ScienceDirect

Chemico-Biological Interactions

Volume 383, 25 September 2023, 110682

Review Article

Indole alkaloids from marine resources: Understandings from therapeutic point of view to treat cancers

Fahadul Islam [a 1], Zerrouki Dehbia [b], Mehrukh Zehravi [c], Rajib Das [d 1], M. Sivakumar [e], Karthickeyan Krishnan [f], Abdul Ajeed Mohathasim Billah [g], Bharadhan Bose [h], Avoy Ghosh [d], Shyamjit Paul [d], Firzan Nainu [i], Irfan Ahmad [j], Talha Bin Emran [a k]

Show more

https://doi.org/10.1016/j.cbi.2023.110682

Get rights and content

Highlights

- This review discussed the anticancer effects of marine indole alkaloids.
- Highlighted SAR of marine indole alkaloids with regard to anticancer effect.
- The mechanism of action of marine indole alkaloids is discussed.
- Focused on clinical trial regarding anticancer effect of indole alkaloids.

Abstract

Cancer is the leading cause of mortality all over the world. Scientific investigation has demonstrated that disruptions in the process of autophagy are frequently interrelated with the emergence of cancer. Hence, scientists are seeking permanent solutions to counter the deadly disease. Indole alkaloids have been extensively studied and are acknowledged to exhibit several bioactivities. The current state of disease necessitates novel pharmacophores development. In recent decades, indole alkaloids have become increasingly significant in cancer treatment and are also used as adjuvants. A substantial amount of pharmacologically active molecules come from indole alkaloids, which are widely distributed in nature. Indole alkaloids derived from marine organisms show immense potential for therapeutic applications and seem highly effective in cancer treatment. A couple of experiments have been conducted preclinically to investigate the possibility of indole alkaloids in cancer treatment. Marine-derived indole alkaloids possess the ability to exhibit anticancer properties through diverse antiproliferative mechanisms. Certain indole alkaloids, including vincristine and vinblastine, were verified in clinical trials or are presently undergoing clinical assessments for preventing and treating cancer. Indole alkaloids from marine resources hold a significant functionality in identifying new antitumor agents. The current literature highlights recent advancements in indole alkaloids that appear to be anticancer agents and the underlying mechanisms.

Introduction

Cancer is the leading cause of morbidity and mortality worldwide [1,2]. The hallmark characteristic of malignancies is the increased proliferation of abnormal cells that surpass their typical confines, subsequently infiltrating adjacent anatomical structures and disseminating to other organs, a process denoted as metastasis [3,4]. During the process of oncogenesis, cancer cells not only evade the body's regulatory mechanisms but also acquire the capacity to disrupt both local and systemic homeostasis. Tumors are capable of producing various substances, including cytokines, classical neurotransmitters, immune mediators, hypothalamic and pituitary hormones, melatonin, biogenic amines, and glucocorticoids, as evidenced by studies conducted on animal as well as human models of cancer. Tumors regulate body homeostasis by releasing neurohormonal and immune mediators influencing the main neuroendocrine centers, including the hypothalamus, adrenals, pituitary, and thyroid [5]. Cancer encompasses a multifaceted set of diseases characterized by the convergence of pathophysiological, genetic, and environmental factors alongside immunological aspects. It includes a diverse spectrum of conditions that exhibit significant variability in their clinical timelines, which extend from remarkably slow growing to aggressive manifestations. The socioeconomic impact of cancer is major, and it is

projected to surpass cardiovascular disease as the primary cause of mortality in the United States shortly [6]. As per the report by GLOBOCAN in 2020, the worldwide incidence of malignancy was estimated to be approximately 19.3 million (apart from non-melanoma skin cancer=18.1 million), with a corresponding mortality rate of nearly 10.0 million deaths (apart from non-melanoma skin cancer=18.1 million) in the same year [7]. According to recent statistics, in 2020, breast cancer in females eclipsed lung cancer as the most frequently diagnosed form of cancer. It is anticipated that breast carcinoma accounted for 11.7% of the total number of cancer diagnoses, and around 2.3 million new instances were discovered worldwide. Lung cancer followed closely behind with 11.4% of diagnoses, while in the case of colorectal cancer, it was 10.0%, for prostate cancer=7.3%, and for stomach cancer=5.6% of all new cancer cases [7].

The earth is predominantly encompassed by seas and oceans, containing over 75% of the planet's total area. These bodies of water are home to a diverse range of creatures, with samples from 34 out of the 36 defined phyla. Marine ecosystems possess a vast phyletic diversity and a significant potential for biotechnology [8,9]. The marine ecosystem is complex, with significant changes in biological habitats, temperature, salinity, salinity, and pressure. These significant changes formed multiple new structures with exceptional pharmacological attributes, some of which aren't common to terrestrial sources [10,11]. Over the last three to four decades, there has been a global attempt to identify the bioactive molecules of the marine ecosystem, with a particular emphasis on marine animals and plants. A small number of marine animals, plants, and microorganisms have produced over 12,000 new chemical components, and thousands of extra molecules are being identified annually. The attempts to find new compounds lead to the isolation of multiple bioactive metabolites, which have been effectively synthesized and utilized by the pharmaceutical sector [[12], [13], [14]]. It has been shown that indole alkaloids are produced from a wide range of marine organisms, including symbiotic bacteria, acorn worms, red algae, tunicates, and sponges. As reported in previous studies, these compounds are the most abundant and complex of all marine alkaloids [[15], [16], [17], [18], [19]]. The therapeutic effect of indole alkaloids is attributed to their basic properties, which result from a pyrrole ring containing nitrogen atoms [20,21]. Indole alkaloids have been shown to display anticancer activity through various antiproliferative mechanisms. Some of these indole alkaloids, for example, vincristine and vinblastine, have already been tested clinically or are now undergoing clinical trials to treat malignancies. Therefore, indole alkaloids have a significant place in the research on the progress of newfound cancer treatments [22,23]. Much evidence supports the notion that melatonin is protective in mitigating the effects of UV radiation and the resulting mitochondrial dysfunction.

The anti-apoptotic actions of melatonin and its metabolites may be due to its modulatory influence on mitochondrial redox and bioenergetic homeostasis [24]. In an in vitro experiment, several marine fungi from the family Trichocomaceae, such as *Aspergillus versicolor*, develop indole alkaloids such as variecolortides and versicamide H. These indole alkaloids have been demonstrated to prevent the growth of many cancer cell lines, such as cervical, colon, and leukemia, myelogenous leukemia [25,26]. Another member of the same fungus family, known as *Neosartorya laciniosa*, includes indole alkaloids. One is Aszonapyrone A, a compound that has demonstrated efficacy in managing many cancers, like skin, lung, and breast [27]. In order to confirm the therapeutic effectiveness discovered in vivo and in vitro research, several drugs are now being tested in clinical settings [28]. For instance, The proteasome inhibitor Salinosporamide A is currently participating in clinical studies for the therapeutic management of multiple myeloma [29].

This study aims to offer a comprehensive overview of the medicinal uses of marine indole alkaloids as cancer-preventive agents and to facilitate finding potential options for developing novel anti-cancer drugs.

Section snippets

Structure-activity relationship

The objective of investigating the structure-activity relationship (SAR) is to pinpoint and improve the structural characteristics of a molecule that are accountable for its activity, such as its potency, selectivity, or mode of action [30]. Researchers can learn more about SAR and establish better medications or chemical compounds by precisely altering various portions of the molecule and analyzing the changes in activity that ensue. Marine sponges, tunicates, algae, and bacteria are a few…

Mechanism of action of marine indole alkaloids

Marine indole alkaloids, which come from fungi, sponges, and other marine species, exhibit various modes of action in the context of cancer [38] (Table 1). Due to their distinct chemical structures and biological activity, these substances have demonstrated considerable promise in the fight against many forms of cancer. Several universal processes have been identified, albeit the precise action methods might differ based on the drug and the kind of cancer [25,27,44,48,57,70]. Interference with…

Breast cancer

Breast cancer is a top contributing factor to mortality in women worldwide (Fig. 1). The incidence rates are comparatively more significant in highly advanced countries, while they are relatively low in emerging economies, albeit on the rise [75]. In recent years, numerous experimental investigations have been carried out to find novel indole compounds derived from marine sources. Eamvijarn and colleagues discovered that Aszonapyrone A, derived from *Neosartorya laciniosa*, can trigger apoptosis…

Updates on clinical trials

Indole alkaloids and their derivatives are widely acknowledged as significant molecules to target in pharmaceutical chemistry and drug development. These compounds are found abundantly in diverse natural sources. Nevertheless, the clinical application of various indole alkaloids remains restricted by associated factors, including inadequate water solubility, limited bioavailability, and toxic adverse effects. Furthermore, most investigations have predominantly relied on animal models, either in …

Conclusions and future directions

Marine indole alkaloids are recognized as significant target molecules in pharmaceutical chemistry and drug discovery. These compounds are plentiful in a diverse range of natural sources. Nevertheless, several indole alkaloids exhibit confined clinical significance owing to inherent factors such as inadequate aqueous solubility, lowered bioavailability, and deleterious side effects. Furthermore, many investigations have been carried out preclinically. These limitations may work as a catalyst…

Authors contributions

Fahadul Islam, Zerrouki Dehbia, Mehrukh Zehravi, Rajib Das, and Talha Bin Emran conceptualized and designed the manuscript, participating in drafting the article and/or acquisition of data and/or analysis and interpretation of data; Fahadul Islam, M Sivakumar, Karthickeyan Krishnan, Abdul Ajeed Mohathasim Billah, and Bharadhan Bose prepared the figures and tables. Fahadul Islam, Zerrouki Dehbia, Rajib Das, Avoy Ghosh, Shyamjit Paul, Firzan Nainu, Irfan Ahmad, and Talha Bin Emran wrote, edited,…

Funding

Not applicable.…

Ethics approval and consent to participate

The reported studies did not involve human participants and human data.…

Consent for publication

This does not involve any individual's data.…

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgments

The authors express their gratitude to the Deanship of Scientific Research at King Khalid University for funding this work through the Large Research Group Project under grant number RGP.02/316/44.…

Recommended articles

References (133)

D. Hanahan *et al.*
Hallmarks of cancer: the next generation

Cell (2011)

R.M. Slominski *et al.*
How cancer hijacks the body's homeostasis through the neuroendocrine system
Trends Neurosci. (2023)

M.J. Costello *et al.*
Erratum: marine biodiversity, biogeography, deep-sea gradients, and conservation (current biology (2017) 27(11) (R511–R527) (S0960982217305055) (10.1016/j.cub.2017.04.060))
Curr. Biol. (2017)

M. Donia *et al.*
Marine natural products and their potential applications as anti-infective agents
Lancet Infect. Dis. (2003)

T.P. Anand *et al.*
Antimicrobial activity of marine bacteria associated with sponges from the waters off the coast of South East India
Microbiol. Res. (2006)

A. Eamvijarn *et al.*
Bioactive meroditerpenes and indole alkaloids from the soil fungus Neosartorya fischeri (KUFC 6344), and the marine-derived fungi Neosartorya laciniosa (KUFC 7896) and Neosartorya tsunodae (KUFC 9213)
Tetrahedron (2013)

K.O. Hansen *et al.*
Kinase chemodiversity from the arctic: the breitfussins
J. Med. Chem. (2019)

K. Iwasaki *et al.*
Croissamide, a proline-rich cyclic peptide with an N-prenylated tryptophan from a marine cyanobacterium Symploca sp
Tetrahedron Lett. (2018)

F. Wang *et al.*
Seven new prenylated indole diketopiperazine alkaloids from holothurian-derived fungus Aspergillus fumigatus
Tetrahedron (2008)

M. Gompel *et al.*
Meridianins, a new family of protein kinase inhibitors isolated from the Ascidian Aplidium meridianum
Bioorg. Med. Chem. Lett (2004)

View more references

Cited by (6)

Comparing antioxidant and cytoprotective effects: Quercetin glycoside vs. aglycone from Ephedra alata
2024, Phytomedicine Plus

Show abstract

Antidiabetic potency and molecular insights of natural products bearing indole moiety: A systematic bioinformatics investigation targeting AKT1
2024, Computational Biology and Chemistry

Show abstract

Indole Compounds in Oncology: Therapeutic Potential and Mechanistic Insights
2024, Pharmaceuticals

Pharmaceutical prospects of pomegranate antioxidants in combating microbial infections
2024, International Journal of Food Properties

Exploring pyrrolidinyl-spirooxindole natural products as promising platforms for the synthesis of novel spirooxindoles as EGFR/CDK2 inhibitors for halting breast cancer cells
2024, Frontiers in Chemistry

Molecular Hybridization of Alkaloids Using 1,2,3-Triazole-Based Click Chemistry

2023, Molecules

1 The authors contributed equally to this work.

View full text