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EFFECTIVENESS OF BROWN SEAWEED *(Sargassum sp.)* AS NATURAL ANTIOXIDANT FOR ENDOTHELIAL CELL PROTECTION IN PREECLAMPSIA: A LITERATURE REVIEW

Lia Arian Apriani* , Ida Ariyanti

Master of Applied Science in Midwifery, Poltekkes Kemenkes Semarang, Semarang, Indonesia

*Corresponding author's email: **arianlia020495 @ gmail.com**

ABSTRACT

Background: *Seaweed as one of the natural resources has many potential bioactive ingredients. One of them is Phaeophyceae which shows the highest antioxidant activity among other seaweed. Sargassum sp has many potential bioactive ingredients in the pharmaceutical field which has been supported by several scientific studies. This study aims to expose all information related to abilities Sargassum sp as an antioxidant for endothelial cell protection in preeclampsia in a comprehensive and systematic manner.*
Methods: *This study was a systematic review that used the prism protocol. Data obtained from Electronic databases Science Direct, Springer, DOAJ, NCBI and Google Scholar that published between 2009 and 2019. By using keywords such as an antioxidants of Sargassum sp, preeclampsia and antioxidants, as well as antioxidants and endothelial cells to find the relevant journal.*
Results: *The search found 963 articles, of which 215 articles were included in the inclusion and exlusion criteria. The final results obtained 8 articles that are suitable for this literature review. Majority of studies used the same method namely experimental, 3 other studies uses meta-analysis randomized controlled trials, and a case-control study. Analysis of the studies found out that Sargassum sp contains phenolic compounds which function as antioxidants in fighting free radicals and as protection against endothelial cells in preeclampsia.*
Conclusion: *Sargassum sp is proven to have the value of high antioxidant effect that is able to fight free radicals and is able to protect endothelial cells in preeclampsia. Therefore, this study is presented to assist researchers in planning their future studies related to seaweed in preventing preeclampsia in the fields of obstetrics and gynecology and with the hope of potential future drug development.*

Keywords: *Sargassum sp, Antioxidants, Endothelial Cells, Preeclampsia*

INTRODUCTION

The indicators of the successful development in a region can be seen from its health state, namely Maternal Mortality Rate (MMR) and Infant Mortality Rate (IMR). In general, there was a decrease in maternal mortality during the period 1991-2015. Initially, IMR in Indonesia shows that 390 out of 100.000 live births in 2019 has decreased to 305 out of 100.000 live births in 2015. However, this figure is considered relatively high compared to IMR in 2007 in which 228 out of 100.000 live births (1,2). High Blood Pressure (HBP) is a complication of pregnancy where a major cause is of 5% -10% morbidity and mortality in pregnancies worldwide. HBP is classified as preeclampsia, eclampsia, chronic hypertension, superimposed preeclampsia and transient hypertension (3).

Preeclampsia is called *Disease Of Theory,* this is due to pathophysiology and uncertain causes (4). One theory that is used as the hypothesis of the causes of preeclampsia is placental ischemia which is a decrease in placental perfusion and endothelial activation that affects the entire organ system (5). Hypoxia and placental ischemia also trigger the formation of free radicals that can damage cell membranes and cause oxidative stress in preeclampsia. This oxidative stress indicates an imbalance in the number of oxidants and antioxidants in the body which is considered the main cause of endothelial dysfunction (5). Therefore, it is necessary to evaluate the potential of antioxidants in preventing complications and improve the prognosis of pregnancy so that the results can improve the quality of maternal health during pregnancy (4).

Natural remedies in modern times are preferred by society because they are considered safer and easily absorbed by the body compared to synthetic medicine. However, the most commonly used antioxidants are synthetic antioxidants whose effects are carcinogenic and can cause liver damage, such as *butylated hydroxyanisole* (BHA), *butylated hydroxytoluene* (BHT), *tort-butyl hydroquinone* (TBHQ) and *propyl gallate* (PG) (6). These natural antioxidants can be obtained from natural ingredients on land and from the sea. Natural materials from the sea are no less potential as a source of active ingredients than natural materials sourced from land.

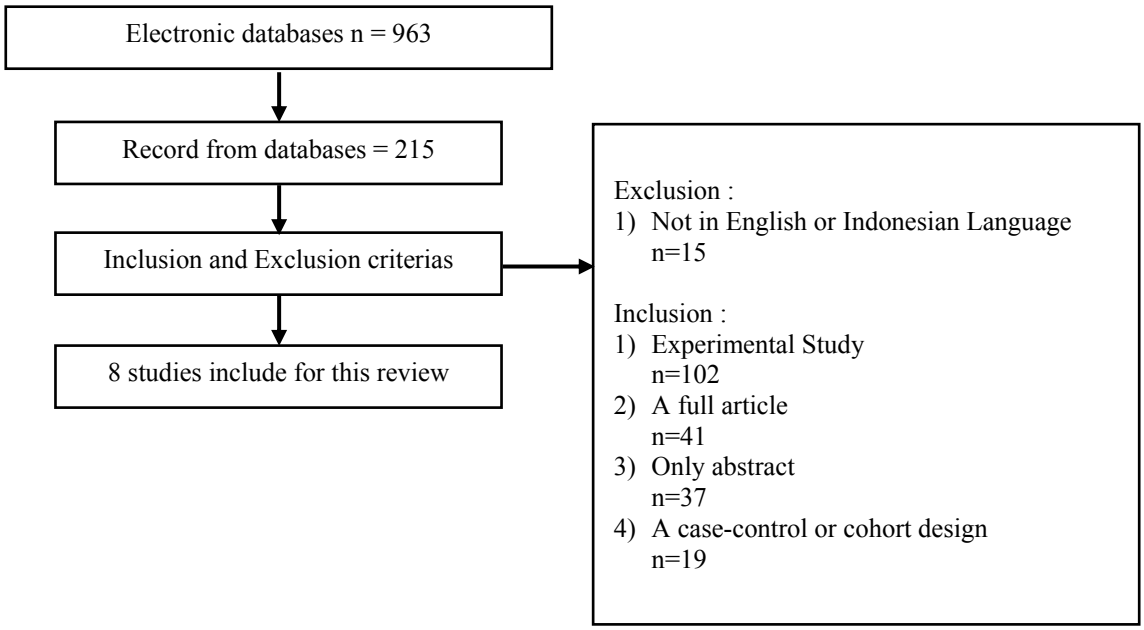
Seaweed as one of the natural resources has many potential bioactive ingredients (7). One of them is brown seaweed *(Phaeophyceae) which* shows the highest antioxidant activity among other seaweed (8). *Sargassum sp.* is a type of brown seaweed whose extraction is in the form of alginate. Alginate is a linear polysaccharide polymer composed of *α-L-guluronate* and *β-D-manuronate* (9). Several studies have been conducted in Indonesia(10), India (11), Hawaii (8), and Thailand (12) showing that extracts of *Sargassum sp.* have been widely used in various industries including the health industry as natural antioxidants.

METHODS

This literature review uses the prism protocol. The search for these articles was obtained from electronic databases namely *Science Direct, Springer, DOAJ, NCBI,* and *Google Scholar,* as well as other related sites. The articles taken are those that discuss brown seaweed, antioxidants and endothelial cells in preeclampsia. The types of articles taken are articles in the form of experimental studies in English and Indonesian which were published from 2009-2019. Article searches are conducted from January to April 2019.

In this literarure review, the criteria for the articles used are adjusted to the inclusion and exclusion criteria. The inclusion criteria are in the form of experimental studies and full articles. The exclusion criteria are studies that do not speak English or speak Indonesian. The article search results using key words antioxidants of Sargassum sp, preeclampsia and antioxidants, as well as antioxidants and endothelial cells. Based on these keywords found articles as many as 963. Of these, 215 articles were included in the inclusion and exclusion criteria. Thus, the final results obtained 8 articles that are suitable for this literature review.

Figure 1. Shows The Characteristics of The Inclusion And Exclusion Studies



RESULTS

From several articles that have been obtained, 5 articles have the same research method and it can be concluded that brown seaweed (Sargassum sp) has the characteristics and content of the active substance phenol compounds function as antioxidants in fighting free radicals in the body. (13) From the several articles that have been obtained, 5 articles have the same research method namely experimental, 3 other studies use metanalysis, randomized controlled trials, and a case-control study. From the 8 journals, it was stated that Brown seaweed (Sargassum sp) contains phenolic compounds which function as antioxidants in fighting free radicals and as protection against endothelial cells in preeclampsia

Table 1. The Characteristics of Research Studies

Authors	Title	Design	Variable	Result
Revathi Chitra S, Syed Ali M, Anuradha V, Shantha M, Yogananth. (14)	Antioxidant activity of polysaccharide from Sargassum sp	Experimental	polysaccharide from Sargassum sp	The obtained results give a significant IC50 Value which indicates that the isolated polysaccharide from the Sargassum sp is able to inhibit the free radicals and can be used to treat tumour cells.
Qifei Cong, Huanjun Chen, Wenfeng Liao Fei Xiao, Peipei Wang, Yin Qi, Qun Dong, Kan Ding. (15)	Structural characterization and effect on anti-angiogenic activity of a fucoidan from *Sargassum fusiforme*	Experimental	fucoidan from *Sargassum fusiforme*	These results suggest that the fucoidan FP08S2 from brown seaweeds *S. fusiforme* could be a potent anti-angiogenic agent.
Wi-Gyeong Gwon, Eun –Ji Joung, Mi-Sung Kwon, Su-Jin Lim, Tadanobu Utsuki, Hyeung-Rak Kim. (16)	Sargachromenol protects against vascular inflammation by preventing TNF-α-induced monocyte adhesion to primary endothelial cells via inhibition of NF-κB activation	Experimental	TNF-α-induced monocyte adhesion to primary endothelial cells via inhibition of NF-κB	These results indicate that SCM may have potential application as a therapeutic agent against vascular inflammation.
Ali Taravati, Fatemeh Tohidi. (17)	Comprehensive analysis of oxidative stress markers and antioxidants status in preeclampsia	Meta-analysis	nitric oxide, superoxide dismutase, glutathione, vitamin E and C was observed in preeclampsia women	In conclusion, it is hypothesized when oxidative stress is established, a protective response is induced by increasing some antioxidants. Further studies are warranted to investigate the role of dietary supplementation and genetic variation in women with different ethnicity.
M.B.Tenório, R.C.Ferreira, F.A.Moura, N.B.Bueno, M.O.F.Goulart, A.C.M.Oliveira. (18)	Oral antioxidant therapy for prevention and treatment of preeclampsia: Meta-analysis of randomized controlled trials	Randomized controlled trials	The antioxidants used in these studies were vitamins C and E, selenium, L-arginine, allicin, lycopene and coenzyme Q10	Antioxidant therapy has no effects in the prevention of preeclampsia but shows beneficial effects in intrauterine growth restriction, when used in the treatment of this condition.

Jacqueline M.Cohen PhD, Michael S.Kramer MD, MSc, Robert W. Platt PhD, Olga Basso PhD, Rhobert W. Evans PhD[f], Susan R. Kahn MD, MSc. (19)	The association between maternal antioxidant levels in midpregnancy and preeclampsia	Case-control study	Associations between antioxidant biomarkers and timing of onset (in weeks) by cox regression, with appropriate selection weights.	Most antioxidants are more strongly associated with early-onset preeclampsia, suggesting that oxidative stress may play a greater role in the pathophysiology of early-onset preeclampsia. Alternatively, reverse causality may explain this pattern. Lutein is associated with both early- and late-onset preeclampsia and may be a promising nutrient to consider in preeclampsia prevention trials, if this finding is corroborated.
James M.Roberts, Paul Speer. (20)	Antioxidant therapy to prevent preeclampsia	Experimental	Trials evaluating prophylactic aspirin and supplemental calcium from early pregnancy suggest that therapy before evident preeclampsia may be successful in selected populations	Antioxidants currently are being evaluated in several larger trials in the United States, Canada, Mexico, England, and in several developing nations. These studies should definitively establish the efficacy and safety of this therapy for the mother and fetus.
Mohamad Gazali, Nurjanah, Neviaty P. Zamani.(13)	The Exploration of Bioactive Compound to Brown Algae Sargassum sp. Agardh as Antioxidant from West of Aceh Coastal	Experimental	The test consisted of proximate analysis, active compound, total phenol, antioxidant activity of DPPH method and calculation of yield of extract.	The results showed the most dominant chemical composition consisted of ash content 52.74% and carbohydrate content 23.77%. The yield ethanol exstract 0.565%, ethyl acetate 0.420% and n-hexane 0.265%. total phenol ethanol extract 563,22 mg GAE / g, ethyl acetate extract 13.48 mg GAE / g, n-hexane extract 30.610 mg GAE/g. Activity of antioxidant ethanol extract IC50 239.51 mg/L, ethyl acetate extract 68,89 mg/L and n-hexan extract 148.16 mg/L. Sargassum sp. extract detected containing phenol, alkaloids and triterpenoids

DISCUSSION

Preeclampsia (PE) is a pregnancy disease that begins with an increase in blood pressure with proteinuria in pregnant women who have not previously experienced hypertension (21). This is indicated by an increase in blood pressure / 140/90 mmHg and the presence of proteinuria ≥ 300 mg / 24 hours or ≥ 1+ in the examination of dipstick in a random urine sample in pregnant women who have not previously experienced hypertension. (5) Preeclampsia (PE) is not a *"One Disease"* but involves all aspects of maternal, placental and fetal (5,22). While the etiology can be grouped into four main groups, namely genetic, immunological, nutritional and infectious, and interactions between them, supported by environmental factors (5,23). According to Sibai (2002) there are several theories adopted as the causes of preeclampsia to date are (5): Theory of placental vascularization abnormalities (abnormal trophoblast

invasion), theory of placental ischemia, free radicals, and endothelial dysfunction, theory of immunological intolerance between mother and fetus, cardiovascular adaptation/vasculopathy, theory inflammation, theory of nutritional deficiency, theory of genetic deficiency (21).

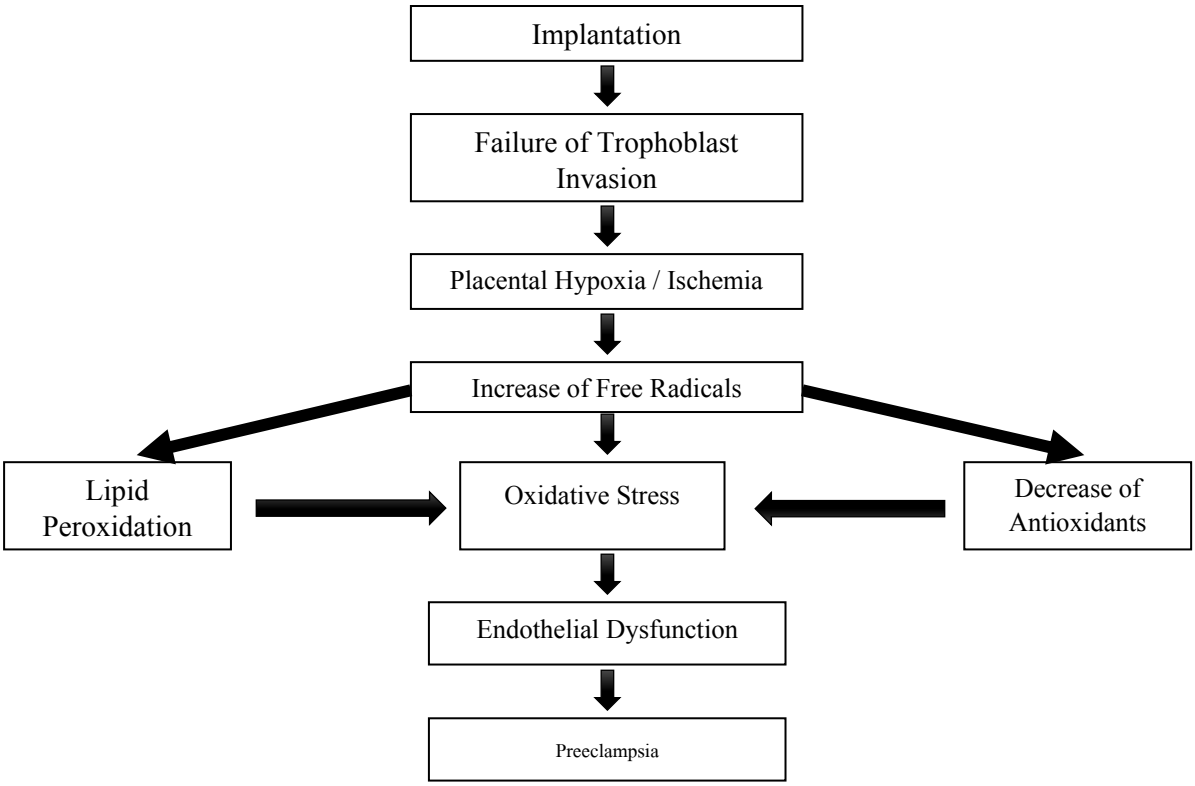
In PE, the presence of proteinuria is an objective sign, which shows extensive endothelial damage, a characteristic feature of the preeclampsia syndrome. Symptoms of PE can be lost or reduced after giving birth so that definitive therapy ends the pregnancy. Preeclampsia can threaten the health of the mother and the fetus it contains (3,22).

Oxidative stress in preeclampsia is caused by a state of hypoxia and placental ischemia. This increases the formation of free radicals that trigger lipid peroxidation processes and decrease endogenous antioxidants to reach oxidative stress state (4). Oxidative stress and endothelial activation can stimulate the release of IL-6 which can increase endothelial permeability and can reduce prostacyclin synthesis by inhibiting cyclooxygenase. As a result, there will be an increase in the thromboxane A2 / prostacyclin ratio, which is found in PE. The free radicals formed can also induce synthesis of IL-6 by the endothelium. Free radicals are involved in PE because they can produce endothelial tissue which reduces NO synthesis and prostaglandin production. Several studies have demonstrated that the presence of IL-6 or an increase in IL-6 can contribute to PE pathogenesis (3).

Free radicals are a group of chemicals in the form of atoms or molecules that have unpaired electrons in the outer layer or lose electrons so that when two free radicals meet, they can use together unpaired electrons to form covalent bonds (24). Biological molecules are basically nothing radical. If non-radical molecules meet with free radicals, a new radical molecule will be formed. It can be said, free radicals are unstable and always try to take electrons from surrounding molecules so that free radicals are toxic to biological molecules/cells that result in endothelial cell dysfunction (17). Free radicals can interfere with DNA production, the lipid layer in the cell wall, affect blood vessels, prostaglandin production, and other proteins such as enzymes contained in the body (25).

Endothelial dysfunction also causes increased vascular permeability resulting in edema and proteinuria. If endothelial dysfunction occurs when the endothelial surface will be expressed adhesion molecules, such as *vascular cell adhesion molecule-1* (VCAM-1), and *intercellular cell adhesion molecule-1* (ICAM-1) (26). Several studies report increasing levels of molecular vascular adhesion and E-selectin cells in the serum of preeclamptic patients (5). VCAM-1 level improvement in preeclamptic patients can be an indicator of endothelial cell activation and soluble adhesion molecules in the serum reflect concentrations of attachment to the endothelium. E-selectin is believed to be more specific than VCAM-1 because E-selectin can bind to initiate neutrophilic granulocytes.(27)

VCAM-1 is also found to be increasing in preeclampsia. VCAM-1 is found in activated cells, including activated endothelial cells. Because the pathological picture of preeclampsia is endothelial dysfunction, one source of circulating adhesion molecules in the endothelium. Increased expression of VCAM-1 reflects the adhesion molecule in the endothelial surface. The expression of VCAM-1 on endothelial cells is induced by IL-1β, IL-4, TNF-α, IFN-γ. Interestingly, IL-4 cytokines produced by the T lymphocyte subset, induce VCAM-1, mediates T-cell bonds in the endothelium without stimulating E-selectin or intracellular cell adhesion molecules that mediate their attachment. VCAM-1 mediates the adhesion of lymphocytes, monocytes, and eosinophils to activate endothelium through integrins (22,24).
Figure 2. Mechanism of the occurrence of preeclampsia (4)



Antioxidants are compounds that can delay, slow down and prevent the lipid oxidation process. In a special sense, antioxidants are substances that delay or prevent oxidation reactions from free radicals in lipid oxidation. Antioxidants are needed to prevent oxidative stress which plays an important role in the etiology of various degenerative diseases, one of which is preeclampsia. Based on the source, antioxidants can be divided into two types of antioxidants, namely enzymatic/endogenous antioxidants (in the body) and non-enzymatic/exogenous antioxidants consisting of natural antioxidants and synthetic antioxidants (28). Under normal circumstances, the human body has the ability to protect itself from oxidative stress, namely in the presence of enzymatic antioxidants. However, under certain conditions, an increase in oxidants and a decrease in antioxidants cannot be prevented, so the balance of oxidants/antioxidants shifts to oxidative conditions and oxidative stress is formed which can damage cells and trigger hypertension (5,29). This is evidenced by Rastini's research (2010) that antioxidant bioactive compounds and polyphenols can inhibit LDL oxidation so that NF-κβ activation expression does not occur, TNF-α protein expression, and ICAM-1 protein (30).

Many authentic Indonesian natural ingredients contain antioxidants with various active ingredients, including vitamins C, E, provitamin A, organosulfur, *α-tocopherol, flavonoids, thymoquinone,* statins, niacin, *phycocyanin,* and others. Various natural ingredients, both those that have long been used as daily food or have just been developed as food supplements, contain various antioxidants (25). Prevention of free radical damage to the human body can be done by producing endogenous antioxidants in the body's defense system. However, the antioxidant level is currently unable to fight free radicals that cause disease, one of which is due to the presence of oxidative stress, which requires additional exogenous antioxidants from outside the body. Based on the source of intake, exogenous antioxidants consist of natural antioxidants and synthetic antioxidants, but the safety of consuming synthetic antioxidants is currently uncertain, so it is necessary to look for sources of natural antioxidants. One source of natural antioxidants is brown seaweed that easy to find in Indonesia and economical price (13)

Flavonoids contained in natural ingredients are widely developed as natural antioxidants because they have great benefits. The presence of flavonoids with high antioxidant activity works as a free radical catcher that can be used to repair/restore vascular endothelial function and provide protection against endothelial cell dysfunction (27,31). The use of authentic Indonesian natural ingredients as antioxidants is needed to improve the quality of public health at a relatively affordable cost. Seaweed is a photosynthetic organism that is often exposed to sunlight and high oxygen, both of which are triggers of the formation of free radicals and strong oxidizing agents. Free radicals and oxidizers have the potential to change cell structure and function, but in reality, seaweed cells do not suffer damage. This phenomenon proves that seaweed has an anti-oxidative defense mechanism and contains antioxidant compounds (32).

Seaweed sargassum duplicated is a type of brown seaweed from Indonesia that has the potential as an antioxidant because it contains active substances such as fucoidan and phenolic components. The type of phenolic component that is often found in brown seaweed is phlorotannin which ranges from 0.74% to 5.06% (33). The results of the Sedjati (2017) proves that water filtrate from *Sargassum sp* has the highest antioxidant potential (32). Total phenolic from *Sargassum* sp has a positive correlation with antioxidant potential (34,35). Vijayabaskar, et al. (2012) also finds that brown *seaweed Sargassum swartzii* shows antioxidant activity. It is known that brown seaweed is a natural product that has no side effects, it is necessary to consider developing this formula in herbal medicine in the community.(13) The research is also supported by several other studies that seaweed contains compounds with relatively high antioxidants and anti-proliferation activity. Low-fat seaweed, but contains vitamins and bioactive compounds, such as terpenoids and sulfated polysaccharides, the latter of which are natural antioxidants that are potentially not found in land plants (36).

CONCLUSION

Increased free radicals in the body can trigger oxidative stress reactions which then result in damage to endothelial cells or endothelial cell dysfunction in preeclampsia. Oxidative stress is a condition of an imbalance between the number of free radicals available and the number of antioxidants in the body. Free radicals are compounds that contain one or more unpaired electrons in their orbitals, so they are highly reactive and able to oxidize the surrounding molecules. Therefore, antioxidants are needed to prevent oxidative stress. In addition, antioxidants are very easily oxidized, so free radicals will oxidize antioxidants and protect/protect other molecules in cells from damage caused by oxidation by free radicals or reactive oxygen (25).

Many antioxidants are found from natural ingredients on land and at sea. One of them is natural ingredients from the sea which are natural sources that are rich in antioxidants and other various active metabolites. Natural marine materials are capable of producing potential bioactive compounds for health so that they are attractive to be developed in the health industry as natural medicine. Seaweed which is a natural material from the sea is considered a biological source rich in active substances such as antioxidants, antiviral, anti-inflammatory, and anticoagulant agents (36). Higher antioxidant ability is found in *Sargassum wightii* (brown seaweed) which has greater phenolic constituents (37).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests..

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