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# PHARMACOLOGICAL POTENTIAL OF GREEN ALGAE *CAULERPA*: A REVIEW

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**Keywords:**

Natural Products, Macroalgae, *Caulerpa*, Pharmacological activities, Drug discovery

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**ABSTRACT:** From the beginning of civilization, humans depend on the natural products for their food and as medical treatment. Diversity in various bioactive compounds from marine organisms has been tested for the multiple pharmacological effects. Marine algae are surviving in a competitive environment with developed defense strategies and significant levels of chemical structural diversity with a wide variety of bioactive secondary metabolites. Therefore, algae are a promising source of novel active biochemical compounds with different pharmacological properties for the prospective development of novel drugs by the pharmaceutical industries. Microalgae (blue-green, dinoflagellates, bacillariophyte, *etc*.) and Macroalgae (green, brown and red algae) are the two groups of algae. *Caulerpa* is the genera of green macroalgae, represent the numerous bioactive compounds like tannin, steroids, flavonoids, terpenoids, sulphated polysaccharides (SP), glycosides, phenolic compounds, and saponins, *etc*., for significant pharmacological effects in the current medicine. Exploration of these compounds for the pharmaceutical and medical purpose, the present review focused on morphological behavior and pharmacological activities of some *Caulerpa species* in current drug research.

**INTRODUCTION:** From the immemorial time, plants act as a source of drugs for several human diseases. Natural Products have been important sources of useful drugs from prehistoric times to the present. In developing countries, plants and their product used as a traditional medicine in their primary healthcare system.

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Coastal marine waters are the most vulnerable and heavily invaded habitats [1]. Marine plants have long been recognized as producers of biologically active substances worldwide and from the 21st century marine algae were considering as medicinal food, the medicinal potential of some marine plants like mangroves, seaweeds, seagrasses, and lichen have been reported from India and elsewhere [2, 3, 4, 5, 6].

Marine algae are the major source for organic compounds, which grown on solid substrates such as rocks, dead corals, pebbles shells, mangroves, and other plant materials in the regions of intertidal, shallow and deep-sea areas, estuaries and backwaters.

Seaweeds composed with the thallus, stem and a foot. Some species have gas-filled structures to provide buoyancy. Amounting more than 844 marine algae species are distributed in Indian coasts among 217 genera. Algae can be classified into microalgae, which includes blue-green algae, dinoflagellates, bacillariophyte (diatoms), *etc*., and macroalgae are very important in the identification and isolation of new biomedical compounds in drug research. As about 2400 natural products have been isolated from three subdivided classes of macroalgae [7], thus the Rhodophytes (Red algae), Chlorophytes (green algae) and Phaeophytes (brown algae) [8] for providing valuable ideas for the development of new drugs against several human disorders like cancer, infectious diseases and inflammation, *etc*. [9, 10, 11]

Marine algae are structurally novel, biologically high concentrated active metabolites which include, flavonoids, saponins, glycosides, tannins, steroids, alkaloids, phenolic compounds and proteins [12] from other marine organisms in marine environment [13] and they were the most potential renewable sources, hence, most of the scientists were focused their research on marine algae for identification and development of new bioactive substances. Therefore, macroalgae become an important source for new bioactive natural substances [14, 15]. Moreover, many isolated metabolites were shown to possess bioactive effects [16, 17] from marine algae. Therefore, Pharmaceutical industries play a major role in developing several new techniques to isolate novel bioactive compounds from edible seaweeds due to their great medicinal value [18, 19].

**2. *Caulerpa*:** *Caulerpa* is one of the most distinctive edible green algae genera come from a *Caulerpaceae* family and *Bryopsidales* order, widely distributed in a range of habitats throughout the tropical and subtropical areas with a group of conspicuous algae [20, 21, 22] and identifiable solely with their growth form and internal morphology. From literature survey reports, there are about 70 to approximately 100 species are exhibit polymorphism, showing different growth forms in different habitats which make them difficult to identify [1, 23, 24].

*Caulerpa* species having with a distinctive suite of anatomical, cellular and biochemical characters with a little relative morphological variation including reinforcement of the saphenous structures of fibrous algal wall materials and expanded their ranges into the more temperate environment [25, 26, 27, 28], characterised compounds including caulerpin [29, 30, 31], caulerpicin [32, 33], palmitic acid, *β*-sitosterol and taraxerol [34], caulerpol [35], flexilin and trifarin [36] and the secondary metabolites of *Caulerpa* shows a variety of biological activities such as antitumor [37], anti-inflammatory [38], antioxidant, antimicrobial and growth regulator [39], *etc*. Hence, the present review focused on brief morphological description and pharmacological properties of some of the *Caulerpa* species.

**2.1. *Caulerpa racemosa*:** *Caulerpa racemosa* is commonly known as sea grapes [English], Parelwier [Dutch], Caulerpa raisin vert [French], Grune Traubenalge [German], found with adjacent to the living coral in many areas of shallow muddy bays to clear water reef environments of warm temperate and tropical seas at 100 m depth around the world. *C. racemosa* also called as *Acropora palmata,* is a multinucleate and nonseptate (coenocytic), chloroplast is free to migrate from any part of the organism to another, and fibrous protein network helps in the movement of organelles. *C. racemosa* has short, erect branches arising from a horizontal stolon attached to the sediment at the interval by descending rhizomes. The erect branches arise every few centimeters to as much as up to 19 - 30 cm in height. Many ovate or spherical body branchlets on the stalk arise from each erect branch, where branches and stolons are close together, the branchlets form a dense mat of seemingly spherical structures [38, 40] **Fig. 1A**. It reproduces vegetatively by fragmentation; growth begins in April continue till December on the sandy substrate in calm and turbid water tend to have long erect branches while those growing on rocky wave exposed water have strong short, erect branches [41, 42, 43].

**2.2. *Caulerpa mexicana*:** *C. mexicana* is feathery green seaweed with about 2 cm long in calmer conditions, it attaches with rhizomes to rocks, coral fragments. *C. mexicana* has a deep green with a beautiful segmented feather like frond with 2-25 cm tall, branchlets are opposite each other, flattened curve upward, pointed tip with 2-4 mm wide, 2-10 mm long and the length of a stem creeps

over the third surface or just under the sand with a flat midrib **Fig. 1B**. This alga also is known as *Caulerpa crassifolia*, is very adaptable in the amount of light it requires to grow and is often observed growing under ledges on seawalls and intertwined with other algae and have many bioactive compounds, such as polysaccharides, terpenes, and flavonoids, *etc*., have different pharmacological activities [44, 45, 46].


***CAULERPA RACEMOSE*** ***CAULERPA MEXICANA***

***CAULERPA TAXIFOLIA (VAHL)*** ***CAULERPA CYLINDRACEA***

***CAULERPA CUPRESSOIDES*** ***CAULERPA SERTULARIOIDES***

**FIG. 1: GENERAL MORPHOLOGY, RHIZOMES, AND BRANCHES OF DIFFERENT *CAULERPA SPECIES***

**2.3. *Caulerpa taxifolia* (Vahl):** *Caulerpa taxifolia (*Killer Algae*)* is a light green macroalgal grow up to 2.8 m height in 40-60 cm deeper of tropical seas, 6-8 mm diameter of flattened upright leaf-like frond arising from the creeping stolons up to 3-15 cm long and from the base, the narrow tip upward small side branchlets are constructed opposite to the midrib [47, 48] **Fig. 1C**. *C. taxifolia* reproduces sexually and vegetatively, maximum colonization is between 2 and 6 m depth, but the algae have

been observed down to 99 m with 350 m of fronds density along with leaves up to 14,000/$m^2$. *Caulerpenyne*, the most potent endotoxins protecting these macroalgae against epiphytes and herbivores, is toxic to mollusks, sea urchins, herbivorous fish, at least during summer and autumn [49, 50].

**2.4. *Caulerpa cylindracea*:** The green macroalgae *Caulerpa cylindracea* is one of the most threatening invasions in the Mediterranean Sea [51] located in the intertidal and shallow subtidal zones (from 1 -70 m depth) and extended up to approximately 100 $m^2$ [52, 53], spread on rocky bottoms, concrete, sand, and mud survive winter temperatures down to 10.5 ºC by fragmentation, sexual reproduction and reduces the diversity of native macroalgae [41, 54, 55]. The spherical branchlets can act as propagules, and long-range dispersal of the alga seems to be a result of human activities like disturbance by anchor and fishing [56, 57] **Fig. 1D**. The 15 cm thick compact multilayer mats of *C. cylindracea*, develops the anoxic layer and sedimentable to increases the organic matters, sulphide levels and microbial activity due to modification in quality and intensity of physical, chemical and hydrodynamical factors [58, 59].

**2.5. *Caulerpa cupressoides*:** *C. cupressoides* also refers as Cactus tree alga [English], Cypres-*Caulerpa* [Dutch], *Caulerpa cactus* [French], *Zypressealge* [German], widely occurs in depth 70.3 m of tropical seas, it consists with grey-green to dark green thallus spreading laterally to 35-40 cm with open spreading habit, thick, heavy, upright branched stolon with 1.5-2.5 mm diameter growing in a shallow subtidal, protected sandy areas, the length is variable, from 2-8 cm to 15-25 cm and consists of a cylindrical or flat narrow or relatively broad central stem and very short, flat pointed tip side branches. The central stem may branch at the tips to from Y-shapes **Fig. 1E** looks like a zipper, maybe long and slender, or short and very broad [60, 61].

**2.6. *Caulerpa sertularioides*:** *C. sertularioides* is a light green, 15-20 cm tall Green feather alga [English], Veerwier [Dutch], Caulerpa plume [French] and Grune federalge [German], distributed in the middle to lower intertidal habitats. The stolon is long, horizontal and flat erect with feather-like branches growing in dense colonies on shallow sandy bottoms with mixed coral fragments, in areas of mangroves and attach to their roots. The upright branches are dark to olive green in appearances and arise from coarse, moderately thick, branching stolons [62, 63] **Fig. 1F**.

**2.7. *Caulerpa scalpelliformis*:** *Caulerpa scalpelliformis* is bright yellowish-green to olive-green seaweed located in intertidal zone, in large associations, algae consist with simple, glabrous, glossy stolons are bilateral, flat, leaf-like with more than equal to 1 cm broad and 8-24 cm long or more, linear-lanceolate in outline, occasionally constricted at middle; upper end broadly rounded; pinnately branched; the erect branches above 15-20 cm or more long with erect assimilators on the upper faces at intervals of 1-2 cm. On the main broad thickened flat rachis, closely pinnate, alternately linear, subacute, plano-compressed; 1-2 cm long, 0.3 mm broad; a section of thallus with a spongy network of anastomosing filaments, filled with semifluid matter **Fig. 2A**, it grows on rocky and sandy bottoms at different depths [64, 65, 66].

**2.8. *Caulerpa brownii*:** *C. brownii* (Sea Rimu) is a green to dark green seaweed commonly occurs on rocks at just below low tide intertidal zone to depth of 35 m, often forming a monospecific community and 31 - 400 mm tall, *stolon* usually robust, 1-3 mm in diameter, moderately densely covered with simple ramuli 0.5-2.5 mm long and in the range of 150–500 µm in diameter, tapering abruptly to a spinous tip, epilithic or on jetty piles. Erect fronds medium to dark green, with simple or several times irregularly branched axes, usually 3-40 cm high and 3-8 mm across; axes terete, 0.5-1.5 mm in diameter, densely covered throughout with irregularly placed ramuli. *Ramuli* simple on basal part of axes and 1.5-4 mm long, becoming basally furcate and often bifurcate over most of the axes, 3-4 mm long and 100-350 µm in diameter, terete, upwardly curved, tapering close to their apices to a spinous tip [65, 67, 68] **Fig. 2B**.

**2.9. *Caulerpa peltata*:** It is a small fleshy umbrella, generally seen on some of the shores, grows on coral rubble near lower intertidal reefs, 1-3 mm diameter. Freely forked stolons giving off rhizoid bearing and foliar branches, 5-50 mm tall, erect branches with one to several peltate branchlets

consisting 1-2 mm long slender pedicels ending with 3-5 mm thick diameter. The thalli consist of horizontally branched stolon and erect branches supporting several short-stalked branchlets each terminating in a disc (fleshy umbrellas) of about 3-9 mm in the more common form and 11-20 mm in the less common form **Fig. 2C**. Some form, loose cluster, bright yellow-green to bluish-green. Growth is seasonal, depending on the turbidity and salinity of the water. *C. peltata* forms thick carpets in a good well-protected environment [42, 69, 70].


*CAULERPA SCALPELLIFORMIS* *CAULERPA BROWNII*

*CAULERPA PELTATA* *CAULERPA MACROPHYSA*

*CAULERPA LENTILLIFERA* *CAULERPA PROLIFERA*

**FIG. 2: GENERAL MORPHOLOGY, RHIZOMES, AND BRANCHES OF DIFFERENT *CAULERPA SPECIES***

**2.10. *Caulerpa macrophysa*:** *C. macrophysa* commonly on coral rock substrates in the lower intertidal and upper subtidal areas exposed to strong water movement in depth of 1.5 m. Coenocytic grass green thalli of this seaweed are 3-5 cm long forming dense clusters with the prostrate terete, naked branched stolon and erect, terete branches on the sandy-muddy substrate by

colorless rhizoidal holdfast **Fig. 2D**. The erect branches are simple or branched bearing crowded stalked spherical to slightly mushroom-shaped ramuli, 2-5 mm in diameter to 2 mm long. This species is like *C. lentillifera* however the branchlets of this seaweed are bigger and without constriction between the base of the spherical head and the stalks [71].

**2.10. *Caulerpa lentillifera*:** *Caulerpa lentillifera* is a "green caviar" edible green tropical food algae were distributed worldwide. It is adaptable to a variety of environments and sensitive to low temperature and osmotic pressure, easily spoilt by storage in a refrigerator or washing with tap water. The grass-green color thalli composed of cylindrical stolon with a rise to erect branches are spaced 3-14 mm above and rhizoidal branches below. Each made up of 2.5-7 cm tall cylindrical axis, beset with ramuli are arranged radially and crowdedly, forming a berry-like structure. The ramuli are 2-4 mm long consisting of a short stalk and globular head of 1.5 mm in diameter; distinct constriction is present between the base of the globular head and distal end of the stalk of the ramuli **Fig. 2E**. It was adaptable to a variety of environments and making it suitable for cultivation in ponds. Naturally, it inhabits a wide range of substrate consisting of rubbles to over 50 meters deep, sand on reef flats and shallow, muddy lagoons and forms beds and meadows in excellent condition habitats. However, *C. lentillifera* is sensitive to changes in salinity being stenohaline; poor growth in salinities lower than 30 ppt and mortality in lower than 25 ppt salinity[72].

**2.11. *Caulerpa prolifera*:** *Caulerpa prolifera* is a distinctive dark-green, slender, oval-shaped flat bladed complex alga than other members of the green alga order Bryopsidales, which resembles turtle grass, long twisting leaves grow from a single rhizome prefers sandy bottoms and ledges in shallow turbulent water. The blades are 1-2 mm diameter and around 1 m lengths, often proliferates to extend upward forming a new blade by fragmentation and it colonization very fast on muddy substrates with low hydrodynamic, when waters cool drastically, an individual can reproduce by holocarpsy, these. *C. prolifera* is a plant consists of a single giant cell with multiple nuclei, these are monoecious, and so each plant produces gametes of both sexual types **Fig. 2F**. It behaves as a shade-adapted species with a low photoprotective capacity due to light is one of the main factors governing its distribution [74, 75].

Sulphated polysaccharides, terpenoids, poly-acetylenic fatty acid, saponins, steroids, alkaloids, tannins, glycosides, carbohydrates, flavonoids and proteins, caulerpin, caulerpenyne (CYN) are the most common phytoconstituents of these green algae genera with the small range of scientific evaluation and pharmacological activities were discussed in **Table 1**.

**TABLE 1: PHYTOCONSTITUENTS, PHARMACOLOGICAL EFFECT OF *CAULERPA SPECIES* WITH THE POSSIBLE MECHANISM IN DRUG DISCOVERY**

| S. no. | Name of the Algae | Phytoconstituents | Pharmacological activity | Mechanism |
|---|---|---|---|---|
| 1 | *Caulerpa racemosa* | SPs, Terpenoids, Polyacetylenic fatty acid, Saponins, Steroids, Alkaloids, Tannins, Glycosides, Carbohydrates, Flavonoids and Proteins, Caulerpin | Bactericidal | • Interact with sPLA2 [76] |
| | | | Antinociceptive | • Inhibition of COX and LOX,<br>• Partial agonist of adrenergic, serotoninergic, cholinergic and dopaminergic receptors [77] |
| | | | Antitumor | • Apoptosis regulates cell division and intrinsic suicide or programmed cell death [78] |
| | | | Anti-viral | • Selective inhibitor of HSV-1 and HSV-2 [79] |
| | | | Cytotoxic | • Due to the compounds differing in polarity [80, 81] |
| | | | Hypolipidemic, Anticoagulant [82, 83] | ----- |
| | | | Larvicidal | • Toxicity against 4th instar larvae of mosquito [84] |
| | | | Antioxidant and Anti-Arthritic | • Inhibition of nitric oxide radical generation, Inhibition of protein |

| | | | | |
|---|---|---|---|---|
| | | | | denaturation [85] |
| 2 | *Caulerpa mexicana* | Caulerpin, Polysaccharides, Terpenes and Flavonoids, β-carotene and A-tocopherols, indole alkaloids | Antinociceptive, Anti-inflammatory | • Inhibition of pain receptors or COX-3,<br>• Reduce cell migration & edema formation<br>• Negatively regulating the pro-inflammatory cytokine levels [86, 87, 107, 108] |
| | | | Spasmolytic | • Inhibition of $Ca^{2+}$ influx<br>• Non-competitive antagonism [88] |
| 3 | *Caulerpa taxifolia* (Vahl) | Caulerpenyne (CYN) | Antiproliferative | • ↓se intracellular ATP-dependent $Ca^{2+}$ accumulation, a specific inhibitor of reticular $Ca^{2+}$-ATPase and<br>• $^{3}$H-thymidine incorporation into DNA inhibition [89] |
| | | | Toxicity effect studies | • Inhibit or delay the proliferation of several phytoplanktonic strains [90] |
| 4 | *Caulerpa cylindracea* | Caulerpin, Caulerpinic acid | Mitochondrial targeting activity | • Selectively inhibits the respiratory complex II activity, while functional re-modification in complexes I, III, & IV [91] |
| 5 | *Caulerpa cupressoides* | SPs, Lectin, | Antinociceptive, Anti-inflammatory, Anti-thrombotic, Prothrombotic, Anticoagulant, Anti-bacterial | • ↓se in leukocyte migration and Inhibition the inflammatory process<br>• Inhibition the TNF-α and IL-1β inhibition, IL-1β, IL-6 and COX-2 expression and histamine H1 receptors<br>• Preventing reactive oxygen species formation [83, 92, 93, 94, 95, 96, 97] |
| 6 | *Caulerpa sertularioides* | Flavonoids and chlorophylls Polyanionic bioactive compounds | Antioxidant, Antimutagenic, Antiproliferative, Antinociceptive Anti-inflammatory, Antimicrobial | • Inhibition of inflammatory mediators<br>• Lysis of the cells by affecting the lipid packing in the cell wall [86, 98, 99] |
| 7 | *Caulerpa scalpelliformis* | Tannins, Flavonoids, Glycosides, Saponins, Phenolic compounds, Terpenoids, Fatty acids, Alkaloids, Steroids, Amino acids, Proteins, *etc*. | Anti-microbial, Larvicidal effect [100, 101, 102, 103] | ---- |
| 8 | *Caulerpa brownii* | Diterpenoids | Antimicrobial | • Inhibits the cell division [104] |
| 9 | *Caulerpa peltata* | Caulerpin, Caulerpicin, | Antioxidant, Antiproliferative, Antibacterial | • *β*-Carotene bleaching (BCB) inhibition [105, 106] |
| 10 | *Caulerpa macrophysa* | Phenolic compounds | Anticholinesterase, Anticancer Antioxidant | • Induces the DNA damage [109]<br>• Free radical scavenging and inhibitory activities [110] |
| 11 | *Caulerpa lentillifera* | Polysaccharides, Flavonoids | Anti-diabetic | • ↓ the dipeptidyl peptidase-IV and α-glucosidase enzyme activities and effectively inhibited cell death and iNOS expression [111] |
| | | | Antipyretic | • Blocking the COX [112] |
| | | | Immunostimulatory | • Enhanced NO production *via* NF-kB and increased the phosphorylation of p38 MAPK and cytokine induction and |

| | | | | |
|---|---|---|---|---|
| | | | | phagocytosis [113] |
| 12 | *Caulerpa prolifera* | SPs | Antiadipogenic, Antiproliferative, Microbicidal, Immunomodulatory, Antioxidant Activity | • Reducing the differentiation of3T3-L1 in adipocytes<br>• Reducing the proliferation of HeLa and 786-O cells<br>• Increasing the nitric oxide production<br>• Scavenging the oxidant molecules [114] |
| | | | Anti-fungal Larvicidal activity, Antibacterial, cytotoxicity and anticoagulant [115, 116, 117] | ---------- |

HSV – Herpes Simples Virus; sPLA2 - Secretory Phospholipase A2; COX – Cyclooxygenase; LOX – Lipoxygenase; BCB - *β*-Carotene bleaching; SPs – Sulphated polysaccharides

**CONCLUSION:** From the present review, we concluded that the natural products from the marine algae and other marine organisms represent one of the new confines in the exploration of bioactive compounds. India is one of the leading bio-diversity centers with the presence of different plant species. Amongst, the marine algae are least explored for their medicinal properties. In the present days, we must accept the new challenges to the queries of the modern system about the quality and efficacy of the herbal drugs and their cultivation, collection, processing, preservation, and use. Hence, the identification of a bioactive compound from marine algae is a new potential area. *Caulerpa species* have been poorly explored for their pharmacological activities, and the presence of secondary metabolites possess different pharmacological actions. Most of the algal species required further studies for isolation, identification, characterization, and elucidation for their bioactive compounds along with its pharmacologic activity.

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