Callyspongia aerizusa: a brief review of its bioactive compounds and their potential as pharmaceuticals

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Abstract. *Callyspongia aerizusa* (*C. aerizusa*) is a marine sponge discovered in the Indo-Pacific region, with the population majority located in the eastern part of Indonesia. It is known for its rich biodiversity and ability to produce many bioactive compounds with great pharmaceutical potential. This non-systematic review comprehensively explores and focuses on the pharmaceutical activities of *C. aerizusa*, highlighting its anticancer, antitubercular, and antifungal activities. Several bioactive compounds that have been isolated and studied from the species, such as ergost-22-en-3-one, ergost-7-en-3-ol, callyaerin E, and callyaerin H, exhibit cytotoxic activity that has shown strong effects against the lung cancer cell line (A549) and esophageal cancer cells (TE-8), through triggering apoptosis as a programmed cell death. By activating key pathway proteins such as *caspase-3*, *caspase-9*, and *PARP-1*, the cells are disrupted. In addition, cyclic peptide compounds such as callyaerin E, H, and G inhibit the growth of lymphoma cells, potentially by disrupting the cell membranes and their signalling pathways. In the treatment of infectious diseases, callyaerin A has shown a promising role in exhibiting antimycobacterial activity against *Mycobacterium tuberculosis,* while callyaerins A, B, and E show effectiveness in exhibiting antifungal activities against *Candida albicans*. Furthermore, *C. aerizusa* also plays a role in the biodegradation of marine pollutants through the sponge mutualistic symbiosis relationship with bacteria such as *Acinetobacter calcoaceticus (AC)*. This review summarizes the *C. aerizusa* and its bioactive compounds with promising values as a source of novel therapeutic agents, particularly in the development of alternative treatments for cancer and infectious diseases, showing beneficial prospects for biotechnology.

Keywords: *Callyspongia aerizusa, marine* sponge, secondary metabolite, therapeutic effect.

1. Introduction

Indonesia, located at the heart of the coral Triangle, is considered one of the most biologically diverse marine regions in the world. This region supports an extraordinary variety of marine organisms,

including sponges, due to its warm tropical waters, complex reef systems, and varied seafloor topography [1]. Within Indonesia, over 850 sponge species have been documented, many of which remain chemically unexplored [2]. Eastern Indonesia is a hotspot for sponge diversity, hosting numerous unique species with biomedical potential. This biodiversity not only enhances the ecological complexity of marine ecosystems but also provides a treasure trove for drug discovery. Marine sponges have garnered significant scientific interest due to their ability to produce a wide variety of bioactive metabolites, many of which exhibit pharmacological properties. These compounds have been found to interfere with various pathways such as cell proliferation, apoptosis, and angiogenesis [3]. Among these bioactive organisms, species from the genus *Callyspongia* have emerged as particularly promising sources of bioactive agents. One notable example is *Callyspongia aerizusa*, which has been identified as a potential pioneer in the discovery of secondary metabolites effective against lung cancer, particularly non-small cell lung carcinoma. The novel treatments for this cancer type is crucial, as it rises in the leading causes of cancer-related mortality, accounting for 18.4% of total cancer-related deaths worldwide in 2022 [4].

C. aerizusa first introduced by Calcinai et al. [5], is part of the family Callyspongiidae and genus Callyspongia. Morphologically, it typically exhibits tubular or vase-like forms with a smooth spiky surface and a soft yet firm consistency. Its structural form increases surface area for filter feeding which is a mechanism by which it captures microscopic organic particles from surrounding water [6]. *C. aerizusa* often inhabits shallow coral reef environments at depths of 5–30 meters, where it attaches to rocks or dead corals. It thrives in warm, clear, and well-oxygenated waters, making eastern Indonesia an ideal habitat due to its optimal environmental conditions. *C.aerizusa* has a broad distribution across tropical Indo-Pacific regions, with significant populations identified in Indonesia's Spermonde Archipelago and other eastern coral reef systems [7]. The Spermonde Archipelago is divided into four ecological zones based on their proximity to the mainland and ocean depth. Zone I include Lae-Lae Island, the closest to the mainland, with an average depth of about 10 meters. Zone II comprises islands such as Samalona, Barrang Lompo, and Barrang Caddi, located approximately 5 Km from the coast and characterized by depths around 30 meters. Zone III, which includes Kodingareng Keke and Kodingareng Lompo Islands, about 12.5 Km offshore, with depths ranging from 20 to 50 m. Zone IV is represented by Kapoposang Island, the farthest from the mainland at about 30 Km, with western depths exceeding 100 m. *C. aerizusa* was found to be most abundant in Zone III, particularly around Kodingareng Lompo Island, suggesting that this species prefers mid-shelf reef environments with moderate depths [8].

These ecosystems offer not only physical support but also nutrient-rich currents that facilitate the sponge's filter feeding. The sponge also maintains symbiotic relationships with various microorganisms, including bacteria and fungi, which are often responsible for producing its bioactive metabolites. These microbial interactions are essential for both ecological function and pharmaceutical potential [9]. In the case of *C. aerizusa*, specific microbial symbionts have been linked to the production of bioactive compounds. *C. aerizusa* as marine sponge also has a symbiotic mutualism relationship with microorganisms such as bacteria. *C. aerizusa* has a symbiont with *Acinetobacter calcoacetius* and plays a crucial role in the sponge's survival and health. The bacterium produces bioactive compounds that help protect the sponge from pathogens and may also contribute to nutrient cycling within the sponge's ecosystem. The relationship between marine sponge and marine bacteria helps to biodegrade and detoxify the pollutants that are found in the ocean. Some of the pollutants are considered heavy metals which can further disrupt the marine ecosystem balance if it's over the normal range. The study done by Marzuki et al. [10] regarding isolated micro symbionts with *C. aerizusa* allows the insight of knowledge on sponge symbiont to have the potential to produce

enzymes in the form of mucus to defend the sponge itself [10]. This mucus consisting of enzymes help to protect them from predators.

The bioactive potential of various marine sponges has been extensively studied, but no study focusing exclusively on *C. aerizusa* has been conducted. The objective of this brief review is to provide a comprehensive summary regarding the pharmacological activities of *C. aerizusa* through its isolated bioactive compound. *C. aerizusa* bioactive compounds were gathered and classified based on their pharmacological activity. These compounds may exhibit unique mechanisms of action, offering potential treatments for diseases that are resistant to current therapies. Previous studies on marine sponges have revealed a wide array of bioactive compounds with significant pharmacological properties, including antimicrobial, antiviral, and anticancer activities. These studies have highlighted the potential of marine sponge *C. aerizusa* as a source of novel therapeutic agents. By examining the chemical diversity and unique bioactive compounds of *C. aerizusa*, researchers can build on this foundation to uncover new possibilities for drug development. Discovering new bioactive compounds is crucial as they can lead to the development of innovative drugs that address unmet medical needs.

2. Materials and Methods

The review uses keywords such as *Callyspongia* genus, *Callyspongia aerizusa*, pharmacological activity, and bioactive compounds to evaluate previous research on *C. aerizusa*. Initially, there are 58 sources from various databases such as Google Scholar, PubMed, and Scopus from 2015 to 2025 that were used to gather information about the species. This review employs a systematic review methodology to ensure a comprehensive and unbiased analysis of the available literature. By systematically collecting and evaluating data from these sources, the review aims to provide a thorough understanding of the pharmacological properties and potential medicinal applications of *C. aerizusa*. This approach enhances the reliability and validity of the findings, offering valuable insights into the species' therapeutic potential. However, there are some sources that are eliminated and are not used in this brief review. Some of the eliminated sources are duplicated journals, journals with irrelevant topics, book chapters, and insufficient data. The journal and articles that are not eligible was eliminated from the chart. As shown in Figure 1, we were using the PRISMA method, it allows the paper elimination process easier. This method also ensures that the journals that are used in this literature review is relevant, has sufficient data, and reliable.

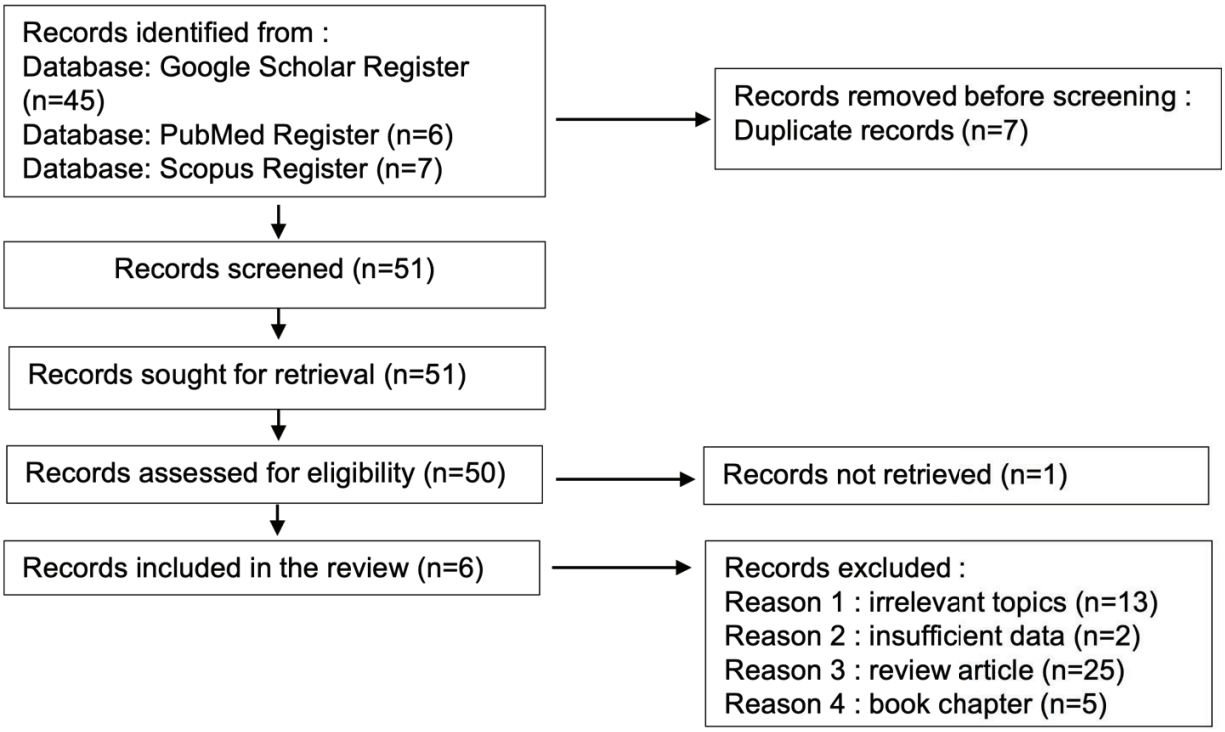


Figure 1. The PRISMA method, it allows the journals that are used in this brief review is relevant, has sufficient data, and reliable.

3. The morphological of *Callyspongia aerizusa*

Callyspongia aerizusa or also known as spiky tube sponge, is a sponge from the class Demospongiae. This species also belongs to the genus Callyspongia and the family Callyspongiidae [11]. The scientific name of this species was published by Desqueyroux-Fandez in 1984 [12]. On the morphology *C. aerizusa* species holds a cylindrical tubular shape with a clustered form arrangement and a spiky like texture on the sponge surface. Specimens of *C. aerizusa* species are found to have several color charactheristic, some may be pink,yelloworange, white, blue-grey, or even pale violet coloured. The different color of the sponges can be affected from the environment due to few factors, such as their symbiotic relationship with algaes and the depth of the water of where they live in. According to Santhanam et al, shallow water sponges like *C. aerizusa* tend to have bright color as their charactheristic, with the color ranging from red, yellow, orange, to violet [26]. The ectosome of *C. aerizusa* is formed by three fibers with various sizes tangentially. Meanwhile the choanosome is composed of thick primary fibers that are reticulated [11]. *C. aerizusa* has a slender oxea spicule which is slightly curved. The spicule is acerate with the tips that are round [13].

Figure 2. A tubular-shaped *Callyspongia aerizusa* is a species of marine sponge found in the Indo-Pacific region. It is known for its unique structure and vibrant coloration, which can range from pale yellow to deep. The image was purchased on shutterstock.com. The blue arrows show the morphology of *Callispongia aerizusa*.

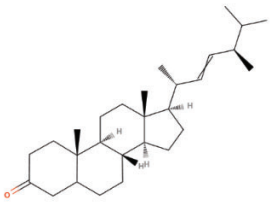
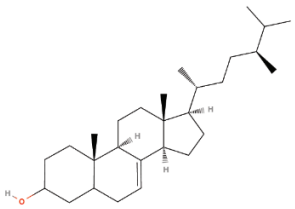
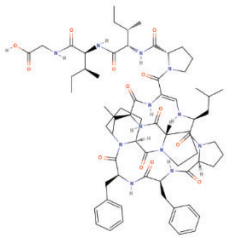
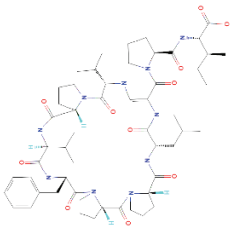
4. The pharmacological activity from *Callyspongia aerizusa*

4.1 An anticancer agent derived from C. aerizusa

The high risk associated with cancer still makes it one of the most malignant abnormal cell growths in the body, causing fear among many people. There is still a low success rate with medications since each kind of cancer and stadium requires a different kind of treatment. Based on the previous research indicates that *C. aerizusa* has a tremendous potential in cancer medications development for lung and esophageal cancers. Several potent anticancer compounds have been identified in *C. aerizusa*, including ergosteroids such as ergost-22-en-3-one, ergost-7-en-3-ol, and cyclic peptides such as callyaerin E, and callyaerin H. These biochemical compounds exhibit powerful antiproliferative properties against L5178Y lymphoma [14]. The IC_{50} values for ergost-22-en-3-one and ergost-7-en-3-ol for TE-8 esophageal cancer cells and A549 lung cancer cells are, respectively, 3.12 and 9.38 μg/mL [15]. Their anticancer activity is mediated by the induction of apoptosis, characterized by *caspase-9* and *caspase-3* activation, cleavage of *PARP-1*, and downregulation of the antiapoptotic protein *BCL-2*. This apoptotic pathway is a key mechanism that leads to reduced colony-forming ability of cancer cells, indicating tumorigenic suppression [15]. These cyclic peptides, rich in proline residues, are believed to exert their anticancer effects through mechanisms that may include membrane disruption and interference with intracellular signalling pathways. The presence of the cyclic peptides such as callyaerin E and H acts in activating the apoptotic pathway in the cancer cell, which leads to triggering a cellular stress response and activating programmed cell death for abnormal cell.

There was also a discovery of another compound that was similar, and it was found to be a natural product called callyaerin G [16]. The first cyclic peptide cycle has been identified through 1D and 2D NMR elucidation. This method identifies a compound's chemical structure [16]. Hadisaputri et al. [17] tested the *C. aerizusa* extract on A549 cells, a type of lung cancer cell, and found significant improvement compared to untreated control cells. This is consistent with the fact that the sponge has a cytotoxic effect that triggers apoptosis in the cells. This is a type of programmed cell death that stops and prevent the potential for results of abnormal cell growth. For example, the lung cancer cell sample A549 is used as the disease sample. During treatment observation after 12 and 24 h, various results confirmed the hypothesis that *C. aerizusa* functions as an anticancer compound. Molecular analysis indicates that the extract activates caspase-3, caspase-9, and PARP-1, which are cell death proteins, and inhibits key cancer pathways like PI3K/AKT/mTOR, leaving cells vulnerable and blocking cell division which shows the compound effective role in supressing tumorigenic cell potential [15]. When cell death proteins is activated, it will trigger and initiate a program of self-destruction on cancerous cell. The cancer key pathway is inhibited, which also leads to decreased cell migration and invasion. Furthermore, the cytotoxic activity is limited to cancerous cells, so non-cancerous cells are not affected, which shows a prospect for controlled and safe cell death. These bioactive compounds in *C. aerizusa* make it a great potential source of new anticancer agents [17]. Several promising chemicals could be developed as cancer medications, such as ergost-22-en-3-one, ergost-7-en-ol, callyerin E, and callyerin H. The bioactivity and chemical structure of ergosteroid molecules differ from those of cyclic peptide molecules. As seen in Table 1, ergosteroid, which includes ergost-22-en-3-one and ergost-7-en-ol with cyclic peptide (callyerin E and callyerin H), differs from cyclic peptide. Ergosteroids are characterized by a steroid backbone structure, which consists of four fused carbon rings, whereas cyclic peptides are made up of sequences of amino acids linked in a circular formation. This fundamental difference in their molecular architecture influences their bioactivity and the mechanisms by which they interact with biological targets. While ergosteroids often interact with receptors in a manner akin to hormones, cyclic peptides tend to form complex interactions with proteins due to their unique conformations.

Table 1. The bioactive compounds isolated from *C.aerizusa* and its anticancer potential.

No	Compound name	Type of molecule	Bioactivity	Chemical structure	Reference
1	ergost-22-en-3-one	Ergosteroid	TE-8 cell lines (IC_{50} 3.12 µg/mL) and A549 cell lines (IC_{50} 9.38 µg/mL)		[15,18]
2	ergost-7-en-3-ol	Ergosteroid	TE-8 cell lines (IC_{50} 3.12 µg/mL) and A549 cell lines (IC_{50} 9.38 µg/mL)		[15,19]
3	Callyaerin E	Cyclic peptide	L5178Y cell lines (IC_{50} 0,39 µg/mL)		[14,20]
4	Callyaerin H	Cyclic peptide	L5178Y cell lines (IC_{50} 0,39 µg/mL)		[14]

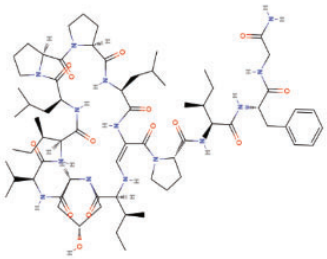
4.2 An antitubercular agent derived from C. aerizusa

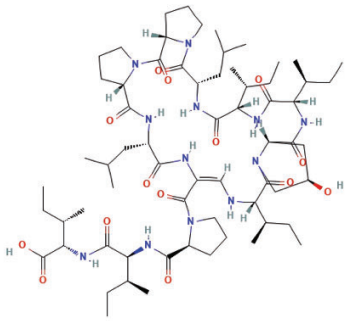
According to Table 2, there is a bioactive compound that exhibits antitubercular properties. A cyclic peptide derived from a marine sponge *C.aerizusa* has been shown to possess selective antimycobacterial activity against *Mycobacterium tuberculosis (Mtb)*. Daletos et al. [21] demonstrated that the bacterial proteome is dysregulated in vitro using the resazurin dye reduction assay. The cyclic

peptide targets specific membrane proteins within the *Mycobacterium tuberculosis* cell, disrupting essential processes such as cell wall synthesis and energy production. This proteomic imbalance will affect the main bacterial function that includes the cell walls integrity and metabolism that plays a crucial role for the bacterial survival. When the bacteria are weakened due to stress condition/response it will lead to system dysregulation and the decrease of the bacteria survival rate, ultimately causing cell death on the *Mycobacterium tuberculosis* cell. According to the study of Zhang et al. [22] it has been developed the first efficient route for the synthesis of callyaerin A, a potent anti-tubercular cyclic peptide featuring a rare (Z)-2,3-diaminoacrylamide moiety. This selective inhibition weakens the bacterium without affecting non-target species, making it an effective antitubercular agent. The specificity is achieved through the peptide's unique structure, which allows it to bind precisely to the bacterial proteins.

This mechanism makes cyclic peptides a promising candidate for developing new treatments against *Mycobacterium tuberculosis*. Its ability to target bacterial proteins specifically reduces the risk of resistance development, a significant advantage in combating this prevalent disease. Callyaerin A binds directly to the non-essential membrane protein Rv2113 in Mtb, triggering a complex dysregulation of the proteome [23]. This binding causes a broad downregulation of various cellular processes, including: (1) reduction in lipid production, which is essential for bacterial cell wall construction and maintenance, (2) impairment of DNA repair mechanisms and replication processes, making it difficult for the bacteria to survive and multiply, (3) inhibition of cell division, further limiting bacterial growth and proliferation [23]. The additionally, its targeted action minimizes disruption of beneficial microorganisms, reducing the side effects commonly associated with broad-spectrum antibiotics. The precision not only enhances its therapeutic potential but also supports its use as a model for designing future antimicrobial agents to address the growing challenge of drug-resistant infections.

Table 2. The bioactive compounds isolated from *C.aerizusa* and its antitubercular potential.

No	Compound name	Type of molecule	Bioactivity	Chemical structure	Reference
1	Callyaerin A	Cyclic peptide	*M. tuberculosis* inhibitor MIC_{90} 2 μM		[20,23]

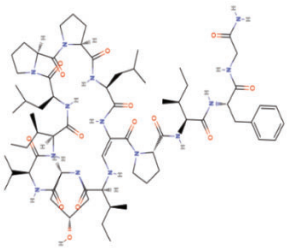
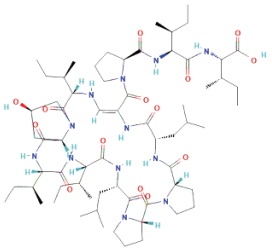
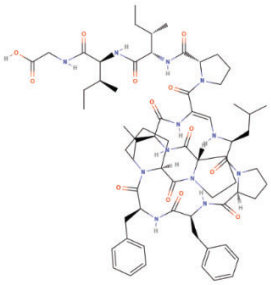
2	Callyaerin B	Cyclic peptide	*M. tuberculosis* inhibitor MIC_{90} 5 μM		[20,24]

4.3 An antifungal agent derived from C. aerizusa

In Table 3, we have summarized the metabolites from *C. aerizusa* that have antifungal activity. The marine sponge *C. aerizusa* produces cyclic peptides A, B, and E that inhibit *Candida albicans* growth. A disk diffusion assay showed that callyaerin A was the most potent inhibitor with a zone of 25–30 mm. It was followed by callyaerin E at 20 mm, and callyaerin B at 15 mm [14]. Several structural characteristics of callyaerins A and E appear to have superior antifungal potency to callyaerin B. These characteristics include the number and positioning of proline residues [25]. These structural characteristics may enhance callyaerin A and E's binding affinity to the fungal cell membrane. This may lead to increased disruption of membrane integrity and inhibition of fungal growth.

This finding highlighted the importance of proline residues in optimizing antifungal activity from cyclic peptides. Disrupting the fungal cell membrane compromises its integrity, leading to vital cellular components and ultimately cell death. This mode of action is particularly effective because it targets a fundamental structure essential for fungal survival. As a result, cyclic peptides like callyaerin A and E that enhance membrane disruption are considered potent antifungal agents. The natural cyclic peptides callyaerins A and E enhance membrane disruption because of their ability to interact with and disrupt the lipid bilayer of the cell membrane. Their ability to insert themselves into the membrane could have a negative effect on the cell, as they could create pores or disrupt the overall structure of the membrane, causing the cell to lyse [27]. A variety of factors play a part in this interaction, such as the composition of the lipids, the concentration of peptides, and membrane defects [28].

Table 3. The bioactive compounds isolated from *C.aerizusa* and its antifungal potential.

No	Compound name	Type of molecule	Bioactivity	Chemical sructure	Reference
1	Callyaerin A	Cyclic peptide	*Candida albicans* inhibitor		[14,23]
2	Callyaerin B	Cyclic peptide	*Candida albicans* inhibitor		[14,24]
3	Callyaerin E	Cyclic peptide	*Candida albicans* inhibitor		[14,20]

5. Conclusion

Callyspongia aerizusa has emerged as a promising marine sponge species that compose a variety of bioactive compounds that shows great potential in addressing as anticancer, antitubercular, and antifungal properties. The bioactive compounds found in *C. aerizusa* such as ergosteroids and cyclic peptides. Researchers could employ solvent extraction techniques, utilizing solvents such as methanol or ethanol to isolate bioactive compounds from *C. aerizusa*. Additionally, advanced chromatographic methods like high-performance liquid chromatography (HPLC) could be used to separate and purify these compounds. Finally, mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy might be employed to identify and characterize the chemical structures of the isolated compounds. Additionally, novel bioactive compounds can inspire the synthesis of new pharmaceuticals with improved efficacy and safety profiles.

6. Acknowledgments

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7. Data Availability

This study's findings are supported by data in the article.

8. Authorship Contribution

Author contributions were comprised of the following: conceptualization, B.A., C.A.S., L.M.Y.; methodology, B.A., C.A.S., L.M.Y..; validation, K.A.; investigation, K.A.; data curation, B.A., C.A.S., L.M.Y.; writing—original draft preparation, B.A., C.A.S., L.M.Y.; writing—review and editing, K.A.; visualization, K.A., B.A., C.A.S., L.M.Y.

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