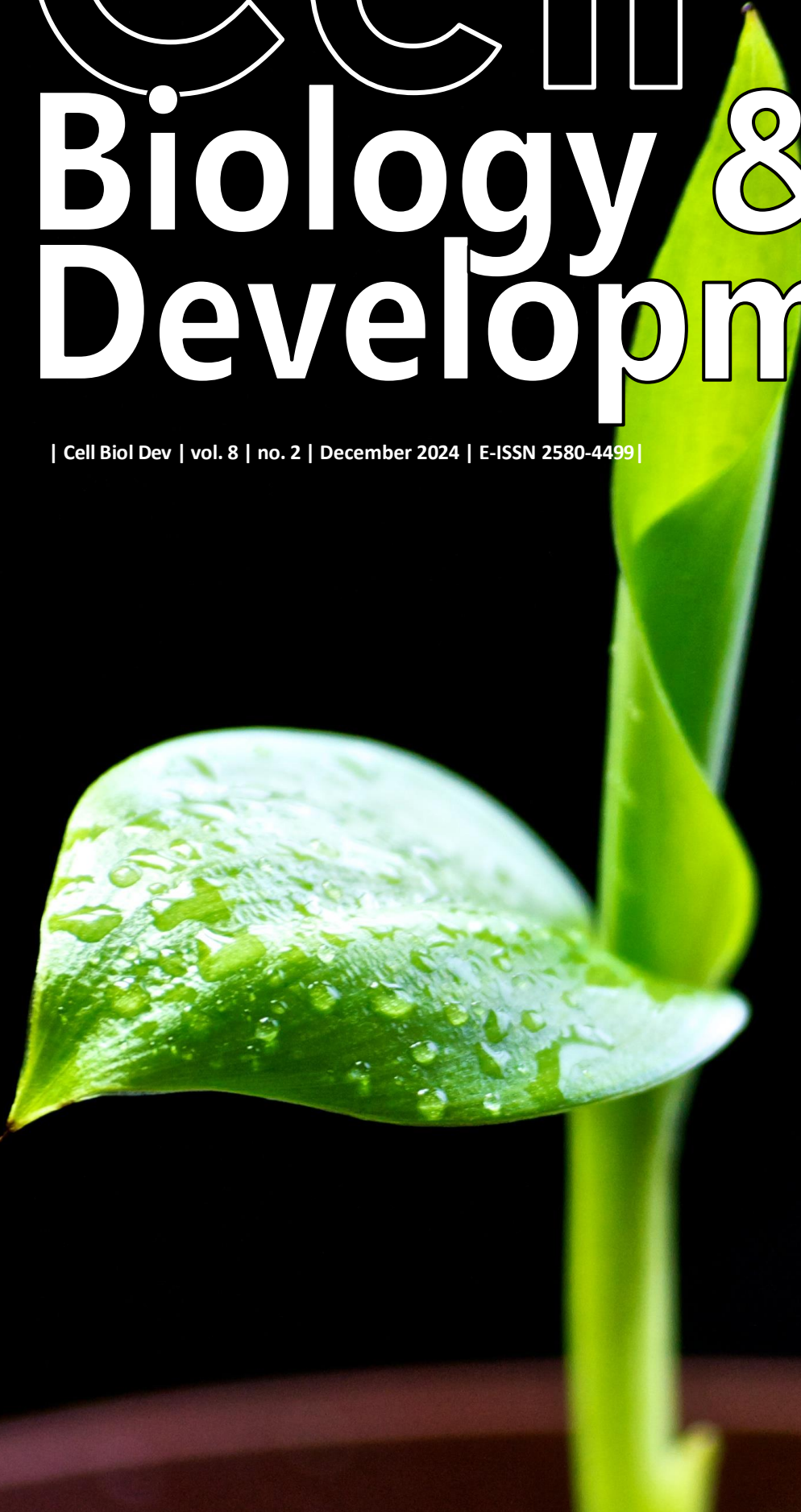


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-
- Effects of light-dark cycle and light-emitting diode (LED) colors on the behavioral and physiological responses of *Phodopus roborovskii*** 51-57
PRINCESS JELIAN S. FUERTES, AUBREY M. AQUINO, NADINE A. BALONES, JOI JANELLE L. PAJILA, MANUEL P. GRANADOZIN JR., SAMUEL C. BRILLO
- Review: Chemical profile and therapeutic potentials of golden sea cucumber (*Stichopus hermanii*)** 58-67
AHMAD ASFAR AULIA, ANGELA REGINA ASTUTI, ARDITA AYU WULANDARI, GILANG DWI NUGROHO, AHMAD DWI SETYAWAN
- Short Communication: Morpho-anatomical and histochemical characterization of four species of Cyperaceae in Rivers State, Nigeria** 68-74
MERCY GOSPEL AJURU, LAURETTA CHINWE-CHIKERE, ASIKIYE IBIYE, BLESSING OKOROMA ELEBACHI
- Review: Medicinal and pharmaceutical uses of skipjack tuna (*Katsuwonus pelamis* Linnaeus, 78)** 75-89
RAISA NOOR SAFIRA, AULIA SYAH HAFIFFAH, BRIGHIA SASTRANI NALURI ALLOBUA, ARUM NUR MUKARROMAH, AZKA DITA AULIA, DARLINA MD. NAIM, AHMAD DWI SETYAWAN
- Review: Bioactive compounds and health applications of *Digenea simplex* (Rhodophyta)** 90-108
AFFANDI FIRMAN SAPUTRA, ALIFIA NAMIRA UTOMO, AMIRA ZAHRA PRAMESTHI, ARDHIAN ABDUL MADJID, GILANG DWI NUGROHO, AHMAD DWI SETYAWAN



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Effects of light-dark cycle and light-emitting diode (LED) colors on the behavioral and physiological responses of *Phodopus roborovskii*

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Abstract. Fuertes PJS, Aquino AM, Balones NA, Pajila JLL, Granadozin Jr. MP, Brillo SC. 2024. Effects of light-dark cycle and light-emitting diode (LED) colors on the behavioral and physiological responses of *Phodopus roborovskii*. *Cell Biol Dev* 8: 51-57. The internal biological clocks regulate the 24-hour cycle of the circadian rhythm. Changes in the quantity or quality of light can disrupt the circadian rhythm as light influences the circadian clock synchronization, affecting the behavior and physiology of an organism. We determined the effects of different light-dark cycles and LED colors, specifically white, blue, and yellow, on the behavior and physiology of *P. roborovskii*. The test subjects were acclimated for one week. Five setups were utilized per LED color, particularly control (12L:12D) and treatment groups (24L:0D, 18L:6D, 6L:18D, 0L:24D). The amount of food intake (g), running wheel usage duration (min), sleep duration (min), and body weight (g) were recorded daily. Inferences regarding the melatonin and corticosterone levels were established from the behavioral assessment. The findings revealed a significant difference in sleep duration and running wheel usage. Results showed that white light at 18L:6D induced longer sleep duration, while blue light at 18L:6D resulted in shorter sleep duration. Moreover, blue light at 24L:0D promoted a longer duration of running wheel usage, whereas yellow light at 0L:24D impeded the use of the running wheel. Based on the behavioral data, it can be inferred that as melatonin levels increase throughout sleep onset, corticosterone levels decrease. Furthermore, there is no significant difference in the amount of food intake and body weight between the control and treatment groups. In conclusion, behavioral and physiological changes following light exposure were observed, disrupting the test subjects' circadian rhythm.

Keywords: Circadian rhythm, LED, light-dark cycle, *Phodopus roborovskii*

Abbreviations: LD cycle: Light-Dark cycle, LED: Light-Emitting Diode

INTRODUCTION

Biological clocks are internal mechanisms that regulate bodily processes, including circadian rhythms-24-hour cycles of mental, physical, and behavioral changes influenced by light and dark (National Institute of General Medical Sciences 2020; Rumanova et al. 2020). Specifically, the suprachiasmatic nucleus (SCN) houses the primary circadian pacemaker in mammals. The photoreceptors in their retina detect photic information. The information is then forwarded to the SCN through the retinohypothalamic tract. The SCN uses the data to synchronize the organism's circadian cycles with the environment (Alves-Simoes et al. 2015). Since light is the most crucial environmental aspect in synchronizing the circadian clock, some variations in exposure to and quality of light can disrupt circadian cycles, which could result in changes in the organism's body homeostasis, affecting everything from behavior to physiology. Bourgin and Hubbard (2016) mentioned that light can indirectly influence the behavior and physiology of mammals through body clock synchronization and the circadian cycle's phase adjustment.

Light can also directly affect organisms by stimulating sleep and alertness in nocturnal and diurnal species. The van der Merwe et al. (2019) study proved that the temporal pattern and light qualities affect rodents' daily locomotor activity. Furthermore, Roborovski dwarf hamsters have been used as experimental animals in biomedical research, especially in theriogenology, endocrinology, and circadian biology (Trimpert et al. 2020). Hamsters, like other rodents, can be valuable animal models in cancer research, infectious diseases, and behavioral studies. Additionally, they have fewer ethical and societal difficulties than when using larger mammals (Dutta and Sengupta 2019).

In the scientific review of Russart and Nelson (2018), it was mentioned that organisms' survival depends on their adaptation to their environment; hence, behavioral and physiological processes developed to correspond with light cycles to minimize the risks of survival and to optimize the accessible resources. Daily changes in the levels of light can be drastic and predictable, as are the behavioral and physiological functions in microorganisms, vertebrates, and invertebrates. As an exemplification in nocturnal rodents, studies show that the presence of light at night can disrupt the regular schedule of daily locomotor activities as well as

alter the timing of food intake to daylight. However, exposure to dim light reduces anxiety-like behaviors such as rearing up often and spending more time in the open. Presented in the following are further discoveries regarding the biological and physiological effects of light on rodents.

Lighting conditions, such as intensity, duration, and wavelength, can disrupt circadian rhythms of metabolism (Wren-Dail et al. 2016). Dauchy et al. (2016) found that rats exposed to blue-enriched LED light consumed less food and water and showed slower growth rates compared to those under standard cool white fluorescent (CWF) light. In contrast, studies by Dauchy et al. (2019) and Voros et al. (2021) reported higher food intake and weight gain in mice exposed to LED lighting versus CWF lighting, indicating that LED light influences dietary habits and body weight. Similarly, Allen et al. (2022) noted that male rats, regardless of the lighting type, consumed more food than females, though no significant weight differences were found between LED and CWF groups.

We assert that there is a need to identify the effects of variations of light-dark cycles and LED colors on organisms, i.e., mammals, because exposure to such has an indirect and direct impact on their behavioral and biological responses. The behavior change affects how they interact with their own and other species within the environment, which may pose disturbances if left unchecked. Therefore, we proposed a study that aims to identify the effects of the light-dark cycle and varying light colors on the circadian control of behavior and physiology of the Roborovski hamster (*P. roborovskii*).

MATERIALS AND METHODS

Ethical statement

In compliance with the Animal Welfare Act of 1998 (RA 8485) and Administrative Order No. 40 Series of 1999 on Rules and Regulation on the Conduct of Scientific Procedures Using Animals, we secured authorization from the Bureau of Animal Industry (BAI) and Department of Agriculture (DOA) prior the conduct of the study. Researchers also underwent a 3-day animal training under the supervision of the Research Institute for Tropical Medicine (RITM). A specially designed housing facility fit for the experiment's set conditions was provided by the De La Salle Araneta University (DLSAU) Veterinary Hospital and utilized during the research. The test subjects, healthy male species of *P. roborovskii*, were purchased from a BAI-accredited facility, MOTS Animal House. In adherence to the RA 8485 and AO No. 40 recommendations, we used carbon dioxide to euthanize the animals at the end of the study.

Research design

An experimental research design was used to assess the effects of the light-dark cycle and different LED colors on the behavioral and physiological responses of *P. roborovskii* and to determine whether there is a significant difference in these responses between the control and treatment groups. Actual experimentation with test subjects

exposed under control and experimental conditions was utilized to determine and establish the cause-and-effect relationship between the independent and dependent variables. Quantitative approaches and statistical techniques were employed to gather and analyze the data.

Test organisms

We used healthy individuals of *P. roborovskii* (n = 19; age, two months; weight, 19 to 25 g; all males), to observe its behavioral and physiological responses to varying light-dark cycles and colors of light. The same set was used to assess each LED color, given that a recovery phase was provided after every experiment.

Samples and sampling procedures

We purposely selected the subjects to form a homogenous population with the same characteristics. The test organisms were randomly grouped using a random wheel picker, with three subjects for the positive control group and four subjects for each treatment group. Specifically, the study population for this research is 19 male *P. roborovskii*, two months old, weighing 19 to 25 g. The sample size was made statistically valid by calculating the E value, which was equal to the total number of animals minus the total number of groups. To yield significant results, the value of E should be between 10 and 20 (Charan and Kantharia 2013). Computing for the E value provided $E=19-5=14$, within the acceptable limit.

Experimentation and data collection

The experiment was conducted at De La Salle Araneta University-Veterinary Hospital, Philippines which was suitable for the set conditions of the experiment. Five experimental setups were used to demonstrate the effects of varying light-dark cycles and different LED colors on the behavioral and physiological responses of *P. Roborovskii*. The experimental setups for each light color, specifically white, blue, and yellow, consisted of 24L:0D, 6L:18D, 12L:12D, 18L:6D, and 0L:24D light-dark cycle periods.

Acclimation

Hamsters were randomly divided into five groups, each with four males, except the 12L:12D standard cycle, which only had three. Each hamster was housed individually in a transparent polypropylene cage with a size of 11.38 × 6.5 inches and, by the minimum enclosure size for laboratory hamsters with a constant ambient temperature of $25.0 \pm 1.0^\circ\text{C}$ and relative humidity at 60% (Housing and Husbandry: Hamster | NC3Rs, 2021). Food (Vitakraft Premium Menu Vital food for hamsters) and water were always available ad libitum. All hamsters were allowed for a one-week acclimation period. They were subjected to a standard light-dark cycle (LD; 12 hours light/12 hours dark) for one (1) week before exposure to treatments of varying light-dark cycles. The light source was installed about 22 inches from the cages. Lighting was provided with a white light-emitting diode (LED), which is currently preferred due to its energy efficiency (Emmer et al. 2018; Dauchy et al. 2016).

Light treatment

To determine the effect of varying light-dark cycles and LED colors on the behavior and physiology of *P. roborovskii*, shelves with installed segments of LED strip lights were used as chambers to expose the hamsters under 400-450 lx of light intensity. Table 1 shows the light-dark cycle schedules introduced to *P. roborovskii* individuals. Following the acclimation period, each setup had four (4) hamsters subjected to 24L:0D, 6L:18D, 18L:6D, and 0L:24D cycles except 12L:12D cycle with three (3) hamsters. They were exposed to designated LED colors per week, specifically white, blue, and yellow, respectively, with an allotted 5-day recovery period after each exposure.

Positive control

Each of the four randomly assigned hamsters was subjected to 24L:0D, 6L:18D, 18L:6D, and 0L:24D cycle treatment, whereas the remaining three subjects were exposed to a 12L:12D standard cycle. The latter is needed to validate the experimental procedures.

Table 1. Light-dark cycles introduced to *P. roborovskii*

Code	Light/Dark (L/D) cycle	Light Period	Dark Period
A	24L:0D	7:00AM-7:00AM	-
B	6L:18D	7:00AM-1:00PM	1:00PM-7:00AM
C	12L:12D	7:00AM-7:00PM	7:00PM-7:00AM
D	18L:6D	7:00AM-1:00AM	1:00AM-7:00AM
E	0L:24D	-	7:00AM-7:00AM

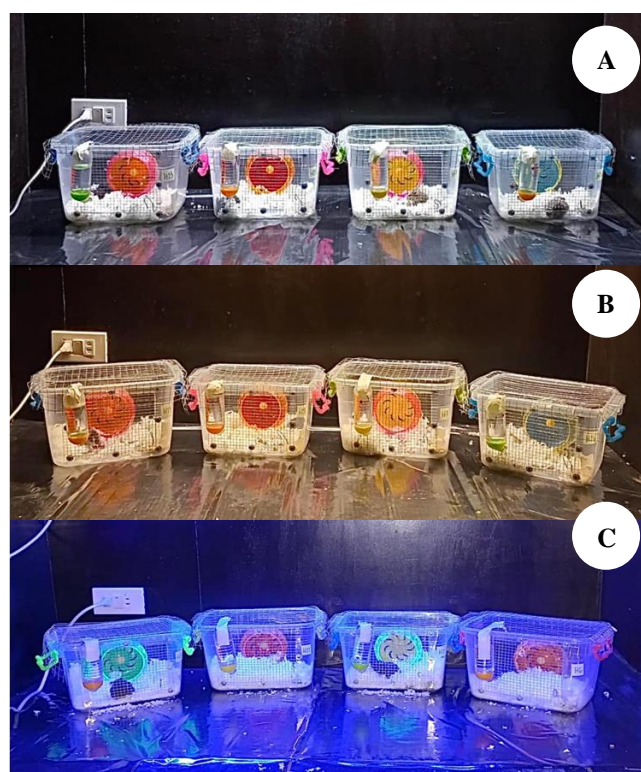


Figure 1. Experimental setups. A. White LED setup; B. Blue LED setup; C. Yellow LED setup

Behavioral testing

To accurately record the behavior of *P. roborovskii*, we used a closed-circuit television (CCTV) located 1.25 to 1.5 m away from the cages. This video trapping enabled us to observe locomotor activity, sleeping behavior, and feeding habits. Moreover, the behavioral responses were assessed daily. Regarding feeding behavior, the hamsters were given 8 g of food, with water provided ad libitum, following their daily food and water consumption based on the guidelines from McGill University Health Centre Research Institute - Laboratory Animal Biotechnology Workshop (2020). Food was provided at night (18:00) daily. To evaluate the amount of food intake, the difference between the allotted and leftover food mass (g) was calculated (Le Tallec et al. 2015).

To evaluate the effects of various lighting conditions on the locomotor activity of hamsters, the individual cages were equipped with running wheels. Based on the camera recordings, the time spent utilizing the running wheel was calculated and expressed in minutes (Bakeche et al. 2021). The usage of running wheels was defined as the time of occurrence of the first use of a running wheel (LA_{onset}) and the time of occurrence of the last use of the running wheel (LA_{offset}) (Le Tallec et al. 2015). The video recordings of sleeping behavior were analyzed to determine their sleeping duration. Additionally, time spent while sleeping was calculated and expressed in minutes (Bakeche et al. 2021).

Physiological testing

To evaluate the effects of varying light-dark cycles and LED colors on the physiology of *P. roborovskii*, we measured the body weight of hamsters to examine the effects on the feeding behavior. The body weight of each hamster was measured and recorded daily during the nocturnal phase.

In addition to the measurement of body weight, inferences regarding the levels of corticosterone and melatonin levels were established from the behavioral data. This is to determine the influence of light in association with variations in hormone levels. The investigation was followed by a recovery phase at the end of the week before conducting the same setups with a different light color.

Statistical analysis

Behavioral testing results: (i) amount of food intake, (ii) duration of running wheel usage, and (iii) sleep duration, and physiological testing results: (iv) body weight were analyzed with one-way ANOVA to determine the statistical difference among varying LD cycles at each of the LED color exposure. The data were represented as means \pm SEM with statistical significance established at P-values of <0.05 . A Post hoc test, particularly Dunnett's t-test, was used to determine which group was statistically significant or insignificant. The above statistical analyses were performed using Statistical Package for the Social Sciences (SPSS).

RESULTS AND DISCUSSION

Fonken et al. (2010) stated that light is the most potent entraining signal for the circadian clock. It is considered the most crucial environmental aspect in its synchronization; thereby, variations in the exposure and quality result in changes in the behavior and physiology of living things. Emmer et al. (2018) maintained that light influences the behavior and physiology of laboratory animals, emphasizing that light-dark cycle disruption disturbs biological rhythms resulting in widespread physiological consequences.

Behavioral responses

Food intake

As seen in Figure 2.A, the highest amount of food intake can be observed under white, yellow, and blue colors in 24L:0D, 6L:18D, 18L:6D, and 12L:12D and 0L:24D setups, respectively. On the other hand, the lowest amount of food intake can be correspondingly noted under

blue and white colors in 24L:0D and 6L:18D, and 12L:12D, 18L:6 D, and 0L:24D setups. There is no significant difference in the average food intake of the subjects between the control and treatment setups (Table 2). This result is similar to Fonken et al. (2010), indicating no significant difference in the total 24-hour food consumption among the groups of mice. From our study, the mean food intake of the test organisms is approximately 2.29 to 3.08, which is within the average daily food consumption of hamsters (Kolynchuk 2015). This is supported by the research conducted by Rouibate et al. (2020), which showed that although there was an increase in food intake under experimental conditions compared to the control group, no statistically significant differences were observed between the groups. López-Espinoza et al. (2021) also produced the same results, depicting no significant differences in the total food consumption in any of the setups and thereby suggesting that the light-dark conditions did not influence the ability of the subjects to maintain the balanced intake.

Table 2. Behavioral responses under different LED colors via one-way ANOVA

LED Exposure	Food intake	Locomotor activity	Sleep duration	Body weight
White LED	0.068	3.949*	4.154*	0.851
Blue LED	0.456	4.988*	12.705*	0.528
Yellow LED	0.320	4.320*	13.572*	0.605

Note: F^P-value; significance level at $P \leq 0.05$ (95%)

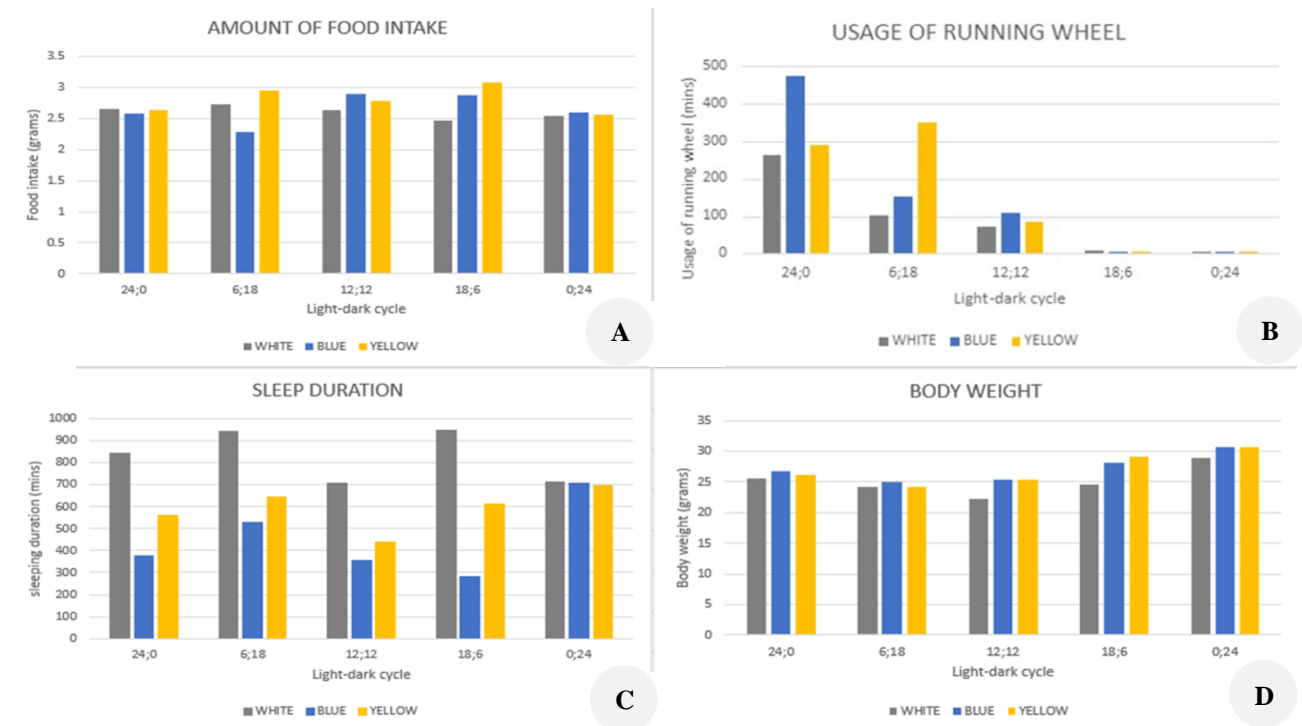


Figure 2. A-C. Mean amount of behavioral, and D. physiological responses measured in this study. A. Food intake; B. Usage of running wheel (locomotor activity); C. Sleep duration; D. Body weight in different light-dark cycles under white, blue, and yellow LED

Table 3. Dunnett's T-test post-hoc analysis results for locomotor activity under blue LED color

LED Exposure	Treatment	Pair	P-value	Interpretation
Blue LED	12L:12D	0L:24D	.830	Not significant
		18L:6D	.835	Not significant
		24L:0D	.045	Significant
		6L:18D	.989	Not significant

Table 4. Dunnett's T-test post-hoc analysis results for sleep duration under the different LED colors

LED Exposure	Treatment	Pair	P-value	Interpretation
White LED	12:12D	0L:24D	1.000	Not Significant
		18L:6D	.044	Significant
		24L:0D	.346	Not Significant
		6L:18D	.048	Significant
Blue LED	12L:12D	0L:24D	<.001	Significant
		18L:6D	.654	Not Significant
		24L:0D	.997	Not Significant
		6L:18D	.107	Not Significant
Yellow LED	12L:12D	0L:24D	<.001	Significant
		18L:6D	<.001	Significant
		24L:0D	.070	Not Significant
		6L:18D	.003	Not Significant

Locomotor activity

It can be observed from Figure 2.B that the highest duration of using the running wheel is depicted under blue, yellow, and white colors in 24L:0D, 12L:12D, and 0L:24D, 6L:18D, and 18L:6D setups, respectively. However, the lowest duration can be distinguished under white and yellow light exposure in 24L:0D, 6L:18D, 12L:12D, and 18L:6D and 0L:24D setups.

Table 2 shows that there is a significant difference in the locomotor activity of the test subjects exposed to white, blue, and yellow LED color, consecutively. There is no significant difference between the control and treatment groups in white and yellow LED colors. However, significant differences were observed among the treatment groups (0L:24D vs. 24L:0D; 18L:6D vs. 24L:0D; 24L:0D vs. 0L:24D; and 24L:0D vs 18L:6D). Table 3 shows that there is a significant difference between the 12L:12D and 24L:0D cycle setups in blue LED color. Overall, LED color and the light cycle duration both play a key role in affecting the locomotor activity of the test subjects, with certain cycle setups, especially continuous light or darkness, driving significant behavioral changes. In the study of Ferraro (2008), exposure of hamsters to constant light produced significantly and similarly longer free-running periods of the locomotor activity rhythm than the exposure of animals to constant dark. In a similar study, Van der Merwe et al. (2019) claimed that the degree of activity on nocturnal rodents is lowest under blue light during the daytime and is active at night. Furthermore, Alaasam et al. (2021) found that artificial light at night (ALAN) was sufficient to disturb nocturnal rest and increase nocturnal locomotor behavior.

Sleep duration

Figure 2.C depicts the average sleep duration for each light-dark cycle under white, blue, and yellow LED exposures. The highest sleep duration can be observed under white color in 18L:6D, 6L:18D, 24L:0D, 0L:24D, and 12L:12D cycles, respectively. On the contrary, the lowest sleeping duration can be seen under blue and yellow in 12L:12D, 18L:6D, 24L:0D, 6L:18D, and 0L:24D, respectively. Based on the findings in Table 4, the P-value resulted in 0.020, <0.001, and <0.001, showing a significant difference in the sleep duration of the subjects between the control and treatment groups under white, blue, and yellow LED color, consecutively.

Table 4 shows a significant difference between the 12L:12D cycle and 18L:6D and 6L:18D cycle setups in white LED color. Additionally, a significant difference in blue LED color can be seen between the 12L:12D and 0L:24D cycle setups. There are also significant differences between the three treatment groups, specifically the 0L:24D, 18L:6D, and 6L:18D cycles, and the positive control group of yellow LED color, which is the 12L:12D cycle setup. This suggests that the lighting cycles have an impact on the sleep duration across different LED colors. These results are supported by the study conducted by Fisk et al. (2018), delineating that the effects of prolonged exposure to white light on nocturnal rodents promote sleep while total darkness results in increased wakefulness. In a similar study conducted by Pilorz et al. (2016), the exposure of mice to blue color showed a significant difference between control and treatment setups. There was an observed delay in the sleep induction of the test subjects when they were exposed to blue light.

Physiological responses

Body weight

Figure 2.D exhibits each light-dark cycle's mean or average body weight subjected to white, blue, and yellow LED colors. The highest body weight was recorded under blue and yellow light colors in 24L:0D and 6L:18D, and 12L:12D and 18L:6D, correspondingly. The lowest body weight was perceived under white light color on all the LD cycles except 6L:18D but with only minimal difference. It can also be noted that in the 0L:24D cycle, blue and yellow light colors attained the same average body weight.

As presented in Table 4, there is no significant difference in the body weight of the Roborovski dwarf hamsters between the control and treatment groups under white, yellow, and blue LED color setup. This result was sustained by Dauchy et al. (2015), who conducted research on Sprague Dawley rats, who were consistently exposed to bright light for 6 to 10 weeks. The study's findings suggest no noticeable alteration in the body weight of the rats because of the light exposure. Unlike our study, Fonken et al. (2010) discovered that subjecting the mice to dim light and bright light increases the body weight and food consumption, in contrast to the standard LD cycle. As opposed, Rouibate et al. (2020) demonstrated that the disruption of the LD cycle affects the metabolism of the rodents characterized by the decrease in body weight of the control and treatment organisms, with a greater decrease in

the latter, as food intake also decreases. In addition, the study of Zhang et al. (2015) concluded that short photoperiods in *P. roborovskii* led to decreased body mass compared to other long day photoperiods. As different factors may contribute to the body weight of animals, we should take into account other factors that led to varying body weights in our study, given a controlled setup to each animal aside from LED and light-dark cycles.

Melatonin and corticosterone levels

It has been stated that light is the most significant stimulus for the circadian clock. In particular, the light:dark (LD) cycle provides a cue that entrains individual clocks in the suprachiasmatic nucleus (SCN), the brain's central pacemaker, which regulates circadian rhythms and physiology, including humoral outputs. The most well-known circadian humoral outputs are melatonin and corticosterone. Thus, exposure to external lighting cues, depending on their intensity, duration, and wavelength, influences the release and suppression of these hormones. (Rumanova et al. 2020; Meléndez-Fernández et al. 2023).

According to Emmer et al. (2018), light-dark cycle disruption disturbs the biological rhythms of living organisms, inducing widespread physiological consequences. Physiological responses, such as melatonin and corticosterone secretion, are essentially coordinated by exposure to different light-dark conditions. Melatonin, sometimes called the sleep hormone, is an internal zeitgeber responsible for providing information concerning the length of the night (Rumanova et al. 2020). Moreover, melatonin is an important aspect of the circadian rhythm (Meléndez-Fernández et al. 2023).

Based on the findings from the behavioral data, it can be inferred that the melatonin levels increased as characterized by the longest sleep duration of the test subjects from the 18L:6D cycle setup under white LED, indicating that exposure to blue light delays melatonin secretion, increasing the alertness and wakefulness of the subjects. Meanwhile, the 0L:24D cycle setup exhibited longer sleep duration under blue and yellow LEDs. This confirms the results of Farhadi et al. (2016) that high plasma melatonin levels result from prolonged exposure to darkness. In contrast, it was established that continuous light exposure does not affect melatonin levels. These findings are evident in Table 4.

Several studies also implicated the relationship of corticosterone levels to the circadian rhythm of behavior. Pilorz et al. (2016) maintained that light exposure increases plasma corticosterone levels in laboratory rodents, influencing sleep duration and locomotor activity. Regarding the duration of sleep, Balbo et al. (2010) highlighted that sleep onset exerts an inhibitory effect on cortisol secretion while awakenings and sleep offset are accompanied by cortisol stimulation. Based on the findings of the study, as shown in Figure 2, an inversely proportional relationship between locomotor activity and sleeping behavior can be established. Concerning this, it can be inferred that as melatonin increases during sleep onset, the corticosterone level decreases. Results revealed that the 24L:0D setup exhibited the highest recorded

locomotor activity under the blue LED. On the other hand, the 0L:24D setup demonstrated the lowest recorded locomotor activity under the yellow LED color. Contrastingly, the sleep duration of the setups under these light conditions was correspondingly lower and higher.

In conclusion, this study investigated the effects of varying light-dark cycles and LED light colors on the circadian control of behavior and physiology in *Phodopus roborovskii*. Statistically significant differences were observed in sleep duration and locomotor activity across different light-dark setups and LED colors, indicating that light exposure disrupts circadian rhythms. Specifically, blue LED light delayed melatonin secretion, reducing sleep duration and increasing locomotor activity, while prolonged darkness elevated melatonin levels, promoting longer sleep durations. Conversely, no significant differences were found in food intake and body weight between control and treatment groups, suggesting that these variables were less sensitive to changes in light conditions. The findings highlight the critical role of LED color and light cycle duration in regulating circadian behaviors, with continuous light or darkness causing notable disruptions. Behavioral data further inferred changes in melatonin and corticosterone levels, emphasizing the physiological implications of altered light exposure. While the 7-day experimental period yielded valuable insights, future studies should extend the exposure duration, explore additional biological parameters, and investigate the interplay between behavior and hormonal changes to better understand the circadian regulation in *P. roborovskii* under varying photoperiods and light wavelengths.

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Review: Chemical profiles and therapeutic potentials of golden sea cucumber (*Stichopus hermanii*)

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Abstract. Aulia AA, Astuti AR, Wulandari AA, Nugroho GD, Setyawan AD. 2024. Review: Chemical profiles and therapeutic potentials of golden sea cucumber (*Stichopus hermanii*). *Cell Biol Dev* 8: 58-67. The golden sea cucumber (*Stichopus hermanii*) is a species of sea cucumber that has a unique chemical profile and significant therapeutic potential. Traditionally, sea cucumbers have been used in medicine in Southeast Asia for their properties which include anti-inflammatory, antioxidant and antimicrobial properties. The distribution of golden sea cucumbers is dominant in Southeast Asia and Northern Australia, but their populations are threatened due to excessive fishing. Conservation efforts through cultivation are being developed to restore wild stocks. This research aims to determine the hidden chemical profile and therapeutic potential of the golden sea cucumber by collecting information from various literature. Golden sea cucumbers have many chemical profiles, namely protein, saponin, triterpenoid, collagen, GAGs, flavonoid, mineral, glutathione, alkaloid, methanol, and hyaluronic acid. This species also have great potential as therapeutic agents, such as wound healing, antifungal properties, hipertriglyceridemia, hypercholesterolemia, diabetes, bone and tooth regeneration. This research brings various data that showed the importance of golden sea cucumbers in the field of health, such as the ability to increase insulin sensitivity, which is beneficial in the treatment of diabetes. Additionally, the high protein content in sea cucumbers provides additional nutritional value and supports antioxidant function. An in-depth understanding of the chemical composition and therapeutic benefits of golden sea cucumbers can encourage the development of biomedical products and support the economic well-being of coastal communities that depend on this resource. Therefore, conservation measures for this species must continue to be carried out so that it remains sustainable in nature and can be used wisely by humans.

Keywords: Chemical profile, golden sea cucumber, therapeutic potential

INTRODUCTION

The golden sea cucumber (*Stichopus hermanii* Semper, 1868) is a species of sea cucumber that has garnered attention in the health and medical fields due to its unique chemical profile and significant therapeutic potential. Research shows that the population of the golden sea cucumber has significantly declined due to overfishing and ineffective fisheries management (Brown et al. 2022). Conservation and restocking efforts through aquaculture are being developed to help restore wild stocks. Sea cucumbers also serve as a primary source of income for millions of small-scale fishers worldwide (Baker-Médard and Ohl 2019). However, sea cucumbers have become a premium product with high prices in international markets. Consequently, their exploitation has been excessive, disrupting their sustainability (Pangkey et al. 2012). Traditionally, sea cucumbers have been used in Southeast Asian medicine for their anti-inflammatory, antioxidant, and antimicrobial properties. Recent research has revealed the scientific basis behind these traditional claims,

highlighting that the bioactive components in sea cucumbers are promising as therapeutic agents. One of the key components in *S. hermanii* is Glycosaminoglycans (GAGs), which have anti-inflammatory activity and play a role in immune system modulation (Mulawarmanti et al. 2022). GAGs also contribute to wound healing and tissue regeneration, explaining their traditional use in wound care (Mondol et al. 2017). Additionally, the golden sea cucumber contains glycosaminoglycans such as heparan sulfate and chondroitin sulfate, which can benefit the wound healing process (Arundina et al. 2015).

Besides GAGs, this sea cucumber is also rich in other bioactive compounds like saponins, which exhibit anticancer activity (Wargasetia 2018). Research on saponins in *S. hermanii* has shown that these compounds can induce apoptosis, a process of programmed cell death crucial for cancer control. Sea cucumbers contain various bioactive compounds, including phenolics, polysaccharides, proteins (collagen and peptides), carotenoids, and saponins, which exhibit strong antioxidant activity and other therapeutic benefits (Hossain et al. 2022).

The fatty acids in sea cucumbers are known to have anti-inflammatory activity that can help manage chronic inflammatory conditions (Escobar-Sánchez et al. 2015). The high protein content in sea cucumbers provides additional nutritional value, with antioxidant activity that protects against oxidative damage and prevents degenerative diseases like Alzheimer's and Parkinson's (Shan et al. 2011). Sea cucumber extracts have shown antimicrobial properties effective against pathogens, including bacteria and fungi, presenting opportunities for natural antibiotics (Mnif et al. 2011). The golden sea cucumber is a natural marine biota containing proteins and active ingredients that function as antibacterial, anti-inflammatory, and antioxidant agents (Mulawarmanti et al. 2022). Extracts of *S. hermanii* can reduce hyphae count, neutrophils, and TNF- α levels through hyphae, neutrophils, and TNF- α pathways (Yudo et al. 2022). *S. hermanii* extracts contain antioxidants proven to alleviate oxidative stress conditions (Prawitasari et al. 2019). Furthermore, this sea cucumber has potential in diabetes treatment, with bioactive compounds that enhance insulin sensitivity and lower blood glucose levels (Oh et al. 2017). Research findings indicate that sea cucumbers can be developed as functional food products to help combat the onset of diabetes and its complications (Rahmadani 2023). The ability of sea cucumbers to produce bioactive metabolites stems from their response to various ecological pressures and predation avoidance (Telahigue et al. 2020). Sea cucumbers contain various bioactive compounds, including saponins and glycosaminoglycans, associated with their therapeutic properties (Bordbar et al. 2011). Sea cucumber aquaculture is an effective way to meet consumer demand and restore its resources (Ma et al. 2022). These findings suggest that adding sea cucumber polysaccharides or their low molecular weight derivatives to Baijiu has the potential to mitigate alcohol-induced liver damage (Song et al. 2024).

Overall, these marine-derived bioactive peptides have the ability to promote cell proliferation and can be further explored as cell growth-promoting agents for biomedical and bioprocess applications (Pilus et al. 2022). This research aims to determine the hidden chemical profile and therapeutic potential of the golden sea cucumber by collecting information from various literature. The literature review used search engines such as PubMed, Wiley, and Google Scholar with specific keywords. A total more than 100 articles were then selected and excluded. This research is motivated by the lack of unified data on chemical profile and therapeutic potential of the benefits of *S. hermanii*.

Stichopus hermanii

S. hermanii, commonly known as the golden sea cucumber, is named for its cucumber-like shape (Figure 1). *S. hermanii* belongs to the Phylum Echinodermata, Subphylum Echinozoa, and Class Holothuroidea. The golden sea cucumber sustains its life in the food chain by consuming organic matter in the sand, plankton, bacteria,

and aquatic organisms as supplements. Currently, the number of golden sea cucumber species has reached 2000 species with a wide area and distribution (Setiyowati et al. 2016).

S. hermanii is an invertebrate animal with spiny skin, forming a cylindrical and elongated shape. The spines on its skin are small and spread across the epidermal layer, visible under a microscope. Generally, the length of the golden sea cucumber ranges from 2.54 to 90 cm (Hartati et al. 2015). On the anterior part of its body, there is a mouth equipped with tentacles for capturing food, while the posterior part has an anus. According to Hartati et al. (2015), the identification of *S. hermanii* or golden sea cucumber reveals that this species has a trapezoidal or rectangular cross-section and is relatively large in size. The integument is smooth, with folds on the surface and structured papillae spread on both dorsolateral sides. The dorsal side is yellowish-brown with blackish papillae or wart-like protrusions.

The primary habitats of sea cucumbers are coral reefs and seagrass beds. Generally, the golden sea cucumber lives in coastal waters at depths of 1-40 meters. The golden sea cucumber thrives in waters with salinity levels between 30‰ and 33‰, with a seabed of fine sand and protective plants against wave action, such as detritus (decayed algae). In Indonesia, the distribution of the golden sea cucumber can be found in East Java, Madura, Sumba, Bali, Aceh, Lombok, Bangka, and Bengkulu (Pringgengies et al. 2018). The distribution spread across the world can be seen in the Figure 2.

The distribution of *S. hermanii*, marked with yellow-orange dots on a world map, showed a predominant presence in Southeast Asia and Northern Australia, indicating a preference for warm tropical waters (Figure 2). Their presence in East Africa confirms the global range of this species, which may be influenced by international trade. This information is crucial for ecological studies, conservation efforts, and the development of sustainable aquaculture, providing insights into marine ecosystem health and the role of sea cucumbers in bioturbation. Therefore, understanding this distribution can aid in conservation efforts and in selecting suitable aquaculture locations that match the natural conditions of the golden sea cucumber.



Figure 1. *Stichopus hermanii* (inaturalist.org)

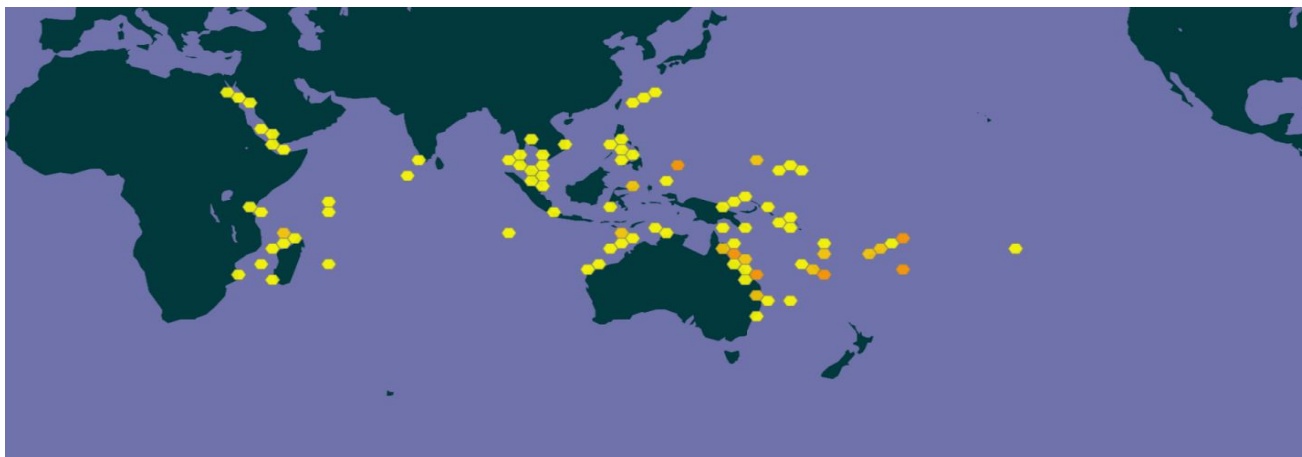


Figure 2. Distribution of golden sea cucumber in the world in 2024 (gbif.org). Note: The more orange the color indicates that the species' presence coordinate points are more numerous and dense in that area

CHEMICAL PROFILES

Protein

S. hermanii contains various beneficial components, one of which is protein (Table 1). The protein in this species is highly beneficial for the body (Prameswari et al. 2020; Safithri et al. 2022a; Taurina and Andrie 2022). The protein content in the golden sea cucumber reaches 86%, which is easily soluble in pepsin enzyme (Rasyid 2018). The golden sea cucumber is considered a marine animal rich in protein and low in lipids, with a large amount of sulfated glycosaminoglycans (De Fretes et al. 2020). Due to its beneficial proteins, the sea cucumber is also known to be used as medicine and is very effective in healing various diseases. It can help with anti-inflammatory, antiviral, and antioxidant processes (Oktaviani et al. 2018; Yatmasari et al. 2021; Rusmini et al. 2023), antimicrobial (Pringgenies et al. 2018), prevent blood clotting, prevent arthritis, accelerate wound healing, serve as a high-protein food source, boost the immune system, combat fatigue, and prevent cancer (Nurwidodo et al. 2018; Rusmini et al. 2023).

Saponin

S. hermanii is known to contain various bioactive compounds, including saponins (Zhafira 2016; Wang and Wang 2017; Pringgenies et al. 2018; Windari et al. 2019; Prameswari et al. 2020; Setianingsih et al. 2020; Monika et al. 2021; Adam et al. 2023a). Initially discovered in sea cucumbers, saponins are classified as holothurins, identified for their broad spectrum of physiological activities. Saponins in *S. hermanii* are found in the skin, flesh, and tubular Cuvierian organs. These high concentrations of saponins act as a defense mechanism against predators and serve as antimicrobial agents. Pure sea cucumber extract tends to contain holotoxins, which exhibit effects similar to antimycin at doses of 6.25-25 µg/mL (Pringgenies et al. 2018). The saponins in golden sea cucumbers stimulate cell regeneration and possess high antioxidant content. Additionally, saponins provide antibacterial functions (Cushnie et al. 2014; Irfan et al.

2014). Safithri et al. (2020b) highlighted that *S. hermanii* contains triterpene glycosides, known antioxidants that can improve hyperlipidemia and hyperglycemia conditions in tested animals like rats. Saponins act as antibacterial agents by breaking down cytoplasmic membranes and killing cells (Cankaya and Somuncuoglu 2021). The antioxidant activity in *S. hermanii* derives from compounds like riboflavin, flavonoids, saponins, tannins, and omega-3. Saponins are a primary component of the antimicrobial properties in *S. hermanii* (Pringgenies 2013).

Triterpenoid

S. hermanii contains triterpenoids that function as antibacterial agents (Cushnie et al. 2014; Irfan et al. 2014). This species has various triterpenoids, particularly holostane types, which possess significant biological activities. Akerina and Sangaji (2019) reinforced that many marine organisms with triterpenoids benefit the body by providing antibacterial, antifungal, and anticancer properties. Zhafira (2016) also confirmed that *S. hermanii* contains triterpenoids, which can reduce blood cholesterol, Low-Density Lipoprotein (LDL), and Triacylglycerol (TAG) levels. Triterpenoids enhance antioxidant functions in plasma and serum, reducing DNA damage, inflammation, and oxidative stress (Han and Bakovic 2015). Testing triterpenoids involves dissolving extracts in 0.5 mL chloroform, adding 0.5 mL acetic anhydride, and 2 mL H₂SO₄ (Anggraeni et al. 2014).

Collagen

All animals contain collagen, a structural protein component in bones, tendons, skin, blood vessels, and the cornea (Marks et al. 2014). Collagen has antioxidant properties and can inhibit tyrosinase activity in melanogenesis. Sea cucumbers are an alternative source of collagen (Safithri et al. 2018). According to Sari et al. (2017) and Siahaan (2017a), sea cucumbers, including *S. hermanii*, are rich in collagen (Sari et al. 2012; Shahrulazua et al. 2013). Additionally, omega-3 and glycosaminoglycans in golden sea cucumbers aid in healing by increasing collagen levels (Damaiyanti et al.

2019). Collagen content in *S. hermanii* can reach 70% of the total protein in the body (Siahaan et al. 2017b). Pringgenies et al. (2018) confirmed that the highest collagen content in *S. hermanii* is in amino acids, chondroitin, and glucosamine. This extracellular collagen is beneficial for dental support tissues (Ratri et al. 2017), shortening the healing time for diseases (Shahrulazua et al. 2013)

GAGs

S. hermanii is rich in Glycosaminoglycans (GAGs) (Sari et al. 2012; Damaiyanti et al. 2019; De Fretes et al. 2020). GAGs in *S. hermanii* offer health benefits such as anti-inflammatory, anticoagulant, and wound healing properties. GAGs enhance skin health by maintaining moisture and elasticity and supporting cell regeneration. They also have potential in repairing connective tissues and cartilage, useful in treating conditions like osteoarthritis and other joint diseases (Rusmini et al. 2023). GAGs

include heparin sulfate and chondroitin sulfate. Heparin sulfate, a complex polysaccharide involved in various biological processes, is found in golden sea cucumbers and has anticoagulant and anti-inflammatory potential. Chondroitin sulfate inhibits the formation of periodontal pathogen biofilms (Ratri et al. 2017) and supports joint and bone health, offering anti-inflammatory effects and protection against cartilage damage (Martel-Pelletier et al. 2015).

Flavonoid

Flavonoids in *S. hermanii* have antioxidant benefits, inhibiting activities like peroxidase and xanthine oxidase (Akerina and Sangaji 2019). Marliza et al. (2022) added that flavonoids in marine animals reduce apoptosis, promoting anticancer properties by inducing programmed cell death. Flavonoids in *S. hermanii* are proven to trigger apoptosis, inhibiting cancer growth (Windari et al. 2019; Prameswari et al. 2020; Marliza et al. 2022).

Table 1. Table of bioactive compounds and their benefits in *Stichopus hermanii*

Main bioactive compounds	Benefits	References
Protein	This species' protein is extremely healthy for the body	(Prameswari et al. 2020; Safithri et al. 2022; Taurina and Andrie 2022)
	The golden sea cucumber has 86% protein, which the pepsin enzyme readily dissolves	(Rasyid 2018)
	The golden sea cucumber is regarded as a marine creature that is high in sulfated glycosaminoglycans, low in lipids, and high in protein It is also well recognized for being used as medication and for being highly successful in curing a variety of illnesses. It can support antioxidant, antiviral, and anti-inflammatory functions	(De Fretes et al. 2020)
Saponin	Act as a high-protein food source, prevent blood clotting, prevent arthritis, hasten wound healing, strengthen the immune system, fight weariness, and prevent cancer	(Oktaviani et al. 2018; Pringgenies et al. 2018; Yatmasari et al. 2021; Rusmini et al. 2023)
	Saponins, which are categorized as holothurins and were first found in sea cucumbers, are known for a wide range of physiological functions. Saponins in <i>Stichopus hermanii</i> are found in the skin, flesh, and tubular Cuvierian organs. These elevated levels of saponins function as antibacterial agents and a defense mechanism against predators. Holotoxins, which are found in pure sea cucumber extract, have effects comparable to those of antimycin at dosages of 6.25-25 µg/mL	(Nurwidodo et al. 2018; Rusmini et al. 2023)
	Golden sea cucumbers' saponins have a high antioxidant concentration and promote cell regeneration. Moreover, saponins have antimicrobial properties Antioxidants that have been shown to alleviate hyperglycemia and hyperlipidemia in test animals, such as rats. By dissolving cytoplasmic membranes and destroying cells, saponins function as antibacterial agents. Compounds like riboflavin, flavonoids, saponins, tannins, and omega-3 fatty acids are responsible for <i>S. hermanii</i> 's antioxidant properties Saponins are a primary component of the antimicrobial properties in <i>S. hermanii</i>	(Pringgenies et al. 2018) (Cushnie et al. 2014; Irfan et al. 2014) (Safithri et al. 2020b)
Triterpenoid	Triterpenoids with antimicrobial properties	(Pringgenies 2013)
	Triterpenoids found in a variety of marine creatures have antibacterial, antifungal, and anticancer effects that are beneficial to the body	(Cushnie et al. 2014; Irfan et al. 2014) (Akerina and Sangaji 2019)
	It can lower levels of Triacylglycerol (TAG), Low-Density Lipoprotein (LDL), and blood cholesterol	(Zhafira 2016)
	Triterpenoids improve antioxidant properties in serum and plasma, lowering oxidative stress, inflammation, and DNA damage	(Han and Bakovic 2015)
	Triterpenoids are tested by dissolving extracts in 0.5 mL chloroform, then adding 2 mL H ₂ SO ₄ and 0.5 mL acetic anhydride	(Anggraeni et al. 2014)

Collagen	<p>Tyrosinase activity in melanogenesis can be inhibited by collagen, which also possesses antioxidant qualities. Another source of collagen is sea cucumbers. Collagen is abundant in <i>S. hermanii</i>.</p> <p>Golden sea cucumbers' omega-3 and glycosaminoglycans also promote healing by raising collagen levels.</p> <p>Collagen content in <i>S. hermanii</i> can reach 70% of the total protein in the body. The amino acids, chondroitin, and glucosamine in <i>S. hermanii</i> include the most collagen.</p> <p>The tissues that support teeth benefit from this extracellular collagen.</p> <p>Reducing the duration of illness recovery.</p>	<p>(Safithri et al. 2018)</p> <p>(Shahrulazua et al. 2013; Sari and Wahjuningsih 2017; Siahaan 2017a)</p> <p>(Damaiyanti et al. 2019)</p> <p>(Siahaan et al. 2017b)</p> <p>(Pringgenies et al. 2018)</p> <p>(Ratri et al. 2017)</p> <p>(Shahrulazua et al. 2013).</p>
GAGs	<p>There are a lot of Glycosaminoglycans (GAGs) in <i>S. hermanii</i>.</p> <p><i>S. hermanii</i>'s GAGs have anti-inflammatory, anticoagulant, and wound-healing qualities, among other health advantages. By preserving skin suppleness and hydration and promoting cell renewal, GAGs improve skin health. Moreover, they may be able to restore cartilage and connective tissues, which would be helpful in the treatment of illnesses of the joints and osteoarthritis.</p> <p>Heparin sulfate and chondroitin sulfate are examples of GAGs. Golden sea cucumbers contain heparin sulfate, a complex polysaccharide with anticoagulant and anti-inflammatory properties that is involved in many biological processes. The development of periodontal pathogen biofilms is inhibited by chondroitin sulfate.</p> <p>Promotes bone and joint health by providing anti-inflammatory benefits and defense against cartilage degradation.</p>	<p>(Sari et al. 2012; Damaiyanti et al. 2019; De Fretes et al. 2020)</p> <p>(Rusmini et al. 2023)</p> <p>(Ratri et al. 2017)</p> <p>(Martel-Pelletier et al. 2015)</p>
Flavonoid	<p>Possess antioxidant properties via blocking enzymes such as xanthine oxidase and peroxidase.</p> <p>Reduce apoptosis to induce planned cell death, which will promote anticancer qualities. It has been demonstrated that flavonoids in <i>S. hermanii</i> cause apoptosis, which stops the growth of cancer.</p>	<p>(Akerina and Sangaji 2019)</p> <p>(Prameswari et al. 2020; Windari et al. 2019; Marliza et al. 2022)</p>
Mineral	<p>The golden sea cucumber <i>Simplisia</i> had zinc (Zn) levels of 9.32 mg/kg, according to testing conducted by the Pontianak Standardization and Industrial Research Institute. Zinc influences bacterial activity and is essential for optimal cell growth, DNA polymerase synthesis, and wound healing.</p> <p><i>S. hermanii</i> also contains other minerals, such as silicon and calcium, which aid in the synthesis of its structural materials.</p>	<p>(Sari et al. 2020)</p> <p>(Floren et al. 2023)</p>
Glutathione	<p>Glycine, glutamate, and cysteine are amino acids found in <i>S. hermanii</i> that are precursors to glutathione, the body's main antioxidant.</p> <p>Glutathione prevents cancer by lowering oxidative activity.</p> <p>By giving free radicals electrons, you can stop cell damage.</p> <p>With the aid of glutathione peroxidase, it transfers electrons to hydrogen peroxide (H₂O₂) and superoxide (O₂^{-*}), creating H₂O.</p>	<p>(Espinosa-Diez et al. 2015)</p> <p>(Wardhani 2019)</p> <p>(Cahyati et al. 2018)</p> <p>(Safithri et al. 2022)</p>
Alkaloid	<p><i>S. hermanii</i>'s alkaloid content gives it antibacterial qualities.</p> <p>Alkaloids are secondary chemicals with nitrogen atoms in their structure that are produced from amino acids. Alkaloids from <i>S. hermanii</i> can suppress both Gram-positive and gram-negative bacteria, although they can be harmful if taken in excess.</p> <p>They help treat diabetes by stimulating the hypothalamus, which lowers blood sugar, gluconeogenesis, and insulin needs.</p>	<p>(Cushnie et al. 2014; Irfan et al. 2014; Zhafira 2016; Susanto et al. 2018; Rahmadani 2023)</p> <p>(Tamara et al. 2015)</p> <p>(Rasouli et al. 2020)</p>
Methanol	<p>Bioactive substances such as alkaloids, saponins, and triterpenoids are present in the methanol extract of <i>S. hermanii</i>, promoting strong antioxidant activity.</p> <p>By generating molecules with pharmacological effects, such as those that treat pain, arthritis, AIDS, and cancer, these bioactive compounds have an impact on organisms. Additionally, they improve antioxidant activity, anti-inflammatory, anti-diabetic, anti-obesity, and anti-aging properties.</p>	<p>(Zhafira 2016)</p> <p>(Pringgenies 2019)</p>
Hyaluronic Acid	<p>Other beneficial components of <i>S. hermanii</i> include hyaluronic acid.</p> <p>Also contains chondroitin sulfate, heparinsulfate, and dermatan sulfate which can help activate and bind GFs, especially FGF-2. In order to create healthy collagen, <i>S. hermanii</i> also contains unsaturated fatty acids, which are the primary agents in regulating fibroblast proliferation, collagen production, and the inflammatory process in wound healing. Another benefit of having unsaturated fatty acids is that they strengthen connective tissue and reduce the creation of scars.</p>	<p>(Sari et al. 2012; Prameswari et al. 2020)</p> <p>(Sari et al. 2012)</p>

Mineral

S. hermanii contains various minerals. Testing by the Pontianak Standardization and Industrial Research Institute identified zinc (Zn) levels at 9.32 mg/kg in golden sea cucumber *Simplisia*. Zinc is crucial for normal cell growth, DNA polymerase production, and wound healing, influencing bacterial activity (Sari et al. 2020). Other minerals like calcium and silicon are also present in *S. hermanii*, contributing to its structural mineral formation (Floren et al. 2023).

Glutathione

S. hermanii contains amino acids like glycine and glutamate, precursors to glutathione, a primary antioxidant in the body composed of glycine, cysteine, and glutamate (Espinosa-Diez et al. 2015). Glutathione reduces oxidative activity, preventing cancer (Wardhani 2019) by donating electrons to free radicals, thus preventing cell damage (Cahyati et al. 2018). It transfers electrons to superoxide (O₂^{-*}) and hydrogen peroxide (H₂O₂), forming H₂O with the help of glutathione peroxidase (Safithri et al. 2022).

Alkaloid

S. hermanii has antibacterial properties due to its alkaloid content (Cushnie et al. 2014; Irfan et al. 2014; Zhafira 2016; Susanto et al. 2018; Rahmadani 2023). Alkaloids are secondary compounds derived from amino acids, categorized by nitrogen atoms in their structure. Despite their toxicity when improperly consumed, alkaloids from *S. hermanii* can inhibit both Gram-positive and gram-negative bacteria (Tamara et al. 2015). They stimulate the hypothalamus, reducing gluconeogenesis, blood sugar, and insulin requirements, beneficial for diabetes treatment (Rasouli et al. 2020).

Methanol

The methanol extract of *S. hermanii* contains bioactive compounds like alkaloids, saponins, and triterpenoids, supporting high antioxidant activity (Zhafira 2016). These bioactive compounds influence organisms by producing chemicals with pharmacological effects, such as treating cancer, AIDS, arthritis, and pain. They also offer health benefits, enhancing antioxidant function, anti-obesity, anti-diabetes, anti-inflammatory, and anti-aging activities (Pringgenies 2019).

Hyaluronic acid

S. hermanii has various other good ingredients, such as hyaluronic acid (Sari et al. 2012; Prameswari et al. 2020). Apart from hyaluronic acid, *S. hermanii* also contains chondroitin sulfate, heparinsulfate, and dermatan sulfate which can help activate and bind Growth Factors (GFs), especially Fibroblast Growth Factor-2 (FGF-2). *S. hermanii* also contains unsaturated fatty acids which are the main agents in controlling the inflammatory process in wound healing, regulating fibroblast proliferation and collagen synthesis to produce healthy collagen. Another advantage of the presence of unsaturated fatty acids is that it minimizes scar formation and increases connective tissue strength (Sari et al. 2012).

THERAPEUTIC POTENTIAL OF GOLDEN SEA CUCUMBER

Golden sea cucumber has numerous therapeutic potentials. Therapeutic pertains to the treatment of diseases or the healing of patients. The golden sea cucumber can be used as a medicinal ingredient for various diseases. It possesses high-value-added compounds that are functional as biomedical materials and derivatives. Its use as a natural medicine is supported by the significant benefits and potential of the organism as an alternative to chemical drugs, which often have high side effects (Adam et al. 2022a). Its therapeutic properties include fatty acids, vitamins, amino acids, glycosaminoglycans, keratin, glucosamine, triterpene glycosides, carotenoids, peptides, chondroitin, cell growth factors, mucopolysaccharides, glycosides, lectins, minerals, omega-3 and 6, and collagen. Research shows that the golden sea cucumber can regenerate tissues, relieve pain, and act as an antimicrobial, fungicide, antioxidant, and anticancer agent (Utami and Yudho 2022).

Wound healing and antifungal properties

Several researchers have found that golden sea cucumber is effective in wound healing, with 13.48% of sea cucumber researchers focusing on this hidden benefit (Mulawarmanti et al. 2019). When combined with extracts of snakehead fish, stingless bee honey, green betel leaf, and clove oil, it can enhance wound healing speed due to its strong adhesion effect (Lestari et al. 2023). In angiogenesis, golden sea cucumber increases the expression of Vascular Endothelial Growth Factor (VEGF) in wound healing (Soesilawati et al. 2019). The wound healing process can be observed through the increase in lymphocytes in ulcers (Arundina et al. 2015). Golden sea cucumber contains glycosaminoglycans and omega-3, which can accelerate wound healing of physiological disturbances or pain in soft mouth tissues (Sari and Wahjuningsih 2017). Extracts of golden sea cucumber containing hyaluronic acid combined with calcium carbonate from blood clam shells stimulate the healing process of tooth extraction complications and periodontal diseases (Sari et al. 2017). Extracts used as raw materials for wound healing drugs must undergo specific standardization such as organoleptic, water and ethanol content, phytochemical screening, protein content, and non-specific standardization (Rusmini et al. 2023). Standardization is done according to applicable Indonesian National Standards (SNI) to ensure reproducibility and maintain the quality of wound healing drugs (Taurina and Andrie 2022). Golden sea cucumber has also been extensively studied for its antifungal and anti-inflammatory properties, which are implemented in treating inflammatory diseases such as *Candida vaginitis* (Yudo et al. 2022). Variegatuside D and E have shown significant inhibition against *C. albicans*, *C. parapsilosis*, *C. neoformans*, *C. tropicalis*, *C. pseudotropicalis*, and *Nannizzia gypsea* (Carodoso et al. 2020). The antifungal properties of golden sea cucumber are due to its body wall and coelomic fluid, which inhibit the growth of *C. albicans*, *Aspergillus*

brasiliensis, *A. flavus*, *A. niger*, and *A. fumigatus* (Adipour et al. 2014).

Hipertrigliseridemia and hiperkholesterolemia

Hypercholesterolemia is a condition of the body that experiences too high an increase in cholesterol levels in the blood. This cholesterol has the potential to increase the risk of heart attack or stroke due to narrowing of blood vessels from the accumulation of fat. The body needs cholesterol as a constituent of healthy cells, Vitamin D producer, and produces various hormones. Cholesterol is produced by the liver and comes from food. However, if the cholesterol level is too high hypercholesterolemia is the term for elevated levels of total cholesterol, LDL cholesterol, and triglycerides in the blood, which exceed normal limits (Angelina et al. 2022).

Blood triglyceride levels exceeding normal limits can trigger coronary artery disease and cardiovascular disease. One bioactive compound in sea cucumbers is steroids, which function as aphrodisiacs and sex reversals (Meydia et al. 2016). Golden sea cucumber extract can reduce triglyceride levels in hyperlipidemic test rats, proving its potential as a supportive treatment for hypertriglyceridemia (Angelina et al. 2022). According to Hartono and Mukono (2020), the antioxidants in golden sea cucumber can lower cholesterol levels, which are a cause of hypercholesterolemia. This cholesterol reduction also lowers the potential for cardiovascular diseases and other life-threatening conditions.

Diabetes

Diabetes is a chronic disease characterized by high blood sugar levels. Glucose is the main source of energy for human cells. However, in people with diabetes, the glucose cannot be used by the body. Blood sugar (glucose) levels are controlled by the hormone insulin produced by the pancreas. However, in diabetics, the pancreas is unable to produce insulin according to the body's needs. Without insulin, the body's cells cannot absorb and process glucose into energy (Mariyanti 2017). Golden sea cucumber extract can treat diabetes (Fajarwati 2017; Setianingsih et al. 2021). *S. hermanii* powder used in Hyperbaric Oxygen (HBO) therapy acts as an antioxidant and antibacterial agent. Tests on 20 male Wistar rats treated with HBO therapy and *S. hermanii* powder showed a reduction in blood sugar levels, indicating its potential in treating diabetes mellitus characterized by hyperglycemia (Darojati et al. 2017). Golden sea cucumber powder has been shown to increase osteoprotegerin expression in diabetes mellitus with periodontitis (Aziza et al. 2016). Diabetes mellitus can cause metabolic disorders due to increased lipolysis, known as hyperlipidemia. The EPA-DHA, saponin, and flavonoid content in golden sea cucumber can act as anti-hyperlipidemic agents (Setianingsih et al. 2020). In addition to diabetes mellitus, golden sea cucumber can inhibit free radical oxidant activity and protect muscles in diabetic patients by activating Glut-4 and IL-6 proteins (Purwanto et al. 2019).

Bone and tooth regeneration

Research indicates that golden sea cucumber has strong potential in bone and tooth regeneration (Hlaing and Compston 2014; Hienz et al. 2015; Sheikh et al. 2017; Ho-Shui-Ling et al. 2018; Jalaluddin et al. 2018; Kruger 2019; Liu et al. 2019; Sari and Kurniawan 2019; Djais et al. 2020; Battafarano et al. 2021). Golden sea cucumber contains rich bioactive components (Fawzya et al. 2020). These bioactive components are beneficial as biocompatible materials in bone grafting, restoring adhesion, filling bone effects, and regenerating bone (Adam et al. 2022b). Golden sea cucumber bone graft can be used as a regenerative bone therapy and an effort to regenerate periodontitis (Adam et al. 2023b). Untreated periodontitis can lead to tooth loss (Adam et al. 2021). Through its content, including flavonoids, heparan sulfate, chondroitin sulfate, collagen, and hyaluronic acid, golden sea cucumber can prevent orthodontic relapse by increasing osteogenesis of the periodontal ligament in cases of orthodontic relapse or unwanted tooth movement (Sangian et al. 2024).

Traditionally, sea cucumber processing is done by manual cleaning and preservation techniques in the form of drying or smoking (Herliany et al. 2016). Sea cucumbers have traditionally been used as medicine by eating them directly in the form of food. Medicinal processed foods come in the form of steamed dishes and soups with traditional kitchen spices such as turmeric, ginger, and pepper. Another traditional processing involves kneading it into a paste as a wound ointment (Hanifaturahmah et al. 2024). This is in contrast to modern processes such as bioactive extraction which are more diverse and functional. Bioactive extraction is processed in aqueous solution to preserve collagen, saponins and fatty acids. The use of tools also tends to be more modern, more hygienic and guaranteed.

Currently, research on the therapeutic efficacy of golden sea cucumber is still limited due to the lack of literature on clinical trials. The literature found is still in the in vitro or in vivo stage. In chemical tests, it is difficult to determine the standardization of raw materials because the composition of the tested golden sea cucumber bioactive compounds is highly dependent on habitat, season, and diet. In addition, due to the small number of participants in studies using human samples, the statistical significance of the conclusions was not tested. Further research and development is recommended to identify new compounds that may not have been previously identified. This can also be done by analyzing the molecular structure of the active ingredients to determine their specific effects on the human body. Research may include metabolomics techniques to study potential contributing metabolites. Various extraction models equipped with up-to-date information and tools can be used to produce highly pure bioactive compounds and conduct large-scale, multidimensional clinical studies. Interaction studies with other drugs can be conducted to investigate various reactions and discover new drugs. To facilitate research, optimizing sea cucumber cultivation using genetic

engineering is one way to increase high-quality biomass so that it can provide meaningful data for research.

CONCLUSION

Golden sea cucumber (*S. hermanii*) contains many bioactive compounds that provide various therapeutic benefits. The chemical profiles, namely protein, saponin, triterpenoid, collagen, GAGs, flavonoid, mineral, glutathione, alkaloid, methanol, and hyaluronat acid. This species also have great potential as therapeutic agents, such as wound healing, antifungal properties, hipertrigliseridemia, hypercholesterolemia, diabetes, bone and tooth regeneration. With this compound content, golden sea cucumbers can serve as a basis for developing innovative and sustainable biomedical products. Utilizing these compounds for health could lead to improvements in regenerative therapies, diabetes management, and protection from infection. Apart from its promising health benefits, processing golden sea cucumbers can improve the welfare of coastal communities through industrial cultivation and biotechnology. Therefore, conservation measures for this species must continue to be carried out so that it remains sustainable in nature and can be used wisely by humans.

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Short Communication: Morpho-anatomical and histochemical characterization of four species of Cyperaceae in Rivers State, Nigeria

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Abstract. Ajuru MG, Chinwe-Chikere L, Ibiye A, Elebachi BO. 2024. Short Communication: Morpho-anatomical and histochemical characterization of four species of Cyperaceae in Rivers State, Nigeria. *Cell Biol Dev* 7: 68-74. This research investigated the morpho-anatomical and histochemical characteristics of four species of Cyperaceae (*Kyllinga erecta*, *Kyllinga bulbosa*, *Pycurus lanceolatus* and *Mariscus alternifolius*) in Rivers State University. They are perennial, monocotyledonous herbs commonly known as erect greenhead sedge, spikesedge, narrow-leaf flatsedge and umbrella sedge respectively. Hand sectioning method and light microscopy were used for both anatomical and histochemical studies, while meter rule was used for quantitative morphological characters and visual observation was used for qualitative characters. The results for anatomy indicated that epidermal cells are one layered and present in the four species studied, the vascular bundles are all scattered, collateral, conjoint and closed in the stems and are also surrounded by parenchyma cells. The results of histochemical studies showed that there were no calcium oxalate crystals in either the stem or rhizomes of the four species. Results from morphological studies showed that the four species have triangularly shaped stems and are tufted and herbaceous perennial sedges. The four species also have fibrous roots and their leaves are all simple, alternate, glabrous and tristichously arranged. The results also showed that the four species of sedges exhibited a wide range of morphological features that distinguish them from another group of plants, and the characters showed some level of similarities amongst themselves. There were no calcium oxalate crystals in both the stem and rhizomes of all four species studied. Also, the presence of fibrous roots and umbel inflorescence authenticated their classification as monocotyledonous plants. The results of this research would help to improve upon the already existing information about the four species.

Keywords: Cyperaceae, histochemistry, *Kyllinga*, *Mariscus*, morpho-anatomy, *Pycurus*

INTRODUCTION

The family Cyperaceae, commonly called the Sedge family is documented as the third largest monocotyledon family, with approximately 5000 species distributed into 109 genera (Pal and Choudhury 2017; Xu and Zhou 2017). Two hundred and thirty (230) species distributed into 23 genera have been identified in Nigeria. They can be found in different habitats, but more than 80% exist in damp or wet places (Goetghebeur 1998; Pal and Choudhury 2017). The genus *Carex* L. contains about 2000 species and is said to be the largest genus in the family followed by *Cyperus* L. (Bruhl 1995; Goetghebeur 1998; Muasya et al. 2002; Tantwai 2017).

Kyllinga erecta, which is a perennial, erect, tufted, glabrous sedge grows up to about 12-45 cm high, possess thick segmented rhizomes with numerous inter-twisted fibrous roots. It has tough stem made up of an underground rhizome that gives rise to above ground stem and shoots. In some regions, *K. erecta* is a source of nutrition for animals in form of fodder (Burkill 1985). It also plays a role in restoring degraded ecosystems (de Moraes and Sennikov 2021).

Kyllinga bulbosa, a vivacious herbaceous plant, possesses fairly long, creeping, slender rhizomes. It has a creeping stem, which holds the slender inflorescence, but it

is swollen at the base in the form of bulbs or tubers, measuring up to 35 cm high. *Kyllinga bulbosa* has been reported to be used for heart problems (Bussmann and Sharon 2006). It is also a good candidate for groundcover, soil stabilization, or erosion control because of its rhizomes and ability to grow in different environments (Bryson and Carter 2008).

Mariscus alternifolius is commonly called umbrella sedge. It is a grass-like, erect, glabrous, tufted perennial plant that grows up to 60 cm high and reproduces from seed. The leaves, linear in shape and up to 30 cm long, arise from the base of the stem and have purplish red leaf sheaths. *Mariscus alternifolius* has attractive foliage and, therefore is used as an ornamental plant. It is also tolerant of wet conditions and it is used for erosion control along water bodies and in landscaping projects (Huxley 1999).

Pycurus lanceolatus is commonly called lance leaf umbrella-sedge. It is a densely tufted perennial sedge which grows up to about 20-60 cm high and reproduces from seeds and slender rhizomes. The linear shaped stem is 3-angled in cross-section, with a dark brown colored leaf sheath (Goetghebeur 1998). This plant provides food and serves as shelter for different wildlife species. It is also used in the treatment of stomach aches, diarrhea and skin

infections (Andrew 2007). Also, the plant is used as a forage for goats and cattle in some regions.

The study of morphological and anatomical structures of plants is highly essential and can be used in plant breeding programs and different agricultural activities. Knowledge of plant morphological characteristics can help breeders select desirable characteristics for crop improvement and weed management strategies. Several studies have demonstrated the use of morpho-anatomical characters in the taxonomy of closely related species. Importance of morpho-anatomical study for taxonomy was emphasized by Standley (1990) and Hejazi et al. (2012), who used anatomy of leaves for the taxonomical and phylogenetic classification within the genus *Carex*. Based on the qualitative and quantitative morpho-anatomical characters, Plunkett et al. (2013) recognized a new species of *Lepidosperma* (Cyperaceae) from the mountain of Tasmania. Pashrizad et al. (2014) used morphological and anatomical data in identification of Iranian *Cyperus*. The four species of Cyperaceae in this study: *K. erecta*, *K. bulbosa*, *P. lanceolatus* and *M. alternifolius* are used extensively for different medicinal purposes, and several studies have shown that they all have triangularly shaped stems, fibrous roots and several other similarities. This may lead to drug adulteration if not properly identified. Also, literature review indicated that structural studies on this plant species are very scanty, making it difficult to easily differentiate among them. Therefore, this research was carried out to fill the gap by providing more morphological and anatomical characteristics that can aid in distinguishing these four species for taxonomic and medicinal purposes.

MATERIALS AND METHODS

Study area

This study was conducted on the Rivers State University (RSU) campus within the Port Harcourt metropolis, Rivers State, Nigeria, which was established in October 1980. Port Harcourt is an industrialized cosmopolitan city located in the health of Niger Delta. The study area RSU lies south-south of the Niger Delta within latitude 4° 31' - 4° 40' N and longitude 7° 01' - 7° 10' E. It is on an elevation of about 10-15 m above sea level (Ubong et al. 2015).

Sources of sample collection, identification and preparation

The research study took place from June to August 2024. The samples of the four species of Cyperaceae were freshly collected from biology laboratory field of the University (4°31'-4°40' N, 7°01'-7°10'), Nkpolu-Oroworukwo, Rivers State (Table 1). They were taken to

the Department of Plant Science and Biotechnology in polythene bags with tags. They were identified and authenticated by Dr. M.G Ajuru, a plant taxonomist in the Department and given the Accession numbers RSUPbH0196-0199. The samples were rinsed in distilled water several times and placed in a sample bottle containing Formalin-Acetic Acid-Alcohol (FAA) mixture in the ratio of 1:1:18 percent of 70% ethanol in preparation for morphological, anatomical and histochemical studies.

Procedures

Morphological procedure

The morphological features of the four selected species, which are of taxonomic importance, were noted on matured living plant samples. Qualitative morphological studies include visual observation of the vegetative and reproductive parts of the plant species. Quantitative morphological traits include the measurement of leaf width, leaf length, petiole length and plant height using a meter rule and a measuring tape. Qualitative morphological plant features studied includes the leaf shape, leaf type, leaf arrangement, plant habit, stem size, color etc.

Anatomical procedure

This was done using the methods of Akomolafe et al. (2017). Plant samples were fixed in FAA to remove excessive pigments. Transverse sections were made by hand using commercial razor blades. They were stained using 2 drops of 1% safranin on clean slides and then rinsed with water. Thereafter, the specimens were mounted on 25% glycerol and observed using digital compound photomicroscope. The observed features include thickness of epidermis, thickness of cortex, diameter of vascular bundles, number of trichomes, length of trichomes and number of cells per mm.

Histochemical procedure

The specimens were fixed in FAA and were rinsed in distilled water before sectioning. The hand sectioning method was employed. Plants were sectioned with sharp razor blades held on the right hand horizontally while the plant part was held with the left hand. Thin sections were made and fixed in petri dish filled with distilled water. After sectioning, good sections were placed on clean slides with the use of a Carmel hair brush. The sections were stained with hydrogen peroxide and silver nitrate for 5 minutes in bright light supplied by 100Watt electric bulb following the method of Silver and Price as modified by Osuji et al. (2013). The stain sections were mounted in glycerin with a coverslip. The microscope slides were observed under a light microscope.

Table 1. Sources of collection of plant materials used for the study

Plant samples	Accession number	Date of collection	Location of collection
<i>Kyllinga erecta</i>	RSUPbH0199	15 th -06-2024	Rivers State University
<i>Kyllinga bulbosa</i>	RSUPbH0196	15 th -06-2024	Rivers State University
<i>Pycneus lanceolatus</i>	RSUPbH0198	15 th -06-2024	Rivers State University
<i>Mariscus alternifolius</i>	RSUPbH0197	15 th -06-2024	Rivers State University

RESULTS AND DISCUSSION

Morphological features of the four species of Cyperaceae studied

The morphological features of the four species of Cyperaceae studied are summarized in Figures 1 and 2, Table 2. *Kyllinga erecta*, *K. bulbosa*, *P. lanceolatus* and *M. alternifolius* are all herbaceous, perennial, tufted sedge plants with fibrous root systems. *Kyllinga erecta* and *K. bulbosa* are vivacious plants mostly found in the terrestrial habitat, while *P. lanceolatus* and *M. alternifolius* are found in marshland and swampy habitats respectively. They all possess underground stems modified to be rhizomes. The rhizome is slender and slightly long in *K. erecta* and *K. bulbosa*, robust and yellowish in *P. lanceolatus* and woody and aromatic in *M. alternifolius*. The stem of *K. erecta* measures up to 35-50 cm long, has sharp angles, smooth with a trigonal shape and is light green; *K. bulbosa* stem measures up to 35-49 cm long, smooth, thick at the base, with a trigonal shape and is light green; the stem of *P. lanceolatus* measures up to 40-52 cm long. It is trigonal in shape, erect and light green, while the stem of *M. alternifolius* is about 25-40 cm long, trigonal in shape, grooved and lignified in nature and purplish green. The leaves of the four species are all simple, alternate,

tristichously arranged at flower base, narrow, glabrous, entire and sessile, with *K. erecta*, *K. bulbosa* and *M. alternifolius* having acute leaf apices, while the leaf apex in *P. lanceolatus* is acuminate. The inflorescence in *K. erecta* and *K. bulbosa* is a spike, and spikelets in *P. lanceolatus* and *M. alternifolius*; it is greenish in *K. erecta*, light green in *K. bulbosa*, golden green in *P. lanceolatus* and greenish to reddish in *M. alternifolius*.

Anatomical structures of the four species studied

The stem anatomical features of the four species of Cyperaceae studied are summarized in Figure 3. Stems of all the four species studied are triangularly shaped with epidermal cell that is one layered, followed by 1-2 layers of hypodermal sclerenchymatous cells in *K. bulbosa*, *P. lanceolatus*, and *M. alternifolius*, but 3-4 layers in *K. erecta*. The ground tissue in all the species is filled with parenchyma cells with large intercellular air spaces. There is no epidermis, pericycle and pith cavity. Vascular bundles are scattered through the ground tissue, with the larger ones towards the center and the smaller ones towards the periphery. The vascular bundles are collateral, conjoint and closed. Each vascular bundle is surrounded by a bundle sheath of parenchyma cells. The phloem tissue is towards the outside, while the xylem tissue is towards the center.



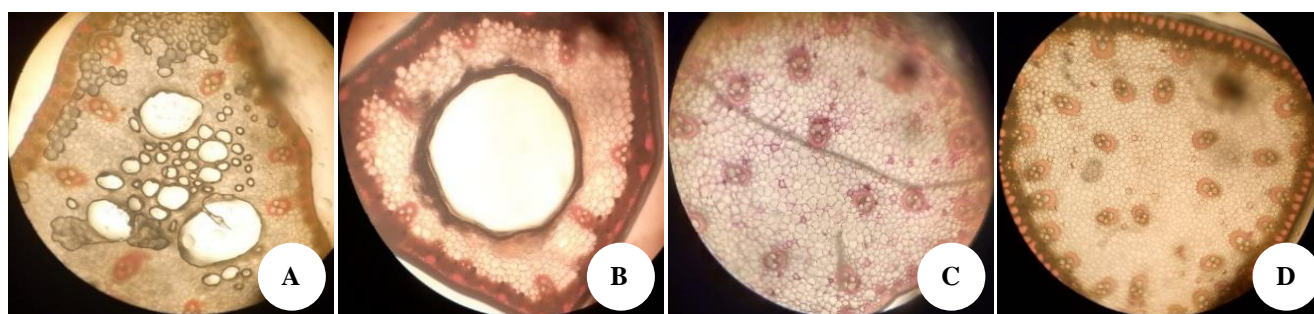
Figure 1. Morphological characters of the four species of Cyperaceae: A. *Kyllinga erecta*; B. *Kyllinga bulbosa*; C. *Pycurus lanceolatus*; D. *Mariscus alternifolius*



Figure 2. Morphological characters of the four species of Cyperaceae in the field: A. *Kyllinga erecta*; B. *Kyllinga bulbosa*; C. *Pycurus lanceolatus*; D. *Mariscus alternifolius*

Table 2. Morphological structures of the four species of Cyperaceae studied

Character	<i>Kyllinga erecta</i>	<i>Kyllinga bulbosa</i>	<i>Pycurus lanceolatus</i>	<i>Mariscus alternifolius</i>
Duration	Perennial	Perennial	Perennial	Perennial
Habit	Herbaceous	Herbaceous caespitose tuft	Herbaceous and tufted	Herbaceous and tufted
Growth form	Sedge	Sedge	Sedge	Sedge
Habitat	Terrestrial	Terrestrial	Marshland	Damp places, swamps
Biological cycle	Vivacious	Vivacious	Vivacious	Robust
Root type	Fibrous	Fibrous	Fibrous	Fibrous
Rhizome	Present, slender and slightly long	Compact underground stems	Present, yellowish in color	Present, woody and aromatic
Stem				
Size	Small (35-49 cm long)	35-50 cm	40-52 cm	25-40 cm
Shape	Trigonal	Trigonal	Trigonal	Trigonal
Nature	Thick at the base, smooth	Sharp angles, smooth	Erect	Grooved and lignified
Color	Light green	Light green	Light green	purplish green
Leaf				
Type	Simple	Simple	Simple	Simple
Arrangement	Alternate	Alternate	Alternate	Alternate
Nature of arrangement	Tristichously arranged at flower base	Tristichously arranged at flower base	Tristichously arranged at flower base	Tristichously arranged at flower base
Petiole	Absent, sessile	Sessile	Sessile	Sessile
Shape	Narrow	Linear	Linear	Linear
Size				
Length	10-23 cm	25-35 cm	30-42 cm	20-35 cm
Width	0.5-0.7 mm	0.3-0.8 mm	0.4-0.8 mm	0.2-0.9 mm
Apex	Acute	Acute	Acuminate	Acute
Surfaces	Glabrous	Glabrous	Glabrous	Glabrous
Margin	Entire	Scabrous	Rough	Scabrous
Color	Deep green	Light bright green	Deep green	Reddish brown purple
Leaf sheath	Deep green	Deep green	Deep green	Purple
Inflorescence				
Type	Spike	Spike	Spikelets	Spikelets
Nature	Dense	Dense	Dense	Subtended by leaf-like bracts
Shape	Ellipsoid to globular	Conical to globulose	Capitate cluster	Cluster
Size				
Length	3-5 mm	2-5 mm	2-4.5 mm	2-3.7 mm
Diameter	2-4 mm	8-10 mm	2-4.3 mm	2-4.1 mm
Color	Light green to whitish	Green	Golden green	Greenish to reddish

**Figure 3.** Stem anatomical structures of four species of Cyperaceae: A. *Kyllinga bulbosa*; B. *Kyllinga erecta* stem; C. *Pycurus lanceolatus*; D. *Mariscus alternifolius* (X100)

Rhizome anatomy

This is summarized in Figure 4 below. The epidermal cell in all the species is one layered, followed by their ground tissue filled with parenchyma cells. There are starch/ food droplets all over the parenchyma cells and intercellular air spaces. The central portion of the rhizome is filled with vascular bundles made up of phloem and xylem tissues, surrounded by bundle sheath of parenchyma cells. There are starch/ food droplets all over the parenchyma cells and intercellular air spaces.

Histochemical studies

Stem histochemistry

There were no calcium oxalate crystals in the stem of all the species, as shown in Figure 5.

Rhizome histochemistry

There were no calcium oxalate crystals in the rhizomes of all the species.

Discussion

The stems of the four species of Cyperaceae studied are triangularly shaped, tufted and herbaceous perennial sedge as stated by Govaerts et al. (2007). The stems of *K. bulbosa*, *K. erecta* and *P. lanceolatus* are light green, as reported by Gordon-Gray (2006) while the stem of *M. alternifolius* is purplish green. The four species of Cyperaceae studied all have fibrous root types, as stated by Simpson (2011). They are all vivacious sedges except *M.*

alternifolius which is robust, and they all possessed underground rhizomes, which conforms with the study by Metcalfe and Gregory (1971), who stated that rhizome is the main underground stem of Cyperaceae.

Kyllinga erecta and *K. bulbosa* are found in terrestrial habitats, while *P. lanceolatus* is found in marshland habitat, which aligns with the study of Govaerts et al. (2007), who stated that *Kyllinga* species usually grow in dry, terrestrial environments while *P. lanceolatus* thrives in marshy places, and *M. alternifolius* is found in damp places and swamps. As stated by Metcalfe and Gregory (1971), that *M. alternifolius* can easily be found in swampy environment. The rhizome is present in all four species studies, and it aligns with the study of Govaerts et al. (2007).

Kyllinga erecta, *K. bulbosa*, *P. lanceolatus* have light green stem color, while the stem color of *M. alternifolius* is purplish green. Their leaves are all simple, alternate, tristichous arranged at the flower base, glabrous and thus are in conformity with the study of Holm et al. (1979) on morphological structures of some species of Cyperaceae.

Kyllinga erecta, *K. bulbosa*, *P. lanceolatus* and *M. alternifolius* have linear leaf shapes, while *K. bulbosa* has narrow leaf shape and this aligns with Govaerts et al. (2007) description in his research work on the vegetative morphology of Cyperaceae family. They all possess sessile petiole, and this aligns with the study of (Holm et al. 1979). They all have dense inflorescence except *M. alternifolius*, which has inflorescence subtended by leaf-like bracts.

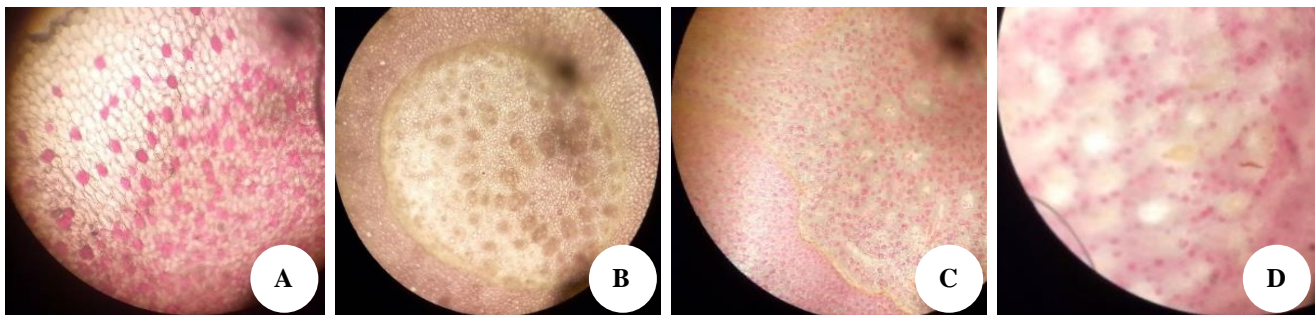


Figure 4. Rhizome anatomical structures of four species of Cyperaceae: A. *Kyllinga bulbosa*; B. *Kyllinga erecta* rhizome; C. *Pycneus lanceolatus*; D. *Mariscus alternifolius* (X100)

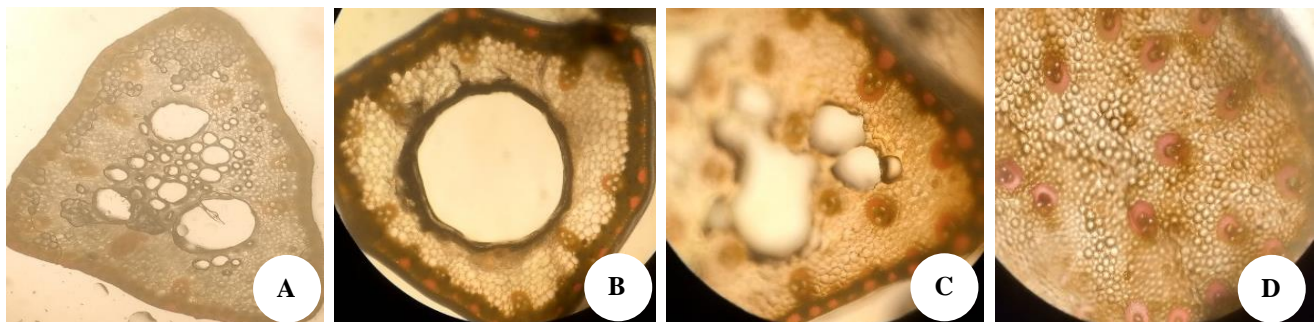


Figure 5. Histochemical localization of crystals in stems of four species of Cyperaceae: A. *Kyllinga bulbosa*; B. *Kyllinga erecta* stem; C. *Pycneus lanceolatus*; D. *Mariscus alternifolius* (X100)

The stem anatomical structures of the plants studied showed that the stem of the four species is triangularly shaped. Their epidermal cell is one layered followed by hypodermal cells which are made up of sclerenchyma tissues as stated by Govaerts et al. (2007) in his study of the anatomical features of Cyperaceae. They all have ground tissues, which are made of parenchyma cells. There is no endodermis, pericycle and pith cavity in *K. erecta*, *K. bulbosa* and *P. lanceolatus*, but there is in *M. alternifolius* which are not differentiated. The vascular bundles in all four species are collateral, conjoint, closed, scattered all over the ground tissues and are made up of xylem, phloem and lacking cambium. The phloem tissues in the four species are towards the periphery while the xylem is towards the center as reported by Metcalfe and Gregory (1971) and Dickson (2000), who stated that monocotyledons usually have numerous vascular bundles, with the xylem tissues facing the central portion of the stem, while the phloem tissues are usually towards the periphery.

In the rhizome, there is only one layered epidermal cell in the four species, followed by one ground tissue filled with parenchyma cells. There are starch/ food droplets all over the parenchyma cells and this is in alignment with the research of Singh et al. (2015), who stated that rhizomes in plants are modified food storage organs. Several authors like Rodrigue and Estellita (2002), Alonso and Moraes-Dallaqua (2004), made reference to the endodermis in rhizomes.

There was a total absence of calcium oxalate crystals in the stem and rhizomes of the four species of Cyperaceae studied. This may be as a result of environmental conditions which may affect the chemical contents in plants. This is in support of the findings by Fodor (2002), Krupa et al. (2002), and Friday and Ajuru (2014), who stated that toxic metals may cause deficiency of elements essential for plants. Calcium oxalate crystals are very important for plant's overall metabolism because the crystals are essential in calcium homeostasis, calcium storage and removal of excess oxalate, which might have a toxic effect when in excess (Franceschi and Horner 1980; Çalışkan 2000).

In addition, calcium oxalate crystals help support plant tissues and protect plants from attack by herbivores since they are associated with chemicals that cause irritation (Rupali 2012). Therefore, plants that grow in polluted environments will not thrive well as a result of little or absence of these crystals. Also, the presence of these crystals has been reported in leaves and stems of plants (Horner and Whitmoyer 1972; Genua and Hillson 1985; Doaigey 1991; Wu and Kuo-Huang 1997; Meric 2009; Aybeke et al. 2010).

In conclusion, the research study on the morphological and anatomical features of *K. erecta*, *K. bulbosa*, *P. lanceolatus* and *M. alternifolius* was carried out. The quantitative and qualitative morphological characters were studied, as well as the description of the transverse sections of stem and rhizomes of the species. The present study will help to improve the existing data for identification and taxonomic purposes, and might be further used to develop a

regulatory document on these species for proper identification to avoid adulteration since the plants are essentially used for medicinal purposes. Further work on molecular analysis should be carried out to authenticate the classification of these species for taxonomic purposes.

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Review: Medicinal and pharmaceutical uses of skipjack tuna (*Katsuwonus pelamis* Linnaeus, 1758)

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Abstract. Safira RN, Hafiffah AS, Allobua BSN, Mukarromah AN, Aulia AD, Naim DM, Setyawan AD. 2024. Review: Medicinal and pharmaceutical uses of skipjack tuna (*Katsuwonus pelamis* Linnaeus, 1758). *Cell Biol Dev* 8: 75-89. Skipjack tuna or skipjack fish or cakalang (*Katsuwonus pelamis* Linnaeus, 1758) belongs to the Scombridae family. The skipjack tuna has a fusiform, round, elongated body, gill segments, small conical teeth, dark purplish-blue with a silvery underside and abdomen, and an elongated dark line. The body length of the skipjack tuna can reach 1 meter, with the weight reaching more than 18 kg. Skipjack tuna is widely spread from the western and central Pacific to the Indian Oceans, including Indonesia. Skipjack tuna can only live in salt water and live off the continental shelf in the open sea. Ecologically, this fish is an indicator of the environmental conditions in the habitat of skipjack tuna. Seasonal variations in productivity and temperature are critical in influencing reproductive factors. They underscore the significance of spatial and temporal compatibility among ecosystems regarding egg hatching, which is crucial for the survival of new fish progeny. Skipjack tuna is widely processed and is a protein source for the community. The use of tuna fish can be done in traditional and modern ways. Besides being used as processed food, skipjack tuna is also used as a natural medicine that is beneficial for the health of the human body. Skipjack tuna has various pharmacological properties, such as antioxidant, anticancer, anti-inflammatory, and antidiabetic.

Keywords: Medicine, pharmaceuticals, skipjack tuna, utilization

INTRODUCTION

Skipjack tuna or skipjack fish or *cakalang* (*Katsuwonus pelamis* Linnaeus, 1758) belongs to the genus *Katsuwonus*, Scombridae family (Artetxe-Arrate et al. 2021a). Scombridae has a high natural mortality rate but can travel long distances (Cunha-Neto et al. 2022). The skipjack tuna has an elongated body that is somewhat round and fat. The pectoral and dorsal fins are black and have a short and stocky tail; the upper body is dark blue and has a gray parallel line behind the ventral fin, the tip of the pectoral fin, and the caudal stalk (Aly et al. 2022).

Skipjack tuna is a cosmopolitan species widespread in tropical and subtropical oceans. Skipjack tuna is widespread in the western and central Pacific oceans (Ashida 2020). Skipjack tuna is also distributed in the Atlantic and Indian Ocean regions and is spread almost throughout the waters of Indonesia (Ridwan et al. 2020). Its geographical boundaries are 55°-60° N and 45°-50° S, and are abundant in the equatorial region throughout the year (Grande et al. 2014). Skipjack tuna is the most dominant tuna species in the Indian Ocean. However, tuna fishermen in the Indian Ocean still have difficulty determining the

potential of skipjack fishing areas due to limited geographical information (Semedi et al. 2023).

Skipjack tuna can only live in salt water and off the continental shelf in the open sea, with the water temperature ranging from 18-31°C (Mulyadi et al. 2017). The spatial boundary of the habitat is determined from the stratification of the upper ocean based on mixed layers and dissolved oxygen (Zhou et al. 2022). Skipjack tuna are limited to water with very high dissolved oxygen concentrations, at least 3.0-3.5 mL/L (4-5 ppm), for long-term survival. Skipjack larvae emerge from the bottom of the mixed layer to the top of the thermocline in the 20-25°C temperature range and the salinity range of 33.6-35.5 ppt (Collette et al. 2021). The habitat of skipjack tuna based on fishery data includes warm waters with sea surface temperatures above 24°C between the coasts of Africa and the Asian continent, as well as around the northern boundary of the South Indian Ocean Gyre. Trawlers rarely catch skipjack tuna in the Indian Ocean, but incidental catches show extensive habitat potential for adult skipjacks (Fonteneau 2014). The 1982 United Nations Convention on the Law of the Sea required semi-closed coastal states to coordinate and comply with regulations on

fisheries issues. Asian scientists overcame this obstacle by developing the Common Fisheries Resource Analysis (CFRA) for skipjack tuna (Prince et al. 2023).

Skipjack tuna are sensitive to environmental changes because they can move on a large scale to find suitable habitats and meet their physiological needs (Yen et al. 2016). Climate change significantly influences the adaptation processes of skipjack tuna, with these adaptations closely tied to population dynamics. As a result, the vulnerability of skipjack tuna species may increase under changing environmental conditions; (Kifani et al. 2019). Skipjack tuna act as an opportunistic predator of medium trophic level that consumes prey of about 1.2-5.5% of body weight per day to support their high energy needs (Fuller et al. 2021). In the spawning process, the influence of water temperature affects the assessment of spawning habitat in the wild and the development of skipjack tuna eggs. A high hatching rate of >50% occurred at 23-31°C. Since the spawning period is vulnerable to predators, a shorter hatching time in warm water provides an ecological advantage for skipjack tuna, as its main spawning grounds are in tropical areas (Fujioka et al. 2024).

Skipjack tuna is currently vulnerable; therefore, its conditions, including its ecosystem, must be considered (Wakamatsu and Managi 2019), such as the Atlantic bluefin tuna, *Thunnus thynnus*, which has been categorized as an almost endangered species according to the IUCN red list criteria (Soares et al. 2019). It threatens skipjack tuna and tuna-like species because the threats endanger the population of these species (Aranda et al. 2017).

Skipjack tuna is widely used in food processing and as a food source (Setyowati and Rahayu 2018), so its fishery products have good economic value locally and as an export commodity. Furthermore, the current utilization of tuna fish waste has not been maximized. By repurposing skipjack tuna's skin and bone waste to produce gelatin, we can significantly enhance its economic value, owing to the substantial collagen content in these materials (Panjaitan 2017). Skipjack tuna waste, such as fish heads, meat, and bones, can produce powdered broth (Indrastuti et al. 2022).

SPECIES DESCRIPTION

Taxonomy

Kingdom : Animal
 Phylum : Chordata
 Class : Actinopterygii
 Order : Perciformes
 Suborder : Scombroidea
 Family : Scombridae
 Genus : *Katsuwonus*
 Species : *Katsuwonus pelamis* (Linnaeus, 1758)

(GBIF 2024)

The skipjack tuna is a pelagic fish (Luhur and Yusuf 2017), the only species in the genus *Katsuwonus* and is classified as a medium-sized fish (Suara et al. 2014).

Morphological character

The skipjack tuna has a body with a very distinctive shape. They generally have a fusiform body, which is ideal for quick movement in the water. The body of this fish also tends to be round and elongated, with a pointed head and a body shape that extends back to the tail. This slightly rounded (fusiform) elongated body shape helps skipjack tuna to adapt to the dynamic marine environment and move nimbly in the water. There are two separate dorsal fins in skipjack tuna. The first dorsal fin has 14-16 sharp fingers, followed by the second dorsal fin, which has 7-9 finlets (additional small fins) (Figure 1). Skipjack tuna generally have a purplish-blue to dark back color, with a silvery belly. The body of skipjack tuna is not scaly except for the body butt (corselet) and sidelines. In general, skipjack tuna is between 40-200 cm long and weighs between 3-130. The combination of its long body shape makes it an efficient predator in chasing prey and avoiding predators in the ocean. Moreover, this distinctive body shape also helps in their extensive migration processes and long-distance travel in the ocean. With a body designed for movement efficiency and adaptation to the marine environment, skipjack tuna are an interesting example of evolution adapted to life in the open sea. It has 53-63 gill segments on the first gill arch. It has small conical teeth with a single series and small conical gill spines with a single series. The skipjack tuna is dark purplish-blue with a silvery underside and belly and has 4-6 prominent, elongated dark stripes (Rukshana et al. 2021). The size of skipjack tuna varies, with lengths that can reach 1 meter and weigh up to more than 18 kg. Skipjack tuna have scales only found on lateral lines and scars (Purwiningsih and Sakriani 2021).

Reproductive cycle

Skipjack spawns year-round in warm-water tropics, but the area is difficult to forage. It makes skipjack tuna move to colder subtropical regions to find food. However, not all skipjack tuna make these movements; some remain around the spawning area. Skipjack tuna is a fast-growing, early-maturing species with high reproductive potential, which makes this species more resistant to fishing pressure than other tuna species (Artetxe-Arrate et al. 2021b). Skipjack tuna can lay eggs many times throughout the year. Skipjack tuna's spawning or spawning process usually occurs in waters with a sea surface temperature of at least 24°C. These warm temperatures support the development of fish eggs and larvae (Mawarida et al. 2022). The reproductive strategy of laying eggs in large numbers is common in skipjack tuna that have a short life cycle and a high mortality rate in the early stages. The main goal of producing large quantities of eggs is to increase the likelihood that some eggs will successfully hatch into strong larvae and survive in harsh marine environments. A female skipjack can produce between 80,000 and 2 million eggs in a single reproductive period (Yetisen 2021). Due to the importance of skipjack tuna as a food and economic source, sustainable fisheries management is critical. Several countries have implemented regulations to manage skipjack fishing, including catch quotas, no-catch zones, and spawning habitat protection (Adam 2016). The

summary of skipjack tuna (*Katsuwonus pelamis*) distribution, chemical constituents, pharmacological properties, and medical utilization can be seen in Table 1.

HABITAT DISTRIBUTION

Environmental factors

The existence and movement of skipjack tuna are greatly influenced by various environmental factors that can determine favorable places of feed. Some ecological factors related to the movement of skipjack tuna are ocean currents, sea surface temperature, depth, chlorophyll-a, and other environmental factors, such as salinity, oxygen availability, and predators and competitors (Hidayat et al. 2020). Sea surface temperature and chlorophyll-a are two key factors that significantly affect the behavior and distribution of skipjack tuna. Sea surface temperature is important for thermoregulation; the optimal temperature ensures skipjack tuna maintain efficient metabolic activity. In addition, physiological adaptations allow skipjack tuna to live in a wide range. Sea surface temperature changes trigger skipjack tuna to move to areas more suitable for their biological needs. Chlorophyll-a concentrations are an important indicator of primary productivity in the ocean, indicating food-rich areas for skipjack tuna, and skipjack tuna often follow migration routes based on food distribution (Abudarda and Zainuddin 2021). Additionally, oceanographic parameters play an important role in the life and growth of skipjack tuna, which can affect their various physiological and behavioral aspects. Some oceanographic parameters affecting skipjack tuna are metabolism, spawning, fish feeding speed, and other activities (Nurani et al. 2022).

The distribution and abundance of skipjack tuna in coastal and offshore areas is not static but fluctuates following complex patterns. Various interrelated oceanographic factors control these dynamics and create a network of interactions (Hasyim et al. 2022). Tropical species such as skipjack tuna are distributed in waters with temperatures up to 30-32°C, preferably at temperatures around 16°C, with relatively high oxygen content, relatively strong currents in corals, reefs, and shallow waters. This skipjack tuna is very sensitive to temperature changes. They can also be found in waters with abundant food sources, such as plankton and crustaceans (Muhling et al. 2015). Climate is one of the factors affecting the life of skipjack tuna. Climate change that results in global warming may affect the productivity of medium and high trophic levels, which can potentially impact marine resources such as tropical skipjack tuna (Kim et al. 2015). Oceanographic parameters such as Sea Surface Temperature (SST) and variability of climatic factors become limiting factors for fish distribution and even their survival. At the same time, while climatic phenomena such as El Niño and La Niña can also have negative or positive impacts on fish (Putri and Zainuddin 2019). In response to changes in temperature, food availability, or other environmental factors, skipjack tuna can travel

considerable distances and even across oceans. Their ability to move widely helps them survive and reproduce in various environmental conditions, making them one of the most adaptive marine predators (Yen et al. 2016).

Distribution

The distribution and migration pattern of skipjack tuna is very wide because skipjack tuna are fast swimmers that travel a long distance from the waters of the archipelago to sea waters but not too far from the coastline; the temperature ranges from 17-23°C, with a swimming layer between 0-40 meters. Skipjack tuna migrate in groups to find spawning grounds, waters with plenty of food, and variations in environmental factors. Skipjack tuna can be found in shallow waters and warmer temperatures than other tuna (Putri et al. 2021). The more suitable habitat influences skipjack tuna's distribution, movement, and vulnerability. The survival of skipjack tuna was affected by the presence of prey, appropriate temperature, and sufficient oxygen. As a result, the distribution of skipjack tuna is annual and seasonal (Restiangsih et al. 2020). Skipjack tuna is found in the tropical and subtropical regions of the Pacific, Indian, and Atlantic Oceans, particularly in the equatorial areas of the western and central Pacific, known for their significant fishing activities (Matsumoto et al. 2014). The annual production of skipjack tuna in the southwestern Atlantic has consistently averaged approximately 25,000 tons from 1979 until 2018. However, a notable decrease in catch volumes was recorded in 2018 (Cardoso et al. 2020). The current distribution areas for skipjack include the Maluku Sea, Halmahera Sea, Banda Sea, Flores Sea, Indian Sea, Aceh Sea, Northern Aceh Waters, South Java, North Sulawesi, West Sumatra, Cendrawasih Bay, Tomini Bay, and Arafura Sea.

Despite their wide geographical distribution, uncontrolled exploitation can lead to regional population declines, ultimately affecting global populations. Furthermore, large stocks do not guarantee availability if fishing technology continues to develop. Fishing activities can change community structure and reduce the biodiversity and resilience of marine ecosystems. Although fish species have a wide distribution, they are still vulnerable to the negative impacts of intensive fishing (Ortuño Crespo and Dunn 2017).



Figure 1. Morphology of skipjack tuna (Fishbase 2025)

Table 1. Summary on skipjack tuna (*Katsuwonus pelamis*) distribution, chemical constituents, pharmacological properties, and medical utilization

Name	Distribution	Chemical constituents	Pharmacological properties	Medical utilization	
				Traditional	Modern
English & Scientific Names Scientific name: <i>Katsuwonus pelamis</i> (syn.: <i>Euthynnus pelamis</i>) Primary name: Skipjack tuna Alternate names: Striped tuna, Oceanic bonito, Arctic bonito (rare)	Tropical, subtropical, and warm-temperate waters Pacific Ocean Western Pacific: Abundant near Japan, the Philippines, Indonesia, and Australia. Eastern Pacific: Found from California to Peru, including the Galápagos Islands. Central Pacific: Common around Hawaii, French Polynesia, and other Pacific island nations. Atlantic Ocean Western Atlantic: From the Gulf of Mexico to Brazil, including the Caribbean. Eastern Atlantic: From Spain and Portugal down to South Africa, including the Canary and Cape Verde Islands.	Macronutrients Water content: 68-75% of fresh weight High-quality protein: 23-28 g/100 g (contains all essential amino acids) Fat content: 0.5-2.5 g/100 g (varies seasonally) Minimal carbohydrates: <0.5 g/100 g Ash (minerals): 1.2-1.8 g/100 g Essential amino acids Lysine: 85-95 mg/ g protein Leucine: 75-85 mg/ g protein Valine: 50-55 mg/ g protein Histidine: 45-55 mg/ g protein (histamine precursor) Taurine (free amino acid): 100-300 mg/ 100 g Fatty acid profile EPA (omega-3): 5-12% of total lipids DHA (omega-3): 15-25% of total lipids Palmitic acid: 15-20% of total lipids Oleic acid: 10-15% of total lipids Excellent omega-3 to omega-6 ratio: 5:1 to 10:1 Vitamin content Vitamin B12: 8-12 µg/100 g (300-500% DV) Niacin (B3): 10-18 mg/100 g Vitamin B6: 0.5-0.9 mg/100 g Vitamin D: 2-5 µg/100 g Vitamin E: 0.5-1.2 mg/100 g Mineral composition Selenium: 40-70 µg/100 g Potassium: 350-450 mg/100 g	Antioxidant properties Selenium helps neutralize free radicals. Vitamin E protects cell membranes from oxidative damage. Bioactive peptides (e.g., anserine and carnosine) exhibit radical scavenging activity. Omega-3 fatty acids (EPA & DHA) reduce lipid peroxidation. Anti-inflammatory effects EPA & DHA modulate NF-κB and COX-2 pathways, reducing pro-inflammatory cytokines (TNF-α, IL-6). Anserine and carnosine suppress neuroinflammation. Cardiovascular protection Reduces triglycerides and increases HDL cholesterol (via omega-3s). Lowers blood pressure (ACE-inhibitory peptides from tuna protein). Anti-atherogenic effects (reduces plaque formation in arteries). Anti-thrombotic (reduces platelet aggregation). Neuroprotective & cognitive benefits DHA supports neuronal membrane integrity and synaptic function. Anserine enhances brain-derived neurotrophic factor (BDNF) levels. Anticancer potential Selenium induces apoptosis in cancer cells (e.g., prostate, colon). Omega-3s inhibit tumor angiogenesis and metastasis. Bioactive peptides (e.g., KPH-41 from tuna hydrolysate) show cytotoxic effects on cancer cell lines. Antimicrobial & antiviral activity Antibacterial peptides (e.g., defensin) active against <i>E. coli</i> , <i>S. aureus</i> ,	Japanese kampō medicine <i>Katsuo</i> (fermented skipjack) used to: Improve digestion Treat fatigue and weakness Boost energy (as invigorating tonic) Pacific Island remedies Raw liver applied topically for: Skin infections Wound healing Fish oil used for: Joint pain relief Ear infections (as ear drops) Southeast Asian folk medicine Broths/soups prescribed for: Post-illness recovery Lactation support in nursing mothers Fever reduction Coastal African traditions Smoked flesh used as: Protein supplement for malnutrition Anemia treatment (iron source) Eyes consumed for: Improving night vision Mediterranean traditional use Preserved in olive oil for: Heart health tonic Respiratory ailments	Cardiovascular health Source of omega-3 for: Hypertension management Triglyceride reduction Prevention of atherosclerotic plaque Neurological support DHA-fortified foods for: Cognitive development in infants Alzheimer's disease prevention Depression/anxiety Sports nutrition Protein isolates for: Muscle recovery supplements Athletic performance Creatine source for strength training Metabolic health Bioactive peptides used in: Anti-diabetic functional foods Obesity management products Omega-3 formulations for metabolic syndrome Geriatric nutrition High-quality protein for: Sarcopenia prevention Age-related muscle loss Combined EPA/DHA supplements for joint health Clinical nutrition Elemental diets for: Post-surgical recovery Cancer patient nutrition Low-purine protein sources for controlled diets Ophthalmic health DHA extracts for: Dry eye syndrome treatments Macular degeneration
Asia-Pacific East & Southeast Asia: Japan: カツオ (<i>Katsuo</i>) - standard, スジキ (<i>Sujiki</i>) - less common Korea: 참치 (<i>Chamchi</i>) - general term, sometimes refers to skipjack China: 鲣鱼 (<i>Jiān yú</i>) - standard, 正鲣 (<i>Zhèng jiān</i>) - in Taiwan Philippines: <i>Gulyasan</i> (Tagalog), <i>Bariles</i> (Visayan) - may also refer to yellowfin tuna Indonesia/Malaysia: <i>Cakalang</i> (Indonesia), <i>Kayu</i> (Malaysia), <i>Debuk</i> (Aceh), <i>Fufu</i> (North Maluku) Thailand: ทูน่าเกดิก (<i>Thoo gati</i>), ทูน่าลาย (<i>Thoo lai</i>) - "striped tuna" Vietnam: Cá ngừ vàng Myanmar: <i>Ngā myīn htwet</i> (ငါးမြင်းထွတ်)					
Pacific & Oceania: Hawaii: <i>Aku</i> Tahiti: <i>'Ahi pa'i'i</i> Fiji: <i>Walu</i> Samoa/Tonga: <i>Atu</i> New Zealand: Skipjack or Striped tuna					

<p>Indian Ocean Maldives: ދިވެހި (Fiyala) Sri Lanka: බලාය (Balaya) Seychelles: Katwal (Creole) India: Bangdo (Gujarati); Kuppa (Telugu/Andhra Pradesh)</p>	<p>Indian Ocean Found throughout, especially near the Maldives, Seychelles, Sri Lanka, and western Australia.</p>	<p>Phosphorus: 200-280 mg/100 g Magnesium: 30-50 mg/100 g Iron: 1-2 mg/100 g (heme iron) Zinc: 0.5-1.5 mg/100 g</p>	<p>and <i>Vibrio</i> spp. Antiviral potential (omega-3s may enhance immune).</p>	<p>(mixed with honey) Polynesian healing practices Fermented preparations used for:</p>	<p>prevention Immunonutrition Selenium-rich supplements for:</p>
<p>Atlantic Ocean & Africa West Africa: Senegal: Yaboy (Wolof) Ghana: Ammoon (Fante) Nigeria: Eja ori (Yoruba), Kifi (Hausa)</p>	<p>Seasonal migrations Skipjack tuna prefer surface waters (0-260 m deep) with temperatures between 15-30°C (59-86°F). They follow warm currents and are often associated with FADs (Fish Aggregating Devices) and floating debris.</p>	<p>Bioactive compounds Anserine: 150-300 mg/100 g (antioxidant) Creatine: 300-500 mg/100 g Antihypertensive peptides (Val-Tyr, Lys-Tyr) Inosinic acid (IMP): increases during fermentation</p>	<p>Antidiabetic & metabolic benefits Improves insulin sensitivity (via omega-3-mediated reduction of inflammation). Low glycemic impact (high protein, low carbohydrate content). Taurine may protect against diabetic complications.</p>	<p>Digestive disorders Internal parasites General traditional applications Whole fish consumption for:</p>	<p>Immune system modulation Antioxidant enhancement Functional food development Fortification of:</p>
<p>East & Southern Africa: Swahili: Jodari or Sangara Madagascar: Antsiva (Malagasy) South Africa: Skipjack (English)</p>	<p>They follow warm currents and are often associated with FADs (Fish Aggregating Devices) and floating debris.</p>	<p>Potential contaminants Mercury: 0.1-0.3 ppm Cadmium: 0.01-0.05 ppm Lead: <0.02 ppm PCBs: 0.05-0.3 ng/g Dioxins: <0.1pg TEQ/g Histamine: may exceed 50 mg/100 g in spoiled fish</p>	<p>Hepatoprotective effects Reduces liver fat accumulation (non-alcoholic fatty liver disease, NAFLD). Taurine and selenium support detoxification pathways.</p>	<p>General traditional applications Muscle development (athletes/workers) Sexual vitality (aphrodisiac) Fish skin applied for:</p>	<p>Baby foods (brain development) Elderly nutritional products Heart-healthy food lines Pharmaceutical applications</p>
<p>Caribbean & Latin America: Brazil: Bonito-listrado or Gaiado Mexico: Barrilete Cuba: Bonito Haiti: Bonit (Haitian Creole)</p>	<p>They follow warm currents and are often associated with FADs (Fish Aggregating Devices) and floating debris.</p>	<p>Processing effects Drying increases umami compounds (IMP) Canning improves protein digestibility Fermentation generates bioactive peptides Heat processing reduces omega-3 content by 10-20%</p>	<p>Wound healing & skin health Collagen peptides promote tissue regeneration. Zinc and omega-3s reduce skin inflammation (e.g., psoriasis, eczema).</p>	<p>Burn treatment Eczema relief Key traditional beliefs: Considered "warming" food in Asian medicine</p>	<p>Anti-inflammatory agents Neuroprotective formulations Nutraceutical industry Collagen peptides for:</p>
<p>Europe & Mediterranean Spain: Bonito del norte (caution: refers to a different species) Portugal: Gaiado Italy: Tonnetto striato Greece: Παλαμιδα (Palamida) - also used for other small tunas Turkey: Yazılı orkinos France: Bonite à ventre rayé</p>	<p>They follow warm currents and are often associated with FADs (Fish Aggregating Devices) and floating debris.</p>	<p>Processing effects Drying increases umami compounds (IMP) Canning improves protein digestibility Fermentation generates bioactive peptides Heat processing reduces omega-3 content by 10-20%</p>	<p>Muscle growth & performance Protein (complete amino acid profile). Creatine (naturally occurring) improves muscle strength and recovery.</p>	<p>Burn treatment Eczema relief Key traditional beliefs: Considered "warming" food in Asian medicine</p>	<p>Anti-inflammatory agents Neuroprotective formulations Nutraceutical industry Collagen peptides for:</p>
<p>Middle East Arabic: تونة مخططة (Tuna mukhattat) - "striped tuna", جَنّ (Jinn) - in some dialects Iran: تن مخطط (Tuna khatdar)</p>	<p>They follow warm currents and are often associated with FADs (Fish Aggregating Devices) and floating debris.</p>	<p>Processing effects Drying increases umami compounds (IMP) Canning improves protein digestibility Fermentation generates bioactive peptides Heat processing reduces omega-3 content by 10-20%</p>	<p>Bone health support Calcium, phosphorus, vitamin D aid in bone mineralization. Omega-3s reduce osteoporosis risk.</p>	<p>Believed to strengthen qi/vital energy Used ceremonially for healing rituals in some cultures Note: Many traditional uses now have scientific support (e.g., omega-3 content validating cardiovascular benefits), while others remain part of cultural heritage without clinical verification.</p>	<p>Wound healing accelerants Taurine extracts for energy Preventive medicine Regular consumption recommended for:</p>
<p>Note: Names: Johannes (1981), Collette and Nauen (1983), Sainsbury et al. (1985), Lehodey et al. (2008), Dueri et al. (2014), Eveson et al. (2015). Distribution: Collette and Nauen (1983), Lehodey et al. (2008), Fonteneau et al. (2013), Eveson et al. (2015), Dueri et al. (2014). Chemical constituents: Balogun and Talabi (1985), Sala (2009), Intarasirisawat et al. (2013), Nurjanah et al. (2015), Klomklao and Benjakul (2016), Chakraborty et al. (2017), Yoon et al. (2018), Shin et al. (2024). Pharmacological properties: Dyall (2017), Ouellet et al. (2017), Chen et al. (2018), Hossain et al. (2019), Mozaffarian and Wu (2018), Najafian and Babji (2018), Guo et al. (2019), Kohen et al. (2019), Tapiero et al. (2019), Holick (2020), Zainal et al. (2020), Yan et al. (2021). Traditional medical utilization: Johannes (1981), Nakamura (1985), Dyer and McGoodwin (1994), Ruddle (1994), Hviding (1996), Hamilton and Walter (1999), Zann (1999), Johannes and Yeeting (2001), Miyake et al. (2004). Modern medical utilization: Hsu et al. (2007), Burri et al. (2012), Ding et al. (2019), Zhang et al. (2019), Pateiro et al. (2020), Cai et al. (2022), Rungruang et al. (2024)</p>					

One of the distribution areas of skipjack tuna in Indonesia is the waters of Sadeng, in which the fish can be found all year around if the fishing season is right, namely from February to March or September to October (Noegroho and Chodrijah 2015). The Sadeng Coastal Fisheries Port is the center of economic activities. It plays a role in developing fishing technology, capturing fisheries business, and other activities related to the fisheries and marine sectors. Capture fisheries business is a commercial activity that involves catching fish and other aquatic organisms (Suharyanto et al. 2024).

Invasiveness and environmental impact

Annual cycles in productivity and temperature are critical in determining reproductive time, and the spatial and temporal compatibility between their ecosystems and egg hatching for the survival of new fish offspring are important (Reglero et al. 2018). The movement of skipjack tuna on a large scale may be caused by the convergence of the ocean, a foraging area. Ocean convergence can draw large amounts of plankton and fish to the surface, creating highly productive conditions for marine predators such as skipjack tuna. The accumulation of abundant food resources, such as plankton and small fish, attracts predatory fish species to move to the area. This phenomenon often occurs offshore, where continental ocean currents meet open ocean currents or near the confluence of different ocean currents. The movement of skipjack tuna on a large scale could also aim to gather in large numbers, increasing their chances of reproduction and survival. In addition, rich food resources in the ocean convergence area make this movement an efficient strategy for meeting skipjack's nutritional and energy needs (Wang et al. 2014). Understanding the reproductive biology of tuna, including skipjack tuna, is essential for managing and conserving this species. However, knowledge about reproductive biology is still relatively limited. Many aspects of life cycle and reproduction are still limited, especially in the wild (Carnevali et al. 2019). The tuna population has increased, and the number of global catches has tripled in the last 20 years, based on estimates of the population from the Indian Ocean. However, the catch of long-tailed tuna that exceeds the target tuna species (*Thunnus obesus* and *Thunnus albacares*) has resulted in the conclusion that the species has been overfishing for several years (Griffiths et al. 2019).

The exploitation of fishery resources often harms the environment. The exploitation process that does not pay attention to environmental carrying capacity is detrimental to the country and the marine and fisheries community. It can be the beginning of habitat loss due to environmental damage (Nugroho and Budianto 2021). The decline in biodiversity and biodiversity of fish resources in the wild can be associated with several factors, including uncontrolled overfishing and irresponsible and environmentally harmful fishing gear (Pratama et al. 2023). According to Indra et al. (2019), one of the efforts to reduce the negative impacts of fish exploitation is to develop environmentally friendly fishing gear. The Food Agriculture Organization (FAO 1995) issued a procedure

for responsible fishing activities (Code of Conduct for Responsible Fisheries - CCRF). In this CCRF, FAO sets a series of criteria for environmentally friendly fishing technology that are (i) fishing gear must have high selectivity; (ii) the fishing gear used does not damage the habitat; (iii) the fishing gear does not endanger fishermen; (iv) produces good quality fish; (v) the fish products produced do not endanger consumer health; (vi) the bycatch and discard results are as minimal as possible; (vii) the fishing gear used must have a minimum impact on the diversity of biological resources (biodiversity); (viii) does not catch species that are protected by law or are threatened with extinction; and (ix) the fishing gear is socially acceptable.

Mortality causes a decreasing number in a population. According to the results of Mawarida's research (2022), the total mortality value of skipjack tuna is 1.13 per year, natural mortality is 0.47 per year, and fishing mortality is 0.66 per year, with an exploitation rate of 0.59 per year. This exploitation rate indicates significant fishing pressure on the skipjack tuna population in the area. Differences in mortality values, especially fishing mortality, are caused by the number of different fishing activities in each region and at other times. Sari and Nurainun's research (2022) emphasizes that fish stocks are influenced by the population's ability to recover through reproduction and fishing pressure. Uncontrolled exploitation can decrease skipjack tuna stocks, so sustainable management is needed to maintain ecosystem balance and the sustainability of fish resources.

TRADITIONAL USE OF SKIPJACK TUNA

Ethnozoological of skipjack tuna

Skipjack tuna is one of the ingredients in processed cuisine in Spain. There is a celebration in May/June when fattier and tastier fish enter the Mediterranean to lay eggs. The activities include the best bluefin tuna tapa competition made from traditional recipes and the most innovative presentation by many local chefs (Pérez-Lloréns 2019). In Japan, processed skipjack tuna is a specialty food, such as smoked and dried *katsuobushi*, the main ingredient in fish soup and other Japanese specialties (Adolf 2019). Japan is the leading importer of bluefin tuna, the most preferred species to be processed into Japanese specialties, such as sushi/sashimi (Esteves and Aníbal 2019). In Sri Lanka, skipjack tuna is cooked as a curry with coconut milk or fried in palm oil, which is considered a delicacy and has become a tradition (Devadawson 2021).

Creating many facilities for processing and marketing marine products is necessary in communities with economic limitations. Developing seafood processing and marketing facilities is an important step to improving the economy of coastal communities. Through an integrated approach, including infrastructure development, marketing, government support, community empowerment, and sustainability, coastal communities can improve their living standards and create a more stable and sustainable economy (Antriyandarti et al. 2023). The calcium content

in skipjack tuna bones reaching 60-70% means that tuna fish has a high calcium content. The calcium in the bones of skipjack tuna can replace the role of fluoride, which functions to strengthen teeth. Calcium hydroxide (Ca(OH)₂) is used in herbal toothpaste. These antibacterial compounds (Calcium hydroxide) can prevent the growth of dental plaque (Hariyanto and Antasionasti 2023).

In India, tuna soup powder is prepared from three traditional recipes, selected based on taste tests by the panels. The ingredients include dried tuna powder, wheat flour, milk powder, salt, black pepper, tomatoes, onions, garlic, ginger, coriander, fennel, carrots, sweet corn, and oil. During a 50-day cold storage, the soup powder contained 13.48% moisture, 38.43% protein, 0.0518% dry fat, and 12.65% ash content (Patel et al. 2023). Tuna broth supports cell growth and repair due to its richness in protein, adds umami flavor to soups and sauces, and serves as a healthier alternative to artificial flavors.

Pindang is a fishery processing product that plays an important role in post-harvest activities. Its products have a relatively short shelf life, less than two days at room temperature. Smoking is a drying technique that maintains the shelf life of fish by using wood fuel as a smoke producer. Pindang tuna that has gone through the smoking process is named *Sei-Pindang Ikan Tongkol* (Pandit et al. 2023).

The use of body parts of tuna

Several body parts of the fish have been commonly used. The meat in skipjack tuna is the most common part to be consumed. Skipjack meat has a dense texture and is rich in protein; therefore, it is the main ingredient in various types of seafood. The fish fin is used in making soup or fish broth, where collagen content can make the dishes delicious. The tails are used in various processed dishes, such as fried or stir-fried, and are often used in making processed fish soup. Fish gills are rarely consumed directly, but they can be used as a basic ingredient in making processed fish sauces and as an additional taste in processed dishes. Skipjack tuna bones are used to make broth and processed into fishbone chips. Fish oil is extracted from offal or specific body parts and is often used as a source of omega-3, which is good for health. Skipjack tuna can be made into *arabushi* (a semi-finished product of *katsuobushi*) by a gradual smoking process using varying temperatures. The manufacturing process involves removing the fish entrails, boiling them at 60°C, removing the bones, and smoking them 7 times at different temperatures (Doe et al. 2020). Skipjack tuna account for 60% of the worldwide commercial tuna catch and are mainly used for canning because skipjack tuna can be stored longer and transported to various markets. This process involves processing, distilling, and pressing the fish in containers that maintain the integrity and freshness of the fish and protect it from contamination. Canning also allows skipjack tuna to be a raw material for various food products such as canned tuna, tuna in sauce, and other canned tuna. These products have become popular in the global market due to the ease of use, availability, and high nutritional value of skipjack tuna (Küçükakin et al. 2016).

In addition, skipjack tuna head bones contain gelatin extracted using the acid hydrolysis. Good quality gelatin produced from skipjack head bones can be a potential food source for pharmaceutical applications (Jalili et al. 2022). Gelatin is usually made from collagen, a protein in animals' skin, bones, and tissues. Gelatin is often used to give texture and consistency to foods such as candy, marshmallows, jellies, yogurt, ice cream, and other dishes. In addition, gelatin is also used to manufacture medicinal capsules, wound dressing materials, hair and skin care products, and photographic films (Minah et al. 2016). Gelatin contains amino acids essential for joint health, such as proline and hydroxyprolin (Suryanti et al. 2017). Gelatin consumption can help maintain cartilage structure and strength, vital for preventing joint diseases such as osteoarthritis. Gelatin contains nutrients supporting bone health, such as calcium and phosphorus (Raeatya and Rosida 2024).

Regular consumption of gelatin can help maintain bone density and prevent the risk of osteoporosis. Although often considered a part of the less desirable, skipjack head contains many vital nutrients with health benefits, such as high protein, which is essential for the growth and repair of body tissues and muscle building. Skipjack head also contains omega-3 fatty acids, such as DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid), which are essential for the health of the heart, brain, and nervous system (Apituley et al. 2020). The head of skipjack tuna contains essential minerals such as calcium, phosphorus, and selenium. Calcium is good for bone and dental health, while phosphorus is vital for energy metabolism and bone formation. Selenium is an antioxidant that can help protect the body's cells from oxidative damage. Gelatin can be obtained from the partial hydrolysis of collagen from animal skins (Aris et al. 2020).

Skipjack tuna liver, often discarded, is a valuable source of protein for human consumption. The preparation methods influence the physical, chemical, and functional properties of the skipjack tuna liver protein powder. Grinding and drying can influence the particle size and texture of protein powder. Additionally, the heating or drying may alter the powder's color and affect its final texture (Jeerakul et al. 2024). The preparation process can affect the nutrient content due to nutrient degradation and change the amino acid profile in proteins (Pawestri and Syahbanu 2023). The cooking process of skipjack tuna is determined based on color differences, texture properties, and sensory evaluation. Its nutritional quality is evaluated by measuring reduced sugar and protein levels, pH values, etc. Next, the reduced sugar and amino nitrogen content changes in the spice solution are analyzed. Boiling had the highest concentration of gradient sugar (92.5 points), and reducing sugar and non-protein nitrogen were 6.22 and 3.63 g/100 g, respectively (Zhang et al. 2023).

CHEMICAL CONTENT OF SKIPJACK TUNA

Nutritional composition

Fish is one of the most common food ingredients in Indonesia. However, fish consumption in Indonesia in 2018 was still relatively low at 50.69 kg/capita (The Ministry of Maritime Affairs and Fisheries 2023). Skipjack tuna has a high protein content and low fat. The protein content of the meat is 22.6-26.2 g/100g of meat, and the fat is 0.2-2.7 f/100 g of meat (Zulistina 2019). It has a high content of EPA and DHA. Skipjack tuna has essential amino acids such as histidine (11.37%), leucine (9.25%), lysine (7.78%), valine (7.16%), isoleucine (4.85%), threonine (4.51%), phenylalanine (3.39%), methionine (2.34%), and tryptophan (1.29%) (Canti et al. 2022). In addition, skipjack tuna contains minerals (phosphorus, sodium, iron, calcium), Vitamin A (retinol), and Vitamin B (niacin, thiamin, riboflavin). The nutritional content of skipjack tuna can vary is influenced by species, age, type, metabolic rate, season, movement activity, maturity level, and the skin and meat of skipjack tuna, which, of course, have different nutritional values (Hadinoto and Idrus 2018).

Skipjack tuna is a rich source of nutrients, containing various essential chemical components such as proteins, fatty acids, enzymes, vitamins, and minerals (Josef et al. 2019). Omega-3 fatty acids, such as eicosapentaenoic acid (EPA, $C_{20}H_{30}O_2$) and docosahexaenoic acid (DHA, $C_{22}H_{32}O_2$), are highly beneficial for heart and brain health (Pandiangnan 2016). Enzymes such as pepsin and lipase play an essential role in the body's digestive and metabolic processes; skipjack tuna also contains vitamins D ($C_{27}H_{44}O$) and B12 ($C_{63}H_{88}CoN_{14}O_{14}P$), as well as minerals such as selenium (Se), all of which support optimal body function (Damongilala 2021). Combining these various nutrients makes skipjack tuna an excellent food choice for a healthy and balanced diet.

The nutritional profile of skipjack tuna includes high protein (20% of the meat weight), omega-3 fatty acids whose fat content varies depending on age, type, and season, rich in vitamin B12 and vitamin B6, as well as several minerals such as selenium, phosphorus, iron, magnesium, and potassium. This content is important for the growth and repair of body tissues, maintains brain health and heart function, reduces the risk of cardiovascular disease, and has a significant antioxidant effect (Ali et al. 2016). The fatty acid profile found in tuna fish includes Omega-3s such as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid); omega-6 plays a role in helping the immune system and cell function. Unsaturated fatty acids in tuna fish are good for health. Omega-6 is a type of polyunsaturated fatty acid that is essential for the health of the human body and essential for the body's normal functioning, including cell growth, brain function, inflammation regulation, and hormone formation. Hence, omega-6 fatty acids are recommended for body health (Fitriyani et al. 2020).

Skipjack tuna also has the potential to contain heavy metals such as cadmium (Cd), lead (Pb), and Polonium-210 (^{210}Po). However, the levels of heavy metals in skipjack tuna are usually low, especially under normal conditions.

Nonetheless, consumption of fish contaminated with high amounts of heavy metals can lead to exposures harmful to human health, such as heavy metal poisoning, and long-term exposure to heavy metals can lead to a variety of health problems (Ruelas-Inzunza et al. 2014).

Skipjack tuna is also the best choice among other tuna options to reduce the risk of mercury exposure. It is due to several factors, such as a relatively small body size, a short life cycle, and different eating habits. In contrast to other large tuna species, skipjack tuna tend to have a smaller body and live a shorter life cycle. Therefore, the period of their mercury exposure tends to be lower. In addition, skipjack tuna prefer smaller prey and are at lower trophic levels in the seafood chain, contributing to lower mercury accumulation levels in their bodies (Gunathilaka 2016). Vitamins and minerals are essential nutrients needed in small amounts to maintain health and support various vital body functions, from maintaining healthy bones and muscles to supporting the immune system and energy metabolism (Damongilala 2021). Skipjack tuna is high in omega 3, essential fat for supporting brain memory (Muchtart 2022). Omega-3s are a group of polyunsaturated fatty acids that have the benefit of reducing the risk of heart disease by lowering triglyceride levels, blood pressure, and the risk of blood clotting and supporting brain development in fetuses and children as well as cognitive function and mental health in adults (Famimah et al. 2017).

The dominant fatty acid content in skipjack tuna meat and muscle is docosahexaenoic acid (DHA), and palmitic acid is a saturated fatty acid generally associated with increased cholesterol in the blood. This fish's palmitic acid is balanced with healthier unsaturated fatty acids, such as DHA and EPA. Stearic acid ($C_{18:0}$), also a saturated fatty acid, is found in smaller amounts than DHA and palmitic acid but still contributes to the lipid profile of these fish. Generally, fish have a high protein content of up to 20%. The protein content of fresh skipjack tuna is 21.45-25.29%; this content is greater than other species (*Thunnus tonggol*), which contains a protein of 21.8%; fresh skipjack tuna contains 0.60% fat (wet base), which is classified as low-fat fish which has a fat content of <5%, Carbohydrate content (db) of fresh skipjack tuna ($3.067 \pm 0.953\%$) and ($3 \pm 0.991.19\%$) (Nurjanah et al. 2015). The boiling process can indeed affect the nutritional content of fish, including the protein in skipjack tuna. A decrease in protein levels of about 2% after boiling for 0 to 30 minutes is a relatively small reduction. Some factors that can affect the decrease in protein levels in skipjack tuna after the boiling process are the duration of boiling, the boiling temperature, the size of the fish pieces, and the type of boiling (Pundoko et al. 2014). Skipjack tuna is known to be safe to consume because it generally has a low level of toxic metal. Factors affecting metals' low toxicity in skipjack tuna include short-lived animals, fast metabolism, feeding habits, and habitat distribution (Jinadasa et al. 2015).

Tuna bones contain about 30% collagen and 60-70% minerals in dry matter. Therefore, collagen extraction from tuna bones can be a promising way to obtain value-added products and lower environmental pollution (Yu et al. 2014). Collagen is a protein abundant in animal tissues

with a proportion of 30% of all body proteins. Collagen plays a role as the main component of connective tissue, muscles, gums and also skin. Collagen is the main connective tissue of animal proteins that has been widely used as a biomedical material. Skipjack tuna is one type of fish that is rich in collagen (Arfiani et al. 2023). Collagen is a very abundant protein in the human body, playing an important role in providing structure and strength to various tissues. Specifically, collagen is found in the skin, bones, tendons, ligaments, and other connective tissues. Collagen production decreases with age, leading to signs of aging, such as sagging and wrinkled skin and joint problems. Therefore, many supplement and skincare products contain collagen or ingredients that stimulate collagen production. One can consume collagen-rich foods such as bone broth, fish, and seafood to get the benefits of collagen.

Physico-chemical characteristics

Organoleptic characteristics

Skipjack tuna generally have white muscles. However, some tuna species have dark muscles that are red or brown. These dark muscles contain more myoglobin, a protein that binds oxygen, than white muscles. This myoglobin turns the tuna meat red or brown (Kannaiyan et al. 2019). The organoleptic value of skipjack tuna follows the SNI standard 01-4110.1-2006. The quality of raw materials is influenced by several factors, such as cold temperatures handling throughout the supply chain, which can maintain the quality of fresh skipjacks for up to 10 days of storage. Fish texture greatly influences consumers' choice of fresh fish products rather than aroma (Sumandiarsa et al. 2020).

Bacteria and parasites are potential contaminants in tuna

In China, around 200,000 tons of tuna are processed annually. In the production of tuna fillets and cans, 25-30% of the weight of the fish is fish bones (spines and skull). Currently, some of the bones are processed into fishmeal or used as a component of animal hair feed, and the rest is disposed of as hazardous waste, increasing environmental pollution. Skipjack tuna stored at cold temperatures is still suitable for consumption for up to 4 days compared to storage at room temperature. Temperatures not correctly controlled during storage can accelerate the growth of microorganisms, leading to spoilage and deterioration of fish quality. Growth of bacteria such as *Pseudomonas* spp. and *Shewanella* spp. can cause decay by producing a foul odor and mucus on the surface of the fish. In addition, some bacteria, such as *Morganella morganii*, *Proteus* spp., and *Klebsiella* spp., can produce histamine from the amino acid histidine in fish meat, causing scombroid (histamine) poisoning (Wally et al. 2015). *Salmonella* sp. is a pathogenic bacteria in fresh and frozen fishery products. The source of the *Salmonella* sp. contamination could have originated from the equipment, poor sanitation, and poor hygiene. Provisions of SNI 2729:2013 concern about quality standards for tuna, cob, and skipjack tuna for *Salmonella* sp. suggesting minimal levels of *Salmonella* sp. to maintain the quality of fishery products (Ratnaningtyas et al. 2023). *Anisakis* sp. is an endoparasite found in fish

that can cause zoonotic or anisakiasis diseases in humans. Endoparasites infest the body of fish in the form of third-stage larvae. Infection begins with the ingestion of crustaceans contaminated with *Anisakis* sp. larvae. *Anisakis* sp. larvae were found in the fish's body in the digestive tract, muscles, and fish eggs. A previous Takubak et al. (2022) study showed that 27 fish from 120 samples were positive for *Anisakis* sp.

Secondary metabolite compound contents

Secondary metabolites in skipjack tuna include steroids and triterpenoids, with a cycloalkane basic structure and diverse substituents. These compounds are vital in regulating various biological functions and demonstrate significant anti-inflammatory and antibacterial properties (Hutajulu 2022). In the test of the content of secondary metabolite compounds in tuna, it was shown that the presence of saponins was able to damage bacterial cell membranes, and glycosides consisting of sugars bound to non-carbohydrates, had various biological activities, including antibacterial activity (Kaunsui et al. 2023). The combination of these secondary metabolite compounds contributes to the ability of skipjack tuna to fight bacterial infections, making it a potential source for developing natural antibacterial agents.

Chemical structure formulas

An antioxidant collagen peptide was obtained from skipjack tuna bone by combining trypsin and chymotrypsin as the catalyst. Based on the liquid chromatography-electrospray ionization quadrupole time-of-flight mass spectrometry (LC-ESI-QTOF-MS) analysis, the amino acid sequence of the peptide was identified as Ser-Ser-Gly-Pro-Pro-Val-Pro-Gly-Pro-Met-Gly-Pro-Met-Gly-Pro-Arg (SSGPPVPGPMGPMGPR). We found that the as-prepared collagen peptide can efficiently scavenge DPPH radical (IC₅₀ value was 3.149 mM), superoxide anion radical (IC₅₀ value was 3.803 mM), and ABTS radical (IC₅₀ was 9.489 mM). In addition, it has been found that the methionine (Met) residue in the collagen peptide could provide a precise active site during the scavenging of DPPH radicals by Fourier transform infrared spectroscopy (FTIR) analysis and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry analysis. Ding et al. (2019) suggest that the peptide can be used in the food, cosmetic and pharmaceutical industries.

MODERN USE OF SKIPJACK TUNA

Skipjack tuna is vital in maintaining fishery resources essential for global food security. As a member of the tuna family, skipjack represents one of several commercially important species that contribute significantly to the fishing industry. Nearly 7.7 million tonnes of tuna have been caught worldwide, accounting for 4.6% of all catches and aquaculture production (Sculley 2016). The highest output of skipjack tuna was in Bitung, North Sulawesi, in 2009, with around 6,132 tons, with a 398 billion rupiah (Asia et al. 2015).

Dried skipjack tuna or *katsuobushi* is a processed product of dried fish or smoked fish produced by boiling and drying. The production process of dried skipjack uses a fish drying oven with a drying time of 1.5 hours to reduce the water content by 50% and evenly cooked. The evenly cooked fish produces a texture of fish meat that is not too hard or mushy, and the color of the fish meat becomes reddish-brown, creating a savory taste. Dried skipjack tuna can be packaged using plastic packaging (Pamungkas and Irawan 2023).

Skipjack tuna is widely used as smoked fish. The organoleptic tests required for smoked fish include the acceptability of an ingredient, product quality, physical properties of the product, and moisture content contained because it can affect the texture and determine the durability (Ibrahim et al. 2014). Monitoring the quality of smoked skipjack tuna is very important to ensure that the products are safe and high-quality, following the Indonesia National Standard (SNI) 2725.1:2009 concerning smoked fish. This quality monitoring aims to protect consumers, build consumer trust, and increase product competitiveness (Hadinoto et al. 2016). Product competitiveness refers to the ability of a product to compete effectively with similar products from its competitors. It includes several factors, such as product quality, price, innovation, marketing, and customer service. Products with high competitiveness tend to have an advantage in one or several of these factors, making them more attractive to consumers than similar products from their competitors. A product with strong competitiveness tends to maintain or increase its market share and create sustainable profits.

In fish processing, salting and drying is the type of preservation most often used by the community for fishery products. It aims to remove some of the water in the fish body to inhibit the growth of microorganisms and bacteria that can damage fishery products (Nurhandayani et al. 2023). Currently, traditional fish processing still has prospects for development. Salted fish is an extensive, conventional fishery product in Indonesia due to its easiness, cheapness, and fast processing methods. It has the advantage of not requiring ice and storage at low temperatures, but the disadvantage is the lack of innovation for fishermen who process dry salted fish. However, synthetic chemical preservatives such as formalin, bleach, and borax affect the salted fish produced.

The other preservative ingredient is *atung* (*Parinarium glaberrimum*) seeds, which have broad-spectrum antibacterial and antioxidant properties. The seeds of the *atung* fruit are removed from the fruit, grated, and dried in the sun. Then, it is mashed by blending and put into plastic. An innovation breakthrough is low salt content technology in salted fish using a combination of salt and *atung*. The preservation process is done by soaking in a solution containing a salt concentration of 5 and 10%, followed by soaking in *atung* with the same concentration.

To make a 3% *atung* solution, mix 30 grams of *atung* with 1,000 mL of water. The *atung* solution can also be made at 4 and 5%. Combine 50 grams of salt with 1,000 mL of water. It can be adjusted to a 10% salt solution for use with the *atung* solutions on skipjack tuna. Clean and

cut the fish (2.5-10 kg) into long fillets. Soak the fillets in a 5% salt solution for 30 minutes, then in a 10% salt solution for another 30 minutes. Next, soak the fillets in 3, 4, and 5% *atung* solutions for 30 minutes each. After soaking, dry the fillets in the sun for 7-8 hours daily over 2-3 days. Finally, the dried fillets are weighed, and their moisture, protein, salt content, and total plate count (TPC) are tested according to Moniharapon et al. (2022). It can be used as a dietary supplement derived from unsaturated fatty acids, offering various health benefits. It is an anti-inflammatory and antiarrhythmic agent essential for heart health (Yulianto et al. 2022). Another processed fish is tuna nuggets from fresh tuna fish of high nutritional quality. With the development of current technology, skipjack tuna can make a variety of delicious processed food ingredients and contain many nutrients. Skipjack tuna nuggets combine flour, spices, and other ingredients such as flour, herbs and others mixed with fish meat (Prabowo et al. 2023).

PHARMACOLOGICAL PROPERTIES

Skipjack tuna is a very healthy food and has many health benefits. Consuming skipjack tuna can help maintain heart health, lower high blood pressure, increase immunity, prevent cancer and kidney function, and improve blood circulation (Huang et al. 2023). Skipjack tuna contains high levels of the amino acid histidine, which microorganisms can convert into histamine during deterioration. Excessive consumption of histamine may lead to allergic reactions or poisoning. Following the fish's death, proteins break down into amino acids, including histidine. This histidine can react with the enzyme histidine decarboxylase produced by certain bacteria, resulting in the formation of histamine (Ismail 2024). The sodium content in various types of salted fish, including skipjack tuna, tude, roa, deho, and oci fish, ranges from 200 to 400 mg per 50 grams. Research indicates that individuals consuming more than 6 grams of salt per day have a significantly higher risk—approximately 5 to 6 times greater—of developing hypertension compared to those who maintain a lower salt intake. The World Health Organization (WHO) recommends limiting salt consumption to a maximum of 6 grams daily, equivalent to 2,400 mg of sodium. In light of this information, it is prudent to limit the consumption of salt-preserved foods, including salted fish varieties such as skipjack tuna, tude, roa, deho, and oci fish (Manikome et al. 2016). However, consuming skipjack tuna in reasonable quantities is still important to avoid the potential risk of heavy metal contamination (Anggraini et al. 2022). Skipjack tuna has many health benefits due to its rich nutrient content, including omega-3 fatty acids, selenium, and high-quality protein. These benefits include the prevention of arteriosclerosis, anticancer properties, anti-inflammatory effects, and the ability to lower blood cholesterol levels (Zheng et al. 2022). Consuming skipjack tuna regularly can have health benefits, including prevention of cholesterol disease, prevention of heart disease, and improved cardiovascular system health. In addition, skipjack tuna is an excellent food choice to support a diet program because

it is low in calories, high in protein, and rich in nutrients (Jemri and Jannah 2022).

Pickled skipjack tuna skin extract had strong antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, and *Streptococcus*) and Gram-negative (*Escherichia coli*, *Salmonella typhimurium*, and *Pseudomonas aeruginosa*). The antibacterial activity is due to the extract's antimicrobial peptides and proteins. It could treat bacterial infections, food conservation, and health products.

Antioxidant properties are very important for the body because they help fight the adverse effects of free radicals. Free radicals are unstable molecules and can damage the body's cells, causing oxidative stress, which is linked to various health problems, including premature aging, cancer, heart disease, and neurodegenerative disorders (Arifin and Ibrahim 2018).

In addition, bioactive peptides in skipjack tuna also show antihypertensive, antioxidant, and immunomodulatory potential, which can be used to treat hypertension, inflammation, and degenerative diseases (Aluko 2015). Research is ongoing to explore the benefits of bioactive compounds from skipjack tuna, including omega-3 extraction, bioactive peptides for the treatment of hypertension, and the potential of antioxidant compounds to support the immune system and fight free radicals.

Skipjack tuna can prevent arteriosclerosis, anticancer, anti-inflammatory, and lower blood cholesterol levels, where the content of skipjack tuna includes omega-3 fatty acids, high-quality protein, and essential vitamins and minerals. They can help lower triglyceride levels in the blood, reduce inflammation, and slow down plaque formation in the arteries. They can also increase HDL cholesterol (good cholesterol) levels, which helps clear the arteries (Zheng et al. 2022). These nutrients work together to maintain human health, prevent diseases, and support optimal body function (Balami et al. 2019). Bogati (2018) explained that consuming skipjack tuna can help lose weight while maintaining appetite and muscle mass. It is known that DNA damage is hazardous and can give rise to various deadly diseases such as cancer, coronary heart, diabetes, etc. However, the antioxidant ability of skipjack tuna protein hydrolysate is shown by the ability to prevent DNA damage caused by hydroxyl radicals.

Skipjack tuna also contains anti-inflammatory compounds derived from eyeball oil (TEO). Eye oil (TEO) is a natural source of anti-inflammatory components, especially omega-3 fatty acids that effectively reduce nitric oxide (NO) levels and pro-inflammatory cytokines by up to 50% in a dose-dependent manner. Taking TEO may provide various health benefits, including reduced inflammation, support for autoimmune diseases, improved heart health, and protection against neurodegenerative diseases (Jeong et al. 2016). Extracting bioactive compounds from skipjack tuna must be considered efficient without wasting resources. Inefficient practices can lead to huge waste. Developing methods for synthesizing bioactive compounds or using other materials that do not rely on fish can reduce pressure on fish stocks.

CONCLUDING REMARK

Skipjack tuna is an important fisheries resource that impacts global food security. Its wide distribution pattern, spawning throughout the year, and being found in many parts of the world make skipjack tuna the main commodity in world fisheries. The body parts of skipjack tuna have various benefits for humans. Skipjack tuna is prized for its flesh, while the fins are used for soups and stocks, adding flavor. The tail can be fried or used in fish soups. Gills are key for fish sauce, and bones are utilized for stock or fish bone chips. Tuna skipjack tuna can be processed in various ways and offers numerous health benefits, such as supporting heart health, lowering blood pressure, boosting immunity, preventing cancer, and improving blood circulation. All parts of the skipjack tuna—meat, fins, tail, gills, liver, skin, and bones—are edible and possess health advantages, making it valuable for diet and pharmaceuticals. This utilization is due to a large amount of protein, fatty acids, enzymes, vitamins, and minerals owned by skipjack tuna more than other fish, which makes skipjack tuna fish one of the types of fish that has many benefits and is widely used until now, this shows that there is a maximum level of utilization of skipjack tuna.

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Review: Bioactive compounds and health applications of *Digenea simplex* (Rhodophyta)

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Abstract. Saputra AF, Utomo AN, Pramesthi AZ, Madjid AA, Nugroho GD, Setyawan AD. 2025. Review: Bioactive compounds and health applications of *Digenea simplex* (Rhodophyta). *Cell Biol Dev* 8: 90-108. *Digenea simplex* (Rhodophyta), a red macroalga widely distributed in tropical and subtropical coastal waters, has gained attention due to its unique chemical profile. However, scientific studies on this species remain scattered and limited. This review aims to consolidate current knowledge on the bioactive compounds present in *D. simplex*, their bioactivities, and their potential applications in various industries. Phytochemical investigations have revealed that *D. simplex* contains a variety of secondary metabolites, including kainic acid, dimethylallyl pyrophosphate, carotenoids (such as astaxanthin), essential amino acids, and tannins. These compounds have demonstrated several pharmacological effects, including antioxidant, antidiabetic, antitumor, antimicrobial, and anti-inflammatory activities. The presence of kainic acid, for instance, highlights the neuroactive potential of the species, while carotenoids and phenolic compounds contribute significantly to its antioxidant capacity. In addition, the nutritional profile of *D. simplex*, comprising proteins, dietary fibers, vitamins, and minerals, supports its use as a functional food ingredient. The cosmetic industry also benefits from its bioactive constituents, which exhibit moisturizing, anti-aging, and skin-protective properties. Despite its promising profile, further studies are necessary to standardize extraction methods, evaluate toxicological safety, and elucidate the mechanisms of action of its bioactive compounds. This review provides a comprehensive reference for future research and valorization of *D. simplex* as a valuable marine resource for health-related applications.

Keywords: Bioactive compounds, *Digenea simplex*, marine natural products, red algae

INTRODUCTION

Marine ecosystems, covering around 70% of the Earth's surface, represent the planet's most extensive and diverse habitat (Dayanidhi et al. 2021). Among their components, red algae (Rhodophyta) are especially valued for their pigments, nutrients, and secondary metabolites with pharmacological and industrial significance (Bhuyar et al. 2021; Kumar and Arunkumar 2023). These include polysaccharides, flavonoids, alkaloids, and terpenoids with antioxidant, antimicrobial, and anti-inflammatory properties (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). Sulfated polysaccharides like carrageenan are especially notable for their biomedical and cosmetic uses (Cicinskas et al. 2020; Sahin and Ozturk 2021; Aboeita et al. 2022; Abd El-Aziz et al. 2023).

One species of interest is *Digenea simplex* (Wulfen) C. Agardh (Rhodomelaceae), found in tropical and subtropical intertidal zones (Betancor et al. 2015; Boo et al. 2018). Known for its red pigments—phycobiliproteins and carotenoids (Schneider et al. 2018; Gljušćić et al. 2022)—*D. simplex* has long been used in Asian traditional medicine, though scientific research remains limited (Chekan et al.

2019; Chen et al. 2020). A key compound, kainic acid, is widely used in neuroscience to model epilepsy and study neurotoxicity (Connell et al. 2017; Maeno et al. 2019; Asakawa et al. 2020), and may function as a natural defense molecule (Vezzani et al. 2016; Jiang et al. 2018).

In addition, *D. simplex* participates in isoprenoid biosynthesis via Dimethylallyl Pyrophosphate (DMAPP), yielding essential pigments like chlorophyll and carotenoids such as astaxanthin and β -carotene—potent antioxidants with protective cellular roles (Sathasivam and Ki 2018; Chekan et al. 2019; Ganley et al. 2020; El-Malek et al. 2022; Dini 2022; Bayomy and Alamri 2024). Nutritionally, *D. simplex* offers essential amino acids, fibers, vitamins, and minerals (Chalid 2010; Ward and Deyab 2021), with tannins contributing to its antioxidant and anti-herbivore defenses (Ibraheem et al. 2017; El-Rafie et al. 2023).

Red algae, including *D. simplex*, also demonstrate antidiabetic activity due to compounds like phlorotannins and sulfated polysaccharides that inhibit enzymes linked to glucose metabolism (Chia et al. 2018; Van Weelden et al. 2019; Luthuli et al. 2019; Pradhan et al. 2020). This supports the search for safer, natural antidiabetic agents (Alam et al. 2021; Hasan et al. 2022). However, despite its

potential, *D. simplex* remains underexplored. Existing studies are often fragmented, lack standardized methods, and provide limited toxicity or mechanism data (Alves et al. 2018; Dhanalakshmi and Jayakumari 2018).

This review aims to synthesize available knowledge on the phytochemistry, bioactivities, and applications of *D. simplex*, emphasizing its value and identifying research gaps. With further study, this species could offer novel compounds and support sustainable development in health-related industries.

TAXONOMY AND MORPHOLOGY

The genus *Digenea*, classified under the Rhodomelaceae family (Ceramiales, Florideophyceae, Rhodophyta), was traditionally considered monotypic, with *Digenea simplex* as its only recognized species. However, recent molecular phylogenetic studies have identified additional taxa, such as *Digenea mexicana* G.H.Boo and D.Robledo and *Digenea rafaellii* G.H.Boo, G.Andrade-Sorcia and S.M.Boo, highlighting the need for a taxonomic reassessment using DNA-based tools. Historically, the identification of *D. simplex* relied heavily on external morphological traits like branching patterns and pigmentation, which are often influenced by environmental factors. This phenotypic plasticity has complicated species delimitation, underscoring the importance of combining morphological, anatomical, and molecular data for accurate classification. The absence of preserved reference specimens in older records further hinders current taxonomic resolution.

Morphologically, *D. simplex* features a prostrate base with discoid holdfasts and an erect, pseudo-dichotomously branched structure forming tufts or mats (Figure 1). This arrangement enhances mechanical stability and light acquisition in high-energy intertidal zones. The thallus is composed of central axial cells encircled by pericentral and cortical cells, contributing to structural integrity and herbivore defense. A mucilaginous surface layer protects against desiccation and microbial intrusion, while pigmentation dominated by phycoerythrin and carotenoids (e.g., astaxanthin, lutein) aids in photosynthesis and antioxidant activity. The cell wall is composed primarily of cellulose and sulfated galactans such as carrageenan, which enhance flexibility, osmotic tolerance, and commercial value. Reproductive elements, including tetrasporangia (asexual) and cystocarps (sexual), are consistent with Florideophyceae characteristics and crucial for life cycle and species recognition. These morphological and biochemical features reflect the species' successful adaptation in dynamic coastal ecosystems and support its promise for future biotechnological applications.

HABITAT AND DISTRIBUTION

Digenea simplex is commonly found in tropical and subtropical coastal regions, typically inhabiting intertidal and shallow subtidal environments with rocky substrates (Betancor et al. 2015). It adheres firmly to hard surfaces

such as rocks, coral rubble, and tide pool walls, where it forms dense mats or tufts. These habitats are characterized by moderate to high wave action, periodic exposure to sunlight, and fluctuating salinity, requiring physiological adaptations such as mucilage production and UV-resistant pigments (Boo et al. 2018; Gljušić et al. 2022). In many locations, *D. simplex* coexists with other macroalgal species, such as *Cystoseira humilis*, forming complex intertidal algal communities (Betancor et al. 2015).

Historically, *D. simplex* was first described in the Adriatic Sea near Trieste in the early 19th century, but subsequent reports have recorded its occurrence across the Atlantic, Indian, and Pacific Oceans (Collins et al. 1913; Boo et al. 2018). It is commonly found along the coasts of the Canary Islands, Bermuda, the Mediterranean, the Red Sea, and Southeast Asia, including Indonesia and the Philippines (Dumilag et al. 2022). The species is known for its broad pantropical distribution, though detailed molecular and morphological studies suggest it may represent a complex cryptic species rather than a single cosmopolitan taxon (Díaz-Tapia et al. 2017; Boo et al. 2018). As such, modern records of distribution should be interpreted with caution unless supported by voucher specimens or DNA barcoding.

Environmental conditions strongly influence the local abundance and vertical distribution of *D. simplex*. It is typically most abundant in shallow rock pools, especially in areas with high light availability and moderate water movement (Betancor et al. 2015). The species can occur from the upper subtidal zone down to depths of approximately 4 meters, depending on light penetration and substrate availability. In intertidal pools, *D. simplex* demonstrates strong resilience to desiccation and salinity fluctuations, partly due to its thick mucilaginous coating and antioxidant pigment systems such as phycoerythrin and carotenoids (Fernando et al. 2016; Sathasivam and Ki 2018), which enable it to demonstrate strong resilience to desiccation and salinity fluctuations. These adaptations allow it to maintain photosynthetic activity and structural integrity in environments with highly variable abiotic conditions, showcasing its remarkable adaptability.



Figure 1. *Digenea simplex* (Schneider et al. 2018)

Anthropogenic pressures such as coastal pollution, tourism, and habitat modification can significantly affect the distribution and health of *D. simplex* populations. Because it is sensitive to changes in water quality, particularly turbidity and nutrient enrichment, *D. simplex* has the potential to serve as a bioindicator of intertidal ecosystem health (Pereira 2015). Studies have also shown that macroalgae like *D. simplex* can accumulate heavy metals, making them useful in monitoring marine contamination (El-Rafie et al. 2023). However, excessive eutrophication or sedimentation can smother rocky substrates and reduce light availability, limiting its growth and distribution.

Seasonal variation may also influence the abundance and reproductive cycles of *D. simplex*. While it can be found year-round in tropical environments, peak growth and reproductive activity often occur during warmer months with higher irradiance (Zongo et al. 2022). In some regions, reproductive structures such as tetrasporangia and cystocarps have been observed during summer, suggesting temperature and photoperiod as key regulatory factors (Boo et al. 2018). These phenological patterns may vary geographically, emphasizing the need for region-specific ecological studies to inform conservation and cultivation efforts.

D. simplex occupies a broad but ecologically specific niche in warm, rocky coastal environments. Its distribution is influenced by a combination of abiotic factors (light, substrate, salinity, temperature) and biotic interactions (competition, herbivory), as well as anthropogenic impacts. The species' resilience to environmental stressors, combined with its ecological specificity, highlights its value both as a subject of scientific study and as a potential biomonitor for intertidal ecosystems.

CHEMICAL DIVERSITY

The biochemical profile of *Digenea simplex* comprises a wide spectrum of primary and secondary metabolites produced via amino acid, isoprenoid, and phenolic biosynthetic pathways, contributing to its physiological function, ecological adaptation, and biotechnological value. These include neuroactive amino acid derivatives, antioxidant pigments, isoprenoids, phenolics, and proteinaceous compounds, many of which have recognized therapeutic and functional food potential (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018; Bayomy and Alamri 2024), with kainic acid standing out as a well-studied neuroexcitatory compound of pharmacological significance.

Kainic Acid (KA)

Kainic acid is a naturally occurring pyrrolidine dicarboxylic acid first isolated from *D. simplex* in the mid-20th century and is one of the most well-known bioactive compounds derived from marine red algae (Chekan et al. 2019; Maeno et al. 2019). The compound exhibits strong neuroexcitatory activity due to its ability to act as an agonist of kainate-type ionotropic glutamate receptors in the central nervous system (Connell et al. 2017; Asakawa et al. 2020). Because of this activity, kainic acid has been

extensively used in neuroscience research, particularly in the development of rodent models of epilepsy and excitotoxic neurodegeneration (Vezzani et al. 2016). Its structural uniqueness among marine-derived amino acids has made it a subject of interest not only for pharmacology but also for synthetic chemistry and neurobiology.

The biosynthesis of kainic acid in *D. simplex* involves the coupling of glutamic acid with a pyrrolidine ring, forming a highly polar molecule that mimics endogenous excitatory neurotransmitters (Chekan et al. 2019). Recent studies have identified key enzymes involved in its biosynthetic pathway, including *kabA* and *kabC*, which are part of a modular gene cluster unique to certain red algae (Chekan et al. 2019). This discovery has opened up new possibilities for the heterologous expression of kainic acid in microbial systems and synthetic biology platforms. The localization of kainic acid within algal tissues suggests its ecological role as a chemical defense against herbivory, deterring invertebrate grazers and possibly influencing microbial colonization (Jiang et al. 2018).

Although kainic acid is neurotoxic in mammalian systems at high concentrations, its potential therapeutic applications are under investigation. Studies have explored its effects on inducing seizures for anti-epileptic drug screening and in evaluating neuroprotective agents that can counteract excitotoxicity (Connell et al. 2017; Asakawa et al. 2020). Moreover, modified derivatives of kainic acid have been synthesized to reduce toxicity while preserving receptor selectivity, offering avenues for safer pharmaceutical development. The controlled use of kainic acid and its analogs may contribute to the treatment of disorders related to glutamatergic dysfunction, including epilepsy, Alzheimer's disease, and chronic pain (Vezzani et al. 2016; Chekan et al. 2019).

Despite its biomedical relevance, the natural abundance of kainic acid in *D. simplex* varies depending on geographical location, environmental stressors, and possibly life cycle stage (Chen et al. 2020). Most existing reports focus on algal populations in the Indo-Pacific and Mediterranean regions, with few comparative studies on seasonal or spatial variation in metabolite content (Betancor et al. 2015; Boo et al. 2018). There remains a need for comprehensive ecological and biochemical surveys to determine the environmental cues that regulate kainic acid production in natural populations. Such insights could inform both sustainable harvesting practices and the development of aquaculture strategies to optimize yields of this valuable compound.

Kainic acid thus represents a rare example of a marine algal metabolite with clearly defined pharmacological targets and widespread use in biomedical research. Its presence in *D. simplex* underscores the species' unique phytochemical profile and its relevance beyond ecological roles. Continued investigation into the biosynthesis, regulation, and biotechnological production of kainic acid will not only enhance our understanding of red algal chemistry but also expand the pharmacopeia of marine-derived neuroactive agents.

Dimethylallyl Pyrophosphate (DMAPP) and isoprenoids

Dimethylallyl Pyrophosphate (DMAPP) is a key precursor in the isoprenoid biosynthetic pathway, serving as a universal five-carbon building block for the synthesis of terpenoids, sterols, carotenoids, and other prenylated compounds (Ganley et al. 2020; Dini 2022). In red algae such as *Digenea simplex*, DMAPP is synthesized through the mevalonate (MVA) pathway or the Methylerythritol Phosphate (MEP) pathway, both of which contribute to the diversity of isoprenoid end-products (El-Malek et al. 2022). These pathways are tightly regulated and compartmentalized in plastids and cytosol, enabling algae to generate a wide spectrum of terpenoid metabolites critical for survival and interaction with their environment. The isoprenoid pathway is evolutionarily conserved and represents one of the most chemically diverse biosynthetic systems in nature.

In *Digenea simplex*, isoprenoid derivatives derived from DMAPP include carotenoids, phytol, sterols, and chlorophyll side chains, many of which play essential roles in photoprotection, membrane stabilization, and oxidative stress responses (Sathasivam and Ki 2018; Bayomy and Alamri 2024). Carotenoids such as β -carotene, lutein, and astaxanthin, for instance, are formed through sequential condensations involving DMAPP and Isopentenyl Pyrophosphate (IPP), catalyzed by prenyltransferases. These pigments not only contribute to the characteristic coloration of red algae but also exhibit potent antioxidant activity, making them valuable in nutraceutical and cosmetic applications (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). Furthermore, isoprenoids serve as precursors for plant hormones and volatile organic compounds, which may have ecological signaling functions.

Biotechnological interest in DMAPP and isoprenoid biosynthesis from marine algae has grown in recent years due to the industrial relevance of terpenoids, particularly for pharmaceuticals, flavors, and biofuels (Ganley et al. 2020). Microbial production systems are now being engineered to express red algal enzymes involved in DMAPP synthesis, with the goal of producing high-value compounds such as artemisinin and taxadiene sustainably (El-Malek et al. 2022). Understanding the genetic regulation of DMAPP biosynthesis in algae like *D. simplex* is critical for optimizing these biotechnological platforms. Advances in genome sequencing and transcriptomic analyses may eventually uncover novel enzymes and regulatory elements unique to red algal isoprenoid pathways.

Ecologically, isoprenoids in *D. simplex* also function as chemical defenses, UV protectants, and osmoprotectants, supporting algal survival in intertidal habitats exposed to fluctuating salinity, temperature, and light (Betancor et al. 2015; Bayomy and Alamri 2024). The multifunctional nature of these compounds reflects their evolutionary significance and explains the metabolic investment required for their biosynthesis. Moreover, certain volatile isoprenoids derived from DMAPP may serve as allelopathic agents or chemical signals to neighboring organisms, although this role remains understudied in red algae. Future ecological studies are needed to clarify the role of isoprenoids in mediating species interactions and community dynamics in coastal ecosystems.

The presence and diversity of DMAPP-derived compounds in *D. simplex* emphasize the alga's rich metabolic plasticity and highlight its potential for bioprospecting in the field of marine natural products. Given the increasing demand for sustainable sources of bioactive terpenoids and pigments, *D. simplex* offers both ecological and industrial value. Detailed characterization of its isoprenoid pathway, supported by metabolomic and genomic tools, will pave the way for the development of novel compounds with therapeutic and commercial applications.

Figure 2.A illustrates the carotenoid biosynthetic pathway in *D. simplex*, starting from dimethylallyl pyrophosphate (DMAPP) and leading to astaxanthin. It emphasizes its role in antioxidant function and pigmentation.

Carotenoids

Carotenoids are lipid-soluble pigments derived from isoprenoid precursors, including dimethylallyl pyrophosphate (DMAPP), and are essential components of red algal metabolism (Fernando et al. 2016; Sathasivam and Ki 2018). In *D. simplex*, carotenoids contribute not only to the reddish pigmentation of the thallus but also to various physiological functions such as photoprotection, antioxidation, and membrane stabilization (Bayomy and Alamri 2024). The predominant carotenoids identified in red algae include astaxanthin, β -carotene, lutein, zeaxanthin, and violaxanthin, many of which have potent biological activities (Ganley et al. 2020; Dini 2022). These compounds are known to quench singlet oxygen and scavenge Reactive Oxygen Species (ROS), protecting cellular components from oxidative damage caused by UV radiation and environmental stressors.

Astaxanthin is among the most biologically significant carotenoids found in red algae, including *D. simplex*, due to its superior antioxidant capacity and ability to modulate immune responses (Fernando et al. 2016). It is widely used in the nutraceutical and aquaculture industries as a pigment and health enhancer, and its biosynthesis in marine organisms has attracted considerable commercial interest (Sahin and Ozturk 2021). Astaxanthin also exhibits anti-inflammatory and anti-aging properties, making it a valuable ingredient in functional foods and cosmeceuticals (Agatonovic-Kustrin and Morton 2018). The presence of astaxanthin in *D. simplex* adds significant value to this alga as a potential source of high-demand bioactive compounds.

β -carotene, another major carotenoid in *D. simplex*, serves as a precursor to vitamin A (retinol) and has important nutritional relevance (Dini 2022). It plays a dual role in protecting photosynthetic systems from photooxidative stress and acting as an antioxidant in human health applications. Studies have demonstrated the ability of β -carotene to reduce lipid peroxidation, modulate immune responses, and lower the risk of chronic diseases such as cardiovascular disorders and certain cancers (Alves et al. 2018; Bayomy and Alamri 2024). The bioavailability and efficacy of β -carotene depend on factors such as molecular configuration, cellular matrix, and coexisting lipids, making algae-based delivery systems a topic of growing research interest.

Digestibility is another critical aspect of *D. simplex* protein utilization. The cell wall of red algae contains complex polysaccharides such as carrageenans and cellulose, which can impede enzymatic access to intracellular proteins. However, processing methods such as fermentation, enzymatic hydrolysis, and mechanical disruption have been shown to improve digestibility and protein extraction. These approaches enhance bioavailability and expand the range of food and feed products that can incorporate algal proteins. Technological advances in preprocessing thus play a pivotal role in unlocking the nutritional and functional potential of *D. simplex* as a sustainable protein source.

In addition to nutritional value, proteins from *D. simplex* exhibit bioactive properties that contribute to health promotion. Marine-derived peptides have demonstrated antioxidant, antimicrobial, and anti-inflammatory activities. Some hydrolysates inhibit Angiotensin-Converting Enzyme (ACE), suggesting potential for managing hypertension. These multifunctional properties increase the attractiveness of *D. simplex* for use in functional foods and nutraceuticals. Analytical techniques such as high-performance liquid chromatography (HPLC), nuclear magnetic resonance (NMR), and mass spectrometry (MS) have facilitated the identification of these peptides and their post-translational modifications. Omics-based methods—especially proteomics and metabolomics—provide powerful tools to elucidate the protein landscape of this species further.

As global interest in alternative protein sources grows, *D. simplex* presents a compelling case for inclusion in sustainable food systems. Its cultivation requires minimal inputs no arable land, freshwater, or synthetic fertilizers—making it compatible with circular economy and blue biotechnology principles. Combining *D. simplex* protein with other marine resources could yield novel food products with superior nutritional and functional profiles. Overall, the amino acid and protein composition of *D. simplex* reflects its ecological adaptability and multifunctional potential, positioning it as a valuable candidate for diverse applications in food, feed, and health-related industries.

Tannins and phenolic compounds

Tannins and phenolic compounds are widely recognized as important secondary metabolites in marine algae, including red macroalgae such as *D. simplex*. These compounds are synthesized primarily through the shikimate and phenylpropanoid pathways and serve various ecological and physiological functions, including defense against herbivory, microbial infection, and oxidative stress (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). In *D. simplex*, phenolic constituents contribute significantly to the alga's antioxidant capacity and are considered among its key bioactive constituents (Bayomy and Alamri 2024). Phenolics in red algae exist in both free and bound forms, often localized within the cell wall matrix or vacuoles, and their composition can vary with environmental conditions.

Tannins, a subset of polyphenols, are high-molecular-weight compounds capable of binding to proteins and metal ions. Their presence in *D. simplex* has been associated with

anti-nutritional effects in some contexts, but more importantly, with health-promoting properties such as antioxidant, antimicrobial, and antidiabetic activities (Ibraheem et al. 2017). Marine algal tannins, although less studied than their terrestrial counterparts, have shown unique structural features such as sulfation, which may enhance their biological activity and solubility in aqueous environments (Chia et al. 2018). These features differentiate red algal tannins from those of higher plants and may contribute to their effectiveness in aqueous biological systems.

Phenolic acids such as gallic acid, protocatechuic acid, and ferulic acid have been reported in various Rhodophyta species and are likely present in *D. simplex* as well (Fernando et al. 2016; Pratita et al. 2023). These low-molecular-weight phenolics act as potent radical scavengers, metal chelators, and inhibitors of lipid peroxidation, which are critical mechanisms in preventing oxidative damage in both algal tissues and potential human applications. In addition, red algal phenolics may exhibit synergistic effects with other antioxidants, such as carotenoids and phycobiliproteins, enhancing the overall bioactivity profile of the species (Alves et al. 2018). Such synergism is particularly relevant in the development of functional food ingredients or nutraceutical formulations.

Environmental stressors such as high light intensity, UV radiation, nutrient limitation, and salinity fluctuation are known to modulate phenolic content in red algae (Betancor et al. 2015). These stress conditions can stimulate the upregulation of phenolic biosynthetic enzymes, leading to increased accumulation of protective metabolites. Therefore, controlled cultivation of *D. simplex* under specific abiotic stress regimes may be strategically employed to enhance phenolic yields for industrial or pharmacological purposes. Moreover, the variability in phenolic profiles due to habitat or season may serve as a chemotaxonomic marker, aiding in species or population-level differentiation (Pereira 2015).

The extraction and characterization of phenolic compounds from *D. simplex* typically involve solvent-based methods using aqueous ethanol or methanol, followed by analytical techniques such as HPLC, LC-MS, or NMR (Dini 2022). Recent developments in green extraction technologies, such as supercritical CO₂ and ultrasound-assisted extraction, offer more sustainable approaches for isolating phenolics from marine biomass. Understanding the phenolic composition of *D. simplex* not only advances its value as a functional ingredient but also opens avenues for the discovery of novel marine-derived antioxidants with therapeutic potential.

Altogether, *D. simplex's* presence of tannins and phenolic compounds highlights the alga's biochemical versatility and pharmacological relevance. These metabolites contribute to its ecological fitness and bioactivity profile, making it a promising candidate for further exploration in antioxidant, anti-inflammatory, and antimicrobial applications. Ongoing studies on the environmental modulation, structural diversity, and bioavailability of these compounds will be crucial to unlocking their full potential in health-related industries.

BIOLOGICAL ACTIVITIES

The bioactive compounds identified in *Digenea simplex* are associated with a wide range of pharmacological and physiological effects. These biological activities reflect the multifunctional nature of the alga's secondary metabolites, which have been shown to act on multiple targets such as oxidative stress, inflammation, tumor progression, microbial infection, and metabolic dysregulation. The synergistic interactions among phenolics, carotenoids, sulfated polysaccharides, and amino acid derivatives contribute to a broad-spectrum therapeutic potential. A summary of these key chemical constituents and their associated bioactivities is presented in Table 1, highlighting their relevance to traditional and modern medical applications. Investigating these effects in detail is essential for understanding the mechanisms underlying the health benefits of *D. simplex* and for identifying applications in pharmaceutical, nutraceutical, and functional food development.

Antioxidant activity

Oxidative stress, defined as an imbalance between the production of Reactive Oxygen Species (ROS) and the body's antioxidant defenses, is a major contributing factor in the development of chronic diseases such as cancer, cardiovascular disorders, neurodegeneration, and diabetes (Di Meo and Venditti 2020). Natural antioxidants play a

critical role in neutralizing ROS and reducing oxidative damage at the cellular level. Marine macroalgae, including red algae such as *D. simplex*, have been increasingly recognized as rich sources of antioxidant compounds with therapeutic potential (Fernando et al. 2016; Alves et al. 2018). The antioxidant activity of these algae arises from a combination of bioactive constituents such as phenolics, carotenoids, amino acids, and sulfated polysaccharides.

Several studies have demonstrated the strong antioxidant capacity of red algae through various in vitro assays, including DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging, ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) activity, Ferric Reducing Antioxidant Power (FRAP), and metal chelation tests (Agatonovic-Kustrin and Morton 2018). Although specific data on *D. simplex* remains limited compared to more extensively studied species such as *Palmaria palmata* or *Chondrus crispus*, available evidence suggests that *D. simplex* exhibits comparable radical scavenging activity, likely due to the presence of polyphenols and pigment antioxidants such as astaxanthin and β -carotene (Bayomy and Alamri 2024). These compounds are well-known for their ability to quench singlet oxygen and scavenge free radicals, thus protecting cellular components such as lipids, proteins, and DNA from oxidative damage (Sathasivam and Ki 2018).

Table 1. Summary on *Digenea simplex* chemical constituents, pharmacological properties, and medical utilization

Name	Chemical constituents	Pharmacological properties	Traditional medical utilization	Modern medical utilization	References
<i>D. simplex</i>	Kainic acid (pyrrolidine dicarboxylic acid)	Neuroexcitatory, antiparasitic, glutamate receptor agonist	Used as an anthelmintic in traditional Japanese medicine	Tool for epilepsy research; potential neuromodulator in neurodegenerative disease models	Maeno et al. 2019; Chekan et al. 2019; Asakawa et al. 2020
<i>D. simplex</i>	Sulfated polysaccharides (e.g. carrageenans)	Antiviral, immunomodulatory, anti-inflammatory, antioxidant	Folk use for digestive balance and wound application (limited documentation)	Topical antiviral gels, immune-support supplements, drug delivery materials	Cicinskas et al. 2020; Aboeita et al. 2022; Sathasivam and Ki 2018
<i>D. simplex</i>	Carotenoids (astaxanthin, β -carotene, lutein)	Antioxidant, photoprotective, anti-aging, anticancer	-	Functional food ingredients; cosmeceuticals; anti-aging skincare	Fernando et al. 2016; Bayomy and Alamri 2024; Dini 2022
<i>D. simplex</i>	Polyphenols and tannins (e.g., gallic acid derivatives)	Antioxidant, antidiabetic, anti-inflammatory, antimicrobial	Used in decoctions or compresses in traditional contexts (poorly documented)	Natural α -glucosidase inhibitors; active ingredients in antioxidant nutraceuticals	Ibraheem et al. 2017; Agatonovic-Kustrin and Morton 2018
<i>D. simplex</i>	Amino acids and peptides (methionine, lysine, leucine, cysteine)	Nutritional; precursor for antioxidant and antihypertensive peptides	Nutritional use implied in seaweed-based diets	Protein supplements; functional peptides with metabolic effects	Ward and Deyab, 2021; Alves et al. 2018
<i>D. simplex</i>	Isoprenoids from DMAPP pathway (e.g., phytol, carotenoid precursors)	Antioxidant, anti-inflammatory, membrane-stabilizing	-	Biosynthetic precursor for terpenoid production; cosmetic stabilizers	Ganley et al. 2020; Dini 2022

Phenolic compounds, including tannins, flavonoids, and phenolic acids, are major contributors to the antioxidant properties of *D. simplex* (Fernando et al. 2016; Ibraheem et al. 2017). These compounds can donate hydrogen atoms or electrons to neutralize free radicals and also chelate transition metals such as Fe^{2+} and Cu^{2+} , which catalyze ROS formation through Fenton-type reactions. Furthermore, phenolics are often upregulated in response to environmental stressors, suggesting their dual role as both protective agents and bioindicators of algal stress adaptation (Betancor et al. 2015). The variability of phenolic content among *D. simplex* populations may reflect differences in habitat conditions, such as UV exposure, salinity, or nutrient availability.

In addition to phenolics, carotenoids in *D. simplex* notably astaxanthin, lutein, and β -carotene—also contribute significantly to its antioxidant profile (Dini 2022; Bayomy and Alamri 2024). These pigments stabilize lipid membranes and inhibit lipid peroxidation, a process that is strongly associated with cellular aging and degenerative diseases. Astaxanthin, in particular, has been shown to be several times more effective than vitamin E in scavenging ROS and protecting mitochondrial function (Fernando et al. 2016). The combined action of hydrophilic (phenolics) and lipophilic (carotenoids) antioxidants in *D. simplex* offers broad-spectrum protection, making this species a promising candidate for antioxidant supplementation.

Proteins and amino acid derivatives in *D. simplex* may also contribute indirectly to antioxidant activity. Certain peptides produced through enzymatic hydrolysis have demonstrated radical scavenging and metal-chelating properties (Alves et al. 2018; Pradhan et al. 2020). Moreover, amino acids such as cysteine, methionine, and histidine contain functional groups capable of interacting with ROS. The role of these nitrogen-containing compounds complements the antioxidant activity of polyphenols and carotenoids and may be enhanced through processing techniques such as fermentation or enzymatic extraction (Calvo et al. 2019; Hung and Trinh 2021).

Sulfated polysaccharides, including carrageenans found in red algae cell walls, have also been shown to possess antioxidant properties, particularly in terms of reducing power and inhibition of lipid peroxidation (Cicinskas et al. 2020; Aboeita et al. 2022). While these compounds are primarily known for their gelling and immunomodulatory properties, their ability to scavenge radicals and protect against oxidative stress has been increasingly reported. The structural features of these polysaccharides, such as degree of sulfation and molecular weight, can influence their antioxidant efficacy. Their water solubility also allows them to function in aqueous environments, enhancing their bioavailability in food or pharmaceutical formulations.

Environmental and cultivation factors greatly influence the antioxidant potential of *D. simplex*. Light intensity, UV exposure, and nutrient levels are known to regulate the biosynthesis of antioxidant compounds, particularly phenolics and carotenoids (Betancor et al. 2015; Gljušćić et al. 2022). Manipulating these factors in aquaculture or bioreactor systems could optimize the yield of antioxidants for commercial purposes. Additionally, post-harvest processing methods, including drying, solvent extraction, and

encapsulation, affect the stability and activity of antioxidant components. Therefore, standardization of extraction protocols and quality control measures is crucial for the development of *D. simplex*-based antioxidant products.

The antioxidant activity of *D. simplex* underscores its potential application in functional foods, dietary supplements, cosmetics, and therapeutic formulations aimed at preventing or mitigating oxidative damage. Its diverse antioxidant constituents acting through complementary mechanisms provide a robust foundation for health-promoting interventions. Continued exploration of *D. simplex* under various environmental conditions, along with advances in metabolomic profiling and bioassays, will be essential to harness its antioxidant potential for commercial and clinical applications fully.

Antidiabetic potential

Diabetes mellitus, particularly Type 2 Diabetes (T2DM), is a global metabolic disorder characterized by insulin resistance, impaired glucose metabolism, and chronic hyperglycemia. The disease has been associated with oxidative stress, inflammation, and mitochondrial dysfunction, which contribute to long-term complications such as neuropathy, nephropathy, and cardiovascular diseases (Di Meo and Venditti 2020; Alam et al. 2021). Conventional antidiabetic drugs such as sulfonylureas and metformin are widely used but often present limitations, including gastrointestinal side effects and decreased efficacy over time. As a result, there is growing interest in marine natural products, particularly from macroalgae, as alternative or complementary therapies for diabetes management (Chia et al. 2018; Van Weelden et al. 2019).

Red macroalgae such as *D. simplex* are rich in compounds with potential antidiabetic properties, including polyphenols, sulfated polysaccharides, carotenoids, and amino acid derivatives. These metabolites may act through multiple mechanisms, such as inhibition of carbohydrate-digesting enzymes, enhancement of insulin sensitivity, protection of pancreatic β -cells, and modulation of glucose uptake (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). Although specific studies on *D. simplex* are still limited, related species in the Rhodophyta group have shown promising *in vitro* and *in vivo* results. The structural similarities in metabolite composition suggest that *D. simplex* may also exhibit comparable bioactivities, warranting further exploration.

One of the most widely investigated mechanisms in marine algae-based antidiabetic studies is the inhibition of α -glucosidase and α -amylase enzymes responsible for the breakdown of dietary carbohydrates into absorbable sugars. By inhibiting these enzymes, algal extracts can delay glucose absorption, reducing postprandial blood glucose spikes. Extracts from red algae have demonstrated competitive and non-competitive inhibitory activity against these enzymes, often attributed to the presence of phlorotannins and sulfated polysaccharides (Chia et al. 2018; Pradhan et al. 2020). Although phlorotannins are more typical of brown algae, red algae like *D. simplex* are known to contain bioactive tannins and phenolics that may exert similar

inhibitory effects (Ibraheem et al. 2017; Bayomy and Alamri 2024).

Sulfated galactans such as carrageenans, which are abundant in red algae cell walls, have also shown hypoglycemic effects through immunomodulatory and gut microbiota-modulating pathways (Cicinskas et al. 2020; Aboeita et al. 2022). These polysaccharides may improve insulin sensitivity and glucose uptake by enhancing signaling in insulin-responsive tissues. Additionally, carrageenans may reduce inflammation in adipose tissue and the pancreas, thereby preserving insulin secretion and improving metabolic function. Their biocompatibility and safety profile make them attractive for incorporation into functional foods or as adjuvants in diabetes therapy.

Carotenoids present in *D. simplex*, particularly astaxanthin and β -carotene, also contribute to its antidiabetic potential by reducing oxidative stress and improving mitochondrial function (Fernando et al. 2016; Sathasivam and Ki 2018). Oxidative stress has been strongly implicated in pancreatic β -cell dysfunction, and antioxidant therapy has been proposed as a strategy to preserve β -cell integrity and function. Astaxanthin has been shown to enhance glucose metabolism by activating AMP-Activated Protein Kinase (AMPK) and reducing inflammatory cytokines in insulin-resistant cells (Ganley et al. 2020). These mechanisms could synergistically improve glycemic control when combined with other bioactive compounds from *D. simplex*.

Amino acid derivatives such as kainic acid, while primarily known for their neuroactivity, may also influence glucose homeostasis through modulation of excitatory neurotransmission and gut-brain axis signaling (Chekan et al. 2019). In addition, essential amino acids like leucine and methionine, present in *D. simplex*, have been linked to insulin secretion and glucose uptake in skeletal muscle (Ward and Deyab 2021; Lopez and Mohiuddin 2024). Their role in metabolic regulation suggests that the protein fraction of *D. simplex* should not be overlooked in studies of antidiabetic bioactivity. Bioactive peptides derived from red algae proteins have also demonstrated inhibitory effects on Dipeptidyl Peptidase-4 (DPP-4), an enzyme that inactivates incretin hormones and negatively affects insulin signaling (Alves et al. 2018).

Environmental conditions such as salinity, light, and nutrient availability can modulate the levels of antidiabetic compounds in *D. simplex*, offering possibilities for metabolic optimization through cultivation control (Betancor et al. 2015). For instance, stress-induced upregulation of phenolics and carotenoids under high light or nutrient limitation may enhance the antidiabetic potency of harvested biomass. Cultivation strategies that apply abiotic stressors in a controlled manner could, therefore, improve the consistency and efficacy of algal-based antidiabetic products. Furthermore, advanced extraction methods such as enzyme-assisted extraction or membrane filtration may improve the bioavailability of active compounds (Calvo et al. 2019; Hung and Trinh 2021).

Despite the encouraging pharmacological potential, the clinical translation of *D. simplex* for diabetes therapy requires further validation. Comprehensive in vivo studies and clinical trials are needed to assess its efficacy, optimal

dosage, and long-term safety. In addition, the identification and standardization of specific bioactive markers will facilitate the development of *D. simplex*-derived products with consistent therapeutic outcomes. Integration of metabolomic profiling, bioinformatics, and pharmacokinetics will be critical in advancing this promising red alga as a novel marine resource for diabetes management.

Antitumor and cytotoxic effects

Cancer remains a leading cause of mortality worldwide, characterized by uncontrolled cell proliferation, resistance to apoptosis, and genetic instability. Conventional therapies such as chemotherapy and radiotherapy, while effective in certain cases, often have significant side effects and face limitations such as drug resistance. This has driven the exploration of natural compounds, especially from marine organisms, as alternative or complementary antitumor agents (Agatonovic-Kustrin and Morton 2018). Marine macroalgae, including *D. simplex*, are rich in secondary metabolites with cytotoxic properties that can modulate cancer-related pathways and suppress tumor growth (Fernando et al. 2016; Alves et al. 2018).

Red algae possess a variety of bioactive compounds with potential anticancer effects, such as phenolics, sulfated polysaccharides, carotenoids, and alkaloid-like amino acid derivatives. Among these, phenolic compounds and tannins have been reported to induce apoptosis, inhibit angiogenesis, and interfere with cell cycle progression in several cancer cell lines (Ibraheem et al. 2017). These compounds exert their activity through mechanisms such as ROS generation, caspase activation, mitochondrial membrane depolarization, and inhibition of transcription factors like NF- κ B (Fernando et al. 2016). While direct studies on *D. simplex* are limited, its phenolic-rich profile suggests similar anticancer potential, especially when compared to other Rhodophyta species such as *Laurencia*, *Gracilaria*, and *Gigartina*.

Sulfated polysaccharides such as carrageenans, abundantly found in the cell walls of red algae, have shown antitumor effects both in vitro and in vivo (Cicinskas et al. 2020; Aboeita et al. 2022). Carrageenans can inhibit tumor cell adhesion, migration, and invasion while also modulating the immune response to enhance host-mediated tumor suppression. Low-molecular-weight carrageenans, in particular, are associated with stronger cytotoxic effects and higher cellular uptake. These polysaccharides also exhibit selective toxicity, demonstrating higher activity against cancer cells than normal cells, which is desirable in anticancer drug development (Sahin and Ozturk 2021). The structural features, such as degree of sulfation, chain length, and branching, influence their anticancer activity and bioavailability.

Another compound of interest is kainic acid, originally isolated from *D. simplex*. Though primarily recognized for its neuroexcitatory properties, kainic acid and its derivatives have been explored for antiproliferative effects in certain cancer cell models (Chekan et al. 2019; Maeno et al. 2019). Kainic acid analogs have been shown to induce apoptotic signaling pathways in glioma and neuroblastoma cells, likely through overstimulation of glutamate receptors and calcium influx, leading to oxidative stress and

mitochondrial dysfunction (Asakawa et al. 2020). However, due to its neurotoxicity at high concentrations, structural modifications and targeted delivery approaches are essential to harness its cytotoxic potential safely.

Carotenoids, particularly astaxanthin, and β -carotene, contribute to the antitumor profile of *D. simplex* by functioning as antioxidants and modulators of gene expression (Dini 2022; Bayomy and Alamri 2024). These compounds can downregulate pro-oncogenic factors such as VEGF and COX-2 while upregulating tumor suppressor genes like p53. Astaxanthin has been shown to inhibit cell proliferation in breast, colon, and prostate cancer models by inducing cell cycle arrest and apoptosis (Fernando et al. 2016). Its ability to cross cell membranes and accumulate in mitochondria allows it to act at critical sites of ROS generation and apoptotic signaling.

Recent studies have also investigated the cytotoxic effects of red algal extracts against various human cancer cell lines, including HepG2 (liver), MCF-7 (breast), HT-29 (colon), and A549 (lung) (Alves et al. 2018). These assays often report IC₅₀ values within the micromolar range, indicating moderate to strong antiproliferative activity depending on the extraction method and solvent used. Methanol and ethanol extract generally yield higher cytotoxicity due to the efficient solubilization of phenolic and lipophilic compounds. The cytotoxic profile of *D. simplex* is likely influenced by the combined action of multiple metabolite classes, acting synergistically or additively to induce cancer cell death.

Environmental stressors such as UV radiation, nutrient limitation, and salinity shifts may enhance the production of cytotoxic metabolites in *D. simplex*, offering opportunities for metabolite modulation via stress-based cultivation (Betancor et al. 2015). These adaptive responses involve the upregulation of biosynthetic genes and the accumulation of defense-related compounds, many of which exhibit cytotoxicity. Manipulating environmental parameters during cultivation could thus increase the yield and potency of anticancer compounds in *D. simplex*. This strategy aligns with sustainable marine biotechnology approaches aimed at producing high-value bioactives from algae.

While the preliminary evidence is promising, the clinical translation of *D. simplex*-derived antitumor agents requires more rigorous investigation. In vivo validation, toxicity assessment, and pharmacokinetic profiling are necessary to ensure safety and efficacy. Furthermore, the identification and structural characterization of active constituents, aided by metabolomics and bioassay-guided fractionation, will facilitate drug development pipelines. Future research should also explore nanoparticle-based delivery systems to improve the bioavailability and targeting of *D. simplex*-based anticancer agents.

Antimicrobial and antiparasitic activities

The emergence of antibiotic-resistant pathogens and the global burden of parasitic diseases have accelerated the search for alternative therapeutic agents from natural sources. Marine macroalgae, including red algae such as *D. simplex*, have demonstrated antimicrobial and antiparasitic activities attributed to their rich secondary metabolite

content (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). These compounds include phenolics, halogenated metabolites, fatty acids, sulfated polysaccharides, and alkaloid-like molecules, which collectively provide chemical defense against microbial colonization and parasitic infestation. The ecological function of these metabolites in algae often parallels their pharmacological action in humans, making macroalgae a valuable source of novel anti-infective compounds.

Phenolic compounds and tannins found in *D. simplex* exhibit strong antimicrobial properties by disrupting microbial cell membranes, inactivating enzymes, and chelating essential metal ions (Fernando et al. 2016; Ibraheem et al. 2017). These polyphenols can form complexes with microbial proteins, leading to loss of function and, ultimately, cell death. Additionally, red algal phenolics are known to exhibit broad-spectrum activity against both Gram-positive and Gram-negative bacteria, as well as various fungi. While direct assays involving *D. simplex* are limited, similar Rhodophyta species have shown inhibitory activity against *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa* (Sahin and Ozturk 2021; Bayomy and Alamri 2024).

Sulfated polysaccharides such as carrageenans are abundant in red algae and have been studied for their antiviral and antibacterial properties. These polysaccharides exert antimicrobial effects by forming physical barriers that prevent microbial adhesion and invasion and by interfering with microbial signal transduction pathways (Cicinskas et al. 2020; Aboeita et al. 2022). In viral infections, carrageenans can block virus-host interactions, particularly in enveloped viruses such as Herpes Simplex Virus (HSV), dengue, and even SARS-CoV-2 (Sathasivam and Ki 2018). Though specific studies on *D. simplex*-derived carrageenan fractions are limited, their structural similarity to those from other Rhodophyta species suggests comparable bioactivity.

Halogenated compounds, though more common in genera like *Laurencia*, have also been reported in various red algae and may exist in *D. simplex* in trace amounts. These compounds often brominated or chlorinated demonstrate potent antimicrobial activity due to their ability to penetrate bacterial membranes and disrupt DNA replication or protein synthesis (Agatonovic-Kustrin and Morton 2018). The structural novelty and chemical reactivity of halogenated metabolites have made them attractive for antimicrobial drug development. Although *D. simplex* has not been extensively profiled for halogenated compounds, advanced metabolomics may reveal previously undetected antimicrobial molecules in this species.

Amino acid derivatives such as kainic acid, while primarily recognized for neuroexcitatory activity, also possess antiparasitic potential. Historically, kainic acid was used as a traditional anthelmintic in Japanese medicine to expel intestinal worms, suggesting selective toxicity toward helminths (Chekan et al. 2019; Maeno et al. 2019). The compound is believed to act on glutamate receptor-like sites in parasitic nervous systems, leading to excitotoxic paralysis. Although its clinical use was discontinued due to side effects in humans, its mode of action remains a valuable pharmacological model for developing new antiparasitic

agents with greater specificity and lower toxicity (Asakawa et al. 2020).

In addition to helminths, macroalgae have been shown to exert antiparasitic activity against protozoa such as *Plasmodium* spp., *Leishmania* spp., and *Trypanosoma* spp. This activity is often attributed to terpenoids, alkaloids, and oxidized fatty acids that interfere with parasite metabolism or membrane integrity (Fernando et al. 2016; Dini 2022). Although no direct studies have evaluated the efficacy of *D. simplex* extracts against these parasites, the presence of bioactive isoprenoids and phenolic compounds indicates potential in this area. Exploration of this activity should be prioritized in future research, especially given the urgent need for novel antiprotozoal therapies.

Environmental stressors such as UV exposure and nutrient deprivation may enhance the antimicrobial potency of *D. simplex* by upregulating the biosynthesis of defense-related metabolites (Betancor et al. 2015; Gljušić et al. 2022). Therefore, cultivation of *D. simplex* under controlled stress conditions could be optimized to produce higher yields of antimicrobial compounds. Additionally, extraction techniques such as supercritical fluid extraction and green solvents may improve the recovery and stability of these compounds, facilitating their incorporation into pharmaceutical or personal care formulations (Calvo et al. 2019; Hung and Trinh 2021).

Overall, *D. simplex*'s antimicrobial and antiparasitic potential reflects its ecological resilience and biochemical richness. Although more targeted studies are needed, the combination of phenolics, polysaccharides, carotenoids, and neuroactive amino acids provides a solid foundation for bioactivity. Continued investigation, including bioassay-guided fractionation and in vivo validation, will be essential to fully harness *D. simplex* as a marine resource for novel anti-infective agents.

Anti-inflammatory and neuroactive properties

Inflammation is a complex physiological response to injury, infection, or metabolic dysregulation, which, when chronic, contributes to various pathological conditions such as arthritis, cancer, diabetes, and neurodegenerative diseases (Di Meo and Venditti 2020). Natural anti-inflammatory agents derived from marine organisms have gained increasing attention as safer alternatives to synthetic drugs, which often present undesirable side effects. Red macroalgae such as *D. simplex* contain a wide range of bioactive compounds including polyphenols, carotenoids, sulfated polysaccharides, and amino acid derivatives—that may modulate inflammatory pathways (Fernando et al. 2016; Agatonovic-Kustrin and Morton 2018). These compounds exert their effects through the inhibition of pro-inflammatory mediators, antioxidant protection, and regulation of signaling pathways such as NF- κ B and MAPK.

Phenolic compounds, including tannins and phenolic acids present in *D. simplex*, are potent inhibitors of inflammation-related enzymes such as Cyclooxygenase (COX), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS) (Ibraheem et al. 2017). These enzymes are involved in the synthesis of prostaglandins, leukotrienes, and nitric oxide—all key mediators of inflammation. The

ability of red algal phenolics to inhibit these pathways has been demonstrated in vitro and in vivo using models of carrageenan-induced edema, lipopolysaccharide (LPS)-stimulated macrophages, and oxidative stress-induced inflammation (Alves et al. 2018). Although specific data on *D. simplex* is still limited, the presence of structurally similar phenolics suggests comparable anti-inflammatory potential.

Carotenoids such as astaxanthin, β -carotene, and lutein, all found in *D. simplex*, also exhibit strong anti-inflammatory effects through their antioxidant and gene-regulatory activities (Dini 2022; Bayomy and Alamri 2024). Astaxanthin, for example, has been shown to downregulate inflammatory cytokines such as TNF- α , IL-6, and IL-1 β in various cell types, including macrophages and endothelial cells (Fernando et al. 2016). These carotenoids also modulate the activity of transcription factors involved in inflammation, such as NF- κ B and AP-1, thereby suppressing the expression of pro-inflammatory genes. Importantly, carotenoids have been observed to improve mitochondrial function, reduce oxidative stress, and restore redox balance, providing reassurance about their potential in managing chronic inflammation.

Sulfated polysaccharides from red algae, including carrageenans, are not only effective in modulating immune responses but also highly compatible with biological systems. Their immunomodulatory and anti-inflammatory properties have been validated in animal models and human cell lines (Cicinskas et al. 2020; Aboeita et al. 2022), making them promising candidates for a range of applications. These polysaccharides inhibit leukocyte migration, reduce cytokine production, and enhance antioxidant enzyme activity. Their high solubility and structural variability enable them to interact with immune cells and modulate inflammatory responses at mucosal surfaces. Moreover, their biocompatibility makes them attractive for incorporation into topical formulations for inflammatory skin conditions or as dietary supplements targeting gut inflammation.

Among the neuroactive compounds in *D. simplex*, kainic acid stands out due to its well-documented activity on glutamate receptors in the central nervous system. Kainic acid is a selective agonist of kainate-type ionotropic glutamate receptors and has been widely used in neuropharmacological research to model epilepsy and neurodegeneration (Connell et al. 2017; Asakawa et al. 2020). While kainic acid is neurotoxic at high concentrations, low or structurally modified doses have shown promise in modulating synaptic plasticity and neurotransmitter release. These properties make it a compound of interest in studying excitotoxicity, neuroinflammation, and potential neuroprotective mechanisms under tightly controlled conditions (Vezzani et al. 2016).

Neuroinflammation, a hallmark of disorders such as Alzheimer's disease and Parkinson's disease, involves the activation of microglia and astrocytes, the release of inflammatory cytokines, and oxidative stress. Marine-derived compounds with both antioxidant and anti-inflammatory properties may attenuate these processes, offering therapeutic avenues for neurodegenerative disease intervention.

Polyphenols and carotenoids from *D. simplex* may provide neuroprotection by modulating neuronal signaling, inhibiting oxidative damage to neurons, and suppressing inflammatory cytokine expression in brain tissues (Fernando et al. 2016; Ganley et al. 2020). Additionally, amino acids such as tryptophan and its derivatives may affect serotonin biosynthesis and gut-brain axis communication, further expanding the neuroactive scope of *D. simplex*.

Environmental conditions significantly influence the levels of anti-inflammatory and neuroactive compounds in macroalgae. Light exposure, nutrient status, and seasonal variation can alter the biosynthesis of polyphenols, carotenoids, and kainoids (Betancor et al. 2015; Gljušić et al. 2022). Cultivation under stress-enhancing regimes may increase the production of these valuable metabolites. Integrating this knowledge into aquaculture strategies may help optimize *D. simplex* biomass for targeted pharmaceutical applications. Further omics-based profiling and bioassay-guided isolation are necessary to identify the full spectrum of anti-inflammatory and neuroprotective agents in this species.

D. simplex represents a promising marine bioresource with significant potential for the development of novel anti-inflammatory and neuroprotective agents. Its rich repertoire of phenolics, carotenoids, polysaccharides, and kainoid compounds offers multiple mechanisms for modulating inflammation and neural activity. Future research integrating pharmacodynamics, toxicity screening, and formulation science will be essential for translating these bioactivities into safe and effective clinical or nutraceutical applications.

POTENTIAL APPLICATION

The broad biological activities of *Digenea simplex* including antioxidant, antidiabetic, antitumor, antimicrobial, antiparasitic, anti-inflammatory, and neuroactive effects—are supported by experimental evidence highlighting both individual compounds and synergistic extract mixtures that act on diverse cellular pathways. Tables 2 to 4 summarize the bioactivities, assay systems, mechanisms of action, and real-world applications of its major metabolites, demonstrating the pharmacological relevance of *D. simplex* across therapeutic, nutritional, and cosmetic domains.

Nutraceutical and functional food uses

The increasing prevalence of non-communicable diseases such as diabetes, obesity, cardiovascular disease, and neurodegeneration has spurred global interest in functional foods and nutraceuticals food-derived products offering health benefits beyond basic nutrition. Marine macroalgae, including red algae like *D. simplex*, are emerging as valuable sources of bioactive compounds suitable for incorporation into such health-promoting formulations (Fernando et al. 2016; Sathasivam and Ki 2018). *D. simplex* contains a broad range of compounds, including polyphenols, sulfated polysaccharides, carotenoids, essential amino acids, and dietary fiber, all of which are known to contribute to physiological homeostasis and disease prevention (Ward and Deyab 2021; Bayomy and Alamri 2024). The

combination of macro- and micronutrients with potent bioactivities makes this species a promising candidate for functional food innovation.

One of the key components supporting the nutraceutical value of *D. simplex* is its rich antioxidant profile, including astaxanthin, β -carotene, phenolic acids, and flavonoid-like compounds. These antioxidants help mitigate oxidative stress, which is implicated in the pathogenesis of chronic diseases such as atherosclerosis, cancer, and type 2 diabetes (Agatonovic-Kustrin and Morton 2018; Di Meo and Venditti 2020). When consumed regularly through functional foods, antioxidants from *D. simplex* may help neutralize free radicals and protect cellular components, thereby enhancing immune resilience and slowing age-related degeneration. Their natural origin and high bioactivity make them attractive alternatives to synthetic antioxidants, which may carry safety concerns with long-term use.

The dietary fiber content of *D. simplex*, primarily derived from sulfated galactans such as carrageenan, also supports its functional food applications. These fibers are known to improve gut health by promoting beneficial microbiota, reducing glycemic response, and enhancing satiety, thus aiding in weight management and metabolic regulation (Cicinskas et al. 2020; Aboeita et al. 2022). Additionally, dietary fibers from red algae may reduce serum cholesterol and improve lipid profiles, providing cardioprotective effects. The inclusion of *D. simplex* into baked products, smoothies, energy bars, or capsules may offer new avenues for consumers seeking high-fiber, plant-based supplementation.

The amino acid profile of *D. simplex* further adds to its nutritional value. It contains essential amino acids such as lysine, methionine, and tryptophan, which are often limited in plant-based diets (Stonik and Stonik 2020; Lopez and Mohiuddin 2024). Moreover, its protein fraction includes bioactive peptides with antioxidant, anti-inflammatory, and antihypertensive properties, particularly when hydrolyzed enzymatically or fermented (Alves et al. 2018; Calvo et al. 2019). These properties make *D. simplex* a potentially valuable ingredient for plant-based protein formulations, catering to vegetarian and vegan consumers while also meeting functional health goals.

The antidiabetic potential of *D. simplex* also underlines its value in functional foods. Compounds such as phenolics, carotenoids, and polysaccharides can help regulate postprandial glucose levels by inhibiting carbohydrate-hydrolyzing enzymes like α -amylase and α -glucosidase (Chia et al. 2018; Pradhan et al. 2020). Regular intake of such inhibitors through diet may provide a preventive approach to type 2 diabetes or serve as adjuncts to pharmacological treatment. Functional snacks or beverages fortified with *D. simplex* extract may offer a convenient delivery form for individuals at risk of metabolic syndrome.

Another promising avenue is the prebiotic potential of red algae-derived polysaccharides. Recent studies have highlighted the ability of carrageenans and related oligosaccharides to modulate the composition of gut microbiota, particularly by promoting beneficial strains such as *Bifidobacterium* and *Lactobacillus* (Hung and Trinh 2021). These microbial shifts are associated with

improved digestive function, enhanced nutrient absorption, and reduced inflammation in the gut. Functional food products incorporating *D. simplex* extracts may thus contribute to gut-brain axis health, influencing not only digestion but also mood, cognition, and immune regulation.

In addition to its intrinsic bioactivity, *D. simplex* offers formulation advantages in food systems. Its mucilaginous texture and natural gelling properties derived from its

polysaccharide content can act as emulsifiers, thickeners, and stabilizers in food processing (Sahin and Ozturk 2021). This dual role—functionality plus bioactivity supports its inclusion in a wide variety of formats, from dairy alternatives and gels to edible films and encapsulated supplements. Moreover, its pleasant reddish hue from carotenoids may serve as a natural colorant, reducing the need for synthetic additives.

Table 2. Reported biological activities of *Digenea simplex* and associated bioactive compounds

Bioactivity	Extract/compound	Target or assay model	Biological effect	Experimental evidence	References
Antioxidant	Methanolic extract; carotenoids (astaxanthin, β -carotene)	DPPH, ABTS, FRAP assays	High radical scavenging and reducing power	In vitro antioxidant screening using algal extracts	Fernando et al. 2016; Bayomy and Alamri 2024
Antidiabetic	Polyphenolic extract; sulfated polysaccharides	α -glucosidase and α -amylase inhibition	Moderate-to-strong enzyme inhibition	Enzymatic assay showing delayed carbohydrate hydrolysis	Chia et al. 2018; Pradhan et al. 2020
Antitumor	Crude extract; tannins; carotenoids	HepG2, MCF-7 cell lines	Dose-dependent inhibition of cell proliferation	Cytotoxicity assay with IC ₅₀ in low μ g/mL range	Ibraheem et al. 2017; Alves et al. 2018
Antiviral	Sulfated galactans (carrageenans)	HSV-1, SARS-CoV-2 pseudovirus	Inhibition of viral entry and replication	Viral plaque reduction and pseudovirus neutralization assays	Cicinskas et al. 2020; Aboeita et al. 2022
Antiparasitic	Kainic acid	Intestinal helminths (historical use)	Paralysis and expulsion of worms	Traditional usage; no recent pharmacological model	Maeno et al. 2019; Asakawa et al. 2020
Anti-inflammatory	Methanolic extract; astaxanthin	LPS-induced macrophage activation (RAW 264.7)	Inhibition of NO, TNF- α , and COX-2 expression	In vitro inflammation model using algal extract	Fernando et al. 2016; Sahin and Ozturk 2021
Neuroactive	Kainic acid	Kainate receptor agonist model	Induces seizures; modulates synaptic activity	Widely used in epilepsy and excitotoxicity models	Vezzani et al. 2016; Chekan et al. 2019

Table 3. Summary of major bioactive compounds in *Digenea simplex*, their mechanisms of action, and bioassay models

Bioactive compound	Mechanism of action	Bioassay model	Reference
Kainic acid	Agonist of kainate-type glutamate receptors; induces excitotoxicity	Rodent model for epilepsy and neurodegeneration	Chekan et al. 2019; Asakawa et al. 2020
Astaxanthin	Scavenges ROS, inhibits NF- κ B signaling, modulates cytokines (e.g., TNF- α , IL-6)	In vitro (RAW264.7 cells), in vivo inflammation and oxidative stress models	Fernando et al. 2016; Dini 2022
β -carotene	Antioxidant; precursor to vitamin A; inhibits lipid peroxidation	Cell-based oxidative stress models	Alves et al. 2018; Bayomy and Alamri 2024
Lutein	Photoprotective antioxidant, reduces ROS generation	UV-induced oxidative stress models	Sathasivam and Ki, 2018
Tannins	Protein-binding, metal chelation, antimicrobial and antidiabetic via α -glucosidase inhibition	DPPH, ABTS, α -glucosidase assays	Ibraheem et al. 2017; Chia et al. 2018
Phenolic acids (e.g. gallic acid)	Radical scavenging, metal ion chelation, inhibition of lipid peroxidation	DPPH, FRAP, MIC assays	Fernando et al. 2016; Pratita et al. 2023
Carrageenans (sulfated galactans)	Immunomodulation, inhibition of tumor cell adhesion and viral binding	In vitro cytotoxicity, antiviral assays (HSV, Dengue)	Cicinskas et al. 2020; Aboeita et al. 2022
Essential amino acids (lysine, methionine)	Nutritional support, modulate insulin response, antioxidant via sulfur groups	Nutritional profiling, glucose uptake assays	Ward and Deyab 2021; Lopez and Mohiuddin, 2024
GABA (γ -aminobutyric acid)	Neuroinhibitory neurotransmitter; antihypertensive effects	Enzyme inhibition, neuronal signaling studies	Pratita et al. 2023
DMAPP (dimethylallyl pyrophosphate)	Precursor in isoprenoid biosynthesis (carotenoids, sterols); antioxidant role	Biosynthetic pathway modeling	Ganley et al. 2020; El-Malek et al. 2022

Table 4. Potential applications of *Digenea simplex* bioactives in health and industry

Application field	Key compounds	Mechanism of action	Target / disease area	Reference
Nutraceutical	Astaxanthin, β -carotene, dietary fiber, essential amino acids	Antioxidant, immune modulation, gut microbiota support	Anti-aging, oxidative stress-related disorders, gut health	Sathasivam and Ki, 2018; Ward and Deyab 2021
Functional Food	Carrageenans, polyphenols, amino acids	Enzyme inhibition (α -glucosidase), cholesterol reduction, satiety modulation	Type 2 diabetes, metabolic syndrome, obesity	Chia et al. 2018; Cicinskas et al. 2020
Pharmaceutical - Neurology	Kainic acid (KA), GABA, tryptophan	Glutamate receptor modulation, neurotransmission regulation	Epilepsy, neurodegenerative diseases	Vezzani et al. 2016; Asakawa et al. 2020
Pharmaceutical - Oncology	Phenolics, sulfated polysaccharides, carotenoids	Induction of apoptosis, inhibition of angiogenesis, oxidative stress targeting	Breast, colon, liver cancer	Fernando et al. 2016; Alves et al. 2018
Pharmaceutical - Anti-infective	Tannins, carrageenans, halogenated metabolites	Disruption of microbial membranes, viral entry inhibition	Bacterial infections, HSV, dengue, SARS-CoV-2	Ibraheem et al. 2017; Pradhan et al. 2020; Aboeita et al. 2022
Pharmaceutical - Metabolic Health	Astaxanthin, carotenoids, polyphenols	AMPK activation, reduction of blood glucose and lipids	Diabetes, hyperlipidemia	Bayomy and Alamri 2024
Cosmeceutical	Astaxanthin, β -carotene, sulfated polysaccharides	Antioxidant, skin hydration, UV protection	Anti-aging, skin damage, inflammation	Pereira 2015; Sahin and Ozturk, 2021; Abd El-Aziz et al. 2023
Biomonitoring / Environmental	Heavy metal-accumulating polysaccharides	Bioaccumulation and bioindication	Marine pollution monitoring	El-Rafie et al. 2023;

However, challenges remain regarding the standardization, safety, and regulatory acceptance of *D. simplex* in functional foods and nutraceuticals. Variability in bioactive compound levels due to habitat, season, or processing methods must be addressed through quality control and standard extraction protocols (Betancor et al. 2015; Gljušić et al. 2022). Additionally, sensory acceptance, taste masking, and consumer perception should be considered in product development. Toxicological evaluation is necessary, particularly for high-dose applications, to ensure safety for long-term consumption.

D. simplex represents a versatile and underutilized marine bioresource with significant potential in the nutraceutical and functional food sectors. Its combination of essential nutrients and pharmacologically active compounds aligns well with global trends toward preventative health and natural product-based therapies. With appropriate processing, formulation, and regulatory compliance, *D. simplex* could be successfully integrated into the next generation of health-promoting food innovations.

Table 3 summarizes the major scientific gaps in the study of *D. simplex* to consolidate existing limitations and guide future research directions. These gaps span methodological, biochemical, ecological, and translational domains and provide a roadmap for advancing the utilization of this species in scientific and industrial applications.

Pharmaceutical prospects

Marine macroalgae are increasingly recognized as prolific producers of pharmacologically active compounds, many of which exhibit promising therapeutic potential for modern drug development. *D. simplex*, a red alga rich in chemically diverse metabolites such as kainic acid, phenolics, carotenoids, sulfated polysaccharides, and amino acids, offers multiple opportunities for pharmaceutical exploration

(Fernando et al. 2016; Bayomy and Alamri 2024). These bioactive constituents target a wide spectrum of disease pathways, including inflammation, oxidative stress, microbial infections, and cancer, making *D. simplex* a valuable source for novel lead compounds (Agatonovic-Kustrin and Morton 2018). Its relatively untapped phytochemical profile, combined with traditional medicinal usage, supports the rationale for more in-depth pharmaceutical evaluation.

Among the most historically significant compounds from *D. simplex* is kainic acid, a neuroexcitatory amino acid that selectively activates kainate-type ionotropic glutamate receptors (Chekan et al. 2019; Asakawa et al. 2020). Though known for inducing seizures in animal models, kainic acid has become indispensable in neuroscience as a pharmacological tool for understanding epilepsy, neurotoxicity, and glutamatergic neurotransmission (Connell et al. 2017). Current research also explores structurally modified kainic acid derivatives for safer and more targeted neurotherapeutic applications, such as neuroprotection in ischemia and neurodegenerative conditions (Vezzani et al. 2016). This illustrates how marine-derived natural products, even those with initial toxicity, can inspire pharmaceutical innovation when biochemically modified or administered in controlled regimens (Table 5).

In the area of oncology, several constituents of *D. simplex* exhibit cytotoxic and antitumor properties. Phenolics and tannins have been shown to induce apoptosis, inhibit angiogenesis, and suppress metastasis through modulation of signaling pathways such as NF- κ B and PI3K/Akt (Ibraheem et al. 2017; Alves et al. 2018). Carrageenans, the sulfated polysaccharides abundant in red algal cell walls, exhibit selective cytotoxicity against tumor cells and may act as immunomodulators, enhancing the host's antitumor response (Cicinskas et al. 2020; Aboeita et al. 2022). Carotenoids like astaxanthin and β -carotene also demonstrate

antiproliferative effects and antioxidant support that could protect non-cancerous tissues during chemotherapy (Fernando et al. 2016; Dini 2022). The synergy among these compounds makes *D. simplex* an attractive candidate for combination therapy or adjunct treatment strategies in cancer management.

The anti-inflammatory activities of *D. simplex* also hold pharmaceutical value, particularly in chronic inflammatory disorders such as rheumatoid arthritis, Inflammatory Bowel Disease (IBD), and neuroinflammation. Bioactives such as astaxanthin and sulfated galactans have been found to inhibit key inflammatory mediators, including TNF- α , IL-6, COX-2, and inducible Nitric Oxide Synthase (iNOS) (Sahin and Ozturk 2021; Bayomy and Alamri 2024). The potential for oral, topical, or injectable formulations derived from *D. simplex* extracts or isolated compounds could pave the way for novel anti-inflammatory drugs with fewer side effects than NSAIDs. Furthermore, the dual role of several compounds (e.g., antioxidant + anti-inflammatory) increases their pharmaceutical appeal due to multifunctional therapeutic action.

In the field of infectious disease therapy, *D. simplex* is a treasure trove of metabolites with potent antimicrobial and antiviral properties. For example, polysaccharides like carrageenans have been found to block viral attachment and entry into host cells, particularly in enveloped viruses such as herpes simplex virus (HSV) and SARS-CoV-2 (Sathasivam and Ki, 2018; Aboeita et al. 2022). In antibacterial therapy, phenolics and halogenated compounds from red algae are effective against multidrug-resistant strains like *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Agatonovic-Kustrin and Morton 2018). These

natural compounds, with their relatively low toxicity and good biocompatibility, are not just theoretical marvels but also find practical applications in wound healing products, topical antimicrobial gels, or mucosal delivery systems such as lozenges and sprays.

Red algal polysaccharides are also being investigated for use as drug carriers in targeted delivery systems. Their biocompatibility, water solubility, and ability to form hydrogels position carrageenans and related polysaccharides as ideal biopolymers for encapsulating Active Pharmaceutical Ingredients (APIs) (Calvo et al. 2019; Hung and Trinh 2021). Microencapsulation of poorly soluble drugs or sensitive bioactives using *D. simplex*-derived materials may enhance drug stability, control release rates, and improve bioavailability. In addition, these polymers may confer mucoadhesive properties, enabling prolonged contact with mucosal membranes and increased local therapeutic efficacy.

Modern pharmaceutical research also seeks marine-derived neuroprotectants and cognition enhancers, and *D. simplex* offers significant promise in this realm. The potential neuroprotective effects of kainic acid derivatives and antioxidant carotenoids may support drug development for Alzheimer's, Parkinson's, or age-related cognitive decline (Ganley et al. 2020). Combining neuroactive and anti-inflammatory actions within a single compound or extract aligns with the current paradigm of Multitarget-Directed Ligands (MTDLs) in complex neurological conditions. Metabolomic and transcriptomic profiling of *D. simplex* under varying stress conditions could uncover new neuroactive scaffolds for drug discovery.

Table 5. Current research gaps and recommended future directions on *Digenea simplex*

Identified gap	Scientific importance	Recommended future research	References
Limited in vivo and clinical studies on pharmacological activities	Most bioactivities are demonstrated only in vitro; lacks translational evidence	Conduct in vivo animal trials and early-phase clinical studies on antioxidant, antidiabetic, and anticancer effects	Fernando et al. 2016; Alves et al. 2018
Lack of standardized extraction and quantification protocols	Variability in bioactive yield across studies; hard to compare results	Develop and validate optimized, reproducible extraction and quantification methods (e.g., HPLC-based)	Calvo et al. 2019; Dini 2022
Unclear toxicity and safety profiles of active compounds (e.g. kainic acid)	Some compounds may be neurotoxic; safety data essential for functional/therapeutic use	Perform toxicological assessments (acute, chronic, genotoxicity) and define safe dosage ranges	Vezzani et al. 2016; Asakawa et al. 2020
Minimal genetic and omics-level studies (e.g. transcriptomics, metabolomics)	Biosynthetic pathways remain partially understood; biosynthesis regulation unclear	Apply omics tools to identify genes/enzymes in biosynthesis of kainoids, carotenoids, and phenolics	Chekan et al. 2019; El-Malek 2022
Poor taxonomic resolution and cryptic species uncertainty	Misidentification can bias ecological and biochemical findings	Integrate molecular barcoding (e.g. rbcL, COI) with morphological analyses to revise taxonomy	Díaz-Tapia et al. 2017; Boo et al. 2018
Absence of biotechnological production systems	Wild harvesting unsustainable; limits scalability for industry	Develop algal cultivation, tissue culture, or synthetic biology platforms to produce target compounds	Ganley and Derbyshire 2020; Hung and Trinh 2021
Limited study on structure-activity relationships (SAR) of compounds	Understanding SAR is crucial for drug optimization and analog development	Isolate pure compounds, determine 3D structures, and evaluate SAR using computational and empirical approaches	Agatonovic-Kustrin and Morton, 2018; Bayomy and Alamri 2024

Despite its potential, the pharmaceutical exploitation of *D. simplex* remains limited by gaps in preclinical and clinical validation. Most studies are still confined to in vitro bioassays or crude extracts without identification of active principles. Future directions should prioritize bioassay-guided fractionation, structural elucidation, mechanism-of-action studies, and in vivo toxicity testing. Moreover, collaborations between marine biologists, pharmacologists, and pharmaceutical industry stakeholders will be crucial for translating the pharmacological promise of *D. simplex* into clinically viable products.

Figure 3 illustrates visual synthesis of the relationships between major compounds, their bioactivities, and application fields of *D. simplex*, highlighting this species' integrative potential for health-related industries.

Cosmetic applications

The increasing consumer demand for natural, safe, and sustainable cosmetic ingredients has driven attention toward marine-derived bioactives, particularly those from red macroalgae such as *D. simplex*. Seaweeds have long been utilized in skincare and personal care formulations due to their moisturizing, antioxidant, anti-aging, and UV-protective properties (Sahin and Ozturk 2021; Abd El-Aziz et al. 2023). *D. simplex*, with its rich profile of phenolics, carotenoids, sulfated polysaccharides, and amino acids, presents multiple functional attributes desirable in modern cosmetics. These compounds target key skin-related concerns such as oxidative damage, photoaging, inflammation, and moisture retention.

One of the primary cosmetic values of *D. simplex* lies in its antioxidant potential, conferred by compounds such as astaxanthin, β -carotene, and phenolic acids (Fernando et al. 2016; Bayomy and Alamri 2024). These antioxidants help neutralize Reactive Oxygen Species (ROS) generated by UV radiation and environmental pollutants, which contribute to premature aging, hyperpigmentation, and loss of skin elasticity (Dini 2022). Astaxanthin, in particular, is known to penetrate skin layers and protect mitochondrial membranes, resulting in improved skin elasticity and reduced wrinkle formation. Incorporation of *D. simplex*-derived antioxidant extracts into creams, lotions, and serums can provide protective and reparative benefits to the skin.

Another notable property of *D. simplex* is its anti-inflammatory activity, which can soothe irritated skin and reduce redness, swelling, or allergic reactions. Inflammatory skin disorders such as acne, rosacea, and eczema are often exacerbated by oxidative stress and microbial imbalance. Compounds such as tannins, sulfated polysaccharides, and carotenoids have been shown to inhibit pro-inflammatory mediators like COX-2 and TNF- α , thereby promoting a calmer and more balanced skin environment (Ibraheem et al. 2017; Alves et al. 2018). These effects are particularly valuable in formulations for sensitive skin or after-sun care products that offer hope for those dealing with such conditions.

The hydrating and moisturizing effects of *D. simplex* are largely attributed to its sulfated polysaccharide content, particularly carrageenans, which have practical applications.

These compounds exhibit high water-retention capacity and the ability to form hydrogels, which help maintain skin hydration by preventing transepidermal water loss (Cicinskas et al. 2020; Hung and Trinh 2021). The film-forming ability of carrageenans also contributes to a protective barrier on the skin surface, enhancing texture and smoothness. These properties make *D. simplex*-based ingredients ideal for use in moisturizers, sheet masks, and leave-on hydrating treatments.

D. simplex also offers potential anti-aging and skin-rejuvenating properties, as its carotenoids and peptides may stimulate collagen synthesis and inhibit Matrix Metalloproteinases (MMPs), enzymes responsible for collagen degradation (Sathasivam and Ki 2018). By preserving extracellular matrix integrity, these compounds can help maintain skin firmness and reduce the appearance of fine lines and sagging. Furthermore, phenolic compounds in *D. simplex* may reduce melanin synthesis by inhibiting tyrosinase, suggesting applications in skin-brightening or anti-spot formulations (Fernando et al. 2016). This multifactorial approach to skin aging makes *D. simplex* an attractive botanical in anti-aging product lines.

Another growing trend is the use of algae-derived extracts for UV protection and photoprotection. Although red algae do not produce traditional Mycosporine-Like Amino Acids (MAAs) as abundantly as some other algal groups, their high content of carotenoids and polyphenols offers natural photoprotective effects (Agatonovic-Kustrin and Morton 2018; Gljušćić et al. 2022). These compounds absorb UV rays and prevent UV-induced inflammation and DNA damage. While not intended to replace synthetic sunscreens, *D. simplex* may serve as a complementary ingredient in SPF-boosting formulations and after-sun repair products.

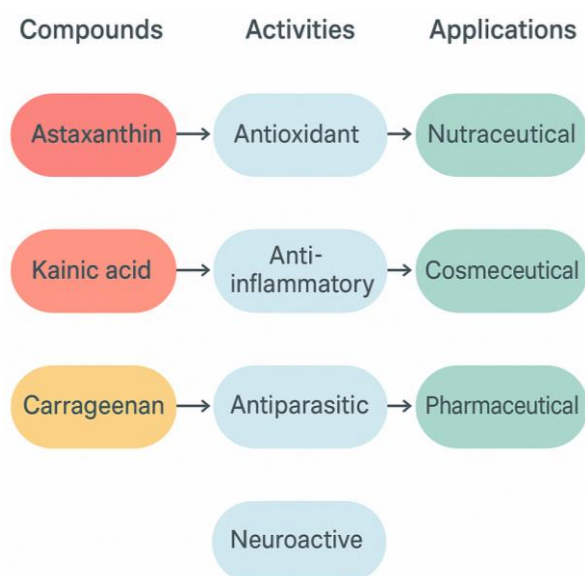


Figure 3. Flowchart illustrating the relationships between chemical constituents of *Digenea simplex*, their pharmacological activities, and corresponding industrial applications

From a formulation perspective, *D. simplex* also brings textural and functional advantages. The viscous and gel-like properties of its polysaccharide content can act as natural emulsifiers and thickeners, improving product consistency and skin feel without the need for synthetic additives (Calvo et al. 2019). This aligns with the clean-label movement in the cosmetic industry, where consumers prefer minimalistic and recognizable ingredient lists. Additionally, the natural reddish hue from carotenoids may offer mild coloring benefits, particularly in tinted moisturizers or serums.

The biocompatibility and low toxicity of *D. simplex*-derived compounds further support their safe application in topical formulations. However, to ensure product safety and consistency, it is necessary to standardize extraction methods, assess stability during storage, and evaluate potential allergenicity through dermatological testing (Betancor et al. 2015; Sahin and Ozturk 2021). Novel green extraction technologies such as ultrasound-assisted or enzyme-mediated extraction can also be adapted to enhance yield and preserve compound integrity (Hung and Trinh 2021).

With growing interest in marine-based skincare and the increasing availability of algal biorefineries, the commercial potential of *D. simplex* in the cosmetic industry is significant. Its multifunctional bioactive profile aligns with current demands for natural, effective, and sustainable ingredients. Future research should focus on clinical evaluation, bioavailability studies, and synergistic formulation with other botanicals to unlock the full cosmetic potential of *D. simplex*.

CHALLENGES AND FUTURE RESEARCH

Despite the promising bioactive potential of *D. simplex*, several challenges hinder its full integration into health-related industries. Species-specific studies remain scarce, with much of the existing literature extrapolated from broader Rhodophyta research, limiting targeted insights and slowing translational application. The lack of standardized cultivation protocols poses a major bottleneck, as wild harvesting is subject to seasonal and ecological variability. Environmental factors such as light, salinity, and nutrient availability significantly affect metabolite yield and composition, making consistency in biomass production difficult without controlled aquaculture systems or stress-induction strategies. In this context, sustainable and scalable cultivation remains a top priority for commercial development.

Another constraint lies in the limited understanding of the biosynthetic pathways responsible for key metabolites such as kainic acid, carotenoids, and sulfated polysaccharides. While kainic acid biosynthesis has been partially elucidated, comprehensive insights into regulatory genes and metabolic flux are lacking for most compounds. Advanced omics-based approaches integrating transcriptomic, metabolomic, and proteomic data could clarify these pathways and identify targets for metabolic engineering. Extraction technologies also require optimization; conventional solvent-

based methods risk degrading thermolabile compounds, reducing both yield and functional activity. Green extraction methods like supercritical CO₂ and ultrasound-assisted systems offer more selective recovery but remain underexplored for this species. Moreover, toxicological data on *D. simplex* are limited. While certain compounds, such as kainic acid, have known neurotoxic effects at high doses, others including polyphenols and polysaccharides lack comprehensive safety evaluations, particularly in terms of allergenicity, bioavailability, and long-term effects. Robust in vivo studies and toxicological assessments are needed for regulatory approval.

Finally, the gap between in vitro bioactivity and in vivo or clinical efficacy continues to impede commercialization. Most pharmacological data derive from cell-based assays, with few follow-up studies in animal models or human trials. Without pharmacokinetic and pharmacodynamic validation, therapeutic relevance remains speculative. Regulatory pathways—such as GRAS, Novel Food, or NHP approval—also demand strong safety and efficacy dossiers. Additionally, *D. simplex* lacks public recognition and a distinct market identity compared to other macroalgae. Addressing these limitations will require interdisciplinary collaboration across marine biology, chemistry, pharmacology, and industrial processing. Coordinated efforts, including public-private partnerships and supportive policy frameworks, are essential to advance *D. simplex* as a viable marine bioresource for food, pharmaceutical, and cosmeceutical innovation.

CONCLUDING REMARKS

Digenea simplex is a promising but underexplored marine macroalga with a diverse spectrum of bioactive compounds that support its use in health-related applications. The presence of kainic acid, sulfated polysaccharides, carotenoids, phenolics, and essential amino acids reflects its multifunctionality across pharmaceutical, nutraceutical, and cosmetic domains. These compounds have demonstrated antioxidant, antidiabetic, antitumor, anti-inflammatory, neuroactive, antimicrobial, and antiparasitic properties in vitro, suggesting potential therapeutic value for chronic and infectious diseases. Despite its rich phytochemical potential, scientific research on *D. simplex* remains limited and fragmented compared to other commercially cultivated red algae. Key challenges include the lack of standardized cultivation systems, inconsistent extraction protocols, limited pharmacological validation, and inadequate safety data. Addressing these gaps through multi-omics studies, bioassay-guided compound isolation, toxicological evaluation, and controlled cultivation may unlock broader utilization of *D. simplex* as a sustainable marine bioresource. Its ecological adaptability and biochemical plasticity make *D. simplex* an excellent candidate for biotechnological innovation. With the growing global demand for natural and multifunctional ingredients, integrating this species into circular bioeconomy strategies could contribute to the sustainable use of marine resources. Interdisciplinary research collaborations and supportive policy frameworks

will be essential to realize the full potential of *D. simplex* in modern health, wellness, and therapeutic industries.

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