Literature and Bibliography Study on Bacterial Proteases in Relation with Marine Algae Symbiosis

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Abstract. Thrombosis is one of the risk factors for cardiovascular disease (CVD) that can cause death, and CVD is the leading cause of death in the world. Bacterial proteases have potential as antithrombosis agents that can be developed into CVD drugs. Indonesia's high marine biodiversity has been recognized worldwide, including the diverse marine algae and symbiotic bacteria. The discovery of new antithrombotic agents is made possible by the high biodiversity of proteolytic bacteria associated with marine organisms. This literature review aims to obtain information about research trends in the last ten years that link protease bacteria with marine algae symbiosis as an alternative source of protease produced by symbiont bacteria. The method of collecting publication data arranged in tabular form in this literature review was obtained from Google Scholar and PubMed. The bibliography study used the search database platform "dimension.ai" with the keyword bacterial protease and the last ten years of publication data from 2014 until 2023. A visualization of the network and density of research worldwide is displayed using VosViewer software. The literature review results, which focused on publications from the previous ten years, showed that there were still very few published studies to research proteases from bacteria symbiotic with marine algae. Based on the information collected, algae have a relatively high protein content, which may indicate that bacteria living in symbiosis with algae are actively producing proteases, with the possibility that some of them have antithrombotic properties. In conclusion, the biodiversity of bacteria isolated from marine algae has significant potential to contribute to identifying new protease sources for antithrombosis. For the utilization and development of proteases to treat thrombosis, it is recommended to investigate protease bacteria that symbionts with marine algae, which are still very limited in research offering novelty.

Keywords: Bacterial Protease, Symbiont Bacteria, Marine Algae.

1. Introduction

Protease enzymes are widely used in various applications, including healthcare, the pharmaceutical industry, food, detergents, and waste management [1][2]. The application

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of protease enzymes in the medical sector can be used for the therapy of cardiovascular disease (CVD), which is the leading cause of death in the world. [3][4]. Proteases act as antithrombosis therapeutic agents [5]. Thrombosis is one of the risk factors for CVD that can cause death [6]. Thrombosis is a life-threatening pathological condition in which a blood clot forms inside a blood vessel, blocking blood flow [7]. Increased thrombosis results in an obstructed supply of oxygen and nutrients to cells and tissues (ischemia) and causes tissue death (infarction) [8].

Indonesia is known as the center of marine diversity, including algae and their symbiont microorganisms [9]. Algae or seaweed is a source of bioactive compounds such as polysaccharides, vitamins, proteins, enzymes, peptides, essential minerals, polyphenolic compounds, and unsaturated fatty acids [10][11]. These bioactive compounds have potential as antibacterial, antiviral, antifungal, anticancer, antioxidants, and anticoagulants [12]. Algae are one of the marine commodities that are widely associated with symbiont bacteria. Studies related to the potential of secondary metabolites of symbiont bacteria are critical to determining the possibility of bacteria, especially those that are symbionts with algae [9][13]. Symbiont bacteria are known to have many biological activities, one of which is enzyme activity [4].

Protease enzymes are produced by microorganisms such as bacteria, known as proteolytic bacteria. The source of proteolytic bacteria is sourced from soil, sea, or bacteria that are symbionts with marine organisms, such as algae [15][16][17]. Proteolytic bacteria have the potential to produce thrombolytic or fibrinolytic proteases that are used as antithrombosis agents [18]. Using microorganisms as enzyme producers has the advantage of faster bacterial growth, growth not affected by the season, and its genetic properties can be manipulated [19].

Treatment of thrombosis generally uses antithrombolytic, anticoagulant, and antiplatelet drugs [20]. However, the use of these drugs has side effects that cause bleeding and are expensive [21]. Therefore, antithrombosis agents sourced from natural products that are safer and have no side effects are needed. The utilization of protease enzymes produced by marine algal symbiont bacteria as antithrombosis agents and potentially developed for therapeutic of CVD.

2. Materials and Method

The bibliography was collected using the search database http://app.dimensions.ai. The research used the keyword "bacterial protease" published in the research range from 2014 to 2023 by searching for titles and abstracts. This bibliography aims to show the research development related to "bacterial protease". By using VOSviewer software, it can visualize bibliometric networks or scientific publication data, which is very much needed at this present time.

Literature reviews were collected using sources from PubMed and Google Scholar databases published from 2014–2023 that discussed "bacterial proteases associated with marine algal symbiosis". The article search used Medical Subject Title Headings (MeSH) with several combinations, including "protease", "protease enzyme", "protease bacteria", "symbiont bacteria", "marine algae," and "marine bacteria". This journal review aims to identify protease-producing bacteria symbionts in marine algae.

2.1. Journal Eligibility Criteria

The determination of journal standardization was based on the inclusion criteria set as follows: (i) algae symbiont bacteria; (ii) protease enzymes; (iii) bacterial proteases; (iv) reported in Indonesian or English; (v) search for review journals published in 2014–2023. All journals were obtained using computerized and manual PubMed and Google Scholar search tools. Journal exclusion criteria in this study were journals unrelated to marine algae symbiont bacteria.

2.2. Journal Selections

Journal selection was based on the guidelines of Pigott and Polanin [22] to identify journals that met the inclusion criteria listed in this journal publication. Careful identification and data analysis resulted in titles and abstracts that could be used to identify inappropriate sources that needed to be excluded. The resulting journal articles were also reviewed and evaluated to see if they met the inclusion criteria.

2.3. Research Bias Control

The risk of bias or quality assessment in this journal review includes (i) the accuracy of the information related to algal symbiont bacterial proteases and (ii) selective reporting of results. The acceptable risk of bias was considered minimal when all requirements were achieved.

3. Result and Discussion

Using the database at http://app.dimensions.ai/ resulted in 875,988 publications of scientific articles or journals published in the data range of 2014 to 2023. Figure 1 shows the number of journals published on "bacterial proteases" annually. The VOSviewer software offers a network visualization map to display the overall data. Figure 2 shows the network visualization of 73 terms. For co-occurrence, VOSviewer also offers a density visualization map. Figure 3 depicts the density visualization of 73 terms.

Figure 1 shows that between 2014 and 2023, there was an increase in the number of studies conducted on bacterial proteases. The peak of such research was in 2021. Figures 2 and 3 show the network and index of research on bacterial proteases, but they do not mention algal symbionts capable of producing proteases. Therefore, research on bacterial proteases associated with algal symbiosis is still relatively new and limited.

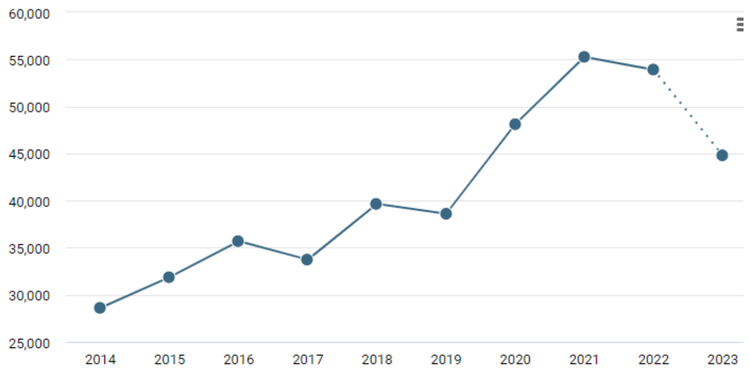

Fig. 1. Total of publications on "bacterial protease" from 2014 to 2023 (source: http://app.dimensions.ai/)

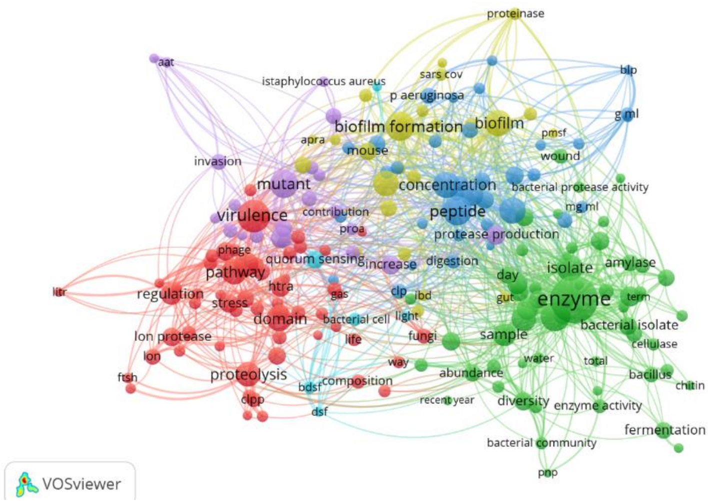

Fig. 2. Network Visualization of "bacterial protease"

(Source: VOSviewer and http://app.dimensions.ai/)

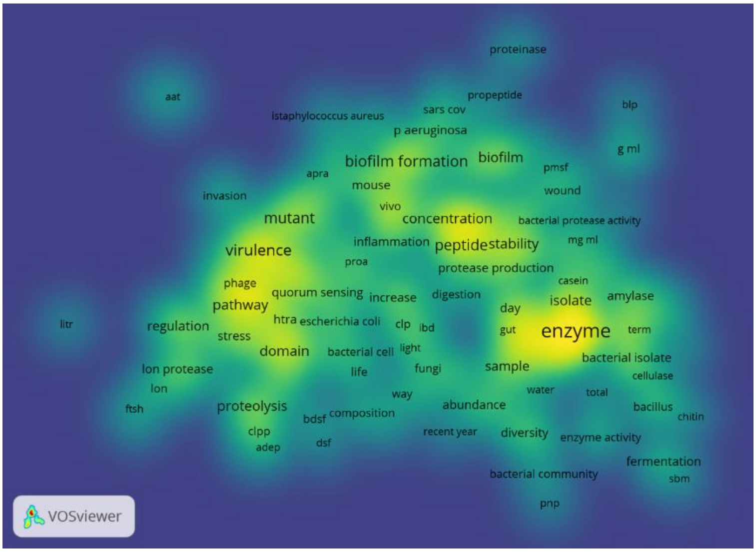

Fig. 3. Index Density Visualization "bacterial protease."
(Source: VOSviewer and http://app.dimensions.ai/)

In the past ten years, many studies have documented proteases produced by bacteria in fermented foods, soil, and marine environments worldwide [23][24][25]. Studies reporting bacteria isolated only from marine environments are summarised in this review specifically. This study uses supporting references published in the last ten years to analyze the possibility of studying proteolytic bacteria symbionts with marine algae, specifically to produce proteases.

According to reports, algae is one of the very rich protein sources and has all the required minerals and amino acids. Based on reports of the three types of algae, brown algae has the highest protein content compared to the red algae and green algae groups. Interestingly, essential metabolites found in brown algae, such as proteins, polysaccharides, carotenoids, and phlorotannins, have been linked to several health benefits for various diseases, including CVD. One of the leading causes of death worldwide is CVD [3][26][27][28][29][30][31].

Table 1. Protein levels of marine algae determined by the Kjeldahl method reported in the last ten years.

No	Algae Species	Protein levels (%)	Weight	Country	Reference
1	Sargassum ilicifolium	43,87	Dry	Sri Lanka	-26
2	Bryopsis corticolans	38,20	Dry	Iran	-27
3	Caulerpa sertularioides	35,06	Dry	Iran	-27
4	Palisada perforate	32,05	Dry	Iran	-27
5	Gelidiopsis variabilis	30,90	Dry	Sri Lanka	-26
6	Jania adhaereus	29,47	Dry	Sri Lanka	-26
7	Caulerpa racemose	29,10	Dry	Iran	-27
8	Acanthophora spicifera	28,89	Dry	Sri Lanka	-26
9	Gracilaria corticata	28,70	Dry	Sri Lanka	-26
10	Gracilaria corticata	26,08	Dry	Sri Lanka	-26
11	Hypnea caroides	25,63	Dry	Iran	-27
12	Ulva sp.	25,11	Dry	Egypt	-28
13	Padina antillarum	24,83	Dry	Sri Lanka	-26
14	Ordo: Bangiales	24,10	Dry	Peru	-29
15	Osmundea pinnatifida	23,80	Dry	Portugal	-30
16	Porphyra sp.	23,70	Dry	Portugal	-31
17	Turbinaria ornate	23,54	Dry	Sri Lanka	-26
18	Grateloupia turuturu	22,50	Dry	Portugal	-30
19	Caulerpa setularioides	22,05	Dry	Sri Lanka	-26
20	Sargassum boveanum	21,33	Dry	Iran	-27

The protein content (dry weight) of algae reported globally over the past five years was reviewed in this study (Table 1) and obtained using the Kjeldahl method. The highest protein content of 43.87% Sargassum ilicifolium, collected from Sri Lanka, had the highest protein content among all reported algae (Table 1). Bryopis corticolans was the green algal species with the highest protein content, at 38.20%. As for the red algae group, Palisada perforata had the highest protein content at 32.05% [26][27].

Algae groups are distributed widely throughout Indonesia, but the bacteria associated with them and their potential to produce therapeutic enzymes are still very little researched worldwide. Given that Indonesian algae or seaweeds have a high marine biodiversity index, obtaining a wide variety of symbiont bacteria from them is possible. Since green algae, red algae, and brown algae have relatively high protein content, it is possible that bacteria associated with marine algae can produce proteases. The bacterial proteases in question can be classified as serine or metalloproteases, which are well known for their therapeutic properties, especially in the treatment of thrombosis. Blood clots called thrombus formed during the thrombosis process can be degraded by antithrombotic protease enzymes [32][33][34].

Table 2. In the last ten years, studies have documented the use of symbiont bacteria of marine algae with biological activity.

No	Microorganism Species	Source	Result	Country	Reference
1	Enterobacter cancerogenous	Euchema spinosum	Enzyme L-Asparaginase	Indonesia	-35
2	Bacillus sp.	Halimeda opuntia	Antibacterial	Indonesia	-36
3	Bacillus cereus	Padina sp.	Antibacterial	Indonesia	-37
4	Pseudomonas guezennei	Halimeda discoidea	Antibacterial	Indonesia	-38
5	Neisseria sp.	Caulerpa racemose	Antibacterial	Indonesia	-39
6	Pseudomonas putida	Sargassum sp.	Enzyme L-Asparaginase	Indonesia	-40
7	Bacillus amyloliquefaciens	Kappaphycus alverezzi	Antibacterial	India	-41
8	Bacillus sp.	Sargassum wightii	Antibacterial	India	-42
9	Metabacillus indicus	Chnoospora sp.	Enzyme Protease	Indonesia	-17
10	Enterobacter cancerogenous	Sargassum sp.	Enzyme L-Asparaginase	Indonesia	-43
11	Idiomarina fontislapidosi	Halimeda macroloba	Antibacterial	Indonesia	-44
12	Lactobacillus plantarum	Turbinaria conoides	Antibacterial	Indonesia	-13
13	Bacillus pacificus	Turbinaria ornata	Enzyme α-Amylase	Saudi Arabia	-45
14	Klebsiella sp.	Sargassum sp.	Antidengue	Indonesia	-46

15	Cobetia sp.	Sargassum fusiforme	Alginate lyase	China	-47
16	Streptomyces albidoflavus	Carpodesmia tamariscifolia	Antibacterial	Morocco	-48

Table 2 reports that various marine bacteria symbionts with algae have been used as sources of biological activities such as antibacterial, anti-dengue, and enzyme-producing globally over the past ten years [13][17][43][35][36][37][38][39][40][41][42][45][46][48][50]. Table 2 shows that very few studies discuss whether marine bacteria are isolated from algae as a source of proteases. This indicates that there is still a significant novelty in studies isolating protease-producing marine bacteria from brown algae. Another conclusion that can be drawn from Table 2 is that Asian countries, especially Indonesia, dominate the research that describes the diversity of marine bacteria in relation to the development of medicines and health fields. Indonesia is followed by China, Saudi Arabia, Morocco, and India. This shows the potential of Indonesia's marine bacterial diversity to produce antithrombosis agents.

To obtain protease enzymes using microorganisms or bacteria that are potentially symbiotic with algae with high algal biodiversity in Indonesia has not been widely studied. Therefore, research on how the biodiversity of algae and their symbiont bacteria in Indonesia can assist further in identifying bacteria that produce proteases as antithrombosis agents is also significant. In the last ten years, very limited research has been reported investigating the synthesis of protease enzymes from tissues or bacteria associated with algae [13][17][43][35][36][37][38][39][40][41][42][45][46][48][50].

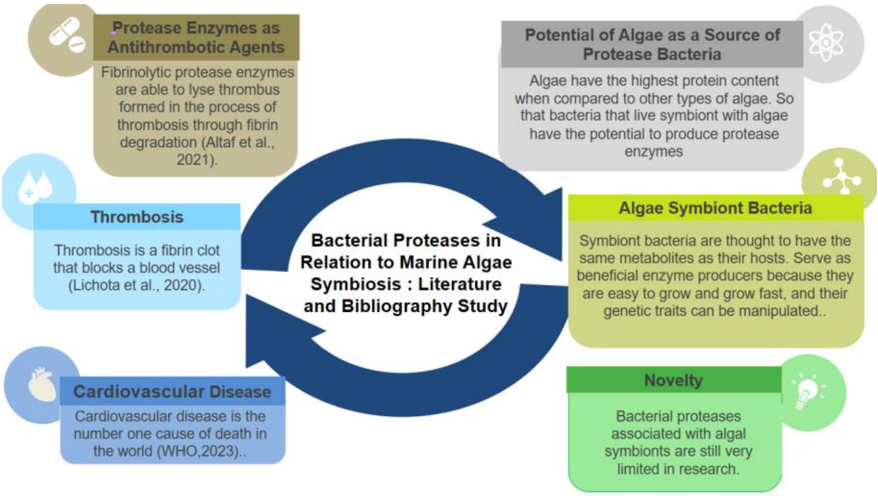

Fig. 4. The significance and potential of studying the biodiversity of bacterial symbionts to marine algae that produce proteases.

A schematic summarizing the factors contributing to the significance and potential of biodiversity studies on protease-producing bacteria symbionts with marine algae is illustrated in Figure 2. The minimum risk factor for death by thrombosis, the potential of marine algae as a source of therapeutic metabolites such as proteins, the role of antithrombotic proteases in medicine, the prospect of algae biodiversity in Indonesia, and the possibility of novelty resulting from the identification of new antithrombotic protease-producing bacteria symbionts with marine algae Based on this Figure 2, it is further recommended to research to explore the biodiversity of protease-producing bacteria that have been isolated from Indonesian marine algae, as it has great potential to result in the identification of new antithrombotic agents.

According to this literature review, there is a high probability that bacteria isolated from marine algae have high biodiversity potential, which may contribute to the finding of new protease sources. Investigating new sources of antithrombosis bacteria to treat CVD is made possible by studies such as this. Therefore, to support the use of proteases in overcoming the threat of thrombosis diseases, research on protease-producing bacteria associated with marine algae that are abundant in Indonesia but have not received much attention is recommended.

Authors Contributions. The entire study was planned by SNE and MZBA, with MZBA gathering, evaluating, screening, and summarizing all the articles it had acquired. SNE and MZBA assess the generated figures, tables, and schemes while examining research bias. MZBA and SNE wrote the majority of the text. SNE proofread the document after MZBA initially wrote it.

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