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Exploring the multiple functions of polyphenols in Mediterranean macroalgae: insights, gaps, and future directions from a systematic review

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ABSTRACT

Macroalgae are a cornucopia of bioactive molecules whose synthesis is modulated in response to environmental variables, allowing macroalgal adaptation and survival. Among these metabolites, polyphenols are worthy of attention because they may represent an informative archive of environmental conditions, given their involvement in several ecological and biochemical functions. This systematic review synthesized the literature from the last two decades on phenolic compounds in Mediterranean macroalgae, focusing on their functional roles, taxonomic distribution, geographical occurrence, and responses to abiotic and biotic stressors, with particular attention to their potential as 'early indicators' of environmental change. Using a Scopus-based search strategy, nearly 6000 records were screened and studies on brown, red, and green macroalgae published between 2003 and September 2025 across the Mediterranean basin were retained.

The reviewed literature highlighted that polyphenols are widely involved in antioxidant defense, photoprotection, stress tolerance, and interspecific interactions, supporting the resilience of macroalgae in a rapidly changing Mediterranean Sea. At the same time, the review emphasizes the significant biotechnological potential of these compounds in the pharmaceutical, cosmetic, food, and agricultural sectors. Overall, the evidence indicates that fluctuations in polyphenol content often reflect rapid physiological responses to environmental stress, suggesting that these compounds may function as early indicators of ecological change in Mediterranean macroalgae.

Despite growing evidence, several important gaps remain. Research from the eastern Mediterranean basin is still limited, most studies focus on only a few model genera, and long-term field studies examining multiple environmental stressors are rare. Future research should therefore include a wider range of geographic areas and species, adopt standardized analytical methods, and investigate how polyphenols respond to combined environmental drivers. This would help clarify and validate their use as early indicators of ecological change.

1. Introduction

The Mediterranean Sea represents the world's largest and deepest inland sea as it covers about 2.97 million km^2, with an average depth of 1.460 m and a maximum depth of 5.267 m. Its strategic position at the crossroads of Europe, Africa, and Asia explains why it has been considered central for Mediterranean history and civilization, fostering cultural exchange, trade, and migration for millennia. Currently, it remains a global maritime hub, supporting dense coastal populations across several countries and attracting nearly 200 million tourists each year. Geographically, a submarine ridge in the Strait of Sicily, separates The Mediterranean into western (0.85 million km^2) and eastern (1.65 million km^2) sub-regions (Coll et al., 2010). Biologically, is a biodiversity hotspot, harbouring about 11% of all marine species in less than 1% of the global marine area (Rodríguez- Rodríguez and Abdul Malak, 2022).

This exceptional biodiversity faces growing threats from human-induced pressures activities, such as habitat loss, coastal urbanization, pollution, overexploitation of marine resources, climate change impacts (e.g., ocean warming, acidification, sea-level rise), and the spread of invasive species (Lejeusne et al., 2010; Mannino et al., 2017). The eastern Mediterranean is particularly vulnerable to climate change

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(Hochman et al., 2018, 2022), with projections indicating significant increases in temperature and humidity. These environmental changes have heightened scientific interest, especially concerning extreme weather events and their impacts on both ecosystems and society (Hochman et al., 2022). For instance, more frequent and intense heatwaves have been linked to increased mortality and disease (Gosling et al., 2009; Lubczyńska et al., 2015), while climate-induced stressors such as prolonged droughts may exacerbate socio-economic instability and trigger migration (Abel et al., 2019). The western Mediterranean, although facing less warming (Garrabou et al., 2022), relies heavily on tourism and face economic risks from rising temperatures and aridity, potentially reducing its appeal to visitors (Agulles et al., 2022).

Elevated CO_2 levels, deriving from intensified anthropogenic pressures, further classify the Mediterranean as a hotspot for climate change. However, the uniqueness and vulnerability of its marine ecosystems are further underscored by the presence of natural CO_2 vents and seeps, which serve as valuable proxies for evaluating the resilience of marine species to ocean acidification (Balzan et al., 2020; Hassoun et al., 2022).

In response to environmental stressors, attention has recently shifted toward the mechanisms that enable marine organisms, particularly macroalgae, as primary producers and habitat-formers, to cope with changing conditions (Fabbrizzi et al., 2023; Manca et al., 2024; Donadio et al., 2025). Macroalgae exhibit a spectrum of responses to environmental fluctuations, either immediate (acclimation) or gradual (adaptation). Adaptation involves genetic changes in populations over generations, enhancing survival in stable environments, while acclimation consists of short-term physiological adjustments to sudden changes like temperature fluctuations, without genetic alterations. However, local environmental contexts also shape both acclimation and adaptation strategies, as site-specific conditions present unique features driving specific biological responses. Over time, repeated acclimation and adaptation cycles can result in the accumulation of traits that enhance resilience to environmental stressors, influencing growth, reproduction, and survival (Duarte et al., 2018; Ji and Gao, 2021).

Among the mechanisms conferring resilience in macroalgae, the production of polyphenols, secondary metabolites with aromatic structures, has emerged as particularly significant.

In higher plants, polyphenols are mainly synthesized through the shikimic acid and phenylpropanoid pathways (Chen et al., 2018). In contrast, macroalgae do not possess a single universal biosynthetic pathway; instead, the pathways differ according to the algal group and the type of polyphenol produced. In brown macroalgae (Phaeophyta), the dominant phenolic compounds, phlorotannins (Ragan and Glombitza, 1986), are primarily synthesized through the acetate–malonate (polyketide) pathway (Li et al., 2011). This process occurs in the Golgi apparatus, where phloroglucinol (1,3,5-trihydroxybenzene) units are polymerized into various structural classes, including fuhalols, phorethols, fucols, and eckols (Carpena et al., 2024).

Compared with brown algae, the biosynthetic pathways of red and green macroalgae (Rhodophyta and Chlorophyta) are less well characterized. Current evidence suggests that these groups use pathways partially analogous to the phenylpropanoid pathway found in terrestrial plants. However, the underlying mechanisms remain poorly understood and are still under investigation (Carpena et al., 2024).

Overall, polyphenols include several groups, such as phenolic acids (e.g., hydroxybenzoic acids, hydroxycinnamic acids), flavonoids (e.g., flavones, flavonols, flavanones, flavanonols, flavanols, anthocyanins), isoflavonoids (e.g., isoflavones, coumestans), stilbenes, lignans, phenolic polymers (e.g., proanthocyanidins, condensed and hydrolysable tannins) (Mazouzi et al., 2023; Carpena et al., 2024). Finally, bromophenols, although not always strictly classified as polyphenols, are widely distributed among red, green and brown macroalgae. Their biosynthesis is catalyzed by bromoperoxidase enzymes, which utilize precursors such as phenol, 4-hydroxybenzoic acid, and 4-hydroxybenzyl alcohol in the presence of hydrogen peroxide and bromide ions (Carpena et al., 2024).

Together, these biosynthetic pathways enable macroalgae to produce a diverse and complex range of secondary metabolites with multiple ecological functions.

These compounds contribute to protection against ultraviolet (UV) radiation and oxidative stress through the scavenging of reactive oxygen species (ROS), deter herbivores through bitterness and toxicity, and inhibit microbial pathogens via antimicrobial activity (Eom et al., 2012; Carpena et al., 2024).

Their synthesis and accumulation are indeed often influenced by light intensity, temperature, nutrient availability, and salinity (Connan et al., 2006; Cruces et al., 2012). Under climate change scenarios, featured by ocean warming, acidification, and increased solar irradiance, polyphenols are increasingly recognized as components of algal adaptive responses. They not only aid macroalgae in surviving extreme environments (Messina et al., 2019), but also shape broader ecological processes, including species interactions, community composition, and habitat stability (Hay, 2009; Jormalainen and Honkanen, 2008). As a result, polyphenols are gaining prominence not only for their ecological functions but also for their potential as 'markers' of environmental change. Their dynamical patterns across space and time may offer valuable insights into the physiological status of algae and the overall health of marine ecosystems facing stress conditions. Consequently, advancing research into algal polyphenols offers a promising pathway for assessing the effects of climate change on coastal environments and for detecting early warning indicators of stress.

Beyond their ecological functions, macroalgal phenolic compounds exhibit a wide range of biological activities, including anti-Alzheimer, anti-inflammatory, anti-allergic, antiproliferative, antioxidant, anti-obesity, hypocholesterolemic, hepatoprotective, and bactericidal properties, among others (Montero et al., 2018; Tziveleka et al., 2021; Ahmed et al., 2023; Cadar et al., 2025; Fonseca-Barahona et al., 2025).

Due to these bioactive properties, macroalgal polyphenols have attracted growing interest for biotechnological applications, particularly as ingredients in nutraceuticals and functional foods, and as active compounds in cosmetic and pharmaceutical formulations (Šimat et al., 2020; De La Fuente et al., 2021; Mirata et al., 2023; Cadar et al., 2025; Golmakani et al., 2025). However, their structural complexity and chemical variability still pose major challenges for their extraction, isolation, and characterization (Santos et al., 2019). This systematic review aims to synthesize recent advances in the research of polyphenolic compounds in Mediterranean macroalgae over the last two decades. Specifically, we aim to: (i) elucidate the multifunctional roles of polyphenols in regulating algal physiology and stress tolerance, (ii) explore potential links between polyphenol occurrence and environmental conditions, (iii) assess the feasibility of using polyphenols as early indicators of environmental changes, (iv) unravel the potentiality of polyphenols in sustaining both ecosystem and human-health.

To this purpose, we conducted a bibliometric analysis of nearly 6.000 scientific articles, refined for relevance to Mediterranean countries and classified by publication year, study site, algal group (brown, red, or green), and research domain. This approach enabled us to identify emerging themes and research priorities, offering insights into current scientific trends, key knowledge gaps, and future directions for studies on polyphenols in the Mediterranean region.

2. Materials and methods

2.1. Analysis on keywords, selection of publications and data collection

The bibliographic search was conducted using the Scopus (Elsevier) database, which was queried through article titles, abstracts and author keywords within the time frame of 2003-2025 (up to September 2025). To maximize sensitivity and minimize the risk of missing relevant studies, we used a broad search strategy based on the keywords "algae" or "macroalgae" combined with "antioxidant" or "polyphenol". This inclusive approach was adopted because the term "algae" is often used in the literature to describe both macroalgae and microalgae, whereas "antioxidant" is frequently used as a general term for compounds involved in redox-related biological activities.

To improve the specificity of the search and reduce the retrieval of irrelevant records, terms specifically related to microalgae were excluded, namely: "microalgae", "micro-algae", "Cyanobacterium", "Cyanobacteria", "Chlorella", "Chlorella vulgaris", and "Spirulina". The search results were exported in csv file format including title, year, DOI, and link of each record. This initial csv file comprised 6068 records.

The screening was performed manually on the full text of each record, without the use of automation tools, by three independent reviewers. At each stage, the reviewers worked first independently and then compared their selections to reach a consensus. During the first screening phase, 5800 records were excluded. Specifically, records that were not accessible, not readable, not written in English, or classified as books, book chapters, or review articles were removed. A record was considered not accessible when the full text could not be retrieved despite repeated attempts through institutional subscriptions, open-access repositories, and author or publisher webpages.

A record was considered not readable when the available file was corrupted, incomplete, or otherwise unsuitable for proper evaluation. Reviews, book and book chapters, were excluded intentionally to limit the bibliometric analysis to original research articles only, consistent with the classification criteria subsequently adopted.

In parallel, studies were excluded when macroalgae samples originated from countries not bordering the Mediterranean Sea. This assessment was carried out through careful examination of the full text to identify the sampling location. Restricting the dataset to Mediterranean-bordering countries was consistent with the aim of investigating a clearly defined biogeographic system. After this first screening step, 268 records remained.

The second screening phase was again conducted independently by the three reviewers, followed by comparison and consensus of the selections.

At this stage, full texts were evaluated to exclude studies focusing exclusively on other bioactive compounds, on overall antioxidant capacity/activity, or on assays unrelated to phenolic constituents. Only studies addressing at least one phenolic compound or phenolic class were retained. To clarify the terminology adopted in the review, Table S1 defines the terms "bioactive compounds", "antioxidant capacity/activity", and "enzyme/enzyme activity", and specifies which terms were included under "polyphenolic compounds" across the 151 selected publications. This second screening step resulted in the exclusion of 117 additional records, leaving 151 full-text articles eligible for inclusion in the review.

These studies were then analyzed and categorized for data extraction, tabulation, visualization, and discussion. The list of included publications is provided in Fig. S1. The review was conducted in accordance with PRISMA guidelines; the study selection process is illustrated in Fig. 1, and the corresponding checklist is available in Table S2 (Moher et al., 2009; Page, 2021). No protocol was developed for this review, and it was not registered in a public registry.

Articles were classified by year of publication to assess how interest in these molecules has progressed over the last two decades. The cumulative publication numbers were represented as vertical bars. Moreover, considering the time required to perform experiments, finalize and publish a manuscript, a 3-year moving average was also calculated to reduce interannual fluctuations while preserving the responsiveness of emerging trends (Christie et al., 2021; Rachuba et al., 2024; Feuchtmayr et al., 2025; Jones et al., 2025).

The full text of each eligible publication was integrally examined to extract the qualitative information required for the analysis and representation of results.

The geographical classification has been established by noting the coordinates of the sampling sites (latitude and longitude), and considering the common division of the Mediterranean Sea provided by the International Hydrographic Organization (1953) (IHO), with the western Mediterranean composed by Strait of Gibraltar, Alboran Sea, Balearic Sea, Ligurian and Tyrrhenian Sea, and the eastern Mediterranean including Ionian Sea, Adriatic Sea, Aegean Sea, Levantine Sea (Coll

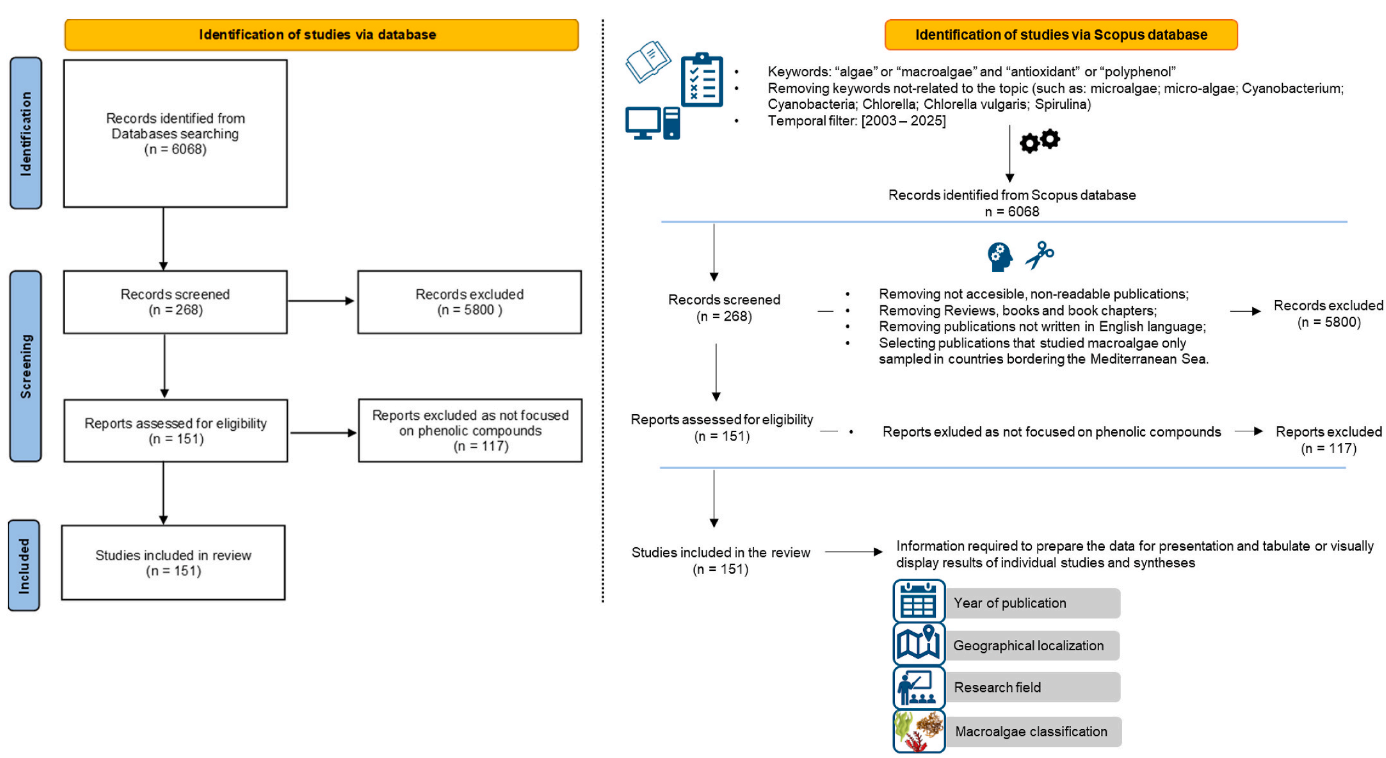

Fig. 1. PRISMA flowchart describing the literature sorting within the systematic review (on the left) and the graphical representation of the flowchart including the list of information required to present and display the results.

et al., 2010; Harding and Palutikof, 2020).

A further classification of the publications was conducted based on the three groups of macroalgae (Chlorophyta, green; Phaeophyta, brown; Rhodophyta, red) and declared species. Specifically, the species classification has been retrieved from Guiry (2024) and Guiry and Guiry (2025). Then, the percentage of studies focusing distinctly on green, brown, or red algae has been calculated. Whenever articles addressed two or more groups, they were counted for each one. The list of documented taxa has been reported, along with the percentage of studies concerning each species within its respective group to highlight which species are the most studied and investigated on phenolic compounds.

Finally, each of the 151 publications was examined and assigned to one or more research domains, namely ecology, agriculture and aquaculture, pharmacology, medicine, chemistry and food, to identify the dominant scientific directions in Mediterranean polyphenol research.

No statistical analyses were performed to validate the trends or patterns identified in the dataset because the study was designed as a descriptive and exploratory bibliometric systematic review. Therefore, temporal, geographic, taxonomic, and thematic patterns were described and interpreted qualitatively rather than statistically.

Similarly, no formal risk-of-bias assessment was carried out, as the main purpose of the review was to provide an overview of the existing literature and identify major research gaps, rather than to quantitatively compare results or assess the strength of evidence across studies.

2.2. VOSviewer analysis on keywords networking and occurrences

The results deriving from publications focusing on ‘polyphenols’ were consolidated into a CSV file, containing three columns: links, abstracts, and author keywords. These data were imported into VOSviewer software (version 1.6.19) and processed. Network maps were generated based on the degree of relatedness between items, resulting in potential cluster formations. Specifically, co-occurrence networks of keywords were constructed by evaluating the number of publications in which the same author keywords appear between two documents (Van Eck and Waltman, 2014, 2018).

For the network visualizations, we applied a minimum threshold of 5 occurrences, which resulted in the identification of 293 terms meeting the threshold. Only relevant terms (136) related to the specific topics have been considered in our analysis. The outcomes are represented by a network map, displaying the co-occurrence of keywords in the document analyzed. This type of graph furnishes the relationships between different terms used by authors in their studies, highlighting how certain concepts are interconnected through publications.

2.3. Geographical distribution of macroalgae sampling sites

All publications have been reviewed to collect the following information: species classified into functional groups according to their dominant pigments (Chlorophyta, green; Phaeophyta, brown; Rhodophyta, red), the sampling site with corresponding coordinates (latitude and longitude, when specified), and the research fields associated with the extraction and analysis of phenolic compounds, including ecology, agriculture and aquaculture, pharmacology, medicine, and food. This information has been entered into a csv. file to generate various distribution maps along the coasts of the Mediterranean Sea. An overall distribution map was produced by plotting all sampling points along the Mediterranean coasts, regardless of the assumed role of the algae. Additional thematic maps were generated while maintaining this same classification and differentiating the research fields. In each map, different symbols were used to distinguish between macroalgae groups. To generate the maps, the obtained csv. files were uploaded into R Studio software (version 4.2.2., R Core Team, 2022). If the study reports multiple algae sampled at the same site or if a species had more than one role (up to three roles simultaneously), they were plotted on every R Studio map. A dedicated shapefile downloaded from the website Marine regions.org (https://marineregions.org/, Accessed September 2025) was used to produce the maps, utilizing the R packages sf, dplyr and ggplot2.

3. Results

Among the various classes of non-enzymatic antioxidants, phenolic compounds are widespread across species and represent as especially informative group, because they are highly responsive to sudden changes in the organism's living environment.

The collection of 151 papers published on Scopus from 2003 to 2025, constitutes a substantial body of evidence, highlighting how phenolic compounds may function as “environmental sentinels” of environmental change.

3.1. Temporal and spatial distribution of scientific publications

Over the last two decades, research on phenolic compounds in the Mediterranean Sea has flourished due to the diverse roles these molecules may play. Analyzing individual years, the highest number of publications was recorded in 2021 and 2023, with 20 and 22 studies, respectively. Note that, since only papers published until September 2025 have been considered, the lower count observed in 2025 is expected and does not indicate a real decline in research activity.

More broadly, the 3-year moving average shows a clear upward trend, with a sharp increase beginning in 2020 (Fig. 2a). This is further supported by the six-year averages, which rise steadily from 2.2 publications per year in 2008–2013 to 7.2 in 2014–2019, and 15.8 in 2020–2025. No relevant publications were found for the period 2003–2007.

Italy, Algeria, Turkey, Spain, Tunisia, and Egypt, contributed with a significant number of publications over the past 20 years. The number of studies recorded in these countries includes 12 from Italy, 16 from Algeria, 20 from Turkey, 21 from Spain, 29 from Tunisia, and 33 from Egypt (Fig. 2b). Overall, the distribution of publications focusing on phenolic compounds is evenly divided, with 54% originating from Eastern Mediterranean countries and 52% from Western Mediterranean countries (see Fig. 2c).

3.2. Distribution of scientific publications across functional groups and species

Among macroalgae from which polyphenols have been extracted, Phaeophyta are the most studied, accounting for 46% of the total, due to the elevated content of flavonoids and phlorotannins. Phaeophyta are followed by Rhodophyta and Chlorophyta with 25% and 29% respectively (Fig. 3).

Considering publications focusing on phenolic compounds, the total number of Mediterranean investigated species Sea amounts to 130, including 28 species of green algae, 42 species of brown algae and 60 species of red algae (Fig. 4a). Although the number of red species exceeded that of brown and green ones, most papers focused on brown macroalgae (46%) with a total of 157 occurrences, compared to red and green macroalgae which accounted for 25% and 26% of the studies, corresponding to 146 and 90 occurrences, respectively. Utilizing the occurrences of each species in the publications, the study percentages for each single species within its respective group (green, brown and red macroalgae) have been calculated, as illustrated in Fig. 4b.

Among green macroalgae of Mediterranean Sea, the genus *Ulva* is the most explored, focusing on the following species: *Ulva lactuca* (24.4%), *Ulva rigida* (13.3%), *Ulva compressa* (7.8%), *Ulva intestinalis* (6.7%), *Ulva fasciata* (6.7%), *Ulva linza* (5.6%). The species *Codium fragile* and *Caulerpa prolifera* account for 4.4%; the 2.2% of interest is focused on *Chaetomorpha gracilis*, *Codium tamentosum* and *Halimeda tuna* and *Codium adhaerens*; several species, namely *Caulerpa racemosa*, *Chaetomorpha aerea*, *Cladophora glomerata*, *Codium bursa*, *Enteromorpha*

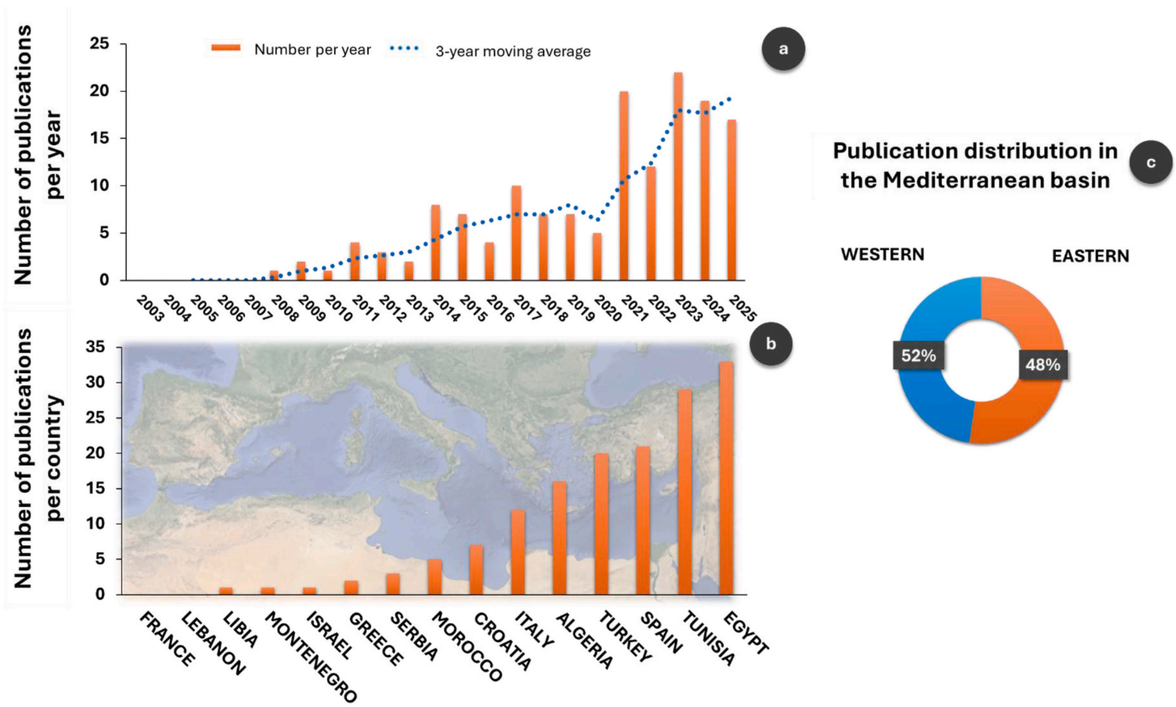

Fig. 2. a) Vertical bars represent the number of publications per year in the time frame 2003-2025, while the blue dotted line represents the moving average with 3-year window; b) Vertical bars represent the cumulative number of publications per country bordering the Mediterranean Sea in the time frame 2003-2025; c) Publication distribution in the eastern and in the western Mediterranean basin. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

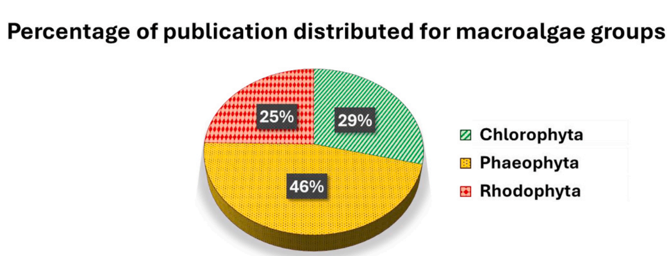

Fig. 3. Pie chart representing the percentage of publications focusing on polyphenols distributed for macroalgal groups: green (Chlorophyta) in striped slice, brown (Phaeophyta) in dotted slice; and red (Rhodophyta) in squared slice. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

multiramosa, *Flabellia petiolata*, *Halimeda incrossata*, *Penicillus capitatus*, *Ulva* sp., *Ulva rotundata*, *Valonia utricularis, Valonia aegagropila, Chaetomorpha linum, Cladophora laeteviren, Cladophora pellucida, Caulerpa cylindrica,* are studied in 1.1% of cases (Fig. 4a and b).

Among brown macroalgae of Mediterranean Sea, the most studied genus is *Cystoseira* which accounts for 36.6% of the total investigated studies, *Padina* (14%), *Sargassum* (14%), *Dyctiota* (10.8%), and *Fucus* (2%). The most studied species is *Padina pavonica* (12.7%), followed by *Gongolaria barbata* and *Dictyota dichotoma* (including *var.intricata*) (8.3%); *Cystoseira compressa* and *Sargassum vulgare* (7%); *Cystoseira amentacea* (*Ericaria amentancea*), *Cystoseira tarmascifolia* and *Halopteris scoparia* which falls into 5.1% of cases. *Rugulopteryx okamurae*, *Colpomenia sinuosa* and *Sargassum muticum* are studied for the 4.5%, 3.8% and 3.2% of cases, respectively. Four species are explored for 1.9%, specifically *Cystoseira mediterranea*, *Cystoseira crinita*, *Cladostephus spongiosum*, and *Petalonia fascia.* Other eight species account for 1.3%, specifically, *Cystoseira foeniculacea, Cystoseira humilis, Sargassum hornschunchii, Sargassum lacerifolium, Scytosiphon lomentaria, Zonaria tournefortii, Fucus virsoides* and *Halopteris filicina*. All the others are studied for 0.6% of cases (Fig. 4a and b).

Concerning red macroalgae, those included in the family *Corallinaceae* are the most studied: *Corallina elongata* (*Elissolandia elongata*) 7.5%, *Jania rubens* (6.2%), *Corallina officinalis* (6.2%), *Jania longifurca* (1.1%). *Pterocladia capillacea* and *Hypnea musciformis* are studied for 4.8%, while *Gracilaria gracilis* and *Laurencia obtusa* (including var. pyramidata) for 4.1%. The species, *Gracilaria bursa-pastoris, Osmundea pinnatifid*a, and *Palisada perforata* (*Laurencia papillosa*) account for the 3.4% of interest. *Asparagopsis taxiformis, Ceramium virgatum, Spaerococcus coronopifolius* amount to 2.7%; *Alsidium corallinum*, *Asparagopsis armata*, *Gelidium spinosum* and *Peyssonnelia squamaria* are studied for 2.1% of interest; *Acanthophora nayadiformis*, *Ceramium ciliatum*, *Gracilariopsis longissima, Jania longifurca, Porphyra umbilicalis, Rhodomela confervoides*, *Gelidium pusillum, Gracilaria cornea* (*Hydropuntia cornea*), and *Porphyra lineaeris* amount to 1.4%, while all the other species are studied for 0.7% of cases (Fig. 4a and b).

3.3. Research topics

Fig. 5 shows that, in the Mediterranean basin, scientific research on phenolic compounds in green, brown, and red algae is predominantly oriented towards pharmacological and medical applications (35.6% and 19.6%, respectively). Ecological research represents 18.5% of the total, whereas the food, chemistry, agriculture and aquaculture are less frequently addressed, accounting for 13.2%,6.8%, 6.3% of the studies respectively.

3.4. VOS viewer bibliometric analysis

The results obtained from the Scopus database were analyzed using the open-source software VOS viewer, performing networking, occurrences and clustering analyses. The software generated a network map based on the co-occurrence of keywords and the degree of relatedness between items, leading to the formation of thematic clusters formations. In the network map, thematic clusters are represented with different

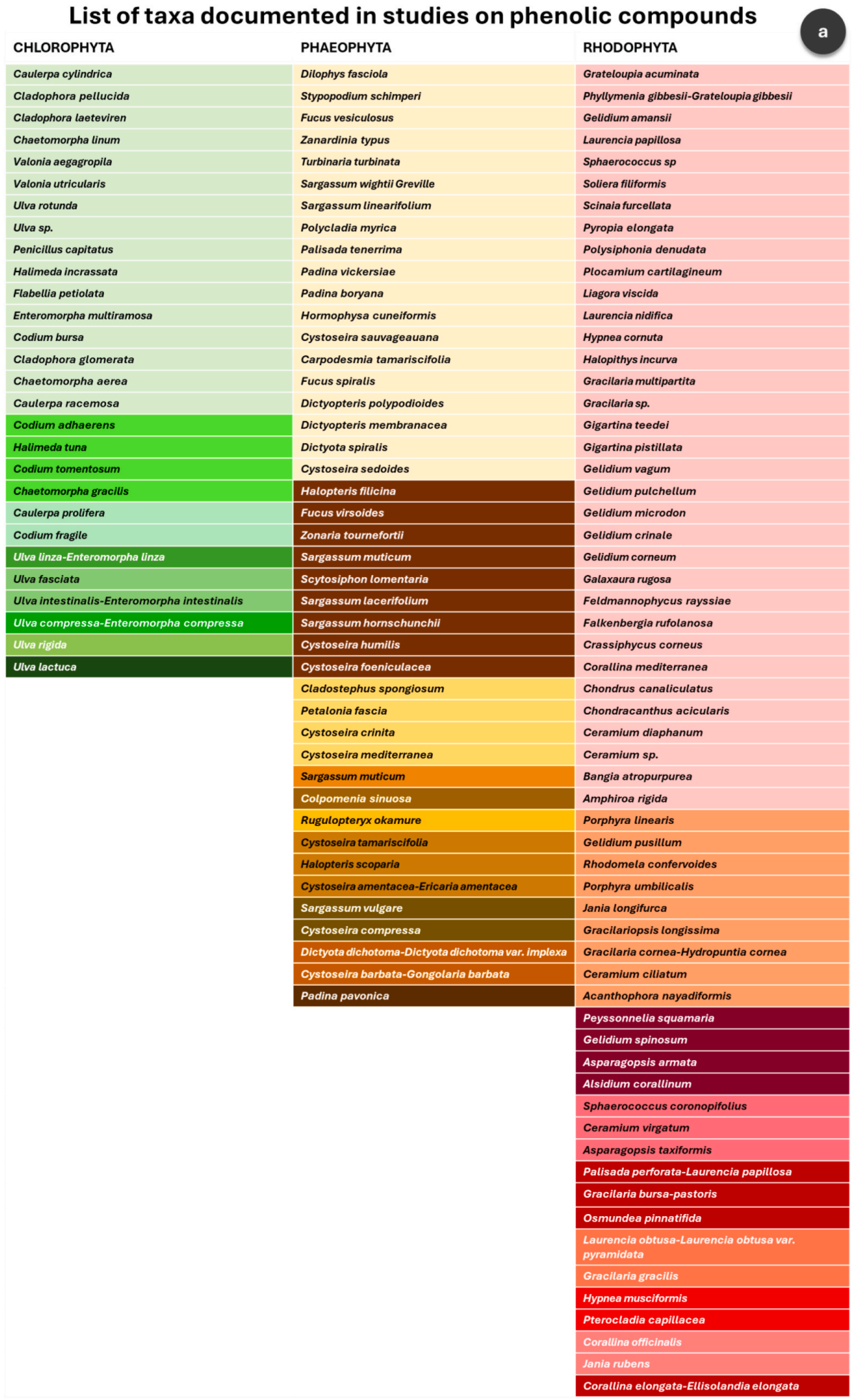

Fig. 4. (a) The upper panel reports the list of taxa documented in the studies focused on phenolic compounds, while (b) the lower panel shows the percentage of study interest relatively to the different macroalgae species (Chlorophyta, green; Phaeophyta, brown; Rhodophyta, red). Colors used to represent each species in the upper panel are also employed in the lower panel to show the percentage of study interest. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

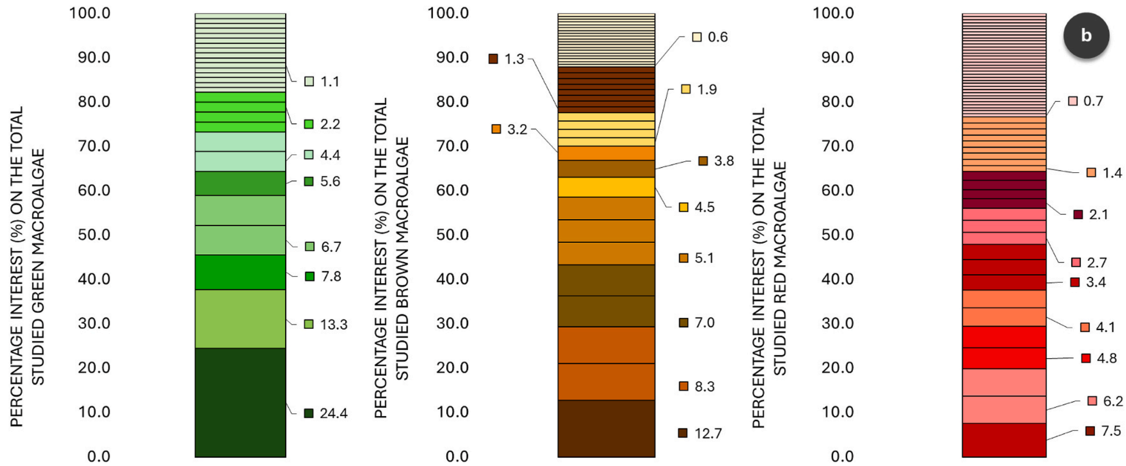

Fig. 4. (*continued*).

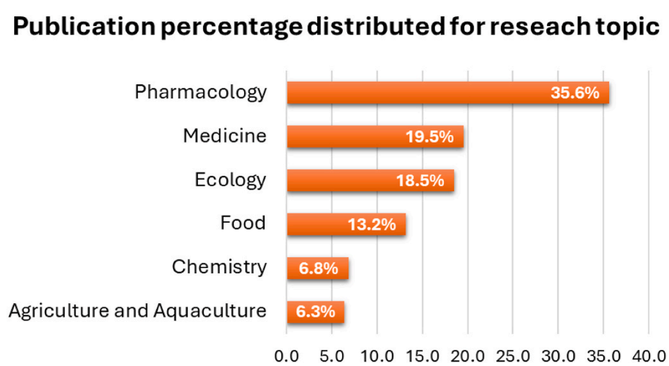

Fig. 5. Percentage of publications distributed for research topic.

colors; the nodes correspond to the terms, with their size proportional to the frequency of each term's occurrence; the distance between two items indicates the strength of the relationship (a smaller distance generally signifies a stronger connection) (van Eck and Waltman, 2010).

The graph (Fig. 6) is composed by 5 clusters, and all terms and occurrences are reported in Table S3.

Cluster 1 (red cluster) includes terms such as "marine algae", "total phenolic - Tpc", "active compound", "flavonoid content - Tfc", "solvent", "ethanol", "methanol-Methanolic extract", "acetone-acetone extract", "dichloromethane", "Chloroform-Chloroform extract", Hexane", "extraction time", "HPLC"; "Ultrasound assisted extraction" and focuses on extraction techniques for active and phenolic compounds, like flavonoids, from marine macroalgae, using different solvents, extraction techniques and timing. The terms "Human health", "Cell line", "Mic", "dose", "ec50"; "Frap", "Abts", "anti-inflammatory", "Strain", "*E. coli*", "*Staphilococcus aureus*", "Antibacterial activity", "Cytotoxic activity", indicate that seaweed extracts are tested on different cell lines and evaluated for their antioxidant, anti-inflammatory, anti-bacterial and cytotoxic activities, supporting research related to human health. Within

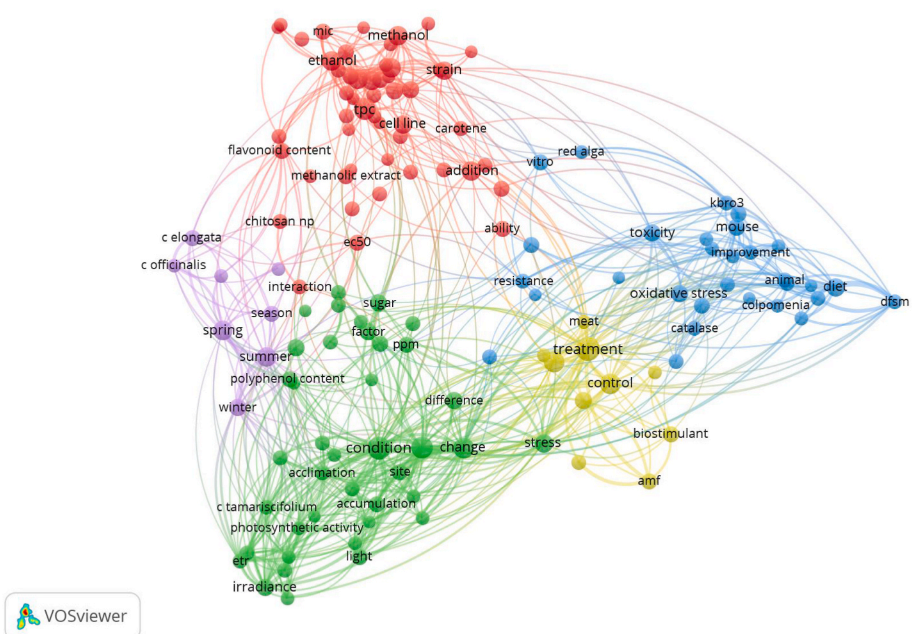

Fig. 6. This representation, obtained using the VOS viewer software, shows a keyword co-occurrence network map based on 151 studies focused on polyphenols in macroalgae sampled in Mediterranean Sea. Nodes represent keywords extracted from scientific articles, with node size proportionated to their frequency of occurrence. Links between nodes show the strength of key-word co-occurrence, while different colors identify clusters of closely related research topics. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

this cluster, the terms "red seaweed", "*Gracilaria bursa pastoris*", "*Cystoseira mediterranea-C. mediterranea*", "*Ericaria*", "*Halopteris scoparia*", "*Dictyota dichotoma*", "*Tunisian coast*" evidenced a particular interest on these macroalgal species sampled along the Tunisian coast.

Cluster 2 (green cluster) is oriented to ecological research and includes terms like "Chlorophyta", "Phaeophyceae", "Rhodophyta", "Mediterranean", "Site", "Lagoon", "Adaptation", "Acclimation", "Condition", "Factor", "Acidification – Ocean Acidification", "pCO_2", "Light", "Irradiance", "UVB radiation", "Nutrient level", "ppm ", "Stress", "Accumulation" and "Difference" related mainly on environmental plasticity across Chlorophyta, Phaeophyceae, and Rhodophyta in response to shifts in environmental conditions across different sites and habitats such as lagoons. The cluster also emphasizes studies on the effects of variations in factors like light and nutrient concentration, as well as of stressful condition, such as ocean acidification. Particular interest is devoted to macroalgal physiology, examining their photosynthetic responses ("photosynthesis", "photosynthetic efficiency" and photosynthetic activity", "ETR" and "ETRmax", "F_v/F_m"), primary and secondary metabolism ("biochemical composition", "Sugar", "Polyphenol content") and antioxidant activity ("high antioxidant activity"), especially in species like "*E.elongata*" and "*C.tamariscifolia*", "*S.vulgare*" and "*U.lactuca*".

Cluster 3 (blue cluster) includes terms like "Oxidative stress", "Malondialdehyde-Mda", "Toxicity", "Antioxidant compound", "Antioxidant enzyme", "Superoxide dismutase-SOD", "Catalase", "Animal", "Mouse", "Bone", "Erythrocyte", "Vitro", "Improvement", "Macrophage", "Potassium bromate-Kbro3"; "Dfsm"; "Hfd"; "Diet", representing a group of studies focused on the potential use of macroalgal extracts in developing anti-cancer and therapeutic treatments tested on animal models, like mouse, supporting medical and pharmacological applications.

Cluster 4 (yellow cluster) includes "Development", "Meat", "Biostimulant", "Plant", "Day", "Combination", "AMF" and "Agricolture", highlighting the scientific interest in macroalgae-deriving products for extending the food shelf-life ("Day"), such as "meat", and formulating of natural biostimulants for plant growth enhancement. These substances may be used alone or in combination with other green approaches like the arbuscular mycorrhizal fungi ("AMF"), comparing the effects of different treatments against control groups to identify sustainable agricultural applications.

Cluster 5 (purple cluster) includes "Season", "Winter", "Spring", "Summer", and "Autumn". It is closely linked to the 'ecological cluster 2' through the 'node' represented by "polyphenol content". Therefore, this cluster mainly encompasses studies on red algae ("*Corallina officinalis* -", "*C. elongata*"), focusing on how polyphenol content may vary across different seasons and habitats.

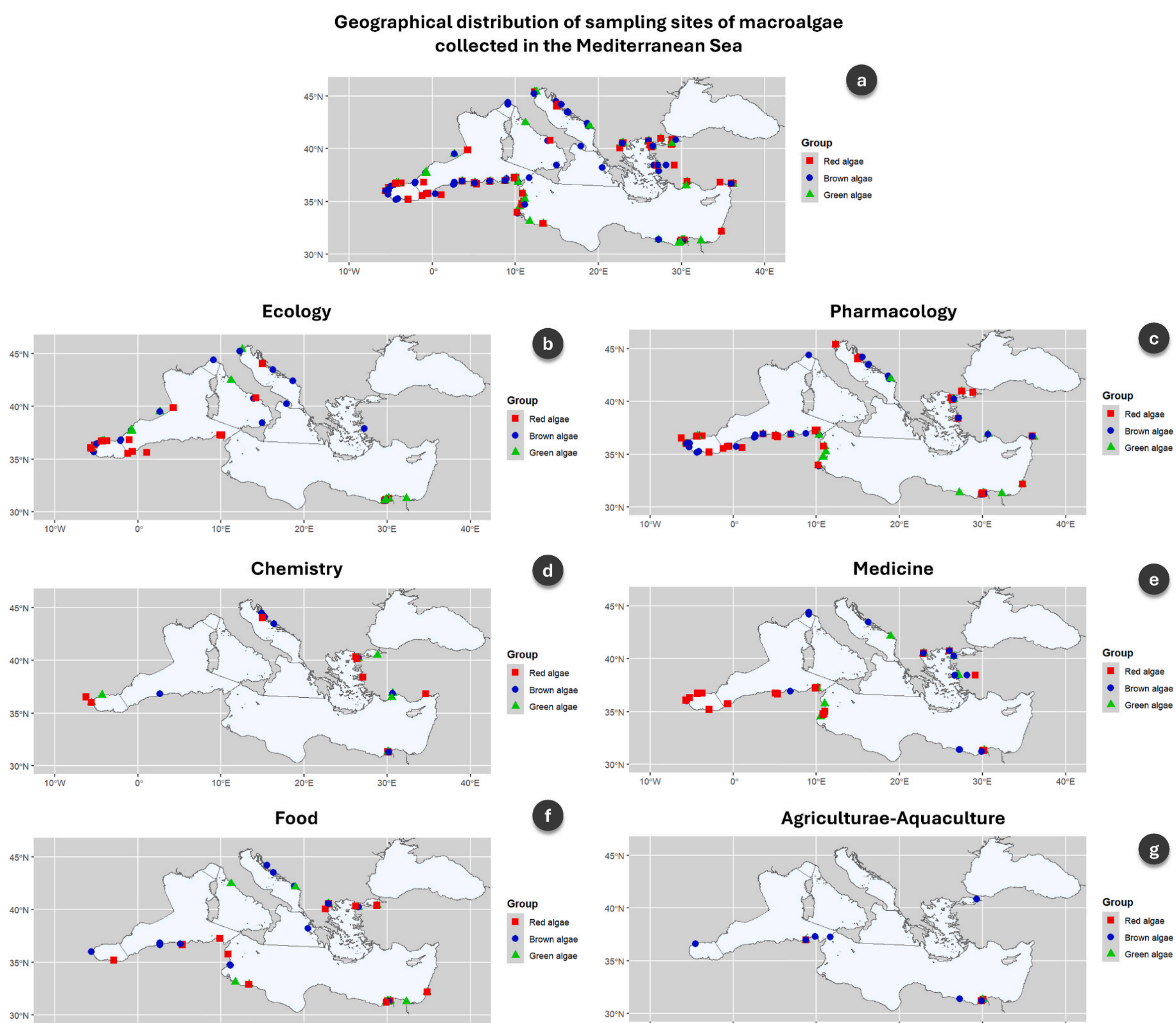

Fig. 7. Geographical distribution of studies on green (Chlorophyta), brown (Phaeophyta), and red (Rhodophyta) macroalgae along the coasts of the Mediterranean Sea (from 2005 to 2025) with a focus on (b) the extraction of polyphenolic compounds for ecological (b), pharmacological (c), chemical (d), medical (e), food (f) and agricultural purposes (g). Blue circles, green triangles and red squares represent brown, green and red macroalgae, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.5. Spatial distribution of macroalgae groups and research topics

Fig. 7a illustrates the overall distribution of studies on macroalgae along the coasts of the Mediterranean Sea between 2005 and 2025. The studies mostly focus on ecological research on brown algae predominantly along the Adriatic and Tyrrhenian Seas, Croatian, Montenegrin and Italian coast, Turkey and Spain. Conversely, red algae have been mainly studied in the western Mediterranean Sea, along the Italian, Spanish, Algerian, Moroccan, Tunisian coasts and eastern Mediterranean in Croatia and Egypt. Finally, green algae have been collected in Italy, Spain and Egypt (Fig. 7b). Studies concerning pharmacological applications have mainly involved red and brown algae from the eastern Mediterranean, along the coasts of Turkey, Greece Croatia and Egypt, as well as the western coasts of Algeria, Morocco, Tunisia and Spain (Fig. 7c). Studies on chemical applications have been documented from countries in the eastern Mediterranean, mainly red and brown algae, and to a lesser extent green algae, in Croatia, Turkey, and Egypt. Sampling locations in the western Mediterranean include Spain, Marocco and Algeria (Fig. 7d).

In the eastern Mediterranean (Croatia, Greece, Turkey, and Egypt), most studies are focused on medical purposes especially from brown macroalgae, along with red and green. In contrast, samplings from Spain, Marocco, Algeria and Tunisia have primarily targeted red algae rather than brown or green (Fig. 7e). Concerning food research, samplings appear homogeneously distributed between the western and eastern regions of the Mediterranean basin (Algeria, Marocco, Tunisia, Italy, Croatia, Greece, Turkey, Lebanon, Israel and Egypt), as well as evenly distributed in terms of macroalgae group. Finally, except for isolated cases observed in Spain and Turkey, research on brown macroalgae have been carried out to explore their potential in agricultural and aquaculture applications, and to a lesser extent on red and green macroalgae (Tunisia and Egypt).

4. Discussion

This study underscores the increasing research attention on the role of polyphenols in influencing ecological processes in the Mediterranean Sea, particularly their diverse functions within macroalgal communities, such as early stress signalling, photoprotection, and protection against herbivory.

Beyond their ecological relevance, polyphenols also exhibit a wide range of applications across fields such as medicine, pharmacology, cosmetics, agriculture, and food production, contributing to the growing global demand for sustainable solutions to pressing environmental challenges, as summarized in Fig. S1.

Their effectiveness and the growing scientific interest in these compounds are mainly related to their antioxidant potential, which depends on their molecular and structural characteristics, including the number and position of hydroxyl groups, the presence of phenolic rings, steric factors, and the degree of polymerization. These features determine their ability to donate electrons or hydrogen atoms and neutralize reactive species in biological systems.

The temporal and geographic distribution of the studies that have been examined in this review shows that the Mediterranean basin is increasingly exploiting its marine resources in response to rising pharmaceutical and biomedical interest. Publications have increased markedly over the past two decades, especially in the last five years, reflecting a shift from preliminary screening studies toward advanced extraction methods, production of higher-quality compounds, and validation of the clinical potential of marine polyphenols against various diseases and disorders.

Although publications were broadly distributed between the eastern and western Mediterranean basin, recent research trends reflect the specific climatic and socio-economic conditions of individual countries and their national priorities. North African countries including Egypt, Tunisia, and Algeria mainly focused on exploiting coastal biodiversity and integrating macroalgae into sustainable food, agricultural, cosmetic, and bioeconomy strategies through screening programs.

In contrast, Italy, Spain, Turkey, Croatia, and Montenegro oriented research toward functional foods, cosmeceuticals, advanced efficacy studies, and the effects of Mediterranean environmental stressors on polyphenol production as algal defense mechanisms. These patterns highlight both the ecological importance of polyphenols in Mediterranean marine ecosystems and their relevance within the One Health framework linking environmental and human health. Accordingly, the following discussion explores the ecological functions of polyphenols within Mediterranean marine ecosystems and their relevance for One Health applications.

4.1. Ecological roles of polyphenols

Ecological studies on polyphenols are relatively limited (18.5% of research) because they are more complex and less standardized, requiring field sampling, seasonal monitoring, and integration of multiple environmental factors. In addition, strong variability in phenolic production across species and environments makes comparisons difficult and hinders clear ecological interpretations. As a result, research has tended to focus more on applied fields such as pharmacology, food science, cosmetics, and agriculture.

However, ecological studies provide critical insights into the interactions between macroalgae and their environment. Studies on the production and fluctuations of phenolic compounds in macroalgae documented how they can be influenced by a variety of abiotic factors, including light intensity, temperature variations, salinity, nutrient availability, CO_2 enrichment, and biotic pressures such as herbivory and interspecific competition. Therefore, special emphasis was given to the species-specific and seasonal patterns of polyphenol synthesis, as these patterns reflect physiological adjustments of macroalgae to variations in light availability, temperature, nutrient conditions, and other environmental stressors. By focusing on this study topic, we aim to provide a comprehensive overview of the ecological role of polyphenols, particularly in photoprotection and antioxidant defence, and to emphasize their value as sensitive, early indicators of environmental change in the unique and fragile Mediterranean Sea.

4.1.1. Seasonal variation: effect of temperature and light in growing environment

Seasonal variation in the production of phenolic compounds in macroalgae is species-specific (Stiger-Pouvreau et al., 2014; Mazouzi et al., 2023), consistently shaped by environmental forcing, particularly fluctuations in sea temperature, light intensity, salinity, location and depth, nutrient availability, and biological pressures such as algae age, size, life cycle, herbivory and competition.

(Celis-Plá et al., 2016; Čagalj et al., 2022).

In the VOS viewer map, the ecological dimension is represented by the green cluster, which indicates that phenolic modulation is closely linked to macroalgal physiological responses to changing environmental conditions. This cluster also highlights the relationship between phenolic accumulation and indicators of metabolic performance, supporting the idea that these compounds function as dynamic mechanisms for photoprotection, antioxidant defense, and stress buffering. The purple cluster further reflects the temporal aspect of these responses by grouping seasonal terms (winter, spring, summer, and autumn), showing that variations in phenolic content are not random but are driven by acclimation processes induced by the environment occurring over time.

Most studies revealed that light and temperature are the main factors in driving seasonal changes in phenolic content, particularly in brown algae, which are richer in polyphenols, especially flavonoids and phlorotannins, than green and red ones.

From these studies emerge that seasonally, polyphenol concentrations are generally highest in winter and spring, and lower in autumn

(Celis-Plá et al. 2014, 2016; Grozdanić et al., 2019; Čagalj et al., 2022; Mazouzi et al., 2023). However, species-specific deviations and summer peaks have also been reported (Kozak et al., 2020; Mazouzi et al., 2023), reflecting differences in taxonomic identity, habitat exposure, the functional roles of polyphenols. In particular, phlorotannins act as key photoprotective compounds, with their synthesis generally peaking in spring and summer. Specific compounds such as eckol and phloroglucinol are often more abundant during summer and show differential distribution within thallus apical and basal regions where they contribute to photoprotection and act as deterrents to epiphytes (Kozak et al., 2020).

Higher phenolic content is often associated with increased electron transport rates and higher carbon and nitrogen levels, suggesting that nutrient availability can enhance both photosynthetic activity and phenol production, supporting primary and secondary metabolism (Celis-Plá et al., 2016).

These patterns are particularly relevant in shallow and intertidal habitats, where macroalgae are exposed to rapidly fluctuating and intense environmental stressors, including strong light, UVB radiation, desiccation, and temperature changes, especially during low tide. Under these conditions, phenolic compounds, namely phlorotannins, help protect thalli from oxidative damage and may also be released into seawater, where they can contribute to UV-absorbing complexes that reduce DNA damage (Figueroa et al., 2014; Celis-Plá et al., 2016; Čagalj et al., 2022; Mazouzi et al., 2023).

Particular conditions can be observed in summer, when nutrient depletion and high irradiance can reduce photosynthetic activity and photoprotective capacity, leading to lower polyphenol content, as more phenols are released from the thalli and the proportion of released phenols relative to internal content can result higher (Celis-Plá et al. 2014, 2016). Depth influences phenolic content: algae from 0.5 m depth typically have lower phenolic concentrations than those from 2.0 m, likely because higher irradiance at shallower depths promotes greater use of polyphenols for photoprotection (Celis-Plá et al., 2014b). At comparable depths, Figueroa et al. (2014) demonstrated that *C. tamariscifolia* exhibits higher resistance to increased UVB, attributed to its high polyphenol and antioxidant content. In contrast *E. elongata* and *Ulva*

rigida have approximately tenfold lower polyphenol levels. *E. elongata* relies mainly on high reflectance for photoprotection, while *U. rigida* shows the greatest degree of photoinhibition. These findings highlight clear species-specific differences in UVB tolerance, where some taxa depend primarily on high polyphenol content for protection, whereas others rely on alternative strategies such as reflectance or structural adaptations. Under prolonged desiccation due to low tide, the antioxidant role of polyphenols becomes crucial for mitigating oxidative damage and supporting recovery after disturbance, as recently observed in *E. elongata* (Donadio et al., 2025).

In the Mediterranean Sea, another important issue is represented by the expected rising seawater temperatures. Thermotolerance studies showed the impact of rising temperature on the decline of *Cystoseira* spp. populations, with repercussion on other populations as well (Kozak et al., 2020). *Cystoseira crinita* from the warmer Eastern Mediterranean tolerates temperatures 2°C higher than those from the colder Northwestern Mediterranean populations, highlighting the role of thermal history (Verdura et al., 2018). More recently, Fabbrizzi et al. (2023) demonstrated that both the duration and timing of marine heatwaves strongly affect the physiological responses of *Gongolaria barbata*, including the production of antioxidant compounds, showing higher levels of polyphenols as a defensive adjustment to counteract oxidative stress after long heatwave exposure and help algae acclimate to harsh environmental conditions. The concentration of studies in the Mediterranean is likely explained by two main factors. First, the region provides strong environmental gradients and high seasonal variability, making it an ideal "natural laboratory" for studying how phenolic compounds respond to changes in light, temperature, and other stressors. Second, Mediterranean Basin hosts well-known model macroalgal taxa such as *Cystoseira*, *Corallina*, and *Ulva*, which are commonly used to study photoprotection, acclimation, and stress tolerance.

Therefore, the spatial pattern of research reflects not only where scientific effort has been concentrated, but also where ecological conditions are most suitable for investigating phenolic metabolism under variable and stressful environments. However, most studies have focused on the western Mediterranean basin, even though the entire Mediterranean Sea shows strong seasonal and spatial temperature variability (Saiz et al., 2014; Garrabou et al., 2022).

Less attention has been paid to the eastern regions where more seasonal studies are needed to clarify how polyphenol concentrations may change across environmental gradients. Sea surface temperatures in European waters have indeed risen by about 0.22°C per decade from 1991 to 2022 (EEA, European Environment Agency 2025), and models predict that, apart from the northern Adriatic, most of the Mediterranean will continue to warm, with average temperatures expected to rise by about 3.1°C by the end of the century.

4.1.2. Lagoon environments

As shown in the VOS viewer map, within the ecology/acclimation group (green cluster), the frequent occurrence of the term "lagoon" indicates that research is increasingly considering macroalgae inhabiting lagoon environments and the role of their polyphenols in these systems.

The geographical distribution of studies along Mediterranean coasts (2005–2025) further supports this pattern, showing that several ecologically relevant investigations are in lagoon systems, particularly in the Adriatic Sea (e.g., the Venice Lagoon) and the Mar Menor. This distribution is consistent with the high number of recent publications from countries such as Italy and Spain over the past five years.

Lagoons attract scientific interest as they differ from coastal and open-sea environments in salinity, temperature, and nutrient availability, conditions that strongly influence macroalgal physiology. In lagoon systems such as the Venice Lagoon, macroalgae (e.g. *Gongolaria barbata*) exhibit age-dependent adaptive responses (Pica et al., 2024) and activate multiple photoprotective mechanisms against PSII photo-oxidative stress, including increase of carotenoids, non-photochemical thermal dissipation processes, and phenolic compounds.

Our results highlight the central role of polyphenols also in the hypersaline Mar Menor lagoon, where elevated temperatures and nutrient concentrations promote enhanced antioxidant and photoprotective responses. In this system, polyphenols contribute to thallus photoprotection, survival, and acclimation, as previously observed in *Cystoseira compressa* and *Padina pavonica* (García-Sánchez et al., 2014). Seasonally, polyphenol concentrations decreased in summer in lagoon and inlet sites, suggesting their involvement in stress mitigation, whereas higher spring levels supported pigment synthesis and photosynthetic performance.

These findings demonstrate that polyphenols are key mediators of photoprotection in nutrient-rich lagoon environments, with a significant seasonal modulation linked to environmental stress intensity.

These findings also suggest that further studies are needed across Mediterranean lagoons. Of the 37 recognized Mediterranean coastal lagoons (Soria et al., 2022), most are shallow systems (<10m) and include well-studied areas in terms of hydrology, pollution and water quality, such as Venice, Mar Menor, Thau, Leucate, Bizerte, Tunis, Marano-Grado and Orbetello. Prioritizing monitoring in eutrophic (Lion gulf, Balearic sea, Sicily basin, Levantine, Adriatic and Tyrrhenian Sea), hypertrophic (Balearic, Alboran, Levantine, Adriatic and Tyrrenian Sea) (Soria et al., 2022) and hypersaline lagoons is especially relevant given that increasing temperature and salinity gradients from the north/west to the south/east Mediterranean are driving declines in productivity and species richness, particularly in the Levantine Basin (Coll et al., 2010).

In this context, seasonal and long-term changes in algal polyphenol content may serve as useful indicators of environmental stress in these priority habitats under the European Union Habitats Directive (Council

Directive 92/43/EEC, of 21 May 1992).

4.1.3. Sea water acidification

Mediterranean Sea acidification is accelerating due to its semi-enclosed nature, with pH declining at about 0.001–0.009 units per year, faster than global and Atlantic averages (0.001–0.0026 units per year) (Hassoun et al., 2022). This trend threatens calcareous macroalgae by affecting their growth, reproduction, and skeletal integrity, and may alter rocky shore habitats, community structure, and ecosystem functioning (IPCC, 2022a). Despite its importance, research on Mediterranean ocean acidification began around 2008 and is still unevenly distributed, with a strong concentration of studies in Western countries such as Italy, France, and Spain. In contrast, the Eastern basin and areas such as the Ionian and Algero-Provençal sub-basins, along with countries like Tunisia, Algeria, and Morocco, remain comparatively understudied (Hassoun et al., 2022). Between 2014 and 2022, interest in the role of polyphenols in macroalgae under acidification has increased, particularly in the Tyrrhenian sub-basin, including volcanic Islands of Ischia (40° 43.84′ N; 13° 57.08′ E) and Vulcano (38° 25′ 01″N, 14° 57′ 36″E), as well as in the Alboran Sea.

This pattern likely reflects the presence of natural CO_2 vents and other acidified field sites, which provide accessible environments for long-term ecological and physiological studies on local adaptation mechanisms.

However, the geographical distribution may also be influenced by the presence of certain species in sufficient abundance to enable repeated sampling.

Similar trends are observed also in other part of the world, where natural CO_2 vents and volcanic acidification sites serve as realistic long-term exposure systems that are difficult to replicate experimentally. As in the Mediterranean, these systems often favor locally abundant, ecologically dominant, or stress-tolerant species, meaning that taxonomic representation is shaped not only by sensitivity but also by site accessibility and sampling opportunities (Hernández et al., 2016; Peña et al., 2021; Hassoun et al., 2022).

In the Mediterranean Sea, the most frequently studied taxa are often relatively tolerant species, making them suitable models for examining phenotypic plasticity and biochemical acclimation under acidification stress. Brown algae such as *Sargassum vulgare*, *Cystoseira tamariscifolia*, *Cystoseira compressa*, and *Padina pavonica* dominate these studies because they are abundant in rocky shore habitats, exhibit strong phenolic plasticity, and have effective antioxidant defenses. In contrast, less attention is given to red and green algae, such as *Jania rubens* and *Ulva rigida*.

Interestingly, the green cluster in the VOS viewer map further suggests that polyphenol production is not solely driven by physiological responses to pH changes, but it indicates that polyphenols act as dynamic biomarkers influenced by the combined effects of carbon and nutrient availability and light conditions.

Long-term exposure experiments in Ischia, such as those conducted on *Sargassum vulgare*, demonstrated that acidified conditions (pH 6.7) reduced levels of caffeic acid, catechins, gallic acid, resorcinol and isoquercitin compared to control conditions (pH 8.2), This reduction is consistent with the overall decrease in polyphenols and flavonoids observed in *S. vulgare* at CO_2-rich sites, as well as in individuals transplanted from acidified to control environments.

It is likely that in *S. vulgare*, antioxidant enzymes likely compensate for redox imbalance under chronic exposure (Kumar et al., 2017, 2018, 2022). Both populations showed indeed similar oxidative enzyme activity and photosynthetic rates, with physiological functions improving after short-term exposure, indicating an adaptation at lower pH, and the ability to employ biochemical and physiological strategies for growth in acidified waters. In the same location, thalli of the corallinae red algae *Jania rubens* bleached at pH 7.5, likely due to a sharp decline in pigments (i.e. chlorophylls, carotenoids, and phycobilins). However, the partial PSII activity observed at pH 7.5 indicated that part of population persisted. The lower polyphenol amount compared to the control (pH 8.1) suggested that these molecules are involved in counteracting unfavourable conditions and preserving photosystem functionality (Porzio et al., 2018). Conversely, in Vulcano island (Italy), Celis-Plá et al. (2015) observed that the short-term exposure (three days) of *Cystoseira compressa* and *Padina pavonica* to different CO_2 levels, significantly increased the antioxidant activity and total phenolic content, especially when coupled with N, P and K nutrient enrichment (oligotrophic vs. eutrophic). The rapid physiological and biochemical changes indicate that the photosynthetic efficiency and algal productivity increase in acidified sites, and polyphenolic compounds could be key indicators of how macroalgae respond to environmental shifts.

Within the Western basin, in the Alboran Sea (Malaga, Spain), other short-term experiments (6 days) (Figueroa et al., 2014b), demonstrated that polyphenol production in *Cystoseira tarmascifolia* and *Ulva rigida* was mainly driven by temperature (+4°C) rather than CO_2 and nitrogen, correlating with protein and fatty acid levels, and suggesting a link between primary and secondary metabolism. *C. tamariscifolia* maintained constitutively higher antioxidant capacity and polyphenols, releasing them at increasing CO_2 and temperature as photoprotective mechanism, while *U. rigida*, decreased polyphenol content at higher temperature. In the same location and always in *Cystoseira tamariscifolia*, Celis-Plá et al. (2017a,b) found maximum polyphenol content and antioxidant activity in ultraoligotrophic waters under ambient temperature (20°C), and ambient (ca. 400–500 ppm) and high (ca. 1200–1300 ppm) CO_2 compared to those from oligotrophic waters, suggesting that ocean acidification may benefit algal photoprotection in response to high irradiance in transparent coastal waters. Additionally, the positive correlation between antioxidant activity and internal nitrogen content emphasised the role of nutrients in polyphenol production and photoprotection.

Finally, in the Eastern basin, in Egypt, *Ulva fasciata* exposed for nine days (sufficient to stimulate biochemical compound synthesis) to four pCO_2 levels (~280, 550, 750 and 1050 μatm), according to the IPCC, A1FI scenario (Houghton et al., 2001), showed that moderate acidification maximized phenolic, flavonoid, antioxidant, and antimicrobial activities, suggesting potential for use as antimicrobial agents and nutritional supplements in aquaculture (replacing microalgae in sea bass aquaculture) (El-Sayed et al., 2022). Conversely, the stronger scenario (pCO_2–1050) negatively affected all parameters. Summarizing, long-term exposure typically reduces polyphenol content and antioxidant activity, while short-term exposure, triggers rapid increases, highlighting a strong resilience capacity in macroalgae. Their production often rises with increased CO_2 and nutrient availability, for photoprotection purpose. However, the combined effects of OA and chronic eutrophication of Mediterranean costs exert specie-specific responses. For example, some brown algae may take advantage and proliferate in shallows waters due to increased CO_2 and anthropogenic nutrient inputs, while others, with a limited reproductive capability, may be replaced by opportunistic species. These contrasting responses indicate that polyphenol dynamics under acidification are both species-specific and time-dependent, and likely reflect differences in metabolic plasticity, habitat exposure, and nutrient availability.

Moreover, it should not be underestimated that changes in polyphenol levels, depending on the ocean acidification (OA) scenario, can significantly impact the nutritional value of macroalgae as well as their protection against grazers and pathogens. These effects can have broader implications for the food web and overall ecosystem functioning, while also offering positive economic benefits in aquaculture due to their antimicrobial properties. Such benefits are particularly relevant along the coasts of the Eastern and Western Mediterranean basins. However, even if the polyphenol concentration and composition in algae tissue responds quickly to several environmental multiple stressors, giving a first alert of change, it remains difficult to associate the pattern of phenol composition to a specific stress in different environments, especially under ocean acidification scenario. Seawater acidity is projected to increase by 0.4 pH units by 2100 (IPCC, 2022) and a higher spatial resolution model forecasting Mediterranean pH changes under intermediate (RCP4.5) and high (RCP8.5) CO_2 emission scenarios predicts a pH decrease of about −0.25 units in the upper waters and −0.2 units in the intermediate waters by 2100, with more pronounced changes in the Eastern Mediterranean (Reale et al., 2022). Given the current trends in pH and these projections, further research is essential to enhance our understanding of the ecological role of polyphenols in macroalgae in different environments.

4.1.4. Invasive species and connections with phenolic compounds

In recent decades, there has been growing concern about the health of marine ecosystems and the introduction of alien species in the Mediterranean, one of the most affected regions (Zenetos et al., 2012). While many alien species remain in favorable habitats, some become invasive, replacing native species, altering trophic relationships, and reducing biodiversity. Invasive species can also introduce parasites and pathogens, impacting cellular responses and long-term ecosystem health (Guzzetti et al., 2019). Their spread is driven by globalization, increased connectivity, and human activities, such as shipping, aquaculture, and aquarium releases, and is facilitated by the Mediterranean's semi-enclosed nature and connections to the Atlantic Ocean through the Strait of Gibiltair and Red Sea through the Suez Canal (Katsanevakis et al., 2014; Coll et al., 2010; Galil et al., 2018; Zenetos et al., 2012). This likely explains why most ecological studies in our dataset are concentrated in these entry corridors, particularly in the western Mediterranean near the Strait of Gibraltar and in the eastern basin near the Suez Canal, where species introductions and secondary spread are most likely to occur. In this context, invasive species and associated epibionts impose biotic stress on native macroalgae, triggering an overproduction of reactive oxygen species (ROS) and potential cell damage (Tang et al., 2007; Sureda et al., 2008; Sureda et al., 2017; Gallardo et al., 2016; Corrales et al., 2018), thereby inducing the activation of antioxidant defenses, including increased production of phenolic compounds. For example, in the Balearic Islands, the red alga *Peyssonnelia squamaria* epiphytized by the alien sponge *Paraleucilla magna,* the first calcareous sponge introduced to the Mediterranean, showed enhanced antioxidant enzyme activity and changes in polyphenols, reflecting an adaptive response (Guzzetti et al., 2019). Similarly, tropical chlorophytes *Penicillus capitatus* and *Halimeda incrassata*, from warm waters of the western Atlantic Ocean, have invaded native algal communities in Mallorca (Balearic Islands), altering ecosystem dynamics (Cerrato et al., 2023), and inducing in *Padina pavonica* the increase in ROS production and the consequent activation of antioxidant responses, including increased polyphenol synthesis. Considering these invasions, it would be valuable to investigate whether polyphenols could also serve as biomarkers in macroalgae such as Halopteris spp. or Corallina spp., given that *P. magna* occurs not only in coralligenous habitats but also on rocky substrates and erect algae. Moreover, because most invasive species are of tropical origin, examining their combined effects with rising seawater temperatures could help clarify how Mediterranean tropicalization may reshape algal communities, particularly in rapidly colonized sandy habitats.

Polyphenols may therefore represent valuable biomarkers of stress and interspecific competition, a hypothesis that needs further investigation across different native species and ecological contexts. In addition, the literature reviewed here highlights their involvement in allelopathic interactions, through which they may inhibit the performance of invasive species and epiphytes, acting as natural chemical mediators of competition. Evidence supporting this role includes the observation that phenolic compounds from *Gongolaria usneoides* can alter photosynthetic activity and biochemical processes in the invasive species *Rugulopterix okamurae*. Furthermore, specific compounds such as caffeic, ellagic, and gallic acids have demonstrated allelopathic effects against epiphytes and other competing organisms (Wang et al., 2011; Chang et al., 2012; Budzałek et al., 2021). Together, these findings reinforce the role of polyphenols in mediating competitive interactions and suggest their potential contribution to natural control mechanisms in marine ecosystems (Pereira et al., 2025). Within this framework, polyphenol dynamics appear not only defensive but also regulatory, potentially influencing community structure and invasions. Further experimental studies are therefore needed to better elucidate these mechanisms and their ecological implications.

The geographic variability in the available literature further reinforce the need for broader investigation, as the Mediterranean Sea hosts nearly three times more alien species than other European seas, especially in the Eastern basin (Galil et al., 2014, 2018).

Currently the major gaps in our understanding of the ecological roles of polyphenols across the basin is because most studies have been conducted in the Western Mediterranean, particularly along the coasts of Spain, North Africa, and parts of Italy. This pattern is probably linked to the greater availability of accessible rocky shores and invaded sandy habitats in these regions, as well as to the presence of abundant invasive taxa such as *Rugulopteryx okamurae* and *Asparagopsis* spp. These species provide suitable natural models for studying stress responses, competitive interactions, and impacts on native communities.

As a consequence, research has mainly focused on the invasive species most frequently reported in the Mediterranean literature, which scientific relevance is not only ecological but also biochemical, since many of these algae are rich in compounds of potential biotechnological, cosmetic, pharmaceutical, and therapeutic interest. For instance, the green algae *Valonia aegagrophila* and *Chaetomorpha linum* collected from Italian coasts contain amino acids, polyphenols, and flavonoids with potential applications in the treatment of hypertension and cardiovascular diseases (Brai et al., 2024). Similarly, the red alga *Asparagopsis taxiformis*has shown antioxidant, antibacterial, and algicidal activities, effects that are associated with its high content of polyphenols, flavonoids, and tannins. These compounds are likely linked to the species' adaptation to highly variable environmental conditions, including fluctuations in salinity, temperature, nutrient availability, and UV radiation in shallow Algerian and Tunisian waters (Mellouk et al., 2017; Ktari et al., 2022). Similarly, Vega et al. (2023) found that the invasive seaweeds *Asparagopsis armata* and *Rugulopteryx okamurae* from Southern Spain are rich in polyphenols and provide anti-inflammatory, antitumoral, antimalarial, antithrombotic, anti-arthritis and anti-microbial effects.

4.1.5. Polyphenols as alert of polluted environment

Anthropogenic activities along Mediterranean coasts release a complex mixture of contaminants, including radionuclides (Praveen et al., 2017), heavy metals (HMs), hydrophobic organic compounds (HOCs) such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and organochlorine pesticides (OCPs) (Poté et al., 2008), creating environmental conditions in which macroalgae serve as bioindicators for water quality changes, and are essential for monitoring contamination levels, by accumulating trace elements or metals (Ryan et al., 2012;Bonanno and Orlando-Bonaca, 2018).

While low concentrations of copper, zinc, and iron are essential for enzymatic reactions in living organisms, high concentrations of these elements can adversely affect seaweed growth and metabolism. Additionally, toxic metals such as lead, mercury, and cadmium can accumulate in algae in high concentration, posing a severe threat to higher consumers, including humans (Manoj and Padhy, 2013; Olivares et al., 2016; Bonanno and Orlando-Bonaca, 2018).

Bonanno and Orlando-Bonaca (2018) reported that, between 1990 and 2016, studies investigating element concentrations in Mediterranean macroalgae were relatively scarce. Most research was conducted in the Aegean Sea (39%) and the Adriatic Sea (18%), while only a single study was reported from regions such as Sardinia, Crete, and Syria with a few species extensively investigated. Even fewer studies have specifically focused on bioactive and phenolic compounds in relation to pollution, despite the importance of considering variations associated with species identity, geographic location, pollutant type, and pollutant concentration (Farasat et al., 2014; Ismail and Ismail, 2017). Our review highlighted that among algal groups, green algae have been most extensively investigated in pollution-related studies, particularly the genera *Caulerpa*, *Codium*, *Enteromorpha*, *Cladophora* and *Ulva* because of their cosmopolitan distribution, rapid growth rates, strong capacity to accumulate heavy metals (Murugan and Harish, 2007), and high tolerance to polluted environments, especially estuaries (Lin et al., 2011; Bonanno and Orlando-Bonaca, 2018). According to our findings, among brown algae, the genera *Ascophyllum, Dictyota*, *Fucus* and *Cystoseira* are the most studied groups, particularly in rocky-shore systems, where they can accumulate metals and radionuclides (Nonova and Tosheva, 2016; Akakçe et al., 2023). Red algae, including the genera *Gelidium, Gracilaria, Porphyra* and *Pterocladia*, are less frequently investigated but remain important for comparing taxon-specific responses to contamination (Boundir et al., 2022; Anteur et al., 2024).

Changes in polyphenol content are particularly significant because these compounds contribute to antioxidant defence and protection against contaminant-induced oxidative stress. For example, exposure of *Ulva* sp. to selenate in the Venice Lagoon increased selenium accumulation, oxidative stress markers, and phenol and flavonoid production, suggesting that phenolic compounds are activated as part of stress-response mechanisms may help maintain membrane integrity and biomass production under contaminant exposure. (Schiavon et al., 2012).

Similarly, studies from the Egyptian coast showed that *Ulva compressa* and *Cladophora glomerata* combine heavy-metal bioaccumulation with strong antioxidant defences, including phenolic compounds, highlighting their phytoremediation potential and reinforcing the role of polyphenols as biomarkers of pollution stress (Ismail and Ismail, 2017; Ismail et al., 2025).

The Mediterranean Quality Status Report (2023) confirms that chemical pollution, eutrophication, shipping and coastal urbanization remain major pressures across the basin, with particularly high impacts in densely populated and semi-enclosed areas, such as lagoons, ports, and trafficked coastal sectors. In this context, the concentration of studies on sites as Venice Lagoon and Egyptian coast reflects the ecological relevance of these environments and the suitability of macroalgae as biomonitors in areas where contaminant exposure is chronic and measurable. However, despite this growing interest, many toxic elements, including arsenic (As), chromium (Cr), mercury (Hg), and nickel (Ni), remain poorly investigated in macroalgae, and a limited number of species have been studied in detail. For this reason, broader monitoring across different Mediterranean locations and algal populations is still required to clarify how polyphenol concentration and composition vary in relation to species, pollutant amount, and anthropogenic impact, and to determine whether these compounds can serve as reliable indicators of contamination and environmental stress.

4.2. Nutraceutical, pharmacological and agronomical benefits deriving from polyphenols in Mediterranean algae

The analysis highlighted the multifunctionality of Mediterranean seaweeds, which owe their bioactivity to a rich and diverse biochemical repertoire including carbohydrates, proteins, lipids, vitamins, minerals, fibers, phytohormones, chlorophylls, carotenoids, and a wide range of specialized metabolites such as phenolic compounds like flavonoids, alkaloids, saponins, coumarins, tannins, terpenes and phytosterols. Collectively, these compounds underpin the broad spectrum of beneficial effects associated with anti-inflammatory, antimicrobial, antitumoral, and hepatoprotective properties (Čagalj et al., 2022; Ahmed et al., 2023). This multifunctionality places algae at the intersection of several applied fields, including agriculture, chemistry, cosmetics, pharmacology, medicine, and food science. As consequence of this cross-sector relevance, the scientific interest of the last two decades accounted for 81.4% of studies in these areas and has led to a pronounced increase in publications over the past five years, particularly in Eastern Mediterranean countries, where both scientific and commercial interests appear to be driving research expansion. This trend is consistent with the rapid increment of the global market of macroalgae, especially for brown and red species. This sector increased by approximately 176% between 1995 and 2012 and the projections estimate an annual global growth rate of 8.4% (Hadjkacem et al., 2023). Currently, algae farming and harvesting are practiced in over 30 countries around the world, using cold, tropical and temperate waters for food, pharmaceutical, cosmetics and even biofuel production (Cadar et al., 2025). This is not surprising given the climatic challenges facing food production, the dependencies on imports, and the socio-economic conditions unique to each European country (IPCC et al., 2019). Given this high demand, the analysis also revealed that, among the different algal groups, brown algae have been the most extensively studied, offering extracts rich in polyphenols and phlorotannins, which often work synergistically to enhance bioactive effects (Kosanić et al., 2019). Red algae, in turn, provide extracts containing catechins, flavonoids, and terpenoids (Abou-Dobara et al., 2023), while green algae are typically richer in carbohydrates and display a more variable phenolic profile, depending on species, metabolic preferences, photosynthetic activity, and growth stage (Ismail and Ismail, 2017). This compositional diversity helps explain the wide range of applications reported across the literature.

From a methodological perspective, the red cluster of the VOS viewer map and the recent literature (Cadar et al., 2025; Golmakani et al., 2025), indicate a strong focus on optimizing extraction protocols to maximize the yield and quality of phenolic extracts while reducing environmental impact. Different studies have used variations in extraction solvents, extraction time and temperature, material to solvent ratio, and advanced techniques such as pressurized liquid extraction, ultrasound and microwave-assisted extraction, high-performance liquid chromatography-based characterization (Grillo et al., 2021; Aboeita et al., 2022; Rashad et al., 2021; Keramane et al., 2023; Dhaouafi et al., 2024; Korkmaz, 2025). Other approaches include the cultivation of local seaweeds (Hmani et al., 2021; Trikka et al., 2021), and the monitoring of seasonal, physiological, and geographic variability which can significantly affect phenolic production (Trigui et al., 2013; Grozdanić et al., 2019; Kozak et al., 2020; Čagalj et al., 2022; Mazouzi et al., 2023). In this context, invasive species, such as *Caulerpa racemosa, Asparagopsis armata, Asparagopsis taxiformis, Rugulopteryx okamurae*, are also emerging as promising sources of valuable polyphenols, reinforcing the idea that even non-native species may contribute to sustainable bioprospecting (Mellouk et al., 2017; Alghazeer et al., 2022; Ahmend et al., 2023; El-Madany et al., 2023; Vega et al., 2023). This methodological focus correlates with the geographical pattern of chemical research field, indicating that studies in the eastern Mediterranean (Croatia, Turkey, Egypt) and western Mediterranean (Spain, Morocco, Algeria) utilize such approaches mainly on red and brown algae (Santos et al., 2019; Cadar et al., 2025). Interestingly, the VOS viewer map suggests that this line of research is not purely analytical but also translational in nature. The identification and extraction of compounds with antioxidant, anti-inflammatory, and antimicrobial properties directly bridges the gap between chemical characterization and therapeutic applications observed at a geographical scale across the Mediterranean basin. The blue cluster further supports this interpretation, as it reflects a progression from chemical profiling to advanced pharmacological validation through both *in vitro* and *in vivo* studies. In different human cell lines and animal model organisms, such as mice, seaweed metabolites, like fucoidans, terpenes and phlorotannins have shown promising effects against cancer, inflammation, allergies, bacterial and fungal infections and other diseases (Mezghani et al., 2013; Saad et al., 2016;Kammoun et al., 2018; Gheda et al., 2021; Dhaouafi et al., 2023; Abdelhamid et al., 2018; Abou-Dobara et al., 2023; Mazouzi et al, 2021, 2023; Abou-Dobara et al., 2023; Mazouzi et al., 2023). The pharmacological investigation of seaweed polyphenolic extracts finds a distinct geographical pattern that aligns with the distribution of medical research activity. A significant concentration of studies is observed in the eastern Mediterranean and is focused on brown algae. The convergence of these data suggests that the eastern Mediterranean serves as a primary hub for *in vivo* experimentation involving brown macroalgal extracts, while western countries, such as Tunisia, exhibit more pronounced research focus on red algae for similar pharmacological and bioactive compound evaluations.

Specific examples illustrate the pharmacological potential of marine macroalgae and their derived compounds. *Dictyopteris membranacea* has demonstrated anti-inflammatory and antibacterial activity against *Staphylococcus aureus* and *Listeria* species (Aoun et al., 2010). Likewise, *Padina pavonica*, *Cystoseira spongiosis*, and *Cystoseira sedoides* have been reported to exhibit antinociceptive and analgesic effects (Abdelhamid et al., 2018; Abou-Dobara et al., 2023; Mazouzi et al., 2023). In addition, several macroalgal metabolites, including fucoidans, diterpenes, and phlorotannins, have shown antiproliferative properties by interfering with cancer cell growth. For instance, *Padina pavonica* has demonstrated anti-tumor activity against human lung and liver carcinoma cell lines (Mhadhebi et al., 2012).

The hydroquinone diterpene mediterraneol, isolated from *Cystoseira mediterranea,* inhibits mitotic cell division, while meroterpenes such as usneoidone E and Z from *Cystoseira usneoides* exhibit notable antitumor properties. Furthermore, *Cystoseira compressa* has shown antidiabetic effects in streptozotocin-induced diabetic rats (Gheda et al., 2021), and *Corallina elongata* has been reported to exert protective activity against pulmonary fibrosis (Dhaouafi et al., 2023).

Beyond their health benefits, edible seaweeds have significant nutraceutical potential, making them promising candidates for application in the food industry. Their use supports sustainability by contributing to waste reduction and promotes public health through the development of functional foods and natural preservatives, thereby extending shelf life and improving food quality without the need for synthetic additives (Amin, 2019; De La Fuente et al., 2022). Their incorporation into products such as fish balls, meatballs, nuggets, broad bean cakes, and stewed horse beans (Amin, 2019; Ozogul et al., 2023) reflects a growing interest in formulating healthier and more sustainable food systems. Polyphenolic extracts from *Cystoseira barbata* have been incorporated into tuna-skin gelatin films to impart antioxidant properties and enhance food quality preservation (Haddar et al., 2012). Furthermore, its polyphenolic-protein-polysaccharide ternary conjugates have shown antimicrobial properties and biopreservatives potential (Sellimi et al., 2018). Similarly, extracts from *Padina pavonica*, *Cystoseira mediterranea*, and *Ericaria selaginoides,* have demonstrated antimicrobial activity against several pathogens, including *Candida albicans, Staphyloccocus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*). These findings support their application in extending the shelf life and improving the safety of degradable fish and meat products.

As evidenced by the yellow cluster, another relevant application area of polyphenols is aquaculture and agriculture, where seaweed extracts are used as biopesticides and biostimulants. However, while pharmacological and medical research shows distinct regional clustering, food and agricultural applications demonstrate a broader, more distributed interest across the Mediterranean. Specifically, food research is relatively homogeneous across the entire Mediterranean basin, reflecting a shared interest in macroalgae as functional food ingredients, regardless of the specific algae group. In contrast, the application of macroalgae in agriculture shows a specialized reliance on brown algae, particularly in Spain, Turkey, Tunisia and Egypt, highlighting a strategic shift toward the utilization of seaweed-based bio-stimulants or fertilizers. The efficacy of algae extracts is due to the presence of polyphenols which often work in synergy with arbuscular mycorrhizal fungi (AMF) or metabolites like sugars, uronic acids, proteins, and sulfate groups, glutathione, ascorbic acid, amino acids. Definitely, the use of brown, green and red algae extracts improve plant metabolism, growth, and productivity, reducing reactive oxygen species and boosting antioxidant response (Latique et al., 2017; Amin, 2019; Drira et al., 2021; Hadjkacem et al., 2023; Mutlu-Durak et al., 2024; Cunha-Chiamolera et al., 2025), thereby supporting crop resilience against abiotic (salinity, drought, heat) and biotic (pathogens, pests) threats (Latique et al., 2017; Drira et al., 2021; Hadjkacem et al., 2023; Soliman et al., 2024). Brown algae such as *Padina pavonica*, *Halopteris scoparia*, and *Fucus spiralis* are emerging as valuable Mediterranean bioresources for sustainable agriculture. Their extracts, naturally rich polyphenols, uronic acids and sulfate groups, enhance plant innate immunity by stimulating phenylalanine ammonia-lyase (PAL) activity, thereby strengthening physical and biochemical defenses mechanisms. These bioactive compounds have shown promising effects in crops such as tomato, Arabidopsis, and wheat, improving resilience to environmental stresses, particularly soil salinity (Hadjkacem et al., 2023). This Mediterranean focus aligns with global interest in *Ascophyllum nodosum*, *Fucus* spp., *Laminaria* spp., *Sargassum* spp., and *Turbinaria* spp. (Drira et al., 2021; Mughunth et al., 2024), as rich sources of bioactive compounds, including phlorotannins, bromophenols, eckol, and phloroglucinol, which contribute to UV protection, herbivore deterrence, and antimicrobial activity (Chouh et al., 2022;Drira et al., 2021; Mughunth et al., 2024).

The green alga *Ulva lactuca* also has emerged as one of the most highly valorized macroalgae due to its broad-spectrum antimicrobial activity against human, fish, and plant pathogens, including *Staphylococcus aureus*, *Candida albicans*, and agricultural fungi such as *Fusarium oxysporum* (Amin, 2019; Latique et al., 2017; Drira et al., 2021; Elshalakany et al., 2023). Among red algae, *Gelidium vagum* has shown potential in enhancing plant resistance under salt-affected soil conditions (Elshalakany et al., 2023). These findings explain the marked increase in publications over the past two decades, particularly since 2018, in Morocco, Greece, Tunisia, and Egypt (Mughunth et al., 2024). This growing interest reflects the urgent need for sustainable agricultural solutions in regions threatened by heatwaves, prolonged droughts, coastal erosion, saltwater intrusion, pests, and emerging plant diseases (EEA, European Environment Agency, 2024).

Global studies indicate that brown and green seaweed extracts are particularly effective in promoting plant growth and alleviating stress across a wide range of crops, more consistently than red algae. This supports their growing role as sustainable tools for enhancing agricultural productivity and strengthening global food security (Aina et al., 2022; Mughunth et al., 2024; Rabhi et al., 2025).

Polyphenol-rich seaweed extracts are increasingly used also in the cosmetic industry due to their versatility, being incorporated into products such as gels, emulsions, lotions, serums, and face masks. Their antioxidant, anti-inflammatory, and photoprotective properties support applications in managing acne, dermatitis, sun damage, and skin aging (Mellouk et al., 2017; Grillo et al., 2021; Rodrigues Moreira et al., 2022; Vega et al., 2023).

Species such as *Carpodesmia tamariscifolia Porphyra umbilicalis, Sargassum vulgare*, and *Ulva Lactuca* have shown good sunscreen potential against UV-induced damage. This effect is largely due to the combined action of phlorotannins and carotenoids like fucoxanthin (Schneider et al., 2020; De La Fuente et al., 2021; Grillo et al., 2021; Rodrigues Moreira et al., 2022; Mirata et al., 2023).

Overall findings indicate that seaweed phenolics show strong potential for advancing a sustainable blue and circular economy, but further large-scale field studies are needed to fully realize their applications in health, food security, and agriculture, especially in Mediterranean contexts.

In particular, the efficacy of seaweed-derived phenolic compounds depends on their chemical structure, extract composition, and application matrix. Their antioxidant activity is influenced by factors such as hydroxylation pattern, polymerization degree, extraction method, and concentration, while translating promising *in vitro* results into real-world applications remains a major challenge (Tziveleka et al., 2021; Cadar et al., 2025).

4.3. Mechanistic linkage between polyphenols and antioxidant activity, integration with biochemical pathways and molecular targets of polyphenols

In Table 1, we summarize and propose the main mechanisms linking polyphenols to antioxidant activity, their integration into biochemical pathways involved in regulating physiological responses, and the molecular targets through which they help preserve cellular functionality. Table 1 highlights that the antioxidant potential of polyphenols in Mediterranean macroalgae is strongly dependent on their chemical structure and redox properties, which determine their ability to donate electrons or hydrogen atoms and thereby neutralize reactive oxygen species.

In macroalgae, this chemical versatility is reflected in their involvement in photoprotection, antioxidant defence, and stress tolerance. Polyphenol accumulation is often associated with changes in photosynthetic performance, carbon and nitrogen metabolism, and the activation of enzymatic antioxidant systems, suggesting that these metabolites are components of an integrated physiological response rather than isolated protective compounds. In this context, polyphenols function as dynamic mediators of acclimation to environmental stressors, including heat, desiccation, acidification, high irradiance, and pollution. However, the molecular mechanisms underlying these responses remain only partially understood, and the relationships between polyphenol biosynthesis, antioxidant activity, and specific biochemical targets are still insufficiently resolved. Future studies should therefore integrate metabolomic profiling with enzymatic assays, transcriptomic analyses, and physiological measurements to better elucidate the biochemical pathways and molecular mechanisms through which polyphenols contribute to stress tolerance in Mediterranean macroalgae.

5. Conclusions: main findings, knowledge gaps and future directions

Polyphenols in Mediterranean macroalgae have multiple ecological and biotechnological roles (Fig. S2). Ecologically, they function as early indicators of environmental stress, photoprotective agents, antioxidants, and mediators of interactions with herbivores, epiphytes, and invasive species. Their effects depend on chemical structure, especially hydroxylation patterns, ring structure, degree of polymerization, and redox-active groups, which determine their ability to scavenge reactive species, chelate transition metals, and support chain-breaking antioxidant reactions. They also interact with endogenous antioxidant enzymes and photoprotective pigments (Fig. S2).

Their synthesis is highly species-specific and strongly regulated by environmental factors such as seasonality, light and temperature fluctuations, salinity, nutrients, CO_2 levels, desiccation, pollution, habitat type, and biotic stressors (Fig. S2). This allows macroalgae to adjust to single or multiple stress conditions through acclimation and adaptation. Polyphenols are integrated into broader metabolic networks involving the shikimate and phenylpropanoid pathways, oxidative stress signalling, and multiple molecular targets.

Biotechnologically, although only 18.5% of studies focus on ecological aspects, 81.5% address applications in food, cosmetics, aquaculture-agriculture, pharmacology, and medicine (Fig. S2). In particular, macroalgal polyphenolic extracts can act as biostimulants that partially replace chemical fertilizers, improving crop resilience and supporting environmental sustainability through better soil and water conservation. Additionally, they have potential uses in human health and wellness products, food security and functional foods, pharmaceuticals, therapeutics, and photoprotective cosmetics due to their antioxidant, anti-age, anti-microbial, anti-tumoral properties, but the gap between *in vitro* assays and validation in real systems remains a major translational challenge (Fig. S2). Other important knowledge gaps emerged from the review. The literature reveals substantial taxonomic and geographical biases. Brown algae (especially *Cystoseira, Sargassum,*

Table 1
Synthesis of the main mechanistic linkages between polyphenols and antioxidant activity, integration with biochemical pathways and identification of polyphenol molecular targets of polyphenols and signaling pathways which contribute to the multiple roles played by polyphenols in Mediterranean macroalgae in the frame of ecological, chemical, pharmaceutical, medical, food, and agricultural research fields.

Mechanistic linkage between polyphenols and antioxidant activity	
Free-Radical Scavenging	
Polyphenols, particularly phlorotannins, act by neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), scavenging harmful radicals such as hydroxyl radicals (·OH), superoxide anions (O2·−), and nitric oxide (NO·) through the donation of hydrogen cations from their hydroxyl groups (-OH), thereby forming stable compounds.	Hamiche et al. (2021); Ahmed et al. (2023)
Structural determinants of activity	
This activity is enhanced by the number and position of hydroxyl groups (-OH) on the aromatic ring. In acylphloroglucinols, a higher degree of hydroxylation of the phenolic structure correlates with a greater ability to donate hydrogen atoms to peroxyl radicals.	Hamiche et al. (2021)
The presence of conjugated double-bond systems and carbonyl groups facilitates electron delocalization, stabilizing the resulting phenoxyl radical and increasing antioxidant potency.	Hamiche et al. (2021);Keramane et al. (2023)
Correlation with antioxidant activity	
There is a direct correlation between increased phenolic compounds/total phenolic content (TPC) and the capacity to scavenge DPPH and ABTS radicals. For instance, in *Caulerpa cylindracea*, a significant correlation (r = 0.87) was observed between polyphenols and ABTS activity.	Mellouk et al., (2017); Schneider et al. (2020); Brahmi et al. (2021); Hamiche et al. (2021);De La Fuente et al., 2021; Chouh et al. (2022); El-Sayed et al. (2022); Boundir et al., 2022; Inoubli et al. (2024); Ismail et al. (2025); Tahar et al. (2025)
Chain-breaking mechanism	
The mechanism that allows the formation of stable aryloxyl radicals, which do not act as chain carriers, known as the "chain-breaking" mechanism, is fundamental for inhibiting lipid peroxidation in cell membranes.	Mellouk et al. (2017); Ismail et al. (2025)
Metal chelation	
Polyphenols reduce oxidative stress by binding transition metal ions such as iron (Fe^{2+}) and copper (Cu^{2+}), thereby preventing the Fenton reaction and the formation of highly reactive radicals. In *Colpomenia sinuosa*, metal-chelating activity of up to 85% has been documented. Chromatographic analyses (HPLC-MS/MS) identified specific phenolic molecules responsible for these activities: • Phenolic acids include gallic acid, caffeic acid (the most abundant in *Ulva lactuca*), p-coumaric acid, vanillic acid, and syringic acid. • Flavonoids include quercetin, kaempferol, catechin, rutin, naringenin, chrysin, and apigenin-7-O-glucoside. • Galloyl derivatives include tetragalloyl-glucose and pentagalloyl-glucose, which are known for their high efficiency in radical neutralization	Celis-Plá et al. (2016); Kumar et al. (2017); Sellimi et al. (2018); Grozdanić et al. (2019); Hamiche et al. (2021); De La Fuente et al. (2022); Rodrigues-Moreira et al. (2022); Dhaouafi et al. (2023); Hadjkacem et al. (2023); Vega et al. (2023); Boundir et al., 2022; Mazouzi et al. (2023); Oumassi et al. (2024); Sayln et al. (2024); Almutairi et al. (2025); El Haci et al. (2025);Ismail et al. (2025); Korkmaz (2025)
Reducing power	
Antioxidant activity is also expressed through ferric reducing antioxidant	Oumassi et al. (2024); Faidi et al. (2025)

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Table 1 (*continued*)

Mechanistic linkage between polyphenols and antioxidant activity	
power (FRAP), where phenolic compounds reduce ferric iron (III) to ferrous iron (II) through electron donation.	
Induction of enzymatic defenses	
The presence of polyphenols, such as flavonoids and terpenes, is often correlated with the up-regulation of endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), ascorbate peroxidase (APX), and glutathione peroxidase (GPx), as well as with the restoration of non-enzymatic antioxidants such as glutathione (GSH) and vitamin C, generating a cooperative response that helps maintain cellular redox homeostasis.	Schiavon et al. (2012); Brahmi et al., 2019; Drira et al., (2021); Kumar et al. (2022); Akakçe et al., (2023); Cerrato et al. (2023); Dalaam et al. (2025); Dhaouafi et al. (2023)
Shielding and photoprotection	
Under radiation stress, polyphenols not only accumulate internally but are also released as exudates into the surrounding medium, where they form UV-absorbing complexes that protect the photosynthetic apparatus from oxidative damage.	Celis-Plá et al. (2014); Figueroa et al. (2014)
Integration with biochemical pathways	
Shikimate and phenylpropanoid pathways	
An increase in aromatic amino acids such as phenylalanine and tyrosine under stress indicates their involvement in this pathway to support the synthesis of secondary metabolites. Elicitors such as alginates and fucoidans stimulate phenylalanine ammonia-lyase (PAL) activity, the key enzyme that initiates phenolic compound production in response to biotic and abiotic stress.	Kumar et al. (2018); Hadjkacem et al., (2023); Pereira et al., 2025
Reduction of oxidative damage	
Polyphenol treatments significantly reduce levels of malondialdehyde (MDA), a final marker of lipid peroxidation, as well as advanced protein oxidation products (AOPP) and protein carbonyls (PCO), thereby protecting membranes, enzymes, and DNA.	Abdelhamid et al. (2018); Brahmi et al. (2021); Feki et al. (2023)
Metabolic reprogramming	
Under stress conditions, macroalgae divert carbon reserves from primary metabolism (biomass and growth) toward secondary metabolism to sustain the production of polyphenols and enzymes. This process is often accompanied by increased levels of precursor amino acids and glycolytic intermediates.	Kumar et al. (2018), 2022; Pereira et al. (2024); Donadio et al. (2025)
Xanthophyll cycle and photoprotection	
Polyphenols act in synergy with photoprotective pigments in the thermal energy dissipation mechanism (NPQ). The accumulation of phenols is positively correlated with NPQ, suggesting biochemical coordination aimed at neutralizing excess light energy that would otherwise generate ROS accumulation.	Garrabou et al., 2022; Celis-Plá et al. (2014); Figueroa et al., (2014); Fabbrizzi et al. (2023); Donadio et al. (2025)
NADPH oxidase	
Molecular docking studies indicate that polyphenolic derivatives such as tetragalloyl-glucose interact directly with the active site of NADPH oxidase, a key enzyme in the generation of reactive oxygen species (ROS).	Oumassi et al. (2024)
Molecular targets of polyphenols and signaling pathways	

Table 1 (*continued*)

Mechanistic linkage between polyphenols and antioxidant activity	
PSII Photosystem	
One of the main protective targets is the D1 protein of photosystem II (PSII). Polyphenols minimize photo-oxidative damage and D1 degradation caused by excess light, UV radiation, or heat, thereby maintaining photochemical efficiency (Fv/Fm).	Porzio et al. (2018); Figueroa et al. (2014); Fabbrizzi et al. (2023); Mughunth et al. (2024); Pica et al. (2024); Donadio et al. (2025); Pereira et al. (2025)
Specific enzyme inhibition	
Polyphenols, including eckol and catechins, target molecular enzymes such as alpha-glucosidase, alpha-amylase, and trypsin. Inhibition occurs through hydrogen bonding or salt bridges between hydroxyl or sulfate groups and the active sites of the enzymes, suggesting potential anti-diabetic and anti-inflammatory applications. Polyphenol-rich extracts from *Sargassum muticum* have shown alpha-amylase inhibition stronger than the reference drug acarbose.	Grozdanić et al. (2019); Hadjkacem et al., (2023); Hamamouche et al. (2024)
Angiotensin Conversion Enzyme	
Phlorotannins, especially pentamers and hexamers, inactivate ACE by binding to the active site or by chelating the zinc atom required for its catalytic function.	Sellimi et al. (2018); Brai et al. (2024)
Nucleic acids and membranes	
By acting as scavengers of hydroxyl radicals (·OH), polyphenols directly protect DNA and membrane lipids from peroxidation.	Celis-Plá et al., 2014; Hadjkacem et al. (2023)
Protein kinases	
Some polyphenols have been shown to target kinases involved in cell-cycle regulation and malignant transformation, conferring cytotoxic properties against tumor cell lines.	Grozdanić et al. (2019)
Inflammatory pathways	
Polyphenol scavenging of ROS acts upstream of inflammatory signaling, inhibiting the activation of transcription factors such as NF-κB and mitogen-activated protein kinase (MAPK) pathways. This leads to the suppression of pro-inflammatory mediators such as iNOS (NO sintetasi inducibile) e COX-2 (cicloossigenasi-2)	Khaled et al., 2012; Abdelhamid et al., 2018; De La Fuente et al. (2021); Rodrigues-Moreira et al. (2022); Vega et al., 2023; Mirata et al. (2023); Rakha et al. (2025)
Redox regulation	
Compounds such as phloroglucinol stimulate the Nrf2 signaling pathway, a crucial regulator that induces the expression of antioxidant and cytoprotective genes. Activation of the AMPK pathway has also been reported.	Dhaouafi et al. (2023); Goksen (2023)
Digestive and tissue-remodeling enzymes	
Polyphenols, especially tannins, inhibit targets such as alpha-amylase and pancreatic lipase through protein-binding effects, thereby modulating carbohydrate and lipid metabolism. In the skin, they inhibit matrix metalloproteinases such as collagenase, elastase, and hyaluronidase, as well as tyrosinase, counteracting aging and hyperpigmentation.	Moussa et al. (2020); Chouh et al. (2022); Rodrigues-Moreira et al. (2022); Mirata et al. (2023)
Apoptosis and cell cycle	
In oncological contexts, polyphenols may target protein kinases and regulate pro-apoptotic genes such as caspase-3, caspase-9, Bcl-2, TP53, and PTEN, inducing cell-cycle arrest and apoptosis in tumor cells.	Grozdanić et al. (2019); Güner et al. (2019) Moussa et al. (2020); Rakha et al. (2025); Dalaam et al. (2025)
Synergy and complex formation	

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Table 1 (*continued*)

Mechanistic linkage between polyphenols and antioxidant activity	
The results show that polyphenols form glycoconjugates, ternary complexes with proteins and polysaccharides, where amino acid residues such as methionine, histidine, and lysine act as additional proton donors, amplifying the overall antioxidant action through a synergistic effect. Their bioavailability and bioaccessibility vary during gastrointestinal digestion, where hydrolysis can release more active aglycones and phlorotannins, increasing iron-reducing capacity and radical scavenging.	Şensu et al. (2023);Brai et al. (2024)

Dictyota) have been more investigated, than green and red ones, although green algae (e.g., *Ulva*), coralline algae, and even invasive macroalgae represent underexplored sources of bioactive compounds with potential for polyphenol extraction. The geographical coverage is uneven, with the western Mediterranean much better represented than the eastern, and several key habitats are still poorly explored. In addition, it remains difficult to link specific phenolic compounds/profiles to specific environmental pressures, especially under multi-stressor conditions (Fig. S2).

Future research should therefore expand taxonomic and geographical coverage (Figs. S2–S3). Short and long-term and multi-site studies are needed to unravel the effects of single and combined stressors on phenolic production, and to determine whether polyphenol profiles can reliably distinguish among different environmental pressures (Figs. S2–S3). Methodological harmonization in extraction and chemical characterization, associated with metabolic, enzymatic, transcriptomic, and physiological approaches are also essential to improve comparability across studies, discover in depth species-specific responses, clarify the mechanisms by which polyphenols are linked to environmental drivers and support stress tolerance in Mediterranean macroalgae, thereby obtaining important ecosystem-level implications (Figs. S2–S3). Finally, the ecological and biotechnological potential of invasive species and the translational value of polyphenol-rich extracts should also be validated through broader field-based and application-oriented research. In conclusion, a wider integrative research approach is essential to fully realize the ecological and applied potential of polyphenols, supporting both marine ecosystem protection and human health (Figs. S2–S3).

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CRediT authorship contribution statement

Ermenegilda Vitale: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rosa Donadio:** Formal analysis, Investigation, Visualization, Writing – review & editing. **Simonetta Fraschetti:** Funding acquisition, Methodology, Supervision, Writing – review & editing. **Carmen Arena:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.marenvres.2026.108244.

Data availability

Data will be made available on request.

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