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Systematic Review of Green Seaweed *Caulerpa racemosa* as an Anti-Inflammatory Agent: Current Insights and Future Perspectives

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Abstract
Background: *Seaweed is a marine biota with many benefits, one of which is C. racemosa. It is one type of seaweed that is quite widely found in Indonesia.* ***Objective*** *This study investigated the anti-inflammatory activity of C. racemosa using various in vitro and in vivo approaches.* ***Methods***: *A literature review was conducted by searching for research data on C. racemosa. The literature was obtained from PUBMED, ScienceDirect, Scopus, SpringerLink, and Google Scholar using the keywords C. racemosa, sea grapes, in vivo, in vitro, and anti-inflammatory. The search identified 1313 articles with 100 articles in Scopus, 100 articles in ScienceDirect, 0 articles in PubMed, 3 articles in SpringerLink, and 1,110 articles in Google Scholar.* ***Results***: *The study showed 12 articles found C. racemosa has the ability as an anti-inflammatory both with in vitro and in vivo study approaches and supported by data on proximate composition which is quite high and substance consisting of various bioactive constituents including flavonoids, phenolics, phytosterols, terpenoids, saponins and alkaloids where the anti-inflammatory active isolate caulerpin was successfully isolated. C. racemosa is able to reduce the inflammatory response by inhibiting NO production and the release of cytokines and inflammatory mediators such as AMPK, mTOR, TNF-α and IL4.* ***Conclusion***: *C. racemosa indicated that this species is a rich source of phytochemicals with many pharmacological activities, one of which is anti-inflammatory. Further research is required to explore the relationship between secondary metabolites and their activities.*

Keywords: *Caulerpa racemosa, marine natural products, anti-inflammatory, in-vitro, in-vivo*

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INTRODUCTION

Seaweed is one of Indonesia's marine and fishery commodities and has a high economic value because of its many benefits. The value of seaweed production in Indonesia in 2022 reached 231,829.70 tonnes (Central Bureau of Statistics, 2023). This shows that there is a lot of market demand for seaweed because every year the Indonesian government always tries to increase seaweed cultivation. One type of seaweed that has many benefits is sea grape (Stuthmann et al., 2023).

Sea grapes (*Caulerpa racemosa*) are a common type of seaweed in Indonesia. It possesses a thallus that exhibits characteristics similar to those of grass and displays green coloration. This thallus is composed of numerous erect branches measuring approximately 2.5-6.0 cm in height. The length of the primary stem ranged from 16 to 22 cm. At the apex of each branch, there are spherical structures similar to grapes, with a length ranging from approximately 2.5 to 10.0 cm. The characteristics of sea grapes include a thallus with stolons measuring approximately 5 cm each. The roots are relatively large and tapered like nails, with ramuli reaching 8 cm in length. Ramuli is a branch organ or branch of the stolon as the main organ, and its substance is rather soft and seems empty. These ramuli are between 2-4 mm in diameter. The ramuli arise on stolons that are branched, have rounded, flattened ends and stalks, and are arranged around and along the ramuli (Yudasmara, 2015).

Sea grapes have an economic function in that they can be used as food ingredients, where the processing process is quite easy. Sea grapes that came from the sea were taken and washed thoroughly using boiled water. It is then boiled to kill pathogenic bacteria in seaweed (Ersalina et al., 2020). Currently, sea grapes are widely used in the food sector as ingredients in jelly candy (Estrada et al., 2020), ice cream, cream soup, and seaweed flour (Stuthmann et al., 2023). In addition to the food sector, seagrapes can be used as medicines in the pharmaceutical sector. In general, the chemical composition of sea grapes has a protein content of 10.41%, ash content of 38.94%, total fat of 1.58%, moisture content of 92.37%, carbohydrates of 35.69%, dietary fiber of 34.08%, energy from the fat of 14.22 kCal/100 g and total energy of 198.58 kCal/100 g (Sedjati, 1999). Furthermore, sea grapes contain minerals such as Na, Ca, and K and amino acids in the form of L-threonine and L-glycine (Sinurat et al., 2021). The secondary metabolite content in sea grapes can be used as an antioxidant (Sinurat et al., 2021), antibacterial (Belkacemi et al., 2020), anticancer (Permatasari, Wewengkang et al., 2022), antidiabetic (Mandlik et al., 2022), antinociceptive (De Souza et al., 2009), antiobesity (Kurniawan et al., 2023), and anti-inflammatory (Worms & Adrian, 2023).

Sea grapes can be used as anti-inflammatory agents because they contain sulfated polysaccharides. This polysaccharide is a negatively charged polysaccharide present in the cell walls of seaweeds and is currently widely used in the food and pharmaceutical industries (Ribeiro et al., 2020). In addition, the most abundant carotenoids in sea grapes are β-carotene and canthaxanthin. The current investigation showed the capability of *C. racemosa* carotenoids as innate suppressors of inflammation through modulation of the AMPK-mTOR-TNF-α signaling cascade. Furthermore, it has been demonstrated that clinical AMPK activation reduces inflammation-related pain by blocking NF-κB, mTOR, and IL-1β activation. (Kurniawan et al., 2023).

Numerous investigations have been conducted on *C. racemosa* to validate and affirm its biological characteristics. Several investigations have been conducted using both in vivo and in vitro models. Therefore, to efficiently conduct future research while minimizing resource waste and maximizing time optimization, retrospective and systematic research methods were employed to outline the technique and present the collected results.

MATERIALS AND METHODS

Focus question

The feasibility of the C. racemosa anti-inflammatory activity test was evaluated through activity tests using in vivo and in vitro model approaches and the mechanisms that occur.

Search strategy

Searching and collecting article data were conducted online from September 2023 to February 2024 using the keywords "*C. racemosa* AND anti-inflammatory AND in-vitro AND in-vivo" in several online databases, such as PubMed, Google Scholar, ScienceDirect, SpringerLink, and Scopus. Furthermore, the collected articles were filtered using EndNote X9.3.3. The initial round of screening involved thorough examination of the article search results to identify any instances of duplication. Subsequently, the duplicate articles that were identified were segregated and separated from the others. After the article separation process, the sorting process continued, including the appropriateness of the title and abstract regarding the research content. The anti-inflammatory activity of C. racemosa was investigated using in vitro and in vivo models. In

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addition, eligibility assessment was conducted by thoroughly reviewing the entirety of the article's content to ascertain its compatibility with the pre-established inclusion criteria. A team of five individuals conducted the method of gathering and categorizing publications, with two additional individuals performing a secondary review. Subsequently, the risk of bias for each article was evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. A comprehensive literature review was conducted to identify relevant studies on the potential anti-inflammatory properties of *C. racemosa*. The search identified 1313 articles with details of 100 articles in Scopus, 100 articles in ScienceDirect, three journals in SpringerLink, and 1110 articles in Google Scholar (Figure 1).

Eligibility criteria

The eligibility criteria employed in this systematic review were established by considering the research questions formulated according to the PICO (population, intervention, comparator, outcome) framework.

•Population: Species *C. racemosa*

•Intervention: In vivo and In vitro study of anti-inflammatory properties

•Comparison: Positive control and negative control

•Outcome: *C. racemosa* species' anti-inflammatory effects both in vitro and in vivo

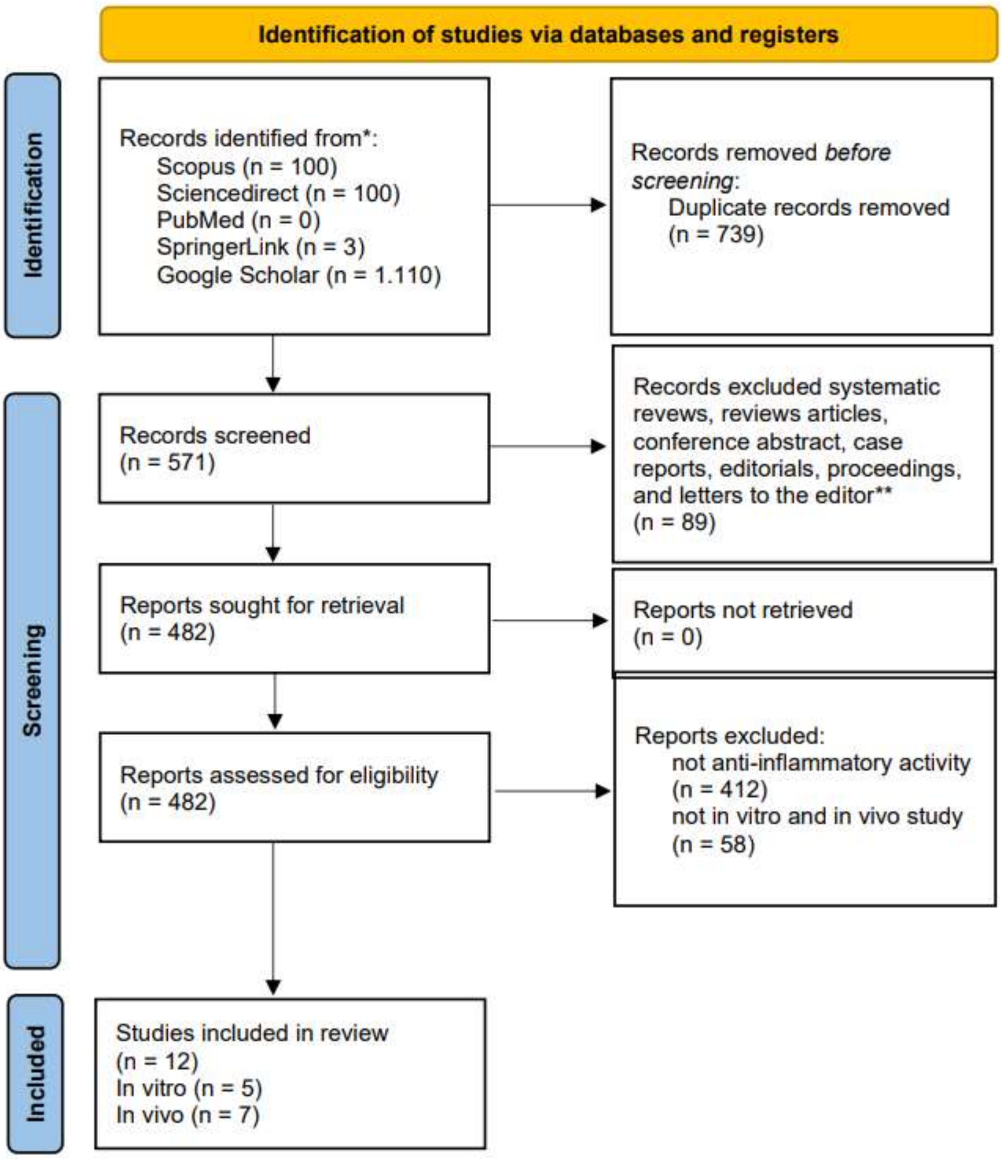

Figure 1. The research PRISMA 2020 flow diagram

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The PICO framework was employed in systematic reviews to construct literature search algorithms that guarantee thorough and unbiased searches. It is commonly employed in evidence-based practice, particularly in the field of evidence-based medicine, to generate clinical or healthcare-related questions and propose answers to the research problem at hand (Methley et al., 2014). In this study, the PICO format was used to specify articles collecting data from several databases.

The inclusion criteria for this study were studies related to *C. racemosa* that have anti-inflammatory activities using in vitro and in vivo models, as well as articles containing comparative analysis and results from both methods from 2000 to 2024. The exclusion criteria were articles in languages other than English and systematic reviews, review articles, conference abstracts, case reports, editorials, proceedings, and letters to the editor.

RESULTS AND DISCUSSION

C. racemosa can be found in shallow waters up to 100 m deep in the warm tropics. It is a type of senositic Chlorophyta with chloroplasts that can migrate inside the cells through a network of protein fibers. This type has a branch morphology or a short, erect rachis originating from the stolon horizontally attached to the sediment or substrate using rhizomes. A branch or rachis appears every few centimeters along the stolon, and the rachis height can reach 30 cm. In murky waters, the rachis erect grows tall, while in waters with sufficient currents, strong, shorter erect rachises. In every branch upright (rachis), the ramuli or small branches are oval to round (Gopi et al., 2019). *C. racemosa* type commonly found in various waters in Indonesia. It is known locally as sea grapes and is widely used by coastal communities as vegetables or lalap. Caulerpa is known to have a high nutritional content, making it a food ingredient (Ridhowati et al., 2016). *C. racemosa* contains fatty acids with higher unsaturation than saturated fatty acids, with the highest acid content fat being oleic acid. The lipid content in *C. racemosa* also has an index of low atherogenicity and thrombogenicity. The amino acid content is relatively more balanced between essential and nonessential amino acids (Magdugo et al., 2020).

Characteristics of study design

A complete list of the studies is presented in Table 1. Twelve studies that satisfied the inclusion criteria were identified, and these studies were published within the time frame of 2009 to 2024. The studies encompassed five in vitro investigations and seven in vivo studies. These 12 studies examined the anti-inflammatory properties of *C. racemosa*, focusing on various activities. The animal species used in these experiments were *Wistar albino* rats (Magdugo et al., 2020), adult female *Mus musculus* Swiss mice, and male *Rattus norvegicus* Wistar mice (Mandlik et al., 2022). The initial utilization of the in vitro anti-inflammatory investigation, as delineated in this review, involved the stimulation of RAW 264.7, through the administration of lipopolysaccharide (LPS). Bacterial LPS is widely recognized as a highly effective stimulus for inducing substantial production of nitric oxide (NO), thereby facilitating the upregulation of pro-inflammatory proteins, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). This experimental approach involving the use of RAW 264.7 cells was employed to evaluate the anti-inflammatory effects of C. racemosa (Vairappan et al., 2013). In a separate study conducted on in vitro cell culture experiments for anti-inflammatory effects, *C. racemosa* increased TNF-α and mTOR expression, as well as decreased AMPK expression after 6 and 24 h of incubation in RAW 2647 cells (Kurniawan et al., 2023). In an alternative in vitro model, the researchers employed CRC HT-29 cells were used to suppress the expression of TGF-β1, a pro-inflammatory protein that stimulates the proliferation of colon cancer cells (Permatasari, Bulain, et al., 2022). The anti-inflammatory activity of *C. racemosa* was assessed using a carrageenan-induced paw edema test as an in vivo test paradigm (Radhika et al., 2012). In additional investigations utilizing acetic acid induction, inflammation was evaluated using the rat abdominal writhing test and the hot plate test to measure the heat-resistant latency time reactivity of rat paws before and after *C. racemosa* treatment. Anti-inflammatory assays using commercial kits for the liver and pancreas after and without *C. racemosa* administration were conducted in streptozotocin-induced diabetic animal models to evaluate the levels of inflammatory biomarkers, including cytokines, TNF-α and IL-4, serum markers (AST and ALT), and ALP (Mandlik et al., 2022). The majority of the research examined the anti-inflammatory activity of C. racemosa in diverse experimental settings, encompassing a range of extract types, fractions, isolates, and doses.

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Table 1. Characterize a study including 12 papers, including 5 articles on in-vitro investigations and 7 articles on in-vivo research regarding the anti-inflammatory capabilities of *C. racemosa*

Types of Extract	Plant sources	Study Type	Conclusion	Ref
Methanol	Sepanggar sea, Kota Kinabalu, Sabah, Malaysia	In Vitro	Extraction: Dried algal thallus was extracted by maceration with methanol for 5 days. The MeOH solution was concentrated in a vacuum and partitioned between diethyl ether and water. The Et2O solution was washed with water, dried over anhydrous sodium sulfate, and evaporated to leave a dark green oil. Method: Samples were tested for anti-inflammatory activity in lipopolysaccharide (LPS) stimulated RAW 264.7 cells. Parameter: Inhibitory effects of nitric oxide (NO) Control: (+) RAW 264.7 cell induced LPS (-) RAW 264.7 cell Results: The green seaweeds, *C. racemosa* var. laete-virens, suppressed 30–40% of NO production.	(Vairappan et al., 2013)
Ethanol 96%	Cultivation pond in Jepara Regency, Central Java Province, Indonesia	In Vitro	Extraction: Simplica powder from each green algae was mixed with 2 L of 96% ethanol solvent in a 1:2 ratio and put into a dark bottle. Simplica was soaked for three days. and the condensed extract was sequentially partitioned into equal volumes using EtOAc and n-hexane solvents. Method: In Vitro Anti-Inflammatory Assays via Mammalian Target of rapamycin (mTOR) Kinase, AMP-Activated Protein Kinase (AMPK), and Tumor Necrosis Factor-Alpha (TNF-α) Assay Parameter: AMPK, mTOR, and TNF-α expression Control: (+) RAW 264.7 cell induced LPS (-) RAW 264.7 cell Results: AMPK expression was generally enhanced while TNF-α and mTOR expression was suppressed by the carotenoid extract of *C. racemosa*. After six or twenty-four hours of	(Kurniawan et al., 2023)

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			incubation, the CrE led to a greater elevation of AMPK expression when compared to the other groups' treatment.	
Ethanol 70%, and Fraction of Hexane, Chloroform, ethyl acetate. Isolated squalane from *C. racemosa*	Southwestern coastal area Sri Lanka	In Vitro	Extraction: Algae powder was extracted four times using 70% ethanol and filtered under vacuum. The filtrate was concentrated by a rotary evaporator to obtain the crude extract. The crude extract (CRE) was suspended in deionized water and fractionated between hexane (CREH), chloroform (CREC), and ethyl acetate (CREE). Method: Samples were tested for anti-inflammatory activity in lipopolysaccharide (LPS) stimulated RAW 264.7 cells. Parameter: Inhibitory effects of nitric oxide (NO) Control: (+) RAW 264.7 cell induced LPS (-) RAW 264.7 cell Results: Solvent fractions, CREE and CREH showed higher potency to dose-dependently inhibit LPS-induced NO production in RAW cells compared to the inhibition by CREC and CREW.	(Fernando et al., 2018)
ethanolic extract	Mantehage, North Sulawesi, Indonesia	In Vitro	Extraction: The extract was macerated in 96% ethanol for 72 hours. The filtrate was concentrated and evaporated at 40°C to obtain a thick extract. Method: Quantitative measurement of apoptosis was measured using flowcytometry and the expression of Bcl-2, BAX, and cleaved-caspase 3 as pro and anti-apoptotic proteins were measured using immunofluorescence Parameter: Pro-apoptosis through expression of Bcl-2 and BAX Control: HeLa cells Results: The TGF-β pathway may be disrupted by the *C. racemosa* extract, which could have several negative knock-on consequences that prevent CRC from progressing. Through the inhibition of TGF-β1 expression and the disturbance of its receptor activation, it modifies growth factors, apoptotic processes, and the cancer microenvironment, offering a possible treatment pathway for colorectal cancer. Extracts that exhibit pro-apoptotic effects correlate	(Permatasari, Bulain, et al., 2022)

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			with anti-inflammatory activity by modulating key signaling pathways and reducing the production of cytokines and inflammatory mediators.	
Methanol (soxhlet apparatus)	Tuticorin coast, Tamilnadu, India.	In Vitro	Extraction: Extracts of the freeze-dried and powdered biomass were prepared using methanol as solvent using a soxhlet Method: Antibacterial activity of seaweed extracts using Disc Diffusion Parameter: Highest inhibition bacterial zone *Vibrio cholera, Salmonella typhoid, Escherichia coli* and *Klebsiella pneumonia* Control: Bacterial agar plates *Vibrio cholera*, *Salmonella typhoid*, *Escherichia coli* and *Klebsiella pneumonia* without extract Results: A peak value of 9 mm zone of inhibition was observed against *Vibrio cholera* with *C. racemosa* extract. Cholera toxin (CT) is the main virulence factor of *Vibrio cholera* that causes the signs and symptoms of cholera. CT production can be inhibited through various mechanisms, some of which also exhibit anti-inflammatory properties	(Radhika et al., 2012)
Methanol and Fraction of hexane, chloroform, ethyl acetate, n-butanol.	João Pessoa, State of Paraiba, Brazil	In Vivo	Extraction: The fresh sample of *C. racemosa* was exhaustively extracted with MeOH at room temperature. The solvent was removed under reduced pressure at <40 °C and a dark green residue was obtained. Part of the crude methanol extract was submitted to solid-liquid partition successively with hexane, chloroform, ethyl acetate, and n-butanol Method: Formalin-induced nociception test. Parameter: Measured the time the animal spent licking the right hind paw from 15 to 30 minutes from the time after injection. Control: (+) Indomethacine (-) control received vehicle-only Results: In assessing the anti-inflammatory activity in formalin-induced experimental animals. In the inflammatory phase, only ethyl acetate (75.43%) and indomethacin (47.83%) induced significant response inhibition in this model.	(Souza et al., 2009)

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N-hexane, chloroform, ethyl acetate, methanol, and water in a Soxhlet device.	João Pessoa, Paraíba State, Brazil	In Vivo	Extraction: Fresh algae were lyophilized and extracted thoroughly with hexane, chloroform, ethyl acetate, methanol, and water in a Soxhlet apparatus, to obtain extracts. Method: The formalin test was performed according to the method of Hunskaar and Hole. Parameter: Measured the time the animal spent licking the right hind paw from 15 to 30 minutes from the time after injection and evaluate the activity of these species in a cell migration model Control: (+) Indomethacine (-) control received vehicle-only Results: In assessing the anti-inflammatory activity in formalin-induced experimental animals, only the ethyl acetate fraction (68,7 % inhibition) and treatment with indomethacin (48.7% inhibition) inhibited the inflammatory phase. In the leukocyte migration inhibition test into the peritoneal cavity, the AE fraction inhibited 71.7%, compared to Indomethacin treatment, which inhibited 65.4% of leukocyte migration.	(Da Matta et al., 2011)
Ethanol (95%)	The coastal area of Okha Port in the Gujarat state of India	In Vivo	Extraction: Fresh algae were lyophilized and extracted thoroughly with hexane, chloroform, ethyl acetate, methanol, and water in a Soxhlet apparatus, to obtain extracts. Method: Measurement of NO, IL4, and TNF-α levels in the serum blood of streptozotocin-induced diabetic rat model Parameter: NO, IL4, and TNF-α levels Control: (+) Glipizide (-) Blank citrate buffer Results: The inhibitory effect of *C. racemosa* (200 mg/kg/day) on serum TNF-α and IL-4 levels was greater than that observed after glipizide (5 mg/kg/day) treatment.	(Mandlik et al., 2022)
Total sulfated polysaccharides (TSP) extraction and Total	From beach at Pedra Rachada in Sa˜o Gonc¸alo-Ce, Brazil	In Vivo	Extraction: The dried algae were hydrated in 250 mL of sodium acetate buffer with papain, cysteine, and EDTA. This mixture was kept at 60°C for 6 hours, filtered, and the residue washed with water. TSP was precipitated using cetylpyridinium chloride (CPC) and centrifuged. The precipitate was washed with CPC solution, dissolved in NaCl-ethanol	(Ribeiro et al., 2020)

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sulfated polysaccharides (TSP) fraction			solution, and re-precipitated with ethanol. The final product was washed, dialyzed, lyophilized. Method: Evaluation the levels of TNF-α, and IL-1β in Wistar rats modeled on TMJ hypernosis that were pretreated (iv) 30 minutes prior to the administration of formalin. Parameter: TNF-α, and IL-1β Control: (-) Formalin Control not treatment Results: *C. racemosa* had anti-inflammatory properties in a TMJ hypernociception experimental model. These effects were associated with a reduction in plasma extravasation, a peripheral stimulation of HO-1, and a decrease in TNF-α, and IL-1β	
Ethanol 50%	From the St. Martin's Island shore in Bangladesh	In Vivo	Extraction: The algae extract was obtained by 50% ethanol maceration with a ratio of 1 gram/10 mL (1:10) for 7 days. Method: To evaluate the reduction of paw swelling/edema, the volume displacement of the left hind paw was re-measured for each rat with a plethysmometer after ½ hours, 1 hour, 2 hours, 3 hours, 4 hours, and 5 hours, 6 hours, and 8 hours after carrageenan induction. Parameter: Reduction of paw swelling/edema Control: (-) Without any treatment (+) Diclofenac Results: A 50% ethanol extract of *C. racemosa* 50mg/kg body weight showed better anti-inflammatory activity at six hours of investigation and inhibited 155.60% of edema.	(Chowdhury et al., 2023)
Aqueous extract	Collected from habitat in Southern, Northern, and North-western coastal areas in Sri	In Vitro In Vivo	Extraction: Each dry powder sample was suspended/dissolved separately in distilled water. Then, the samples were dissolved via sonication for 1 hour using an ultrasonic sonicator. The temperature was maintained at 40°C throughout the process. Then, the samples were shaken in a roller overnight at room temperature, and the extraction results were centrifuged at 15,000 rpm for 10 min at 4°C. Method: Cell migration induction of seaweed extracts was assessed by scratch wound	(Premarathna et al., 2020)

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	Lanka		healing test using the L929 cell line. For in vivo studies to evaluate the whole skin cut to create wounds in mice. as well as the expression levels of Tumor Necrosis Factor (TNF-α) and Transforming Growth Factor-β (TGF-β) through RT-PCR were measured once every three days until the end of the test. Parameter: Cell migration activity, enhanced wound healing activity in mice, and expression levels of TNF-α and TGF-β Control: In Vitro - In vivo (-) Without forming wounds and without providing any treatment. Results: The aqueous extract of C. racemosa has properties that make it able to increase the healing activity of scratch wounds in vitro and in vivo and the evaluation results of cytokine of TNF-α and TGF-β expression	
Isolated caulerpin from *C. racemosa*	Collected in the Northeast of Brazil	In Vivo	Extraction: The methanol extract of *C. Racemosa* was partitioned between H2O and hexane, chloroform, ethyl acetate, and n-butanol. The separation of chloroform fraction resulted in the isolation of orange-red pigment. Based on UV, IR, and NMR spectra data as well as chemical properties, the structure of caulerpine is shown. Method: Formalin-induced nociception Parameter: Measured the time the animal spent licking the right hind paw from 15 to 30 minutes from the time after injection. Control: (+) Indomethacine (-) control received vehicle-only Results: The possible anti-inflammatory activity observed in the second phase in the formalin test of caulerpin (100 μmol/kg, p.o.) was confirmed on the capsaicin-induced ear edema model, where inhibition of 55.8% was presented.	(De Souza et al., 2009)

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Figure 2. *C. racemosa* post-harvesting

The secondary metabolites such as alkaloids, flavonoids, phenolic, phytosterol, tannins, terpenoids, and saponins of various *C. racemosa* extracts are screened in Table 2. These secondary metabolites have many therapeutic applications and are widely used in the pharmaceutical industry. The benefits of alkaloids in the medical field include stimulating and combating microbiological infections, altering blood pressure, and stimulating the neurological system (Vairappan et al., 2013). Flavonoids help the body absorb vitamin C, preventing and treating allergies, viral infections, arthritis, and inflammatory conditions (Pires et al., 2013). Phenolic compounds have antioxidant, antidiabetic, anti-filaria, anticancer, cardioprotective, anti-inflammatory, and antiviral effects against the SARS-CoV-2 virus, which causes severe acute respiratory syndrome (Palaniyappan et al., 2023). Phytosterols have cholesterol-lowering effects by inhibiting the absorption of cholesterol from the intestine, avoiding cholesterol in bile salt micelles, and increasing the excretion of bile salts. Phytosterols also improve blood cholesterol regulation at normal levels (He et al., 2023). Tannin binds and precipitates proteins, treats diarrhea and hemorrhoids, stops inflammation, and is a natural alternative for cleaning dentures (Wu et al., 2022). Terpenoids have interesting pharmacological properties, including antiviral, antibacterial, anti-inflammatory, cholesterol synthesis inhibition, and anticancer effects. Saponins have antibacterial properties, suppress fungi, and shield plants from insect damage. Lipoprotein-lowering saponins are antioxidant, antiviral, anti-carcinogenic, and rumen fermentation manipulators (Hainil et al., 2023).

Table 2. Secondary metabolite of *C. racemosa*

No.	Secondary Metabolites	Presence
1.	Alkaloids	+
2.	Flavonoids	+
3.	Fucoidan	+
4.	Phenolic	+
5.	Phytosterol	+
6.	Tannins	+
7.	Terpenoids	+
8.	Saponins	+

Reproduced from (Palaniyappan et al., 2023)

Analysis of the mineral content showed that calcium had the highest mineral content. According to Khairy and El-Sheikh (2015), sodium, potassium, and calcium are the minerals commonly found in seaweeds. The highest mineral content was calcium which ranged from 149.66-168.64 mg/100 g and the lowest mineral content was magnesium (2.21-2.90 mg/100 g). The results of the analysis showed that mineral content increased with decreasing water content. According to Agoreyo et al. (2011), minerals are not damaged by heat treatment and exhibit very low volatility. The increase in mineral content was caused only by a decrease in the water content of the material. According to Tuteja and Sopory (2008), calcium is a macro element that is very important for plants and acts as a second messenger in the message-delivery pathway, and its concentration increases with stress signals. Calcium is a chemical signal under abiotic stress conditions in plants. Tuteja and Mahajan (2007) also reported that many physiological stimuli stimulate increased Ca^{2+} ion concentrations, such as light, touch or friction, pathogenic elicitors, plant hormones, and abiotic stresses, including high salinity, cold temperatures, and drought. The mineral contents of *C. racemosa* are shown in Table 3.

Table 3. Mineral

No.	Mineral	Fresh (mg/100g)	Semi-Dried (mg/100g)	Dried (mg/100g)
1.	Ca	149.66	163.99	168.64
2.	Fe	9.52	9.95	10.13
3.	K	77.59	86.77	92.50
4.	Mg	2.21	2.56	2.90
5.	Na	13.05	13.85	14.00

Reproduced from (Palaniyappan et al., 2023)

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Table 5. Amino Acid

No.	Amino Acid Compound	Fresh (%)	Semi-Dry (%)	Dried (%)
1.	Aspartic acid	28.99	28.71	73.11
2.	Glutamic acid	32.53	31.46	78.75
3.	Serine	13.73	13.83	32.79
4.	Histidine	1.10	1.21	5.91
5.	Glycine	13.60	8.51	27.74
6.	Threonine	13.12	12.42	31.61
7.	Arginine	13.59	12.21	33.57
8.	Alanine	13.73	19.82	45.03
9.	Tyrosine	18.25	15.89	40.85
10.	Methionine	2.52	2.25	10.38
11.	Valin	13.22	12.01	31.18
12.	Phenylalanine	13.80	13.06	33.97
13.	Ileucine	9.78	8.83	22.69
14.	Leucine	19.90	19.09	49.57
15.	Lysine	8.33	2.89	9.67

Reproduced from (Sanjaya et al., 2016)

Eight fatty acids from semi-dry samples and four fatty acids from dry samples. The dominant PUFA from fresh and dry samples was α-linoleic acid (9.74% and 16.76%, respectively), while that from semi-dried samples was arachidonic acid (10.69%). Blažinareported(that 2009) Reported the most dominant unsaturated fatty acid in *C. racemosa* was α-linoleic acid. The fat content of *C. racemosa* was very low (1.13-2.32% db), but their fatty acids had the potency to contain unsaturated fatty acids, which are essential for the body. According to Farid et al. (2013), seaweed has a very low fat content, but is rich in long-chain unsaturated fatty acids. In the green seaweed group (Chlorophyceae), the main unsaturated fatty acid was C20:5ω3 and the main saturated fatty acid was C16:0. The results in Table 5 show an increase in the relative percentage of the main fatty acids in dry seaweed. This is due to the large amount of fatty acid impurities present in fresh and semi-dried seaweed (Souza et al., 2009). The fatty acid contents of *C. racemosa* are presented in Table 4.

Table 4. Fatty Acid

No.	Fatty Acids	Fresh (%)	Semi-Dried (%)	Dried (%)
1.	Palmitic acid	15.79	11.53	38.41
2.	Linoleic acid	8.42	12.24	12.39
3.	α-Linoleic acid	9.74	8.64	16.76
4.	Arachidonic acid	7.13	10.69	3.31
5.	Oleic acid	3.10	2.40	7.58

Reproduced from (Sanjaya et al., 2016)

The protein content in *C. racemosa* was dominated by glutamic and aspartic acids. They are amino acids that play a large role in the taste of food and have a strong impact on taste (Lewis, 1962; Gunlu & Gunlu, 2014; Santoso & Yoshie, 2004). The amino acid content of dried *C. racemosa* was higher than that of fresh, and fresh and semi-dried *C. racemosa* were unstable because the moisture content of the material was still high (53-90% wb).

Sulfated polysaccharides are polyanionic linear macromolecular compounds that contain sulfate groups. The SPs fraction was isolated from the *C. racemosa* extract collected from the Gujrat Coast and analyzed for sugar content. The results showed that the main sugars were galactose, glucose, arabinose, and xylose. Sugar is widely distributed in–9-11 hemiester sulfate groups. Sulfation and methylation occur in O-6 galactose and O-3 arabinose (Da Matta et al., 2011). This polysaccharide is branched and contains 1,3- and 1,3,6-linked galactose, 1,3,4-linked arabinose, 1,4-linked glucose, and terminal- and 1,4-linked xylose residues (Ragasa et al., 2015). Research has demonstrated that Racemosin C, an alkaloid present in the green alga Caulerpa racemosa, has anti-inflammatory properties. Specifically, it suppresses the activity of protein tyrosine phosphatase 1 B (PTP1B), which plays a detrimental role in regulating insulin and leptin signaling. Such inhibition can result in increased insulin and leptin activity, which may diminish inflammation and enhance metabolic well-being (Dissanayake et al., 2022). Furthermore, racemose C has been investigated for prospective therapeutic use, particularly in relation to inflammatory disorders. This intervention modulates the signaling

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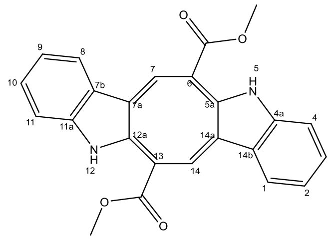
pathways that play a critical role in regulating inflammatory responses, including the NF-κB pathway (Souza et al., 2020). Squalene has been shown to decrease the synthesis of inflammatory mediators, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) in RAW macrophages stimulated by lipopolysaccharide (LPS) (Fernando et al., 2018).

Table 6. Alkaloids and terpenoids compound

No.	Compound	Presence	Reference
Alkaloid			
1.	Caulerchlorin	+	(Liu et al., 2013)
2.	Caulerprenylols A	+	(Liu et al., 2013)
3.	Caulerprenylols B	+	(Liu et al., 2013)
4.	Racemosin A	+	(Liu et al., 2013)
5.	Racemosin B	+	(Liu et al., 2013)
6.	Racemosin C	+	(Liu et al., 2013)
7.	Caulerpin	+	(Ornano et al., 2014)
Terpenoid			
1.	racemobutenolids A, B	+	(Yang et al., 2015)
2.	4,5-dehydrodiodictyonema A	+	(Yang et al., 2015)
3.	α-tocopheroid	+	(Yang et al., 2015)
4.	Squalene	+	(Ragasa et al., 2015)

Environmental factors that affect seaweed growth include temperature, salinity, pH, sunshine, physiological conditions, and CO_2 availability. This is because of different adaptation strategies. The different physiological adaptive properties of seaweeds affect the number of unique structural centers in secondary metabolites, including alkaloids, quinones, polyketides, polysaccharides, cyclic peptides, diterpenoids, glycerol, lipids, and flavonoids. Chlorophytian seaweeds are widely distributed in the intertidal zones.

The anti-inflammatory characteristics of caulerpin make it a highly promising candidate for the advancement of innovative therapeutic medications, particularly for the treatment of diverse inflammatory disorders (Souza et al., 2009). The chemical structure of caulerpin is shown in Figure 3.



d3

Figure 3. Structural of Caulerpin as Anti-Inflammatory

Tumor necrosis factor-alpha (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6) are pro-inflammatory cytokines released by macrophages in response to foreign antigens. These cytokines promote antigen removal and tissue repair by enhancing chemotaxis of mast cells, granulocytes, lymphocytes, and monocytes to the site of injury. However, greater infiltration and activation of these cells increases the possibility of tissue damage because of exaggerated inflammation and its primary symptoms, edema, and pain. During chronic inflammation, an increase in the expression of proinflammatory mediators was observed. iNOS, COX-2, TNF-α, IL-1β, IL-6, and Prostaglandin E2 (PGE2) are primary mediators of inflammation. Changes in cytokine levels may have an impact on cellular reactions and may be related to the anti-inflammatory properties of phytochemicals. NO is another mediator of the inflammatory processes. Inflammation protects against NO levels. However, elevated NO generation also results in cytotoxicity and tissue damage under some clinical circumstances. Cellular responses are governed by a complex network of signaling pathways that govern these processes (Sanniyasi et al., 2023).

T cell activation triggers the production of a diverse range of lymphokines such as interleukin-2 and interferon-γ (IFN-γ). A variety of white blood cells are stimulated to develop, differentiate, and become activated B cells. Overwhelming inflammation gradually ruins the structure of healthy tissue and damages organs. As a result, the demand for safe oral medications with anti-inflammatory properties has increased. Extensive research has been conducted on the qualities of caulerpin, including its antioxidative, anticoagulant, anticancer, anti-inflammatory, and antiviral effects, is one potential contender.

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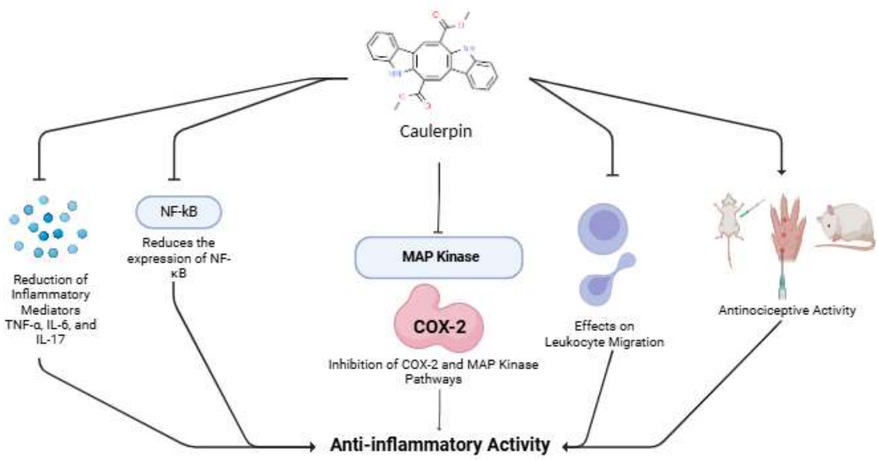

Figure 4. Anti-inflammatory effect of caulerpin

Extensive studies have been conducted on its benefits in malignancies, ischemia, immunological dysfunction, and inflammatory illnesses. Its potential to reduce inflammation may be attributed to a reduction in NF-κB signalling pathway activity (De Souza et al., 2009;Lucena et al., 2018). The function of the mitogen-activated protein kinase (MAPK) cascade in the biological effects of fucoidan has been covered by other studies. Many mammalian cells contain serine/threonine protein kinases, which are members of the MAPK family. The MAPK cascade is involved in gene expression, cell proliferation and differentiation, neuronal survival, and apoptosis, according to numerous studies. Every major MAPK pathway primarily contributes to a specific set of processes. For example, the p38 MAPK pathway controls the production and release of pro-inflammatory mediators; the ERK pathway must be activated for cells to proliferate, survive, and differentiate; and the JNK pathway controls apoptosis (Huang & Ferrell, 1996). Alkaloid Caulerpein substance's mechanism inhibits inflammation with different targets mentioned in the cascade as can be seen in Figure 4.

The anti-inflammatory activities of caulerpine have been thoroughly investigated, and multiple studies have presented comprehensive information on the methodology employed in these tests. The dosage of caulerpine administered orally in in vivo experiments employed different inflammatory models, including carrageenan-induced peritonitis, was 100 μmol/kg. A 100 μmol/kg dose of caulerpine was administered orally to the capsaicin-induced ear edema model (De Souza et al., 2009). In peritonitis and ulcerative colitis models, the efficacious doses of caulerpine were 40 and 4 mg/kg, respectively, administered orally (Schiano et al., 2022). Caulerpin can affect the inflammatory process in many phases, including apoptosis, inhibition of multiple enzymes, and the prevention of lymphocyte adhesion and invasion. The most well-discussed mode of action of caulerpin involves suppression of the NF-κB and MAPK signaling pathways, which lowers the generation of proinflammatory cytokines (Wu et a*l*., 2022), as shown in Figure 3.

Despite extensive reports on the anti-inflammatory properties of caulerpin, several studies have shown an increased generation of pro-inflammatory cytokines. This compound slowed the natural apoptosis of human neutrophils, natural killer cells (NK), and pro-inflammatory cytokines (IL-6, IL-8, and TNF-α). Caulerpin sourced from Fucus vesiculosus facilitates several immunological responses, including Th1 immunity, memory T-cell generation, antigen-induced antibody production, and dendritic cell maturation. Additionally, Caulerpin may stimulate the immune system. Souza et al. (2020) showed how Caulerpin interacts with "toll-like receptors" (TLRs), increasing the expression of MHC molecules and the synthesis of chemokines and cytokines. Increased activity of innate and specialized immune cells is an outcome. The innate immune system and chemicals that bind to TLR to activate the NF-κB signaling cascade are known to have toll-like receptors. Caulerpin improves the immune response by binding to TLR-2 and TLR-4 but not TLR-5 (Huang & Ferrell, 1996).

CONCLUSION

This systematic review shows that Caulerpa is a genus of green seaweed that has been proven to have anti-inflammatory activity across various plant parts and types of herbal medicinal preparations used in experimental settings. The purported anti-inflammatory effect of sea grapes may be attributed, in part, to their capacity to impede the accumulation of pro-inflammatory cytokines at the site of inflammation.

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AUTHOR CONTRIBUTIONS

Conceptualization, R.W.; Methodology, R.W., S., S.D.; Software, E.W.P., I.S.; Validation, R.W., S., S.D.; Formal Analysis, E.W.P., I.S.; Investigation, E.W.P., I.S.; Resources, E.W.P., R.W.; Data Curration; E.W.P., I.S.; Writing - Original Draft, E.W.P.; Writing - Review & Editing, R.W., S., S.D.; Visualization, E.W.P., I.S.; Supervision, R.W., S., S.D.; Project Administration, R.W., S., S.D., I.S.; Funding Acquisition, R.W., S.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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