 2014 [47, 48]. These metabolites displayed significant neuroprotective activity against cell damage induced by $A\beta_{25-35}$ in SH-SY5Y cells and PTP1B inhibitory activity. Racemosin C is the first natural product possessing an 8-hydroxy-2,4,6-cyclooctatrienone ring. Its structure is similar to photoactive π-homotropolons like 5,7-π-homotropolone. A 4-step biosynthetic pathway from caulerpin was proposed [48].

Interplay of *Caulerpa* with cancer signaling

Despite several promising claims of scientists about assured cures of cancer, it still persists as enigmatic trouble. One major reason for this is the notorious survival strategies of cancer cells by modifying multiple signaling pathways [49]. Researchers are now attempting to target cancer cells the same way, so that cancer cells don't survive multiple damages [50]. Secondary metabolites and crude extracts of *Caulerpa* have shown promising results in vitro and in vivo and are considered potential candidates against cancer [51]. Major signaling pathways affected by *Caulerpa* are discussed below.

Microtubule dynamics perturbation

Microtubules, a mainstay of the cytoskeleton, are crucial in various cellular processes like development, maintenance of cell shape, cargo transport, cell signaling, and cell division [52]. These are chiefly synthesised by polymerisation of α-tubulin and β-tubulin heterodimers following non-equilibrium dynamics i.e. 'treadmilling' and 'dynamic instability' [53]. Polymerization dynamics of microtubules are tightly monitored both spatially and temporally by an array of microtubule-associated proteins (MAPs), comprising dynein and kinesin motor proteins as well as other regulatory proteins like survivin, dynactin, stathmin, TOG, MAP4, MCAK, FHIT and RAC1 [54]. Differential expression of some of these proteins is predominant in certain cancer cells, while others are involved in the development of drug resistance. The conventional microtubule drugs like vinca drugs and taxanes stabilize microtubule assembly, thereby inhibiting depolymerisation and disassembling microtubules, leading to paracrystal formation [55]. Although these drugs act in a non-specific manner but are useful in highly aggressive and metastatic cancers. Unfortunately, tumors have developed resistance against these drugs, and probing for novel tubulin binding agents is in progress. The first report of Cyn interfering with microtubule dynamics came in 1998, wherein abnormal DNA replication and metaphase-like cell cycle arrest were highlighted [56]. Another report claims neurite inhibition by dry and wet methanolic extracts of *C. racemosa* on mouse neuroblastoma cells, NA2B [57]. A similar study revealed that Cyn induces compaction of microtubules in SK-N-SH cells (human neuroblastoma), thereby inhibiting their proliferation [44]. Unlike conventional anti-mitotic drugs like paclitaxel or vincristine, which usually disrupt or stabilize the microtubule synthesis, Cyn results in neurite disappearance and peripheral condensation of microtubules, which has never been reported previously [58, 59]. It also inhibits in vitro polymerisation of pig brain tubulin, and MAPs, in time and concentration-dependent manner, revealing a giant cold-irreversible aggregation of tubulin and clustering of microtubules. Interestingly, half inhibitory concentration of Cyn is higher as compared to colchicine, vinblastine, dolastatin or podophyllotoxin, but a pre-incubation with the tubulin is necessary for the desired results [44]. Usually, drugs requiring a pre-incubation period for hindering tubulin assembly as they act by binding on sulfhydryl group of tubulin, but this was not the case with Cyn where two potential binding sites have been proposed i.e. C-terminal domain of α-tubulin, and N-terminal domain of β-tubulin [60].

Endoplasmic reticulum stress and unfolded protein response

Endoplasmic reticulum (ER) stress is another important determinant of cell fate and can either lead to its progression towards survival or death. ER stress may be induced by an imbalance between folded and unfolded proteins, hyper-accumulation of proteins, or altered redox potential [61]. In response, unfolded protein response (UPR) is generated which can be accomplished by an independent or combined action of three trans-membrane signaling molecules viz. IRE1 (inositol-requiring protein-1), PERK (protein kinase RNA (PNR)-like ER kinase), and ATF6 (activating transcription factor-6). UPR may signal cells to shut down the translation process, up-regulate ER chaperones, induce ER-associated degradation, induce rescue response or to trigger apoptosis [62]. In murine leukaemia WEHI-3 cells, Cyn treatment has been reported to upregulate expression of GRP78 (glucose-regulated protein-78) and GADD153 (growth arrest and DNA damage), in a calcium-dependent manner which can further lead to apoptosis (Fig. 2) [63]. GRP78, also known as BiP (binding immunoglobulin protein), is a heat shock protein produced in response to ER stress. Cancer cells consistently produce GRP78 as they are in a constant state of stress resulting from their normal microenvironment i.e. hypoxia, acidity, nutrient deprivation, reactive oxygen species (ROS), and low vascularization [64]. In general, GRP78 has an anti-apoptotic function, but when overexpressed it gets translocated to the cell surface, it behaves as a receptor for pro-apoptotic ligands like kringle-5 (K5) and Par-4, thereby triggers apoptosis [65]. Similarly, GADD153 or CHOP (C/EBP homologous protein) is activated by the PERK pathway and plays multifaceted role in suppression of bcl-2, stimulation of Bim, and/or activation of Ero1, which lead to apoptosis [66]. The exact mechanism of action of Cyn is not clear and needs further exploration.

Inhibition of PTP1B

Protein tyrosine phosphatases (PTPs) constitute an enzyme family that works in a coordinated manner with protein tyrosine kinases (PTKs) and monitors diverse signaling pathways [67]. PTKs mediate the phosphorylation events, mostly initiating the signaling cascade while PTPs are responsible for dephosphorylation and thus, causing cessation of the signal. Normal cells maintain a balance between phosphorylation/dephosphorylation events whereas cancer cells have a dysregulated balance either due to hyper-activated protein kinases or loss of PTPs [68]. PTP1B is one such oncogenic phosphatase protein involved in growth factor signaling and is over-expressed in breast, gastric, prostate and ovarian cancer and hence, receiving renewed interest as a validated target of multiple signaling interactions involved in cancer [69, 70]. Secondary metabolites isolated from *C. racemosa* viz. 4′,5′-dehydrodiodictyonema A (**1**), (23*E*)-3*β*-hydroxystigmasta-5,23-dien-28-one (**2**), *α*-tocopherolquinone (**3**), *α*-tocospirone (**4**), and (3*β*,24*R*)-stigmasta-5,28-diene-3,24-diol **(5)** exhibit PTP1B inhibitory activity with IC_{50} values of 2.30, 3.85, 11.01, 3.80 and 10.34 µM, respectively. Of these the three most potent compounds i.e. **1, 2** and **3** also displayed high selectivity over other homologous PTPs like TCPTP, LAR, CDC25B, SHPs. More structural discernments revealed that the addition of hematinic acid ester group at C(1) hydroxyl group in linear diterpenoids drastically increases their PTP1B inhibitory activity [66]. Another study reported PTP1B inhibitory activity of racemosin-C and caulersin with IC_{50} of 5.86 ± 0.57 and 7.14 ± 1.00 µM, respectively [21, 43]. Interestingly, PTP1B exerts both tumor-promoting and tumor-suppressing effect depending on the surrounding cellular signals [71], for example, in breast cancer, increased PTP1B and ErbB2 expression is associated with tumorigenesis. ErbB2 activation activates the PI3K-Akt signaling pathway leading to cancer progression and down-regulation of anti-apoptotic signals [39]. Various bioactive constituents from *Caulerpa* act up on PTP1B and are believed to shut down these events, thereby, inhibiting cell tumor progression (Fig. 2).

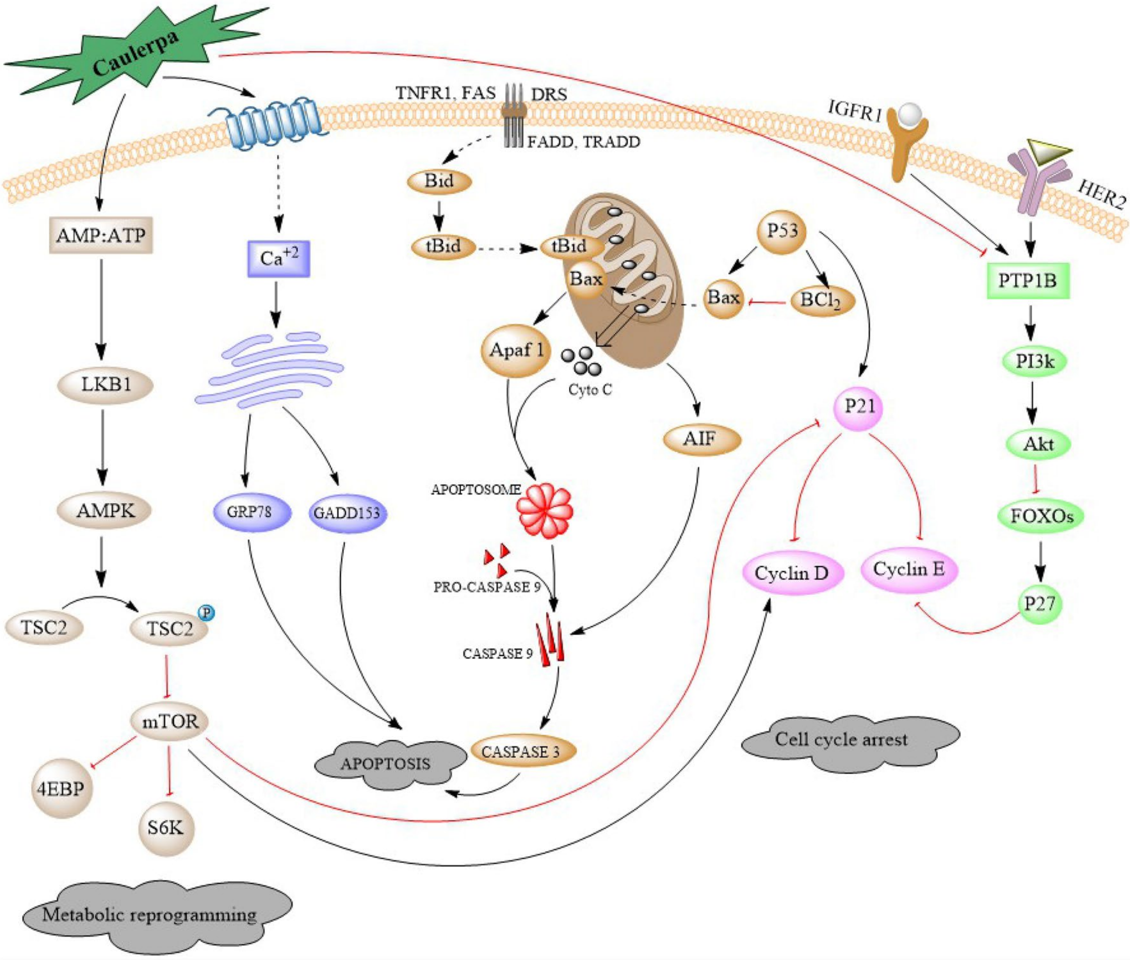

Fig. 2 Proposed mechanism of action of *Caulerpa* in cancer signaling. Complex network of modulations induced by *Caulerpa* on AMPK (light brown), ER Stress (blue), mitochondrial stress (dark brown), PTP1B inhibition (green) and cell cycle arrest (purple) pathways are depicted, that subsequently result in metabolic reprogramming, apoptosis and cell-cycle arrest in cancer cells. Translocation is depicted by dashed arrows, and inhibition by red arrows. (Color figure online)

AMPK pathway modulations and metabolic reprogramming

Dysregulated cellular metabolism or Warburg effect, is one of the cancer hallmarks, which states that cancer cells rely on both mitochondrial oxidative phosphorylation (OXPHOS) and glycolysis as a survival method [72]. Caulerpin is known to induce mitochondrial dysfunctions, thereby, disrupting the crucial energy balance of cells [73]. It incurs inhibitory effects on complex I of electron transport chain (ETC) and decreases oxygen consumption rate in SW480 and LOVO cells (colorectal cancer) with a concomitant elevation of ROS and decrease in ATP production [74]. LKB1, possibly, senses the elevated AMP:ATP ratio and activates the metabolic regulator AMPK, in a CAMKK2 dependent manner [75]. The expression levels of GLUT1, HKII and PFKB3 were reduced after 48 h of caulerpin treatment. The level of glucose, during initial 30 min of treatment increases, in response to AMPK activation to counterbalance the loss of ATP, however, after 60 min the level keeps decreasing until death. Different isoforms of AMPK exhibit differential responses where AMPKα1 mediates the action of caulerpin during cell death while AMPKα2 failed to display any effect [76]. AMPK inactivates mTOR signaling pathway for cellular stress, thereby, resulting in cell death (Fig. 2). Several reports suggest that AMPK attenuates mTOR activity by directly phosphorylating either tumor suppressor TSC2 (tuberin) complex in mTORC1-raptor subunit which blocks the phosphorylation of substrates of mTORC1 kinase viz. eIF4E-binding protein (4E-BPs) and p70S6K (cell growth processes) [77].

Cell cycle arrest

Cell cycle progression is a well-ordered and tightly-monitored process involving several checkpoints ensuring cell size, DNA quality, and integrity. These checkpoints are mediated by cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CKIs), which act as positive and negative regulators, respectively, in cell cycle progression [78]. Cancer is frequently associated with abnormal cell cycle regulation and may originate from genomic instability (GIN), chromosomal instability (CIN), or other changes, that lead to an abnormal expression of positive and/or negative cell cycle regulators [79]. Cyn interferes with DNA replication and causes cell cycle arrest at metaphase-like-stage in sea urchin embryos, as discussed previously [53]. Likewise, CME downregulates the expression of cyclin D, cyclin E, CDK6, CDK2 and upregulates p21, p27, p53 in WEHI cells, inducing cell cycle arrest. It suggests CME-induced cell damage activates p53 protein and subsequently p21 and p27, thus, inhibiting cell cycle check-point-proteins *i.e.* CDK6/cyclin D and CDK2/cyclin E, respectively, blocking the cell cycle at G_0/G_1 phase (Fig. 2) [63]. Another study reports that methanolic extract of *C. racemosa* collected from Sri Lankan coast, induces G_0/G_1 phase arrest in promyelocytic leukaemia HL60 cells, in concentration-dependent manner [80]. CDKs are necessary for driving the cells to next phase and *Caulerpa* causes cell cycle arrest by inhibiting specific CDKs.

Apoptosis

Dysregulated apoptosis disrupts the subtle balance between cell proliferation and cell death leading to cancer [81]. This deregulation can be in terms of mutations in pro-apoptotic proteins, up-regulation of expression of anti-apoptotic proteins, down-regulation of apoptotic proteins or inability to respond to cellular stresses [82]. *C. microphysa* pepsin digested extract (CME) reportedly induces the apoptotic pathway as indicated in myelomonocytic leukemia (WEHI-3) cells. It disrupts the cellular homeostasis by inducing Ca^{2+} release and decreasing mitochondrial membrane potential (MMP), thus, initiating apoptotic events. Downregulation of protein levels of bcl-2 and upregulation of Bid, Bax, AIF (apoptosis inducing factor), caspase-9 and caspase-3, are reported in WEHI cells [63]. In breast cancer MCF-7 cells, apoptosis was indicated by chromatin condensation, chromatin fragmentation and poly ADP-ribose polymerase (PARP) degradation by β-1,3 xylooligosaccharides, obtained from *C. lentillifera* [80, 83]. Likewise, PARP-1, caspase-9, and caspase-3 activation are also reported by caulerpin, in LOVO cells [74]. Mitochondrial pathway of apoptosis largely depends on MMP, which is controlled by a balance of anti-apoptotic and pro-apoptotic signal molecules like Bcl-2, bid, Bax, AIF and others [84]. The membrane permeabilization leads to the release of several inter-membranal proteins including cyto-c, Smac/Diablo, AIF, Endo G etc., of which, our focus will be limited to cyto-c and AIF. Cyto c interacts with the cytosolic monomer of apoptosis protease activating factor-1 (APAF-1) which undergoes an ATP mediated conformational change leading to its oligomerization to an ‘apoptosome’. The apoptosome binds to caspase-9, that further activates executioner caspases *i.e.* caspase-3 and caspase-7, leading to apoptosis. Alternatively, AIF is one of the lethal factor released from mitochondria, and causes cell apoptosis in a caspase-independent manner [85]; the mechanism, however, is poorly understood. CME downregulates bcl-2, and upregulates Bid, Bax and AIF, suggesting its possible role in both caspase-independent and caspase-dependent apoptotic mitochondrial pathway (Fig. 2). In addition, *C. sertularoides* methanolic extract exhibits strong anti-telomeric activity in acute lymphoblastic leukaemia MOLT-4 cells, and thus, causes apoptosis [86]. It is evident that in cancer cells telomerase activity is responsible for the stability and protection of chromosomes from degradation, causing uninterrupted proliferation and its inhibition may contribute to the timely death of cancer cells [87].

Inhibition of hypoxia inducible factor 1 (HIF-1)

Transcription factor, HIF-1, is an imperative target for anti-tumour drugs as it renders them to survive under reduced oxygen conditions by regulating oxygen homeostasis and promoting angiogenesis [88]. HIF-1 is ubiquitously present and consists of HIF-1α (O_2-regulated expression) and HIF-1β (constitutively expressed). At normoxic state, HIF-1 remains inactive, because of prolyl hydroxylases (PHDs) or/and asparaginyl hydroxylases induced degradation of HIF-1α. Hypoxia inhibits these hydroxylases and thus, activates HIF-1 and its downstream signaling pathways [89]. In addition, iron chelators, inactivation of tumour suppressor genes and/or activation of oncogenes can also trigger activation of HIF-1 [90]. Caulerpin treatment results in inhibition of hypoxia, by inhibiting HIF-1α activation and mitochondrial respiration at complex I in ETC, in T47D cells [91]. ELISA based detection of proteins also revealed that caulerpin suppresses the induction of vascular endothelial growth factor (VEGF) and glucose transporter-1 (GLUT-1) in hypoxic conditions but not in normoxic conditions. The anti-angiogenic activity was confirmed by tube formation assay on human-umbilical vein endothelial cells (HUVEC) suggesting that caulerpin suppresses angiogenesis in tumour cells by reducing VEGF levels in hypoxia. It is evident that HIFs help cancer cells to survive under stressed conditions and activate genes utilised for *Warburg effect*. Notably, Warburg described that cancer cells/tissues generally have an increased uptake of glucose (via GLUT-1) and convert this glucose to lactate [72]. Thus, hypoxia inhibiting agents (HIAs) that can reduce ROS and/or reactivate PHDs under hypoxic state can be of great therapeutic value [92].

Anti-oxidants like vitamin C and N-acetylcysteine (NAC) are reported to diminish ROS, genomic instability, and DNA damage, thereby inhibiting tumorigenesis. Cyn inhibits HIF1, GLUT-1, and VEGF, which suggests its intricate role in combating cancer, by disrupting Warburg effect, angiogenesis and hypoxia.

Conclusion and future prospects

This review presents a detailed insight into potential of various *Caulerpa* species on cancer signaling and thus their anticancer potential. *Caulerpa* affects the cytoskeletal framework, cellular metabolism, cell cycle, ER functioning, mitochondrial respiration, and enzymatic machinery of cancer cells, thus inducing multiple damages. The genus is not exploited to the fullest and contains more undiscovered compounds and unexplored biological activities. In addition, no attempts have been made towards the biological effects of its active metabolites with structural modifications and/or their combinatorial effects. Most of the studies reported only in vitro work and very few reports are available about in vivo effects of the metabolites. Systematic screening using in silico approaches followed *by* in vitro and in vivo experiments are suggested to focus on other substantial targets. Additionally, the focus of this review is limited to cancer, but the said genus is also known to affect the immune system, diabetes, and anti-oxidant/ROS balance, well known for their cross-talk with cancer signaling pathways. Infrequent reports about the protective role of anti-oxidants from edible *Caulerpa* species against cancer are also available. Extensive in-depth efforts are warranted to provide further insights into the chemotherapeutic as well as chemo-preventive potential of this marine alga. In order to develop a novel natural cancer-drug and to overcome the global ecologic deficit, genus *Caulerpa* can provide a dual benefit of better alternative food with therapeutic importance. It is believed that this genus holds immense potential than ever thought, but there is a great need of more focussed and collaborated research efforts to dig out a novel promising drug from the sea.

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Author contributions RM and SB contributed equally for the preparation of this manuscript. FB contributed in proofreading and polishing of the manuscript. SS coordinated the work and compiled the manuscript.

Compliance with ethical standards

Conflict of interest Richa Mehra declares that she has no conflict of interest. Satej Bhushan declares that he has no conflict of interest. Felix Bast declares that he has no conflict of interest. Sandeep Singh declares that he has no conflict of interest.

Ethical approval This article doesn't contain any studies with human participants or animal models performed by any of the authors.

Informed consent This study didn't require any formal consent.

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