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RESEARCH ARTICLE

Network Pharmacology Analysis Reveals Bioactive Compounds and Potential Targets of Sea cucumber for Cervical Cancer Therapy [version 1; peer review: awaiting peer review]

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Abstract

Cervical cancer is a leading cause of death among women in many countries, and finding effective anticancer treatments for this type of cancer is challenging due to high rates of HPV infection and low vaccination rates among women of childbearing age. Studies have shown that protein oncogenes produced by HPV stimulate cell growth, promoting tumor development and treatment resistance. It explores the potential therapeutic mechanisms of Scitophus hermanii in treating cervical cancer using network pharmacology, identifying PTGS2, EGFR, and NFE2L2 as targets. Bioactive compounds in sea cucumbers, such as Gangliosides, Stichoposide and variegatuside have the potential to prevent cancer cell proliferation by inhibiting the epidermal growth factor receptor expression. The review suggests that targeting pathways could be a promising strategy for the treatment of cervical cancer. SwissADME also predicted the drug-like properties of the active chemicals in sea cucumbers. This discussion sheds new light on the potential use of marine natural products for the treatment of various types of cervical cancers.

Keywords

Drug discovery, epidermal growth factor receptor, pharmacokinetics, physicochemistry, sea cucumber, schistopus hermanii.

Open Peer Review

Approval Status *AWAITING PEER REVIEW*

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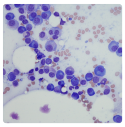

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Introduction

Cervical cancer is a significant public health issue worldwide, with an estimated 604,000 new cases anticipated in 2020, according to the World Health Organisation (WHO).[1] Unfortunately, the majority of cervical cancer-related deaths (approximately 90%) are expected to occur in low- and middle-income countries, with an estimated 342,000 deaths projected for 2020.[1,2] This highlights the urgent need for increased awareness, prevention, and treatment strategies to address this problem. In Indonesia, cervical cancer is the third most common cancer in women, with 36,633 new cases reported in 2020.[3] Human papillomavirus (HPV) is the main risk factor for cervical cancer, with types 16, 18, and 45 being the most common.[4] HPV has several signalling pathways that are involved in signalling pathway transmission via active molecules such as MEK, ERK, and Akt.[5] The virus has several oncoproteins, including E6 and E7, that play a significant role in cancer development. In early stages of cancer, the HPV genome suppresses viral oncoproteins E6 and E7, which maintain Akt phosphorylation status. E6 and E7 activate the Akt/mTOR signalling pathway, promoting viral cap-dependent protein synthesis and leading to carcinogenesis. HPV16 oncoprotein E7 increases keratinocyte migration.[6] E5 plays a role in HPV-related cancer proliferation by regulating myogenic signalling pathways and stimulating VEGF expression through ERK activation, which is involved in angiogenesis.[7] Cancer eventually develops through these pathways.[8]

While various treatment modalities are available, there is still a need for further investigation into the effects of these treatments. The Surveillance, Epidemiology, and End Results (SEER) programme estimates the overall 5-year relative survival rate for cervical cancer to be 67.2%.[9] Therefore, there is a need for continued research to develop more effective treatment strategies. Natural chemicals originating from plants and animals that have potential anti-cancer effects are being researched for new cancer treatments.[10] Teripang, also known as Sea cucumber, is a marine natural product that has shown efficacy in medical treatments.[11] Researchers have demonstrated the anti-cancer properties of seacucumber in previous studies, but its exact mechanism of action remains unclear. Sea cucumber, is a marine natural product that has shown efficacy in medical treatments. According to current research, a specific group of Sea cucumbers has many promising pharmacological properties.[12] This substance is composed of a diverse range of compounds, including various types of polysaccharides, such as glycosaminoglycans, neutral glycans, fucosylated chondroitin sulfates, and sulfated fucans. Studies have shown that Sea cucumber-derived compounds can exhibit cytotoxic activity, induce apoptosis, arrest cell cycle, reduce tumor growth, inhibit metastasis, and prevent drug resistance.[13] Cytotoxic activity prevents cancer cell growth. Bioactive carbohydrate compounds from Holothuria scabra species, such as holothurine A3 and A4, are cytotoxic in Hep-G2 and KB cell lines.[14] Frondanol A5, derived from Cucumaria frondosa extract, induced apoptosis in pancreatic cancer cells S2013 and AsPC.[15] Echinoside A and echonoside A from Pearsonothuria graeffei disrupt the G0/G1 cell cycle of Hep-G2 liver carcinoma cells, preventing DNA replication.[16] Saponins from Pentacta quadrangulari, particularly Philinopsides E and A, inhibit tumour growth in sarcoma and hepatoma mouse models.[17] Pearsonothuria graeffei bioactive's compound, Ds-echinoside A, inhibits hepatocellular carcinoma (Hep-G2) cell migration, invasion, and adhesion, thereby reducing cancer cell metastasis.[18] The bioactive compounds, potential targets, and underlying mechanisms of Sea cucumber in cervical cancer are not well understood.

The article aims to investigate the potential of natural products, specifically sea cucumber, as a novel therapeutic strategy for the treatment of cervical cancer. A network pharmacology analysis of *S. hermanii*, will be presented to identify the active ingredients and targets of *S. hermani*. The findings of this study may provide a better understanding of the bioactive compounds, potential targets, and underlying mechanisms of *S. hermanii*, which may be useful for the development of novel therapies for cancer treatment.

Methods

Screening of potentially active compounds of Sea cucumber

The search for bioactive compounds in Sea cucumbers (*Sticophus* sp.) was conducted using the CMNPD database.[19] Each compound was then searched for its SMILE (simplified molecular-input line-entry system) profile and 3D structure using the PubChem database.[20]

Quantitative Structure-Activity Relationship (QSAR) Analysis

Based on the information provided, the bioactive compounds found in Sea cucumbers or *Schistocopus hermani,* were analyzed for their potential using the WAY2DRUG PASS prediction tool as an anticancer treatment.[21] The WAY2-DRUG Pass Prediction tool uses Structure Activity Relationship (SAR) analysis to compare input compounds with known compounds that have specific potential. The greater the similarity of the structure of the compounds, the higher the prediction value obtained. Compounds with similar structures can be predicted to have similar potential. The Pa value (Probability to be Active) is the output prediction value of the WAY2DRUG PASS, which describes the potential of a tested compound. If the Pa value is greater than 0.7, it indicates that the compound is predicted to have high potential as an anti-inflammatory, for example, because it has a high similarity to compounds in the database. A score of 0.5 is

recommended as the cut-off score. The Pa value provides the accuracy of the obtained prediction function, the higher the Pa value of a function, the better the accuracy.[22]

Toxicity analysis of compounds

The toxicity of bioactive compounds of Sea cucumbers can be predicted using the Protox II database.[23] The parameters analyzed include Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity, and Cytotoxicity, as described by Banerjee *et al*. (2018).[24]

Prediction of proteine targets

The targets of teripang were obtained from SuperPred (with score accuracy and probability > 80%).[25] The target prediction was obtained by entering the SMILES found in step 1. Genes and proteins related to cervical cancer were obtained from the Open Target database (with overall score prediction ≥ 0.1). The Open Target database was chosen because it includes information from other databases and is the most up-to-date (last update February 2023 (Version 23.02)). The targets related to the disease and the teripang target were then mapped using a Venn diagram to determine the intersection target. The function of each target from the best compound (Variegatusdie) was then mapped using the Database for Annotation, Visualization, and Integrated Discovery version 2021. The R package gplot2 was used to visualize the results of functional annotation from DAVID.[26]

Network analysis

The protein target of Variegatuside from teripang was further analyzed using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING DB V.12.0).[27] The following parameters were used: Organism: Homo sapiens; Network type: Full STRING network; Required core: medium confidence (0.4). The data format TSV from STRING was then further processed using CytoScape V.10.0 for network analysis.

Results

Screening of potentially active compounds of *Scitophus hermanii*

Bioactive profile of seacucumber from Comprehensive Marine Natural Products Database (CMNPD).[19] In general, this study extracted 16 compounds from the CMNPD database, which were obtained from samples of sea cucumbers in Table 1.

Table 1. Profile of Bioactive Compounds in Sea Cucumber.[17]

Name	Compound ID
SCG-1	CMNPD13820
SCG-2	CMNPD13821
SCG-3	CMNPD13822
Stichoposide A	CMNPD1722
Stichoposide B	CMNPD1723
Stichoposide C	CMNPD1724
Stichoposide D	CMNPD1725
Variegatuside C	CMNPD25648
Variegatuside D	CMNPD25649
Variegatuside E	CMNPD25650
Variegatuside F	CMNPD25651
Stichorrenoside A	CMNPD29857
Stichorrenoside B	CMNPD29858
Stichorrenoside C	CMNPD29859
Stichorrenoside D	CMNPD29860
Stichorrenoside E	CMNPD31481

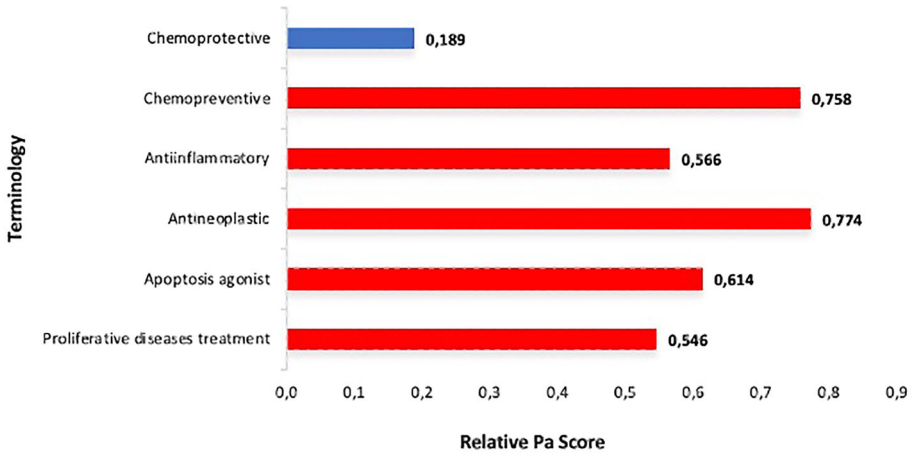

Figure 1. SAR-based Prediction of Sea Cucumber's Potential as an Anticancer Agent.[19]

Quantitative Structure-Activity Relationship (QSAR) analysis

Based on SAR analysis using Way2Drug Pass Online,[21] it is found that bioactive compounds in Sea cucumber have a good potential as Chemopreventive (Pa Score: 0.758), Anti-inflammatory (0.566), Antineoplastic (0.774), Apoptosis Agonist (0.614), and Proliferative diseases treatment (0.546). Chemopreventive is the use of natural or synthetic compounds to prevent cancer. Compounds included in chemopreventive can be used to prevent the occurrence of cancer, for someone with a high risk, and can be used to prevent relapse in patients undergoing treatment. The parameters of anti-inflammatory, antineoplastic, apoptosis agonist, and proliferative diseases treatment are used to see the potential as anticancer based on Hallmarks of cancer. Sea cucumber has the highest potential as Chemopreventive and Antineoplastic toxicity in Figure 1.

Analysis of compound

Toxicity analysis of each Sea cucumber sample using the Protox II webserver demonstrated that all compounds analyzed were predicted to exhibit immunotoxicity, with some also displaying cytotoxic effects. The Protox II immunotoxicity model assesses their ability to inhibit B cell growth. Additionally, mutagens are compounds with the potential to induce changes in an organism's genetic material, while carcinogens can cause cells to become cancerous by altering their genetic structure, leading to uncontrolled cell proliferation. Hepatotoxicity refers to kidney dysfunction or damage associated with an overload of drugs or xenobiotics. Based on the comparison with QSAR data, Variegatuside C and Variegatuside D were identified as potential candidate compounds falling into the toxicity class 4 (range 1 – 6, with lower values indicating higher toxicity), signifying the need for further investigation and evaluation of these compounds as presented in Table 2. Meanwhile, Table 3 displays the profile of the most promising predicted compounds.

Prediction of proteine targets

Figure 2 shows the Functional Analysis Target of Variegatuside in Sea cucumber, while in Figure 3, it is described that there are 11 overlapping targets between cervical cancer and Sea cucumber, namely MTOR, PDGFRA, PIK3R1, KLF5, NTRK3, HIF1A, CCNE1, AR, TRIM24, HSP90AB1, and TOP2A. MTOR is an oncogene that plays a role in promoting proliferative signalling. It is also involved in triggering invasion, metastasis, angiogenesis, evasion of programmed cell death, and altering cellular energetics (Hallmarks of Cancer: Cosmic Database).

Network analysis

MTOR is considered as a potential target because it has the highest values in terms of betweenness centrality, closeness centrality, degree, and cervical cancer overall score compared to other targets (Table 4, Figure 4). Classic centrality calculations such as degree, closeness, and betweenness centrality are used to identify influential nodes (proteins) in biological networks. Degree provides an indication of how many proteins interact with a protein node. Closeness centrality is useful for estimating how quickly information flows through a node, or in other words, how short the fastest path is from node x to all other nodes. Meanwhile, betweenness centrality is based on communication flow. Nodes with high betweenness centrality values play a role in controlling information flow (Scardoni & Laudanna, 2009) Based on these analyses, it is predicted that Sea cucumber, specifically through the MTOR pathway, may be effective in targeting cervical cancer.

Table 2. Profile sea cucumber bioactive compounds in toxicity analysis.[20]

Name	Hepatotoxicity	Probability	Carcinogenicity	Probability	Immunotoxicity	Probability	Mutagenicity	Probability	Cytotoxicity	Probability
SCG-1	Inactive	0.84	Inactive	0.72	Active	0.97	Inactive	0.88	Inactive	0.77
SCG-3	Inactive	0.84	Inactive	0.72	Active	0.98	Inactive	0.88	Inactive	0.77
Stichoposide A	Inactive	0.96	Inactive	0.61	Active	0.99	Inactive	0.91	Inactive	0.58
Stichoposide B	Inactive	0.97	Inactive	0.66	Active	0.99	Inactive	0.93	Active	0.7
Variegatuside C	Active	0.69	Inactive	0.62	Active	0.96	Inactive	0.97	Inactive	0.93
Variegatuside D	Active	0.69	Inactive	0.62	Active	0.96	Inactive	0.97	Inactive	0.93
Stichorrenoside A	Inactive	0.95	Inactive	0.69	Active	0.99	Inactive	0.92	Active	0.56
Stichorrenoside C	Inactive	0.96	Inactive	0.68	Active	0.99	Inactive	0.9	Active	0.79
Stichorrenoside D	Inactive	0.95	Inactive	0.59	Active	0.99	Inactive	0.91	Active	0.69
Stichorrenoside E	Inactive	0.95	Inactive	0.69	Active	0.99	Inactive	0.89	Active	0.71

Table 3. Profile of the most potential predicted compounds.[20]

Name	Hepatotoxicity	Probability	Carcinogenicity	Probability	Immunotoxicity	Probability	Mutagenicity	Probability	Cytotoxicity	Probability
Variegatuside C	Active	0.69	Inactive	0.62	Active	0.96	Inactive	0.97	Inactive	0.93
Variegatuside D	Active	0.69	Inactive	0.62	Active	0.96	Inactive	0.97	Inactive	0.93

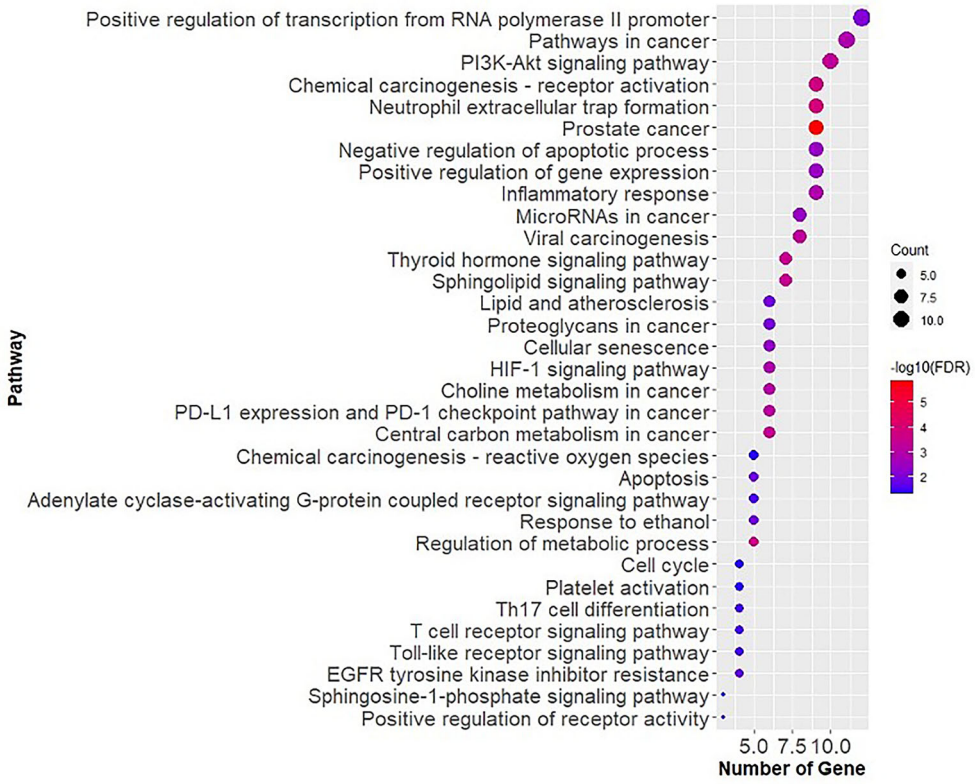

Figure 2. Functional Analysys Target of Variegatuside in Seacucumber.[21]

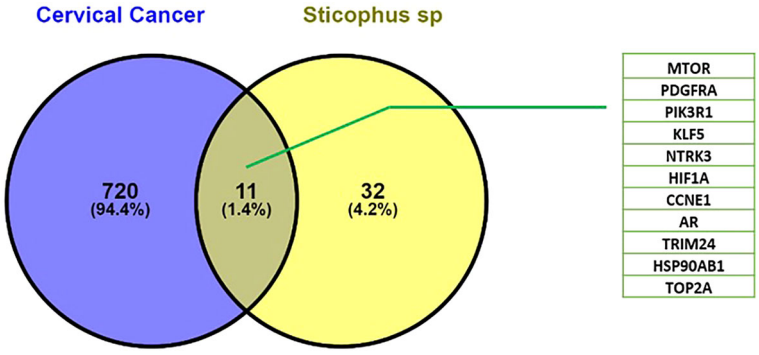

Figure 3. Venn Diagram, Intersection Cervical Cancer and *Sticophus* sp.

Discussion

Our investigation revealed that Variegatuside C and Variegatuside D were the crucial components responsible for its anti-cancer effects. Recent study findings have identified 11 overlapping targets between cervical cancer and Seacucumber. mammalian Target of Rapamycin (MTOR), Platelet-Derived Growth Factor Receptor Alpha (PDGFRA), Phosphoinositide-3-Kinase Regulatory Subunit 1 (PIK3R1), Krüppel-like Factor 5 (KLF5), Neurotrophic Receptor Tyrosine Kinase 3 (NTRK3), Hypoxia-Inducible Factor 1 Alpha (HIF1A), Cyclin E1 (CCNE1), Androgen Receptor (AR), Tripartite Motif Containing 24 (TRIM24), Heat Shock Protein 90 Alpha Family Class B Member 1 (HSP90AB1), and Topoisomerase II Alpha (TOP2A), are crucial proteins with unique roles in promoting cancer growth and progression. PDGFRA is a protein that promotes cell proliferation and survival in several types of cancer.[28] The study conducted by Chang *et al*. regarding miRNA-487a and its role in promoting proliferation and metastasis in hepatocellular carcinoma, demonstrated that PIK3R1 is a fundamental factor in facilitating cellular survival, growth, and proliferation.[29] According to the review conducted by Luo *et al*., the transcription factor protein KLF5, which is implicated in various cancer types, plays a role in promoting cellular proliferation, growth, and survival.[30] Similarly, NTRK3, a receptor tyrosine kinase protein involved in cell survival, proliferation, and differentiation, plays a significant role in cancer

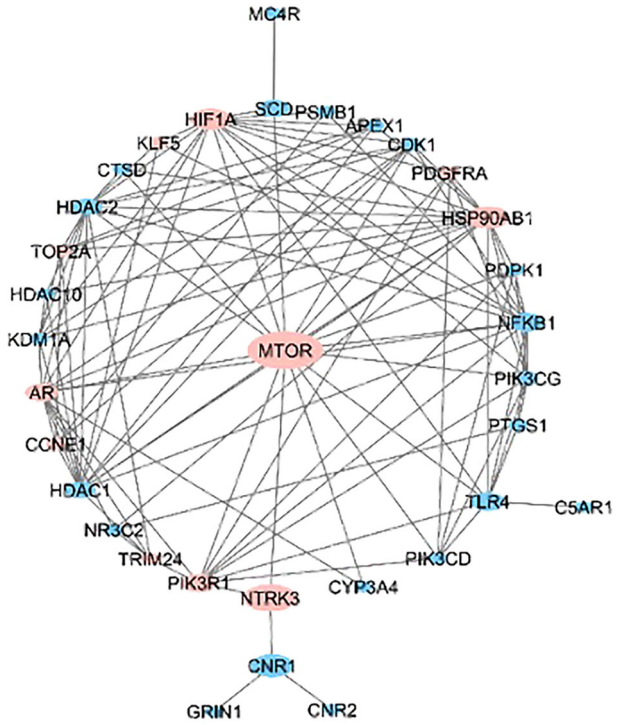

Figure 4. Target pathway network of Sea cucumber (Variegatuside C and Variegatuside D) for treating cervical cancer. The blue nodes represent Sea cucumber targets, while the red nodes represent targets of both Sea cucumber and cervical cancer. The diameter of each node indicates its betweenness centrality score, with larger diameters indicating higher scores.

Table 4. Betweenness centrality score of network analysis.[23]

Name	Degree	Betweenness centrality	Closeness centrality	Cervical cancer overall score
MTOR	**17**	**0.288**	**0.653**	**0.486**
NTRK3	3	0.175	0.444	0.323
CNR1	3	0.123	0.323	0.001
HSP90AB1	17	0.122	0.604	0.185
HIF1A	15	0.113	0.593	0.298
NFKB1	14	0.079	0.571	0.031
PIK3R1	10	0.078	0.533	0.362
TLR4	9	0.077	0.516	0.010
AR	13	0.072	0.552	0.456
SCD	3	0.063	0.438	n/a

development.[31] HIF1A is a protein that plays a crucial role in cancer cells' adaptation to low-oxygen environments, promoting the survival and growth of cancer cells even in challenging conditions.[32] CCNE1 is a regulatory protein that contributes to cell cycle progression and is frequently overexpressed in various cancers, leading to the uncontrolled growth of cancer cells.[33] Meanwhile, AR is a transcription factor protein that is crucial in the development and progression of prostate cancer, promoting cell growth and survival of androgen-dependent cancer cells. TRIM24 is an oncogenic transcriptional activator that regulates gene expression and promotes cancer cell growth.[34] Recent studies have shown that HSP90AB1 is a chaperone protein that plays a critical role in cell signalling pathways related to the growth and survival of cancer cells.[35] This is consistent with the findings of Ujianti *et al.*, which suggest that endoplasmic reticulum stress conditions involving HSP90 as a marker for UPR may contribute to the development of liver carcinoma.[36] These insights help us better understand the complex role that HSP90AB1 plays in cancer biology and could lead to new potential therapeutic targets for the treatment of liver cancer and other cancers in which this protein is involved. Finally,

TOP2A is an enzyme that is often overexpressed in cancer and plays a role in DNA replication and repair, contributing to the proliferation of cancer cells.[37] Understanding the functions of these proteins can help researchers develop targeted therapies for cancer treatment develop targeted therapies for cancer treatment.

The discussion brings attention to the significant potential of MTOR (mammalian target of rapamycin) as a target for cervical cancer treatment. Network analysis, which includes parameters like betweenness centrality, closeness centrality, degree, and cervical cancer overall score, reveals that MTOR possesses the highest values among other targets. These network properties are fundamental in identifying influential nodes or proteins within biological networks. These findings align with the study conducted by Ji *et al.*, which found that MTOR is one of the factors influencing the growth of various cancers, particularly cervical cancer.[38] Degree centrality defines the number of proteins interacting with a protein node, while closeness centrality estimates the efficiency of information flow through a node. On the other hand, betweenness centrality is based on controlling the flow of information.[39] Considering these network properties, the analysis indicates that targeting MTOR may prove effective in the treatment of cervical cancer. MTOR, a serine/threonine kinase, plays a critical role in cell growth, metabolism, and proliferation. It is well-established that mTOR signalling is involved in multiple cancer characteristics, such as cell growth, survival, metabolism, angiogenesis, and metastasis.[40] The activation of mTOR is frequently observed in cancer cells, contributing to their uncontrolled growth. Activation of mTOR signalling can enhance mRNA translation and increase the production of proteins involved in cell cycle progression, thus promoting cancer cell proliferation.[41] Additionally, mTOR activation induces metabolic reprogramming in cancer cells, enabling them to adapt to nutrient-deprived and hypoxic conditions.[42] The mTOR signalling pathway is also involved in regulating essential cellular processes for cancer progression, including angiogenesis and metastasis. By stimulating the production of vascular endothelial growth factor (VEGF), mTOR signalling promotes the formation of new blood vessels (angiogenesis). Furthermore, mTOR signalling facilitates cancer cell migration and invasion, facilitating the spread of cancer throughout the body.[43] Consequently, targeting the mTOR pathway has emerged as a potential therapeutic strategy for cancer treatment. Several mTOR inhibitors, such as rapamycin have been developed and assessed in preclinical and clinical studies. The results are consistent with the SAR analysis conducted in this study using Way2Drug Pass Online, which demonstrated that bioactive compounds found in Sea cucumbers have promising potential as agents for cancer prevention, anti-inflammatory, antineoplastic, apoptosis agonist, and treatment of proliferative diseases. Toxicity analysis using the Protox II webserver showed that Variegatuside C and Variegatuside D are potential candidates, as they belong to toxicity class 4. The use of Protox II as a tool in toxicity analysis is explained in a review study conducted by Benarjee *et al.*[24]

The study suggests that Variegatuside C and Variegatuside D, active ingredients found in seacucumber, show potential as treatment options for cervical cancer. These compounds have the ability to regulate targets associated with the disease, opening up avenues for further exploration and the development of novel therapeutic interventions. However, it is important to consider the limitations of the study. The findings were based on network pharmacology analysis, which relies on computational predictions and may not fully capture the complexities of biological systems. Therefore, further experimental studies, such as in vitro and in vivo experiments on cervical cancer cells and animal models, are needed to validate these findings and provide more concrete evidence. This will help strengthen the evidence presented in the study and provide a more robust understanding of the therapeutic efficacy of Sea cucumber and its active ingredients.

Data availability

Underlying data

Figshare: cmnpd_teripang_final.csv, https://doi.org/10.6084/m9.figshare.23589966.[44]

This project contains the following underlying data:

- CMNPD export.xlsx
- Disgenet.xlsx
- OMIM.xlsx
- QSAR.xlsx
- Target.xlsx
- Target Raw.xlsx
- Venn.xlsx

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Software availability

- A search for bioactive compounds in Sea cucumbers (Stichopus sp) was conducted using the CMNPD database https://www.cmnpd.org/organism-report-card/CMNPD360436
- The compounds found in Sea cucumbers were further analyzed for their potential using WAY2DRUG PASS prediction, http://www.pharmaexpert.ru/passonline/predict.php
- The toxicity of the compounds found in Sea cucumbers was predicted using the Protox II database, https://tox-new.charite.de/
- The targets of the Sea cucumber compounds were obtained using SuperPred https://prediction.charite.de/
- The genes and proteins associated with Cervical Cancer were obtained from the Open Target database https://www.opentargets.org/
- The protein target of Variegatuside, derived from the Sea cucumber, was further analyzed using STRING DB v12.0 https://version-12-0.string-db.org/

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