Biological and Biomedical Journal

Journal homepage: https://bbj.journals.ekb.eg

Therapeutic, chemo-sensitizing, protective effects of natural products against cancerous cells: Preclinical and clinical studies

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ARTICLE INFO

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P-ISSN: 2974-4334
E-ISSN: 2974-4324
DOI: 0.21608/BBJ.2024.263771.1030

ABSTRACT

There are times when it is challenging to stop chemotherapy side effects from happening when the patient is receiving treatment. Nowadays, the treatment with chemotherapy combinations is frequently utilized to treat different forms of cancer. The key benefit of utilizing numerous medications was thought to be the ability to lower dosages, which may result in decrease resistance and the maintenance of the same efficacy or, with a higher efficacy, or a synergistic impact. It has been suggested that pharmacological combinations consisting of natural products (NPs) and dietary supplements can have benefits comparable to those of traditional chemotherapy treatments, but with fewer side effects. Pre-clinical and clinical studies were carried out to evaluate how NPs worked against malignant cells. Thus, the optimal balance between potential side effects and anticancer activity is desperately needed. The therapeutic, chemo-sensitizing, and protective activities of NPs against malignant cells are covered in this review.

Keywords: Pre-clinical, Clinical, Natural products, Cancer, Protection, Treatment

1. Introduction

Uncontrolled cell proliferation is a hallmark of cancer, one of the world's most common causes of mortality (Proksch et al., 2002). Surgery, radiation, chemotherapy, hormone treatment, biological therapy, and targeted therapy are all used to treat cancer. Normal cells are also killed by it in addition to tumor cells (El-Naggar and El-Said, 2020). Chemotherapy medications have a wide range of adverse effects to vital tissues including lung, heart, renal, and nerve tissue tissues damage, and an increased risk of developing cancer again (El-Naggar et al., 2019).

Potential chemotherapeutic agents and lead compounds can be found abundantly in nature. These compounds have served as the foundation and source of inspiration for the partial or complete synthesis of several potent new medications. utilizing natural products (NPs) as a foundation for pharmaceutical research. Bioactive compounds with potential medical use can be isolated from a variety of natural sources, including plants, animals, and microorganisms. Since cancer is the leading cause of death worldwide, finding a more efficient treatment strategy is vital (Anbar et al., 2022). Despite the remarkable breakthroughs in current medication, there are still several negative effects associated with chemotherapy, which has

prompted researchers to search for workable alternatives that have fewer side effects (Altun and Sonkaya, 2018). To solve this issue, novel medications that are more effective and selective are desperately needed; NPs offer a source of novel anticancer medications, particularly those derived from marine, microbial, and plant sources (Newman and Cragg, 2016; El-Said et al., 2022).

More than half of all medications and over 80% of authorized chemotherapeutic medicines are based on bioactive NPs (Muhammad et al., 2022). NPs could combat cancer because they contain natural antioxidants that function as reducing agents, free radical scavengers, and singlet oxygen quenchers. Their antioxidant activity is mostly attributed to bioactive compounds such as lignans, coumarins, flavones, isoflavones, flavonoids, anthocyanins, and isocatechins. Furthermore, by boosting the cancer-fighting properties of radiation and chemotherapy, NPs can reduce or eliminate their hazardous side effects (Zhang et al., 2018).

2. Natural products as anti-cancer agents

2.1. Anticancer agents derived from microorganisms

Some of the most important pharmaceutical industry products have been produced by microorganisms, which are also a plentiful supply of structurally diverse bioactive metabolites. Microorganisms have been found to have secondary metabolites that may have anti-tumor properties (Law et al., 2020). Numerous microbes have been tested to produce natural anticancer chemicals, which may modulate immunological response, stop cell division, and trigger apoptosis (Bakrim et al., 2022). Actinomycetes produce bioactive NPs such as enzymes, antibiotics, immunosuppressive drugs, and anti-tumor agents; actinobacteria have been identified as the principal source of these compounds (Ibrahim et al., 2023). The well-known representative genus of the Actinobacteria family, Streptomyces, is the source of approximately 70% of the antibiotics with anticancer activity that are relevant to commerce. These include antibiotics from the actinomycin, ansamycin, anthracycline, bleomycin, epothilone, and staurosporin families. According to Quinn et al. (2020), streptomycetes have been confirmed to manufacture anticancer medications such doxorubicin (DOX), bleomycin, dactinomycin, and mitomycin C. Carfilzomib, a synthetic substitute for epoxomicin that was extracted from an actinomycete strain, is a proteasome inhibitor that attaches to the chymotryptic subunit of the proteasome via a covalent, selective, and stereospecific bond (Jayaweera et al., 2021).

Numerous novel metabolites with a wide variety of bioactivities are known to be produced by fungi, and many of them are also said to have cytotoxic properties. *Aspergillus* and *Penicillium* species account for more than 30% of the identified metabolites from fungi (Al-Fakih and Almaqtri, 2019). Fumagillin has been developed as an anti-angiogenic drug for the treatment of brain, prostate, and breast cancer because it suppresses angiogenesis both *in vivo* and *in vitro*. To boost efficacy and reduce toxicity at the same time, several semi-synthetic fumagillin analogues have been created (Guruceaga et al., 2020). A new generation of anticancer medications is presently being employed in clinical trials because of advanced technology and substantial study on marine natural ingredients (Khalifa et al., 2019). Through strong growth inhibition of human tumor cells *in vitro*, *in vivo*, and in cancer clinical trials, a sizable number of metabolites originating from marine sources function as anticancer agents (Fakher El Deen et al., 2022). Most marine plant species are algae, and they have a wide range of chemical compositions. Products derived from marine plants, such as mangroves and marine algae, have been demonstrated to have antibacterial, antifungal, analgesic, anti-inflammatory, cytotoxic, hypotensive, and spasmogenic properties (Khalifa et al., 2019). Macroalgae have long been recognized as food, functional food, and potential drug sources. Also known as seaweed, contain numerous pharmacologically important bioactive elements including carotenoids, dietary fiber, protein, essential fatty acids, vitamins, and minerals, in addition to polyphenols. An alcoholic extract of the red alga *Acanthophora spicifera* was supplemented to mice treated with Ehrlich ascites carcinoma (EAC) cells, and to exhibit anti-tumor activity at

an oral dose (Biris-Dorhoi et al., 2020).

More than 400 novel metabolites, including unique, biologically active peptide and polyketide metabolites, are abundantly produced by cyanobacteria, sometimes referred to as blue-green algae. These metabolites can either kill cancer cells by inducing apoptosis or affect cell signaling by activating the protein kinase c family (Nunnery et al., 2010). Roughly 50% of the cyanobacteria strains that were evaluated showed the capacity to kill cancer cells (Robles-Bañuelos et al., 2022).

2.2. Anticancer agents derived from plant sources

The most significant position in terms of the source of novel therapeutic compounds is held by medicinal plants. In order to treat a wide range of illnesses, such as cancer, bacterial infections, and inflammation, plants and their phytoconstituents have been proven to be invaluable (Shrihastini et al., 2021). Many different types of cytotoxic phytochemicals are produced by plants; these phytochemicals can either cause necrosis and apoptosis or block different cell-signaling pathways, which can result in cell death or cell cycle arrest (Ahmed et al., 2022). Considering that more than 60% of anti-cancer medications come either directly or indirectly from plants, with the majority of them being phytochemicals that are cytotoxic. Plant-derived anti-cancerous chemicals fall into four main structural categories: vinca alkaloids, amptothecin quinolone alkaloid derivatives, epipodophyllotoxin lignans, and taxane diterpenoids. Many of their semisynthetic counterparts, such as cabizetaxel, topotecan, irinotecan, etoposide, teniposide, etc. Apoptosis is induced by several naturally occurring plant-derived chemicals, and it has been demonstrated that these products' suppression of cellular proliferation is linked to cell cycle arrest (Bailon-Moscoso et al., 2017).

Phytochemicals and their analogues are present in different parts of the plant for instance seeds, pericarp, flower, sprouts, fruits, roots, stem, leaf, and perform various pharmacological functions (Al Kazman et al., 2022). Several plant products such as alkaloids, flavonoids, lignans, saponins, terpenes, taxanes, vitamins, minerals, glycosides, gums, oils, biomolecules and other primary and secondary metabolites play significant roles in either inhibiting cancer cell activating proteins, enzymes and signaling pathways (Cdc2, CDK2 and CDK4 kinases, topoisomerase enzyme, cyclooxygenase and Bcl-2, cytokines, PI3K, Akt, mechanistic target of rapamycin (mTOR) or by activating DNA repair mechanism (p21, p27, p51, p53 genes and their protein products), Bax, Bid, Bak proteins, stimulating the formation of protective enzymes, inducing antioxidant action, thus showing potent anticancer effects in terms of their efficacy on the above mentioned proteins, enzymes and signaling pathways (Ijaz et al., 2018). *Taxus chinensis* is the source of the popular first-line chemotherapy drug PTX, which is also used as a herbal remedy for breast and ovarian cancer. The aromatic plant *Curcuma longa* is used in nutraceuticals. This plant's root, a vegetal product, is widely used in Indian traditional medicine to treat a variety of illnesses, such as liver disease, wounds, acne, urinary tract infections, parasite infections, and common colds (Siddiqui et al., 2022).

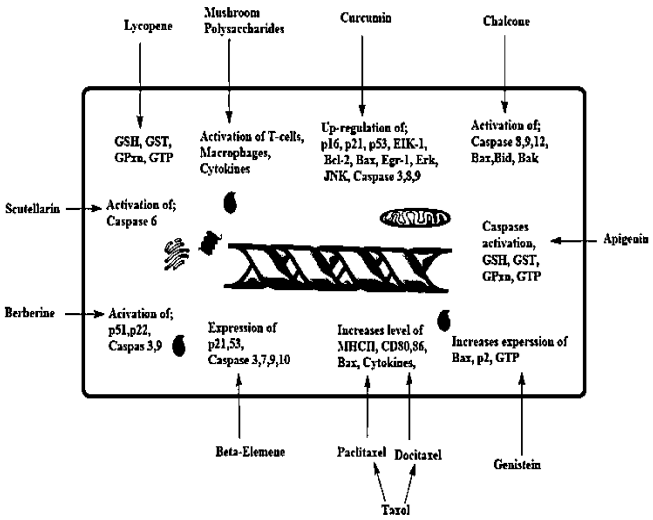

Fig. 1. Different mechanisms of natural products action as anticancer agents (Adapted from Iqbal et al., 2017).

2.3. Anticancer agents derived from animal sources

Bioactive peptides from a variety of marine creatures, including fish, mollusks, sponges, tunicates, ascidians, and invertebrates, that have anticancer properties. Physiological activities such as antibacterial, antihypertensive, and anticancer have been shown for peptides derived from animal sources (Al-Khayri et al., 2022).

2.3.1. Sponges

Sponge members of the phylum Porifera are the most abundant marine species in terms of natural marine compounds; they account for thirty percent of all natural marine products that have been discovered to date. It generates metabolites that enable them to adapt to their surroundings and serve as a self-defense mechanism.

Furthermore, active substances with anticancer potential have been found to include nucleosides, sterols, alkaloids, peroxides, fatty acids, derivatives of amino acids, and cyclic peptides (Calcabrini et al., 2017). The ability of bioactive cyclic peptides from marine sponges to chemosensitize cancer cells to conventional chemotherapy, as well as their impact on various cellular and molecular events such as DNA protection, cell cycle, apoptosis, and inflammation, have drawn the attention of numerous researchers (Ercolano et al., 2019). Seven cytotoxic cyclic peptides isolated from the Indonesian sponge (*Callyspongia aerizusa*) are cytotoxic to murine lymphoma cells, HeLa cells, and pheochromocytoma tumor cells. Two cyclic depsipeptides isolated from a Madagascan sponge (*Homophymia lamellosa*) have been found to exhibit cytotoxic activity against human lung, colon, and breast cancer cells (Yuan et al., 2021).

2.3.2. Cnidaria

Researchers have long been interested in using jellyfish venom to discover and create new anticancer drugs. According to Tawfik et al. (2021) jellyfish venom is a rich source of bioactive proteins and peptides with a variety of biological activities, such as antioxidant, antibacterial, and anticancer properties. Nematocysts, which are specialized venom-containing capsules found mostly in the tentacles of jellyfish, are the principal container for the venom of jellyfish. A combination of bioactive proteins and peptides with hemolytic, cardiotoxic, neurotoxic, musculotoxic, antioxidant, and cytolytic properties can be found in nematocyst venom. The proteins found in jellyfish venom are extremely effective against a variety of human cancer cell lines, which has sparked a lot of interest in tumor research (Lee et al., 2017).

Numerous investigations have unequivocally demonstrated the connection between jellyfish venom's capacity to cause oxidative stress and its activation of cancer cell death (Tawfik et al., 2021; De Domenico et al., 2023). The cytotoxicity of jellyfish venom, such as that of *Pelagia noctiluca* against colon cancer cells and *Cassiopea andromeda* against breast cancer cells, is attributed to the production of reactive oxygen species (ROS), the stimulation of lipid peroxidation, and damage to mitochondria (Ayed et al., 2011). On a variety of cancer cell lines, including those from the brain, colon, lung, and liver, jellyfish venom or isolated peptides have anti-proliferative effects (Zare et al., 2023).

Crude venom of *Rhopilema nomadica* jellyfish inhibited the growth of human hepatocellular carcinoma cell line (HepG2) cells. Similar inhibitory effects against HepG2 cells have been reported for other jellyfish species such as *Nemopilema nomurai*, *Cyanea lamarckii*, and *Acromitus flagellates'* venoms (Salama et al., 2022). Crude venom from nematocyst of Jellyfish *Acromitus flagellates* possesses antiproliferative and antioxidant properties on human lung cancer and HepG2 cell lines. *R. nomadica* venom showed a prominent increase of apoptosis as revealed by cell cycle arrest at G2/M phase, up-regulation of p53, Bcl-2 associated X, apoptosis regulator (BAX) and caspase-3 proteins, and the down regulation of anti-apoptotic Bcl-2 protein and DNA fragmentation. These findings suggest that *R. nomadica* venom induces apoptosis in hepatocellular carcinoma cells (Tawfik et al., 2021).

2.3.3. Echinodermata

One of the many possible aquatic creatures with important nutrients and therapeutic qualities is the sea cucumber (Bordbar et al., 2011). The

presence of bioactive agents with promising biological and pharmacological properties, such as cytotoxic activity, induction of apoptosis, cell cycle arrest, inhibition of tumor growth, anti-metastatic, and anti-angiogenic properties, is thought to contribute to the medicinal value of sea cucumbers (Wargasetia and Widodo, 2017). Vitamins, minerals, fucoidan, triterpenoid aglycones, non-glycosaminoglycan sulfated glycans, sulfated polysaccharides, non-sulphated triterpene glycosides, sphingoid bases, and chondroitin sulfates are among the important nutrients they contain.

Numerous cancers are treated with bioactive chemicals that are extracted from sea cucumbers. For example, the cytotoxic activity of holothurin, which is produced by the *Holothuria scabra* species, has been shown to be highly effective against Hep-G2 cell lines and human epidermoid cancer (Dhinakaran and Lipton, 2014). *Cucumaria frondosa* saponin Frondoside A caused apoptosis in breast cancer cells by upregulating p53, which in turn activated caspases to trigger cell death pathways. Cucumaria japonica-derived cucumarioside showed anticancer properties by inducing programmed death in tumor cells and arresting the cell cycle during the DNA synthesis phase (Wargasetia and Widodo, 2017).

3. Natural products as chemo-sensitizing agents

3.1. Chemo-sensitizing agents derived from micro-organism sources

Extracted from Cordyceps militaris, the main biologically active component identified is a nucleoside analogue called cordycepin. It affects a number of biological functions, including the control of the inflammatory response and platelet aggregation. Furthermore, cordycepin is thought to be crucial in preventing cell invasion, proliferation, and tumor metastasis via a number of signaling pathways (Soltani et al., 2019). When gemcitabine and 5-fluorouracil are used to treat malignant cells, for example, cordycepin increases their antitumor efficaciousness. Therefore, it is possible that cordycepin might improve Cis anti-cancer ability in esophageal cancer. Other studies have discovered that the combination treatment of Cis and cordycepin exerts apoptotic effects in human oral cancer cell lines by activating the JNK/caspase-7/PARP signaling pathway (Gao et al., 2020).

Natural lovastatin is made from rice that has been fermented with monascus. It has anticancer properties, may increase lung cancer cells' susceptibility to ionizing radiation, and may work in concert with DOX to cause ovarian cancer cells to undergo apoptosis. According to Peng et al. (2017), lovastatin may increase the sensitivity of nasopharyngeal cancer stem cells to chemotherapy and prevent the metastasis and epithelial-to-mesenchymal transition (EMT) in triple-negative breast cancer. Paclitaxel is one of the chemotherapy drugs that patients with hormone-independent castration-resistant prostate cancer (CRPC) frequently show resistance to. The CYPs (cytochrome P450 enzymes) are essential for the metabolism of drugs. Combination of paclitaxel with lovastatin decreased the mRNA level of CYP2C8, and CYP3A4 in prostate cancer. This revealed that inhibition of CYP2C8 by lovastatin might decrease the paclitaxel resistance of prostate cancer cells so lovastatin could enhance the sensitivity of drug-resistant prostate cancer cells to paclitaxel (Zhao et al., 2021).

The combination with bacteria, combining cyclophosphamide with bacteriolytic *Salmonella* treatment reduced tumor vascularization and inhibited the tumor in a melanoma model (Mi et al., 2019). In colon cancer xenograft models (HCT116), the *C. novyi*-NT spores and microtubule-interacting drugs, such vinorelbine and docetaxel showed tumor shrinkage. The combined treatment caused the tumor's vascular and avascular components to be destroyed. In a recent research, Saltzman et al. found that the combination of low dosage DOX and immunotherapy from *Salmonella typhimurium* decreased the tumor burden in a mouse breast cancer model. Compared to each treatment used alone, the combination exhibited better tumor reduction and less toxicity (Sawant et al., 2020).

For the treatment of lung cancer, Zhang et al. created paclitaxel liposomes and internalized them in bacteria such as *E. coli* and *L. casei*. These bacterial formulations were administered intratracheally, which resulted in an increase in neutrophils and leucocytes cell migration into the tumor microenvironment and greater levels of TNF-α, IL-4, and IFN-γ in lung tumor tissues than in healthy lung tissues. Successful anti-tumor impact was the consequence of the synergistic interaction between immunostimulation and high levels of paclitaxel distribution in the lungs (Zhang et al., 2020).

To cure cervical cancer, the combined effects of bacterial prodrug therapy using the *E. coli nitroreductase*/prodrug CB1954 and γ–rays were examined. This combination had a notable impact on the cytotoxicity of HeLa cells and considerably increased their radio sensitivity (Teng et al., 2016). *Lactobacillus* strains inhibit cancer cell proliferation and prevent malignant transformation in colorectal cancer cell lines *in vitro*. It is well known that 5-FU is the most used chemotherapeutic agent in colorectal cancer treatment. It has been approved that Uro-A is able to sensitize colon cancer cells to 5-FU (Zhang et al., 2022).

3.2. Chemo-sensitizing agents derived from plant sources

Vitamin B-17, amygdalin (AMY), has a variety of biological functions. It has anti-inflammatory, anticancer, and antioxidant properties. Additionally, in EAC-bearing mice, AMY enhances the anticancer impact of sorafenib (SOR), an efficient chemotherapy drug (Attia et al., 2022). Around the world, cucurbitacin B has been isolated from numerous plants belonging to different families. According to research, pretreating cancer cells with cucurbitacin B and then Cis greatly boosts the killing effect of the former (Alafnan et al., 2022). Flavonoids such as apigenin (APG) are derived from various plant sources, such as grapefruit, oranges, and onions (El-Said et al., 2019). Researchers discovered that in HepG2, Hep3B, and Huh7 liver cancer cell lines, APG increases the anticancer impact of Cis (Papachristou et al., 2021). *Olea europaea* leaves are used to extract oleeuropein. Ruzzolini et al. (2018) discovered that Ole, at a non-toxic level of 250 µM, could augment dacarbazine (DTIC), a DNA-methylating drug, in its lethal effect while treating advanced stage melanoma. Many plant species, including *Bridelia Micrantha*, *Garcinia densivenia*, and *Allan blackia floribunda*, are used to extract gallic acid. Researchers discovered that in human HeLa cells with cervical cancer, gallic acid can enhance the anticancer effects of paclitaxel, carboplatin, and paclitaxel/carboplatin combination therapy (Aborehab and Osama, 2019).

3.3. Chemo-sensitizing agents derived from animal sources

Honey is a naturally occurring product of bees that includes essential vitamins and enzymes along with phenolic compounds. Numerous cancer cell types, including colon cancer, have demonstrated the anti-cancer effects of honey (Erejuwa et al., 2014). It has been demonstrated that local honey from Malaysia, specifically Tualang honey, shows antibacterial activity against *Acinetobacter baumanni* and inhibits the growth of cervical and breast cancer cell lines. Gelam honey therapy was found to induce larger levels of apoptosis than 5-FU alone, according to further research on the induction of cellular apoptosis (Hakim et al., 2014).

To improve the impact of Cis on breast cancer cell lines, bee pollen was harvested from Malaysian stingless bees. Bee pollen extract (BPE) has the potential to increase the effectiveness of chemotherapy medications while perhaps lowering the dosage that is needed. According to Arung et al. (2021) the average percentage of cancer cell inhibition that BPE potentiated was approximately 50%. Tachyplesin is a cationic β-hairpin antimicrobial peptide that was found in horseshoe crab about 30 years ago. It is well recognized for its cytotoxicity to mammalian cells and its antibacterial properties against bacteria that are resistant to drugs. Tachyplesin stimulates apoptosis in resistant lung adenocarcinoma cells caused by Cis and causes programmed cell death in non-small cell lung cancer cells. Tachyplesin functions by triggering the pathways involved in

necroptosis, mitochondria, and Fas. Furthermore, while tachyplesin does not affect tumor cell migration, tachyplesin and Cis together can effectively block migration. Tachyplesin's development hence offers a wide range of potential applications (Wu et al., 2021).

4. Natural products as protective agents against chemotherapeutic injury

4.1. chemo-protective agents derived from microorganism sources

When taken as dietary supplements or as pharmaceuticals, probiotics are live bacteria that help maintain a favorable and healthy microbial balance in the digestive system of humans or other hosts (Bodke and Jogdand, 2022). For patients with pelvic cancers, probiotics, such as *Lactobacillus species*, may help lessen diarrhea brought on by radiation or chemotherapy. Supplementing with *lactobacillus* may be an efficient and well-tolerated method for reducing the severity of diarrhea caused by 5-fluorouracil (5-FU) - based chemotherapy. It is safe to provide probiotics to colorectal cancer patients receiving irinotecan-based chemotherapy, and it may reduce the frequency and intensity of gastrointestinal toxicity. It has been discovered that *Clostridium butyricum* decreased chemotherapy-induced diarrhea in lung cancer patients, reduced the systemic inflammatory response system, and promoted homeostatic maintenance (Feng et al., 2022). Probiotics show promise in the treatment, management, and avoidance of breast cancer-related problems. Probiotic strains such as *Lactobacillus acidophilus*, *Lactobacillus casei*, *B. longum*, and *Lactobacillus rhamnosus* have been shown to be effective when used alone or in combination with other strains as a viable therapeutic approach for common treatment-related side effects in adult oncology patients, such as gastrointestinal side effects, immune or inflammatory side effects, and performance status-related side effects (Mendoza, 2019).

4.2. Chemo-protective agents derived from plant sources

Chemotherapeutic treatments can have a variety of adverse effects, such as cytotoxicity, low potency, and chemo drug resistance. As a result, the combined effects of two medications may be additive, antagonistic, or synergistic when compared to their individual features when used alone. These methods are said to reduce the side effects of chemotherapy drugs (El-Said et al., 2013; Mobasher et al., 2021). Certain plant-derived bioactive chemicals that are combined with chemotherapeutic drugs could reduce the negative effects of chemotherapy for cancer (Cragg and Pezzuto, 2016).

A naturally occurring polyphenol, resveratrol (3,5,4-trihydroxy-trans-stilbene) is present in a wide range of food items, including grapes, wine, nuts, berries, and many other foods consumed by humans. It can lessen the adverse effects of conventional chemotherapy, including gastrointestinal toxicity, renal toxicity, cardiotoxicity, hepatotoxicity, UVR-induced skin cancer, and damage caused by carcinogens, thanks to its antioxidant activity (Cai et al., 2011). Numerous beneficial chemicals can be found in costus (*Saussurea lappa*) and rosemary (*Rosemarinus officinalis*). According to Borrás-Linares et al. (2014), rosemary has three primary active ingredients that are used in the treatment and prevention of cancer: carnosic acid, rosmarinic acid, and donosol. Costus, on the other hand, is a fragrant plant that belongs to the Asteraceae family and is high in antioxidants and anti-hepatotoxic properties. Certain powerful chemotherapeutic medications, like Cis, are used to treat a variety of solid tumors, including cancers of the testicles, bladder, lungs, head, and neck. However, they can have serious side effects, including tumor cell resistance and dose-limiting nephrotoxicity (Ali et al., 2022).

4.3. Chemo-protective agents derived from animal sources

Given that they were responsible for nearly 30% of all discovered marine NPs, marine sponges were clearly the best source of NPs for drug development (Mehbub et al., 2014). The coral rock, *Cliothosa aurivilli* (CA) is a member of the Porifera phylum. In addition to having the innate capacity to avert neuronal loss, neurodegeneration, and neuroinflammation, CA

may be able to reduce the symptoms of neuropathic pain brought on by paclitaxel. This is because CA includes substances such flavonoids, tannins, alkaloids, glycosides, and sterols that are known to have analgesic effects. Moreover, pro-inflammatory markers TNF-α, IL-1β, and IL-6, which represent central and peripheral activity, are decreased by high saponin content's neuroprotective and anti-inflammatory qualities (Karmakar et al., 2022).

Marine molluscs belonging to the family Muricidae naturally contain derivatives of brominated indole that may have chemopreventive effects. Even at the highest dosage, no additional intestinal toxicity effects were noted when muricid extract, which is derived from *Dicathais orbita*, was mixed with 5-fluorouracil (5-FU) as opposed to 5-FU alone. This suggests that during colorectal cancer treatment regimens, crude muricid extract may be a safe and beneficial nutraceutical option (Yazbeck et al., 2015).

The poisonous arthropod *Scolopendra subspinipes* (SS) has been used for the treatment of neurological disorders for several hundred years. Pharmacopuncture with *Scolopendra subspinipes* (SSP) stimulates peripheral nerves in the injected acupoint and activates spinal α2-adrenoceptors, thereby suppressing mechanical allodynia caused by oxaliplatin chemotherapy. Furthermore, SSP increases the analgesic benefits of clonidine on mechanical allodynia generated by oxaliplatin, allowing for a reduction in clonidine dosage and thereby reducing side effects. For the management of chemotherapy-induced peripheral neuropathy, the combination of SSP and low-dose clonidine offers a unique and secure therapeutic strategy (Lee et al., 2020).

Ghrelin has been found in several teleosts and Oncorhynchus keta, the chum salmon. There are two primary types of ghrelin: acyl- and unacylated (Riley, 2013). Salmon-acyl ghrelin (sAG) is a preventive agent against DOX-induced cardiotoxicity due to its antioxidant properties. In DOX-induced heart failure, sAG dramatically lowers the risk of myocardial apoptosis associated with oxidative stress in a non-invasive manner. In neuronal cells, the signalling of ghrelin is mediated via the 5' AMP-activated protein kinase (AMPK)/ Sirtuin 1(Sirt1)/peroxisome-proliferator-activated receptor-γ coactivator-1alpha (PGC-1α)/uncoupling protein 2 (UCP2) pathway after binding to growth hormone receptor, which then reduces mitochondrial oxidative stress and apoptosis. sAG increases food intake as it has food intake-stimulating effects (Kihara et al., 2021). The large, flightless Australian emu (*Dromaius novaehollandiae*), a member of the ratite family, is the source of emu oil (EO). In rat models of chemotherapy-induced mucositis and colitis, it thickens the mucosa in the colon and small intestine; consequently, its anti-inflammatory qualities reduce the action of small intestinal myeloperoxidase, indicating decreased inflammation, the restoration of normal mucosal architecture, and an increase in intestinal barrier function (Mashtoub et al., 2018).

In summary, natural compounds that function as adjuvants for chemotherapy may do so by directly increasing the tumoricidal effect (i.e., sensitizing cancer cells to chemotherapeutic drugs), reversing chemoresistance (i.e., reducing drug efflux or surmounting other mechanisms that increase the accumulation of chemotherapeutic drugs in cancer cells), or reducing the toxicity caused by chemotherapeutic drugs (i.e., encouraging normal cells to repair themselves against damage from chemotherapeutic drugs). Natural chemicals may be used as chemotherapeutic adjuvants or collaborating medications in combination therapy to further boost their application after establishing anticancer effect as monotherapy.

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