REVIEW ARTICLE

Pharmaceutical Active Secondary Metabolites from the Marine Sponges and its Therapeutic Applications in Wound Healing

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ABSTRACT

The healing of a wound is a complicated process that might be impeded by infection and result in a long recovery process and the development of severe complications. Ancient multicellular organisms Marine sponges are ancient, multicellular marine organisms living in a wide range of oceanic habitats which have been shown to produce a wide range of secondary metabolites with high biological activity. This review discusses the wound healing and antibacterial potential of the bioactive compounds alkaloids, peptides and terpenes. Marine sponge metabolites have great antibacterial properties against a broad spectrum of pathogens, which include antibiotic resistant strains with antibacterial activity happening to disruptive mechanisms named synthesis of a cell wall, the loss of membrane stability, and protein and nucleic acid synthesis. Also these compounds have anti-inflammatory and antioxidant properties, which inhibit inflammation and oxidative stress hence promoting an optimum environment in which wound healing takes place. Moreover, they stimulate cell proliferation and angiogenesis, which makes the process of tissue regeneration and repair possible. This diversifies the approach of the marine sponge secondary metabolites, which is useful in developing intermediary wound care preparations with capable effect (control infection and wound healing).

Keywords: Marine sponge, Bioactive Secondary Metabolites, Wound healing, Antibacterial activity, Marine diversity

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INTRODUCTION

The disturbance of the normal composition of structure and functionality of the skin and underlying soft tissue is acknowledged as a wound. It is possible to divide wounds in terms of the reason of their appearance (surgical wounds, traumatic wounds, and pressure ulcers), and in terms of the healing process (acute or chronic wounds)[1]. Wound care is very important because complications might develop, and the healing process takes longer and causes even more pain and can result in serious systemic complications. Infection of the wound may also arise where bacteria gain access to a wound site resulting to local events that include redness, swelling, heat, pain and discharge[2]. The systemic indications of infection are as follows; fever and elevation of white blood cells. This might result in sepsis, which is another lethal condition that must be addressed with promptly medical care in severe cases. The risk of being infected can be avoided by the following: adequate wound cleaning, antiseptic usage, and antibiotic, in certain cases[3].

When wounds fail to heal in a timely manner, they can become chronic. Chronic wounds are often stuck in the inflammatory phase of healing and can persist for months or even years[4]. Common types include diabetic foot, venous leg, and pressure ulcers[5]. Chronic wounds require specialised care, including advanced wound dressings, negative pressure wound therapy, and surgical intervention[6].

Most plants and animals on earth have natural habitats in the open oceans and deep seas. Living organisms of all kinds have been found in the ocean, including prokaryotic bacteria, marine invertebrates, and multicellular complex organisms such as whales and sharks. Harsh marine conditions, which range in temperature from freezing to 350°C in deep hydrothermal vents, in pressure from 1 to 1000 atm, in nutrient ranges, and in photic and non-photic zones, marine organisms have yielded a greater number of novel natural products than other sources.

Marine sponges are an ancient class of simple multicellular organisms found worldwide in oceanic habitats. Marine sponges are grouped into three major classes based on their skeletons: Demospongiae, Calcarea, and Hexactinellida[7]. These organisms are usually sessile, which means they permanently cling to solid underwater surfaces such as rocks or coral reefs, and have a porous structure[8]. As major contributors to the nitrogen cycle and producers of habitats, marine sponges are essential to aquatic ecosystems. Large volumes of water are filtered to remove bacteria and microscopic food particles, which also helps clarify the water and manage bacterial populations. Sponge growth is characterised by a wide range of sizes and shapes resulting from environmental adaptation. They typically grow slowly, with the availability of food, salinity, and water temperature all having an impact. Certain species have the ability to regenerate from tiny fragments, which helps them

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survive but also makes determining their ages and development rates more difficult.
In this review, we systematically examine marine sponges and their diverse applications. We classified various bioactive compounds derived from marine sponges, focusing on their potential uses. The key areas of interest include bioactive compounds from marine sponges, their wound healing properties, and their antibacterial activity. Our research utilised search engines, such as Google, ResearchGate, and PubMed. Multiple statistical analyses of natural products from marine sponges, particularly from PubMed, have revealed that sponges possess a remarkable abundance of biologically active compounds. These analyses underscore the significance of secondary metabolites obtained from marine sponges.

Wound

Infectious wounds, often caused by pathogens, such as bacteria, fungi, or viruses, represent a significant challenge in both clinical and community settings. These infections can arise from various sources, including surgical procedures, traumatic injuries, and chronic conditions such as diabetes. The presence of an infectious agent in a wound can complicate the healing process and lead to adverse outcomes. Infectious wounds can be broadly categorised according to their origin. Surgical wounds are intentionally created during the surgical procedures. While most surgical wounds heal without incident, some can become infected, particularly if aseptic techniques are not followed rigorously. Traumatic wounds result from injuries, such as cuts, abrasions, and punctures. The risk of infection increases if the wound is contaminated with dirt, debris, or foreign objects. Chronic wounds, such as diabetic ulcers, pressure ulcers, and venous stasis ulcers, are prone to chronic infections owing to prolonged exposure to a pathogenic environment and impaired immune response. Infectious wounds begin with the entry of pathogenic microorganisms into skin. These pathogens can proliferate and overcome an initial immune response. The presence of foreign bodies, necrotic tissues, and compromised blood flow can facilitate bacterial growth and biofilm formation. Biofilms are particularly problematic because they provide a protective environment for bacteria, making them resistant to antibiotics and the host immune system. The most common bacteria associated with wound infections are *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Fungal infections, although less common, can occur, particularly in immunocompromised patients. Candida species are the typical culprits in such cases. Complications arising from infectious wounds are manifold and can significantly affect patient outcomes. Infection can prolong the inflammatory phase of wound healing by delaying the formation of new tissue and wound closure. Localised wound infections can spread to the surrounding tissues and enter the bloodstream, leading to sepsis, a life-threatening systemic response to infection. Particularly in chronic wounds, the infection can extend to the underlying bones, causing osteomyelitis, which is difficult to treat and often requires prolonged antibiotic therapy or surgical intervention. Management of infectious wounds involves several key strategies. Debridement and removal of necrotic tissue and foreign bodies are crucial to reduce the bacterial load and promote healing. Use of systemic antibiotics may frequently be necessary, especially in deep or systemic infections. Antibiotic treatment relies on the sensitivity and culture outputs. Antibiotics on wounds Wound dressings can be used to instill antimicrobials topically to the wound, such as silver dressings and honey, to help decrease bacterial burden. Supportive measures, which include proper nutrition, blood sugar control in diabetic patients and

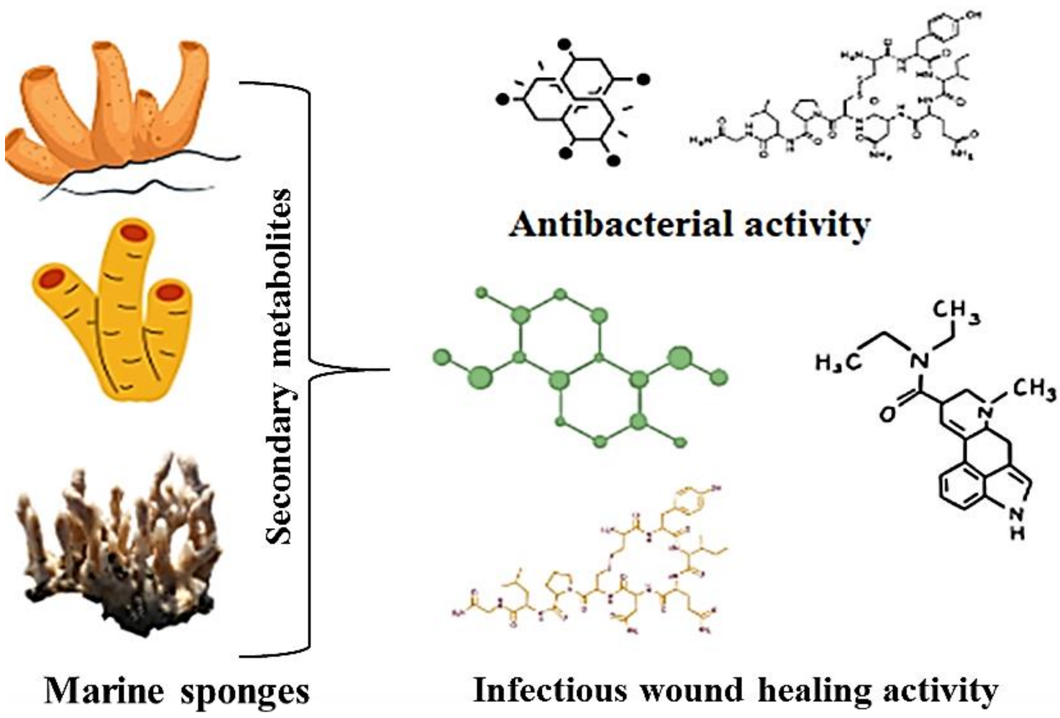

Figure 1: Marine Sponges Anti-bacterial and Wound Healing Activity

improvement of the underlying conditions that predispose patients to wounds that do not heal well should be given. Expensive therapies encompass negative-pressure wound therapy, hyperbaric oxygen therapy and the application of bioengineered skin substitutes. The most important thing to do is prevention to limit the cases of infectious wounds. These entail proper use of aseptic technique in the health facilities, wound management and wound hygiene, early debridement of the dead tissue, teaching the patient to recognize the signs of infection, and the need to consult a health expert on a timely basis.

Pharmaceutical Compounds form the Marine Sponges

Steroids

Aplysina oroides is known to synthesize numerous sterols on the examples of specimen found in Naples and the Northern Aegean Sea. These sterols have been shown to have very strong antiplasmodial, trypanocidal and leishmanicidal effects but they are not cytotoxic to mammalian cells. Likewise, Aplysina flabelliformis on the Bahamas bears sterols that are efficient in inhibiting the action of murine splenocyte in a two-way mixed lymphocyte reaction exhibiting no accompanying toxicity when there was test in levels as varying as 2.0-62.5 and 62.5-2.0 2.0 microgram-milliliters minus one. A third example of sterols is of sterols of various Agelas species, including sterols produced by Caribbean A. schmidtii, ecdysterone, and ajugasterone C in the Little San Salvador Islands A. dispar, and sterols of Jamaican A. sceptrum.

Fused Cyclic Pyrrole Alkaloids

Fused cyclic pyrrole alkaloids are characterised by their common structural features, where fusion typically occurs between C-1 and C-2, often forming a five- or six-membered ring. These alkaloids typically possess a carbonyl group at the α-position relative to the bridgehead atom. These structural similarities are attributed to their biosynthetic origins, likely formed from oroidin and its analogues through cyclisation and oxidation processes. Marine sponges, owing to their remarkable biosynthetic capabilities, produce a diverse array of these compounds, which can be categorised into four families based on the oroidin atoms involved in linkage formation[9].

Agelaspongin

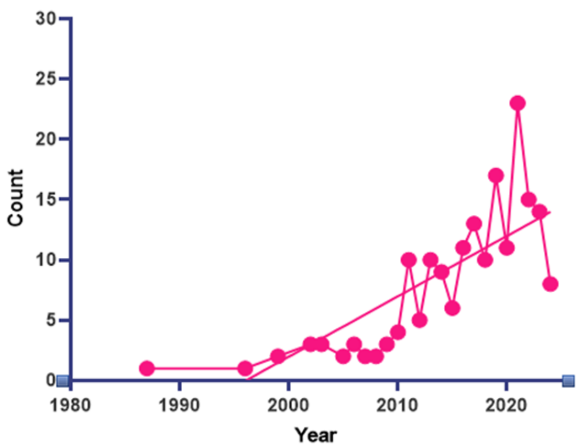

Figure 2: Multiple statistical investigations of marine sponge natural products in the PubMed database

Typically found in Agelas sponges, these tetracyclic PIAs include dibromoagelaspongin hydrochloride (104) from Tanzanian Agelas sp., which stimulates wheat seedling root growth. Caribbean dispar produces dibromoagelaspongin-methyl ether. Monobromo analogues such as monobromoagelaspongin and optically active forms such as monobromoagelaspongin have been isolated from Mediterranean A. oroides.

Phakellin

Bearing a tetracyclic skeleton similar to that of agelaspongins, these alkaloids include dibromophakellin from Phakellia flabellate and various derivatives from Caribbean Agelas sp. Phakellins have shown significant antibiofilm and antifeedant activities, with bromination enhancing their efficacy.

Agelastatin

These compounds, such as agelastatins A and D-F, are derived from the New Caledonian A. dendromorpha. They feature a densely functionalized cyclopentane ring and exhibit potent cytotoxicity in various cancer cell lines. Agelastatin A is also a selective inhibitant of glycogen synthase kinase-3beta.

Longamide

These alkaloids are characterised and synthesised of a pyrroloketopiperazine nucleus and originate in A. longissima and contain longamides, medium-sized antibacterial compounds. Provocative antiprotozoal activity has been observed with a compound like longamide B. Different biological activities are shown by other derivatives including monobrominated mukanadin C and non-brominated nemoechine B.

Dimeric Pyrrole Alkaloids

The alkaloids are characterized by a complex connectivity and by their high nitrogen content. Monomers can cyclise to dimers or dimers may be held together by one chemical bond. As an example, sceptrin derived by A. sceptrum has cyclobutane core and exhibits multiple types of bioactivities such as antiviral and antimicrobial properties. Derivatives of other structure, like ageliferins, possess cyclohexene-derived skeleton sharing actomyosin-activating ATPase and antibiofilm activities.

Terpenoid Alkaloids (9-N-Methyladeninium Terpenoids)

Based on E, E, E-geranylgeranyl diphosphate (GGPP), such compounds are the agelasines of Okinawan A. nakamurai, Na+/K+ATPase inhibitors. They demonstrate several bioactivities such as antimicrobial, cytotoxic and antimalarial properties. The Solomon Island agelasines (A. cf. mauritiana) are also strongly antimalarial.

Terpenoids of Hypotaurocyamine

Agelasidine A was extracted as the first hypotaurocyamine terpenoid and this was able to show antimicrobial properties which were extracted by Okinawan Agelas sp. Other analogues, e. g. agelasidines B and C demonstrated inhibitory activity on microbial growth and Na+/K+-ATPase activity. Caribbean A. clathodes also synthesises other antibacterial analogues (eg. (−)-agelasidine A).

Glycosphingolipids

Agelas sponges synthesise unique glycosphingolipids such as agelasphins, which prolong the lifespan of mice inoculated with melanoma cells. These glycosphingolipids were the first known galactosylceramides with an α-galactosyl linkage. Other notable compounds include coniferoside from A. conifera and clathrosides A–C from A. clathrodes, which feature unusual glycoside structures.

Marine Sponges Secondary Metabolites and its Geographical Source

The geographical marine sources highlighted in the data revealed a significant presence of Aaptos sponges across various regions in the Indo-Pacific, particularly in Southeast Asia. Locations such as Indonesia, Vietnam, and the South China Sea have been recurrently mentioned, indicating that these areas are rich in Aaptos species. Indonesia, specifically North Sulawesi, Manado, Derawan Island, Ambon, Kupang, and the broader Indonesian coast, appears to be a hotspot for these sponges. Similarly, Vietnam, including regions like Tho Chu Island, Ku Lao Re Island, and Vang Fong Bay, is another significant locality. The South China Sea is notable for its recurring role as a source, often in conjunction with Malaysian localities like Terengganu and Sepanggar Island. Okinawa, Japan, appears, as well, an important source, showing the broad spread of Aaptos sponges in these seas. These are also not only productive sources of Aaptos sponges but of the diverse bioactive compounds they yield, and a case can be made that these marine environments are generally important natural product sources and that, therefore, they are of interest into drug discovery.

The Wound Repairing Work of Marine Sponge Bioactive Molecules

Marine sponges have attracted a lot of focus in terms of wound healing prospects owing to the abundance of biological active compounds. These create a combination of the peptides, polysaccharides, sterols, and alkaloids that possess biological activities and add to the complex of wound healing procedures.

Anti-inflammatory Activity

Inflammation is one of the most important wound healing properties. Several kinds of anti-inflammatory agents are secreted by marine sponges and these agents are capable of suppressing inflammation thus creating a more favourable environment to enable wound healing. As an example, sterol molecules such as halistanol sulfate and other sterols found in sponges have demonstrated strong effects of anti-inflammation; this can be used to reduce the inflammation which is chronic and usually impedes the healing process.

Antimicrobial Properties

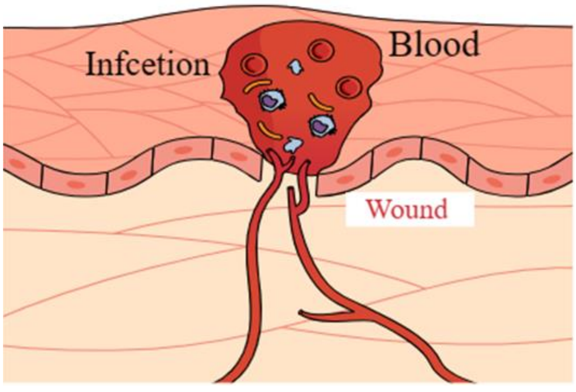

Figure 3: Structure of wound

Sponge is important in the control of infection in wound management and has been identified to have powerful antimicrobial activities. There are sponges like Aaptos aaptos that form compounds like aaptamines with broad-spectrum antimicrobial activity of antibacterial, antifungal, and antiviral action. The compounds are able to prevent infections of wound among them being the healing process without the interference of microbial complications.

Boosting Cell Propagations and Cell Movements

This regenerates the tissue through proliferation and migration of different types of cells e.g. fibroblasts and keratinocytes. Compositions of marine sponges have been proved to excite such processes. As an example, it has been shown that selected polysaccharides that are extracted in sponges can improve the rate of fibroblast proliferation as well as collagen production that is needed to reinforce and remodel damaged tissues. These compounds also have the potential of increasing the movement of the keratinocyte cells to seal the wound surface, and this enables an accelerated process of wound healing.

Angiogenesis

Angiogenesis is also a very important aspect of wound healing as it brings enough blood and nutrients to the wound site. One of the compounds that can trigger this process, marine sponges contain angiogenic compounds. As an example, certain peptides derived out of sponges had been identified to enhance the proliferation of endothelial cells and generation of new blood vessels that aids the vascularization required in wound healing.

Antioxidant Activity

Oxidative stress has the potential to hamper wound healing due to its pro-inflammatory and damage-inducing effect to the cell. Marine sponges can manufacture antioxidants capable of destroying free radicals and eliminating oxidative stress. Some of the compounds, like carotenoids, certain alkaloids present in sponges also assist in the protection of the cell damage courtesy of oxidation and enable a more healthy and productive healing procedure.

Cherishing of Extracellular Matrix Remodelling

Remodeling of the extracellular matrix (ECM), a highly structured network of proteins which offers structural and biochemical support to surrounding cells, is important in wound healing. Enzymes and other bioactive molecules of marine sponges might be able to contribute to the remodelling of an ECM. The compounds contribute in degrading damaged components of the ECM and production of new ones, which determines the good organization and strength of the new tissue formed.

Antibacterial Activity

The marine sponges are known to be the prolific sources of secondary metabolites that have potent antibacterial compounds and thus an excellent resource in identification of new antimicrobial agents. They contain an extensive variety of antibacterial activities, with these compounds having alkaloids, peptides, terpenes, and polyketides. These compounds have a broad antibacterial spectrum towards many pathogens even drug-resistant pathogens.

Mechanisms of Action

Inhibition of cell wall synthesis: Several compounds obtained in sponges destroy the cell wall of gram-negative bacteria. As an example, brominated alkaloids within sponge Agelas conifera have been demonstrated to suppress enzymes that are participating in cell walls of peptidoglycan creating the cell weaker and ensuing cell lysis. Membrane Disruption: Certain sponge metabolites attack the cell membrane of the bacterium raising the permeability level that leads to death. Polyketide characterized macrolide, halichondrin B extracted out of the sponge, halichondins okadai causes a leakage of cell contents through distortion of the membrane. Inhibition to bacterial protein synthesis: Some sponge substances bind to the ribosomal subunits and thus inhibit protein synthesis in these bacteria. For instance, the cyclic peptide theonellamide F from *Theonella swinhoei* binds to the 50S ribosomal subunit, preventing protein translation and bacterial growth. Nucleic Acid Synthesis Inhibition: Marine sponge metabolites can also interfere with DNA and RNA synthesis. The nucleoside analogs from the sponge Cryptotethya crypta, such as ara-C and ara-A, inhibit DNA polymerase and reverse transcriptase, respectively, blocking nucleic acid replication. Aaptamines: These are a class of alkaloids found in the sponge Aaptos aaptos. Aaptamines have shown broad-spectrum antibacterial activity, including against methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli. Their mechanisms include DNA intercalation and topoisomerase inhibition. Manzamine Alkaloids: Isolated from the sponge Haliclona sp. manzamines exhibit strong activity against Gram-positive and Gram-negative bacteria. Their mode of action includes interference with the activity of bacterial cells membrane and cellular enzyme inhibition. Fascaplysin: It is an alkaloid of the sponge Fascaplysinopsis sp. which is strong against Mycobacterium tuberculosis. Fascaplysin binds DNA and eludes bacterial growth because of interrupting biological activities. Halichondrins These sponge-derived macrolides have high antibacterial activity, being isolated rhythmia okadai halichondrida. They interfere with cell membranes of bacteria and prevent generation of essential bacterial proteins. Brominated Isoxazoline Alkaloids: These alkaloids which occur in the sponge Aplysina aerophoba are active against Staphylococcus aureus and Bacillus subtilis. They work by blocking bacterial enzyme in cell wall and protein synthesis.

Antimicrobial Effort Against Dependent Antibiotics Bacteria

Metabolites of marine sponge hold exceptional use in defending against multidrug-resistant (MDR) bacteria. These compounds including manzamine A and theonellamide F work against MDR strains because they inhibit new bacterial routes and processes that are resistant to conventional antibiotics. This is why they can be regarded as promising participants of the development of new antibiotic-resistant infection therapeutics.

Prospect of Clinical Usage

The chemical structures peculiarities and their antibacterial activity of the marine sponge metabolites can serve as the foundation to developing new antibiotics. Such compounds may have different mechanisms of action than the current antibiotics, which may be useful in preventing development of resistance. Nevertheless, additional studies are required to modify their pharmacokinetic profile, decrease toxicity, and warrant efficacy in the clinical role.

Marine Sponge Secondary Metabolites as Candidates of Infectious Wound Healing Activity Mechanism

Secondary metabolites of marine sponges have huge potential in the treatment of infectious wound diseases because of their multi-faceted bioactive characteristic. Such metabolites as alkaloids, peptides, and terpenes have strong antibacterial properties that resist a wide range of pathogenic bacteria, the antibiotics. Not only preventing and treating different types of infections, these compounds enhance healing of different types of wounds by inhibiting bacterial cell wall and interfering on the synthesis of proteins and nucleic acids as well as disrupting membrane integrity. Moreover, they have antioxidant and anti-inflammatory effects, which increase the anti-inflammatory effect and decrease oxidative stress to support wound healing further. The capacity of marine sponge metabolites to stimulate cell proliferation and angiogenesis, is guaranteeing fast tissue regeneration and tissue repair and hence the prospects of using the metabolites as advanced metabolite in wound care therapy applied in treating both the wound healing process and the related infection.

CONCLUSION

Marine sponges, possessing a wide range of secondarily produced productions and with their potent antibiotics bear a future potential of being an improved wound dressing especially in suspecting infectious wounds. These bioactive compounds that are unique to these sponges have a wide range of anti-bacterial properties that are able to effectively deal with and counter a wide range of pathogens (including antibiotic-resistant strains). The modulation of inflammation, decrease oxidative stress, and enhancement of cell proliferation and angiogenesis make them candidates in stimulation of closure of wounds. With the progress of our knowledge and the utilization of the therapeutic potential of these marine-derived compounds, they might become a part of creating new solutions in wound care. This would go a long way to alleviate suffering among patients as infection rates are lessened, healing time takes shorter and prevents the burden of sticking with chronic wounds. Future research and clinical studies will play a vital role in modifying these substances to make them practical in the medical field and this will usher in new invention of medicines in wound care and control of infectious diseases.

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