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Marine natural products for multi-targeted cancer treatment: A future insight

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ABSTRACT

Cancer is world's second largest alarming disease, which involves abnormal cell growth and have potential to spread to other parts of the body. Most of the available anticancer drugs are designed to act on specific targets by altering the activity of involved transporters and genes. As cancer cells exhibit complex cellular machinery, the regeneration of cancer tissues and chemo resistance towards the therapy has been the main obstacle in cancer treatment. This fact encourages the researchers to explore the multitargeted use of existing medicines to overcome the shortcomings of chemotherapy for alternative and safer treatment strategies. Recent developments in genomics-proteomics and an understanding of the molecular pharmacology of cancer have also challenged researchers to come up with target-based drugs. The literature supports the evidence of natural compounds exhibiting antioxidant, antimitotic, anti-inflammatory, antibiotic as well as anticancer activity. In this review, we have selected marine sponges as a prolific source of bioactive compounds which can be explored for their possible use in cancer and have tried to link their role in cancer pathway. To prove this, we revisited the literature for the selection of cancer genes for the multitargeted use of existing drugs and natural products. We used Cytoscape network analysis and Search tool for retrieval of interacting genes/ proteins (STRING) to study the possible interactions to show the links between the antioxidants, antibiotics, anti-inflammatory and antimitotic agents and their targets for their possible use in cancer. We included total 78 pathways, their genes and natural compounds from the above four pharmacological classes used in cancer treatment for multitargeted approach. Based on the Cytoscape network analysis results, we shortlist 22 genes based on their average shortest path length connecting one node to all other nodes in a network. These selected genes are CDKN2A, FH, VHL, STK11, SUFU, RB1, MEN1, HRPT2, EXT1, 2, CDK4, p14, p16, TSC1, 2, AXIN2, SDBH C, D, NF1, 2, BHD, PTCH, GPC3, CYLD and WT1. The selected genes were analysed using STRING for their protein-protein interactions. Based on the above findings, we propose the selected genes to be considered as major targets and are suggested to be studied for discovering marine natural products as drug lead in cancer treatment.

1. Introduction

Cancer is an abnormal growth of cells and tissues which affects people of all age groups and the associated risks may increase with growing age of the patients. Up till now, more than 277 types of cancer have been identified and diagnosed among which prostate, breast, lung, colon, rectum, bronchus and urinary bladder cancers are the predominant ones [1]. Environmental (90–95%) and genetic (5–10%) factors play major role in causing cancer. Lifestyle related factors such as food habits of having carbonated beverages, junk food, tobacco, preservatives intake in food and smoking etc. are the other major factors which may cause cancer [2]. Cancer cells represent a unique property of invasion and metastasis [3].Cancer disrupts cell communication and cell signaling which leads to dysfunction of vital genes. The key cause of cancer has been understood to be a series of mutation in various cancer genes which are basically classified as tumor-suppressor genes, oncogenes and stability genes [4]. These genes act by different pathways involving cancer progression like adenomatous polyposis coli (APC), apoptosis (APOP), zinc finger protein (GLI), hypoxia inducible factor 1 (HIF1), tumor suppression protein (p53), phosphoinositide 3-kinase (PI3K), retinoblastoma tumor suppressor gene (RB), receptor tyrosine kinase (RTK), intracellular mediator (SMAD), base excision repair (BER), chromosomal instability (CIN), DNA mismatch repair (MMR) and nucleotide excision repair (NER) [5–15].

Computational studies are now considered as an interesting tool for generation of bioactive compounds. Computer aided drug design helps us in finding new targets-specific chemical entity, prior to their

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synthesis and biological evaluation. The selection of specific target, drug design, selection and synthesis of hits, structure elucidation, mechanism of action, in vitro and in vivo analysis concludes the completion of a well-designed rational project [16]. Drug design studies have been very useful for proteins to avoid their unwanted/ side effects. As many multitargeted drugs have been reported for their undesirable properties which is understood to be due to the involvement of adverse sites in target specific treatment. According to Anatomical Therapeutic Chemical (ATC) classification, total 21% multitargeted drugs have been approved in 2015-17 for their use as majorly anti-infective and anti-neoplastic agents [17]. In this review, we have used computer based software and online tools i.e. Cytoscape and STRING. Cytoscape 3.6.0 is a free software supported with java 1.8.0 _151, which provides an open source visualization and analysis to study system biology, molecular components and bimolecular interaction networks [18]. STRING database helps with simple and clear coverage of information about predicted and experimental data of protein-protein interaction, confidence score, protein 3D structure and homology models [19]. We used Cytoscape and STRING to study targets including genes, proteins, pathways and natural bioactives which are useful against cancer progression and development.

1.1. Cancer genes and their role

The cancer pathways work by targeting specific genes, which is explained in brief in this section- The APC acts as tumor suppressor and helps in controlling the growth and metastasis of tumor cells. APOP is known to be responsible for programmed cell death, and the hindrance to APOP is caused due to the central dogma of progression of cancer [7]. The GLI protein aberrantly triggers during adult life and result into development of cancer [8]. HIF1 is one of the crucial survival pathways of cancer cells to carry out its biological activities. The hypoxic condition is generally observed due to increased cellular metabolism in cancer cells, which activates many other pathways; high cellular metabolism is also understood to have a role in keeping malignant cells in hypoxic tumor alive [9,18]. p53 gene encoding protein regulates the cell cycle during DNA repair in normal cells and have major role in tumor suppression in multicellular organisms. p53 gene functions get altered by the cancer cells which doesn't allow DNA repair and thus may lead to cancer. p53 mutation has been reported in more than 50% of human cancer, which leads to mutational inactivation being a key molecular mechanism behind p53 gene dysfunction[10]. PI3K gene controls various check points like cell cycle, growth and development in normal cells. The mutation in this gene often induce cancer in normal cells, thus a potent and selective PI3K inhibitor is being looked upon as a best option to improve survival of selected cancer patients [11]. RB protein plays an important role in the first stage of DNA replication. The dysregulation of RB gene has been already reported to cause ocular cancer [12]. The membrane spanning proteins RTK are known for their intrinsic phosphotyrosine kinase activity. They bind with ligands and activate kinase by phosphorylation mechanism. The irreversible binding of ligands to receptor tyrosine kinase protein may block the kinase activity [13]. Smad proteins act as intracellular mediator of signaling once employed by TGF-β cytokines. Upon this stimulation, the cytoplasmic Smads get translocated to the nucleus to regulate target gene expression. The translocation of Smad proteins take place from cytoplasm to nucleus once it gets activated. These activated Smad proteins then regulate the gene expression [14]. The CIN gene helps in regulation of number of chromosomes per cell. The mutation in CIN leads to chromosomal instability which may increase the probability of gain or loss in chromosome number during cell division [15]. DNA damage interferes with normal cell processes, where genes for BER, MMR and NER plays major role in their repair mechanism. These key molecules are involved directly or indirectly in induction or interruption of cell cycle which may lead to metastasis [19]. The molecular targets of cancer include hyper/hypo methylation, deacetylation, histone modification and dysregulation of proteins that bind to DNA [20].

The diverse classes of drugs used in chemotherapy are topoisomerase, mTOR, aromatase and kinase inhibitors, vinca alkaloids, alkylating agents, antimetabolites, anthracyclines, and retinoids. US Food and Drug administration approved a total of 21% multi-targeted drugs in 2015–2017 which kept increasing compared to previous years (16%) [15]. For example palbociclib, ribociclib, abemaciclib [21] midostaurin [22,23], panobinostat are approved by USFDA as anticancer drugs. The cell proliferation, motility, and survival being regulated by multiple pathways and multiple alterations in cellular signaling machinery makes the multi- target approach a viable option in the field of cancer [24–26].

1.2. Bioactive compounds from marine sponges and its symbionts/associates

Marine sponges are considered as one of the richest sources of bioactive compounds among other marine organisms. They are the most prolific producers of diverse bioactive secondary metabolites with valuable therapeutic potential [27,28]. They overcome drastic environmental changes of abiotic factors such as- pH, temperature, salinity, dissolved oxygen etc. and also ecological changes from predator prey interaction which allow them to make a shield of secondary metabolites to fight and survive in benthic ecosystem [29]. The sponge and their associated microbes (bacteria, fungus and actinomycetes) produce many pharmacologically and chemically diverse compounds like peptides, alkaloids, steroids, terpenoids, sesquiterpenes, macrocyclic lactones, polyketides, phosphatidylcholines, triterpenoids, glycoproteins, biopolymers, macrolides, acetogenins, polyacetylenes and tannins [30]. These compounds are responsible for exhibiting various biological activities such as antioxidant, antidiabetic, anti-cancer, anti-hypertensive, antiviral, anti-obesity, and anti-proliferative properties.

In the span of last eight years, we have extensively studied marine sponges from Mumbai coast including *Spongosorites halichondriodes* and its associated microbes for its diverse bioactivity and have reported it in our research findings. The methanol extract of the sponge had shown antibacterial activity against *Proteus vulgaris, Escherichia coli, Bacillus subtilis, Salmonella typhi, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae*; antifungal activity against *Aspergillus flavus, Aspergillus niger* and *Metarhizium anisopliae* and cytotoxic activity in *Artemia salina*. The bioactive compounds were found to be sterol esters and terpenoids in methanol extract by GC–MS analysis [31]. To confirm the bioactive compounds in ethyl acetate and butanol extracts, these extracts were subjected to LC–MS/MS analysis. It showed presence of saturated and unsaturated esters like 7 α, 12β-dihydroxy-5β-cholan24-oic acid methyl ester, 3β, 4β, 7α, 12α-tetrahydroxy-5β-cholan-24-oic acid methyl ester, a triterpenoid glycyrrhetinic acid and novel isocoumarin citrinolactone A as well as nucleoside inosine [32]. Methanolic extract of sponge *S. halichondriodes* exhibited immunomodulatory activity at the concentration of 200 mg/kg in rats showed significant decrease in total WBC count, antibody titer values and prevention of myelosuppression in cyclophosphamide treated rats [33]. The ethyl acetate extract of sponge *S. halichondriodes* also exhibited anti-inflammatory activity in Carrageenan induced paw edema in Wistar rats. The glycyrrhetinic acid was found to be the main bioactive compound responsible for the anti-inflammatory activity [34]. Diverse bacteria were isolated and characterized from sponge *Halichondria glabrata, Cliona lobata* and *Spirastrella pachyspira* with promising antimicrobial activity. The phylogenic analysis concluded the isolates to be gram negative with close resemblance to *E. coli* and *Enterobacteria* [35]. In another study, we also isolated bioactive proteins and characterized them from *S. halichondriodes* [36].

We recently reviewed the diverse bioactive compounds and bioactivity from marine organisms with special mention to marine sponges for their therapeutic applications with bioactive secondary metabolites to update the marine researchers community [37]. Marine sponges are

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