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Marine-derived bioactives from cephalopods for therapeutic use

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Cephalopods, an advanced group within the phylum Mollusca, have emerged as a promising reservoir of bioactive compounds with diverse therapeutic properties. Various body parts of cephalopods, including their ink, skin, muscle, and internal organs, contain a range of biologically active substances, such as peptides, polysaccharides, polyunsaturated fatty acids, chitin, collagen, and glycoproteins. These compounds exhibit potent antimicrobial, antioxidant, anticoagulant and antitumor activities, making them valuable candidates for drug discovery and biomedical innovations. In recent years, research has increasingly focused on the isolation, characterisation, and functional evaluation of these marine-derived molecules, supporting their potential applications in pharmaceuticals, nutraceuticals, and wound-healing formulations. This review provides a comprehensive synthesis of current scientific findings on bioactive metabolites from cephalopods, highlighting their biomedical significance and prospects for therapeutic development.

Keywords: Bioactive compounds, Biological activities, Cephalopods

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Introduction

The fascination among researchers for biologically active metabolites sourced from marine organisms is steadily growing. A plethora of these bioactive metabolites, including peptides, sterols, sesquiterpenes, terpenes, prostaglandins, anti-HIV protein, bursatellanin-P, and more, exist abundantly within marine animals[1]. Cephalopods, a class under the phylum Mollusca, are quite promising sources for new bioactive metabolites. Members of the class Cephalopoda, including squid, cuttlefish, and octopus, are characterised by short life cycles, rapid body growth, early sexual maturity, a quick return to abundance, and the ability to form aggregations. These characteristics make them a reliable raw material for large-scale medicinal uses. There are only 700 cephalopods species have been reported across world which are very low as compared to other animal groups. They consist of two groups: Nautiloidea, which represents Nautilus, and Coleoidea, which represents cuttlefish, octopus, and squids. Squids, the largest members of the cephalopod class, comprise approximately 250 species worldwide. Around 200 squid species inhabit the Pacific Ocean, with roughly 30 species commercially harvested. Cuttlefish, numbering approximately 100 species, and octopus, around 250 species, are primarily concentrated in Eastern waters, spanning the middle Atlantic and Northeastern Pacific Ocean[2,3]. Traditionally, cephalopods have been used as human food in many civilisations, such as the Greeks and Egyptians, in various ways. In Southeast Asian countries, cuttlefish and squid constitute important fishery products. Numerous publications have extensively explored the therapeutic potential held within cuttlefish by-products. A multitude of studies have emphasised that derivatives obtained from cephalopods demonstrate a diverse array of advantageous properties, encompassing activities such as antiseptic, antibacterial, antifungal, antioxidant, anticoagulant, and antiretroviral effects[4]. In Japan, cuttlefish ink has a traditional use in meat preparation due to its antiseptic properties, and it boasts a range of traditional applications in food products[5]. These marine creatures are rich sources of biologically active substances, often present in high concentrations[6].

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Cephalopods have evolved diverse defence strategies due to their lack of an outer shell. They employ methods such as venom release to counteract threats from both prey and adversaries, while their ink serves as a reservoir for numerous bioactive metabolites with diverse medicinal applications[6]. However, it's notable that investigations concerning the exploration of bioactive substances (BASs) from squid, cuttlefish, and octopus are relatively scarce within the Indian biomedical literature. This is particularly intriguing considering the abundant presence of these marine animals in the Indian Ocean. In previous work, marine gastropods, Sea Slug, *Kalinga ornate, Doriprismatica atromarginata, Dolabella auricularia, Aplysia fasciata,* and *Bursatella leachii* have been reported on the south coast along the Bay of Bengal, India[7]. This research gap presents an opportunity to develop the potential biomedical applications of these organisms, thus contributing to a more comprehensive understanding of their therapeutic attributes. These intriguing attributes heighten the enthusiasm for continued research into the medicinal properties of bioactive metabolites derived from cephalopods. The pharmaceutical and food industries have extensively harnessed these by-products. However, unregulated disposal of ink poses ecological challenges. Repurposing these by-products for medicinal use ensures proper management and mitigates environmental pollution and ecological concerns. This review highlights the diverse array of bioactive metabolites found in cephalopods and explores their potential biological properties, underscoring their significance in future drug discovery efforts.

Bioactive metabolites from Cephalopods

Cephalopod by-products such as ink, skin, whole body extract, liver oil, egg mass, hepatopancreas, cuttlebone, etc., are a good source of many bioactive metabolites, and it has been utilised as a source of pharmacologically active compounds that have been used on a vast scale as an alternative medicine and therapeutic drugs[6].

Bioactive metabolites in the ink of cephalopods

Cephalopods secrete ink as an adaptive response to predation. Cephalopod ink is the source of many bioactive metabolites with many biomedical properties[8]. It has been reported that the ethanol extract of *L. duvauceli* ink contains various metabolites, including flavonoids, alkaloids, phenols, saponins, glycosides, and terpenoids[8]. It has been reported that flavonoids contain antioxidant, free radical scavengers, antileukemic, vasodilation, and antibacterial properties and in Alzheimer's patients these metabolites improve blood flow in the CNS. Flavonoids possesses high antioxidants activity with high redox potentials, allowing them to behave as hydrogen donors, reducing agents, and singlet oxygen quenchers. They are well known therapeutic candidate for their capability to reduce risk of cancer and heart disease. Alkaloids are well known for their antioxidant activities, which involve scavenging or chelation processes. It promote activities of antioxidant enzyme and decreases peroxidase synthesis in body. Saponins modify the body's hypersensitivity reaction, provide protection against viral infection and carcinogens.

It exhibits anti-allergic, anti-inflammatory, antibacterial, antifungal, and anticarcinogenic properties. Phenolic acids are also well known for possessing antioxidant activities. They contain one or more aromatic rings with one or more hydroxyl groups and can quench free radicals by forming stabilised phenoxyl radicals. Glycosides are group of steroids with an innate ability to treat many human diseases with highly specific and potent action, primarily administrated through injection into humans or animals.

For example, cardiac glycosides are used as therapeutic agent to treat heart diseases. Tannins have antifungal and antibacterial activities. Terpenoids have antimicrobial, antimalarial, anti-inflammatory and anticytotoxic activities. Jeyasanta and Patterson investigated the antibacterial activities of squid ink against *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*[8]. Studies show that hexadecanoic acid and 1-(15-methyl-1-oxohexadecyl)-pyrrolidine, as the most therapeutic potential bioactive metabolites, exhibit antiproliferative activities against human colorectal (HT-29, HCT116) and breast (MDA-MB-231) carcinoma cells. They induced apoptosis in these cell lines and upregulated the JAK-STAT, PI3K-AKT, and IL-17 signalling pathways, which increase cytokine production, resulting in an anti-inflammatory effect in the cancer cell line. Hernandez-Zazueta *et al.* reported that ozopromide, a metabolite isolated from octopus ink, has antiproliferative and anti-inflammatory activities against human breast (MDA-MB-231), prostate (ZZRv1), cervix (HeLa) and lung (A549) cancerous cell lines[8]. It induced apoptosis in these cell lines by

activating AKT-1 and pro-apoptotic BCL-2 factors[9,10]. Melanin from cuttlefish ink (*S. officinale*) exhibits various biological properties, including cytotoxic, antibacterial, and antioxidant activities[11]. Squid ink extracted melanin inhibits gastric secretion in rats[12]. Melanin from octopuses inhibits gastric secretion and prevents ulcer formation in rats[13]. An enzyme, tyrosinase, was also isolated from cephalopod ink (*S. officinale*, *L. duvauceli*, and *S. pharaonis*), which converts catechols into harmful quinones in cephalopods, acting as a deterrent for predators. Tyrosinase from cuttlefish ink, *S. officinale,* promote programme cell death in PC12 cells by increasing production of caspase 3[11]. The other two metabolites found in the ink of squid, *L. opalascens*, dopamine and dopa, have antioxidant properties as they prevent the rapid oxidation of these metabolites. It was found that millimolar levels of total free amino acids (FAA) and ammonium were present in the ink of six species of cephalopods (Squid, cuttlefish, and Octopus), with the highest concentrations of FAAs being taurine, aspartic acid, glutamic acid, alanine, and lysine. Purified peptidoglycan from cuttlefish ink induced several morphological features of apoptosis, including chromatin condensation, loss of integrity of cell membrane, blebbing of membrane, and DNA damage, all of which contribute to apoptosis in cancer cells[14]. Similarly, peptidoglycan from squid ink (*L. argentinus*) has antitumour activity against MethA fibrosarcoma in mice. Tyrosinase, innexin and peptidoglycan from the ink of squid, *L. argentinus*, have antitumor property against Meth A tumour in BALB/C mice[15]. The ink of cuttlefish promotes both non-specific and specific immunity by increasing cytokine production. Cuttlefish ink is noted for its antiseptic properties, and its richness in taurine and hydroxyproline contributes to increasing the shelf life of food[16]. Ink of *S. inermis* and *L. duvauceli* exhibits antiretroviral activity against Molony Murine Leukaemia Virus Reverse Transcriptase (MMLVRT)[15].

Bioactive metabolites in cephalopod skin

The skin of the jumbo squid (*Dosidicus gigas)* is rich in gelatin and collagen[17]. Gelatin from giant squid skin exhibits antioxidant properties, as demonstrated by the ABTS and FRAP assays[18]. Bioactive hydrolyzates of gelatin have cytotoxic activity against cancer cell lines and act as potent angiotensin-converting enzyme inhibitors. Collagen from giant squid skin enhances anti-osteoporosis in MC3T3-E1 cells[18]. It also increases superoxide dismutase activity, thereby reducing oxidative damage[18]. Ommochromes, a group of pigments found on the skin of cephalopods, act as electron donors and stabilise free radicals. Previous studies have demonstrated the antioxidant activities of ommochromes. Ommatins belong to the ommochrome family, specifically manthommatin and digydroxanthommatin from octopus (*Octopus vulgaris*) and squid (*Loligo duvauceli*, and *Dosidicus gigas*) skin pigment, which exhibit remarkable antioxidant activities (investigated by FRAP, DPPH, and ABTS assay)[18].

Bioactive metabolites in cuttlebone

Calcium phosphate from the cuttlebone of cuttlefish induced osteoblastic differentiation of the human dental pulp stem cell (hDPSCs)[19].

Cuttlebone derived chitin has wound healing effects in the burned injury of a rat. Cuttle bone extract stimulates macrophages to increase the synthesis of TNF-α, TNF-β, and VEGF, which are involved in formation of new blood vessels and activation of fibroblast. Activation of fibroblasts increases the secretion of matrix metalloproteinase-1, which is responsible for wound healing[19].

Bioactive metabolites in hepatopancreas, tentacle, mantle, fin, and liver of different species of cephalopods

The hepatopancreas of jumbo squid contains many bioactive metabolites like trypsin, chymotrypsin, aminopeptidase, carboxypeptidase, etc. It has been investigated that the ideal factors for enzymatic hydrolysis of *D. gigas* tentacle derived collagen have been examined, and the antioxidant activities of the corresponding hydrolyzate have been assessed by DPPH and ABTS assays[17,18]. Mantle, fin, and tentacle of the jumbo squid derived collagen exhibits antioxidant activities[18]. Omega-3 PUFA and omega-6 PUFA are found in squid liver oil. It has been found that administering cuttlefish liver oil (*S. pharaonis*) in conjunction with isoproterenol administration has cardio-protective effects. Feeding of cuttlefish liver oil induced an immune response and platelet aggregation in rats. This liver oil greatly reduced total cholesterol, triglycerides, phospholipids, and LDL cholesterol, whereas it increased HDL cholesterol in the serum. PUFAs from the cephalopod's liver oil prevent free radical generation and enhance the antioxidant defence system in rats[14]. The presence of these bioactive metabolites in cephalopod by-products suggests that further extraction, purification and characterisation of any identified metabolites may serve as a foundation for developing novel pharmaceuticals. The structure of some bioactive compounds from cephalopods is presented in Fig. 1.

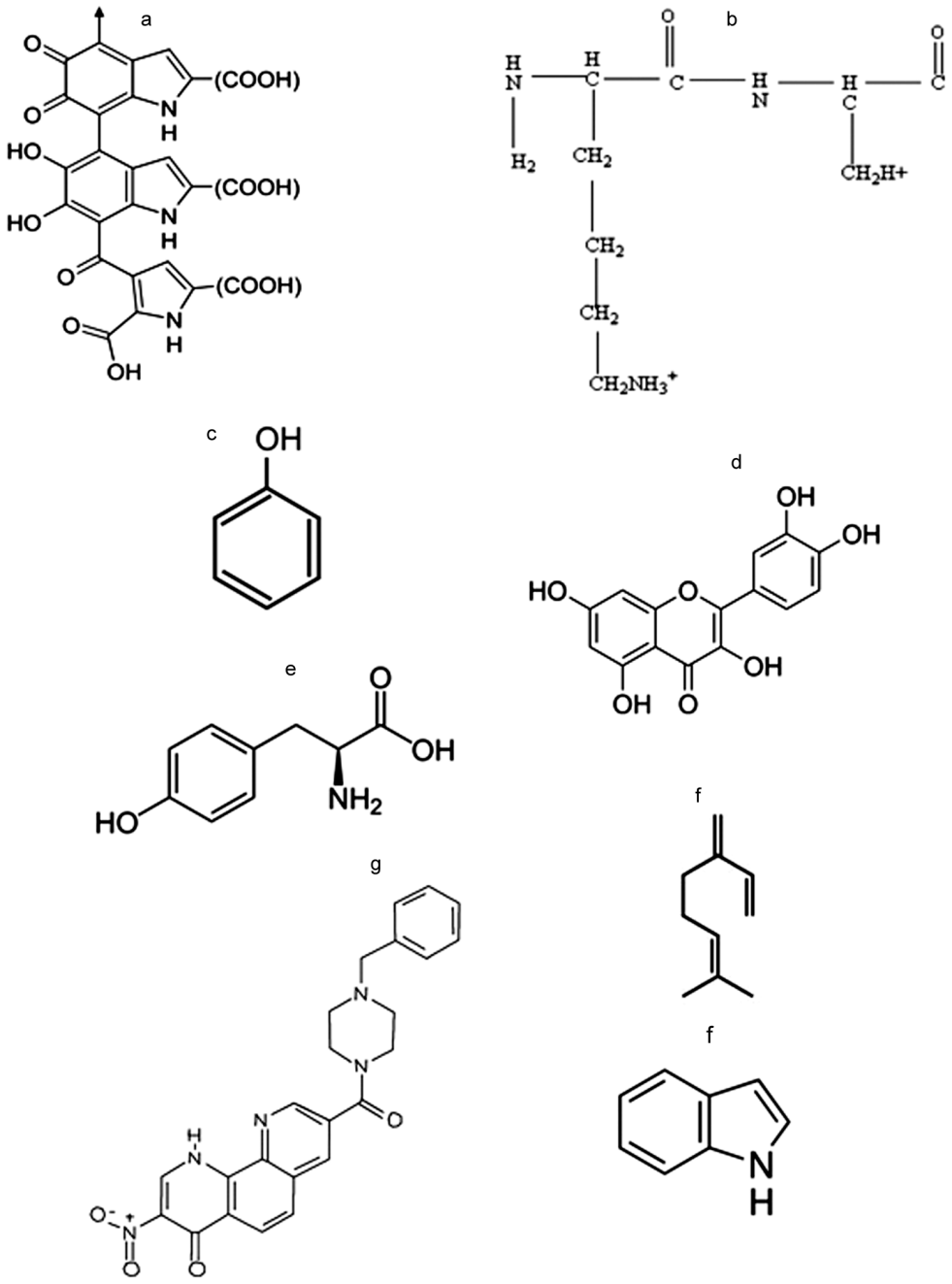

Fig. 1 — Structure of key bioactive compounds isolated from cephalopods known for their therapeutic properties. a) Melanin and b) Gelatin belong to the Polymer group, c) Phenol and d) Flavanols belong to the Phenol group, e) Tyrosine to Amino acids group, f) Monoterpenoids to Terpenoids, g) Collagen to the Protein group and h) Indole to the Alkanoid group.

Biological properties

Antimicrobial activities

The exploration of cephalopod-derived metabolites represents a promising frontier in the development of novel therapeutic agents that could potentially revolutionise the field of antimicrobial therapy. With the growing concern of antibiotic resistance among pathogens, there is an urgent need for alternative antimicrobial agents. The compounds from marine sources are often characterised by low toxicity to human cells, making them safer candidates for drug development compared to some synthetic antibiotics[20]. Research from various regions highlights the potent antimicrobial properties of cephalopod-derived compounds, which remain effective even against drug-resistant pathogens. Numerous publications have

highlighted the abundant presence of antimicrobial compounds within marine creatures, showcasing their effectiveness against a diverse spectrum of bacteria, including but not limited to *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Websiella* sp., *Salmonella* sp., and *Escherichia coli*[14]. *Mycobacterium tuberculosis*, the bacterium responsible for tuberculosis, has developed resistance to first- and second-line drugs. On a more promising note, research has revealed that cuttlefish *Sepiella inermis* derived ink exhibits antituberculosis properties[21]. Furthermore, Omega-3 fatty acids and lipids extracted from cephalopods have been found to disrupt the plasma membranes of microorganisms. In the case of the Indian squid, *L. duvauceli*, its ink exhibits notable antibacterial activity, particularly against gram-negative bacteria such as *Salmonella* spp., *V. cholerae*, *E. coli*, and *Pseudomonas* spp.[12]. While it also exhibits some effectiveness against Gram-positive bacteria, its activity against this group is relatively weaker against Gram-negative bacteria. Cuttlefish ink has been reported to possess dual properties of both antiseptic and antibacterial activity[15,16]. Specifically, it exhibits robust inhibitory effects against *S. aureus*. Bioactive metabolites of ink from Indian squid exhibit both antibacterial and antifungal activities[12]. It has been found effective against pathogens such as *K. pneumoniae*, β-lactamase producing strains of *E. coli*, as well as *Candida albicans*. Furthermore, nervous tissue of the Far Eastern squid derived peptide named tinrostim, exhibits antiviral activity against the tick-borne encephalitis (TBE) virus[14]. Many cephalopod-derived compounds exhibit broad-spectrum antimicrobial activity, against diverse group of pathogens, including bacteria, fungi, and viruses (Table 1). This versatility makes them valuable candidates for drug development.

Table 1 — Antimicrobial properties of bioactive substances from cephalopods (Antibacterial, antifungal and antiviral properties)

Cephalopod species	Mode of by-product used	Active against microbes	References
Antibacterial activity			
Cuttlefish (*Sepia pharaonis*)	Crude ink, fridge-dried ink, partially purified ink, crude ink extracted by acetone, chloroform, butanol, and hexane.	*S. aureus, B. subtilis, E. coli, A. hydrophila, S. pyogenes, K. pneumoniae* and *P. aeruginosa*	45
Indian squid (*Laligo duvauceli*)	Partially purified ink by ammonium sulphate, crude ink extracted with different solvents (Acetone, ether, chloroform, methanol), antimicrobial protein Lolduvin-S isolated from ink, ink precipitated at different pH, Aqueous extract of crude ink	*Pseudomonas aeruginosa, Staphylococcus aureus, V. cholerae, K. pneumonia, Shigella spp., Salmonella enterica, E. coli, Micrococcus spp.,*and *L. acidophilus*	37, 46
Soft cuttlefish (*Sepioteuthis lessoniana*)	Crude ink extracted at different temperatures (Room temp, 40, 60, 80, 100 °C) for 15 minutes	*E. coli, S. aureus, B. subtilis,* and *P. aeruginosa,*	46
Octopus (*Octopus vulgaris*)	Aqueous extract of crude ink	*Pseudomonas aeruginosa, Staphylococcus aureus, V. cholerae, K. pneumoniae, Shigella spp.,* and *Salmonella enterica*	47
Antifungal activity			
Octopus (*Octopus vulgaris*)	Aqueous extract of crude ink	*Fusarium spp.,* and *Aspergillus fumigatus*	47
Indian squid (*L. duvauceli*)	Partially purified ink by ammonium sulphate, crude ink extracted with different solvents (Acetone, ether, chloroform, methanol), and aqueous extract of crude ink.	*Fusarium spp., Aspergillus fumigatus,* and *C. albicans*	37
Soft cuttlefish (*Sepioteuthis lessoniana*)	Crude ink extracted	*A. fumigatus,* and *S. cerevisiae*	46
Cuttlefish (*S. pharaonis*)	Fridge dried crude ink	*C. alcicans*	45
Antiviral activity			
Indian squid (*L. duvauceli*)	Bis (2-ethylhexyl) phthalate (DEHP), a phthalate derivative	Hepatitis C virus	14
Far Eastern squid	Tinrostim, a peptide from the Far Eastern squid	TBE virus	14

Antioxidant activity

Free radicals are highly reactive molecules causing impairment of normal cellular functions, thereby contributing to a range of health issues, including cancer, heart disease, cataracts, diabetes, and infections. These antioxidants help protect their cells and tissues from injury caused by reactive oxygen species (ROS), which are harmful molecules generated during normal metabolic processes. Like many marine organisms, cephalopods produce natural antioxidants as part of their defence mechanisms against oxidative stress. In recent years, a large part of research has been devoted to investigating the antioxidant activities of bioactive metabolites derived from cephalopod extracts[22]. Both melanin and the melanin-free fraction extracted from squid and cuttlefish ink have been found to exhibit antioxidant properties, as reported by many researchers[23-25]. Agustini *et al.* have documented the antioxidant capabilities of melanin-free ink from the squid, specifically *L. formosana*[26]. *In vitro* antioxidant assays, including the ferric reducing antioxidant power (FRAP), ABTS radical scavenging activity, DPPH radical scavenging activity, lipid peroxidation and chelating activity towards Fe^{2+}, have collectively demonstrated the antioxidant potential of splendid squid, *L. formosana* and cuttlefish, *S. officinalis* derived melanin-free ink[25]. The polysaccharide isolated from cuttlefish, *Sepia cobiensis and S. aculeata*, exhibits dose-dependent antioxidant activity[25]. Notably, these polysaccharides demonstrate a remarkably high antioxidant activity when compared to commercially available antioxidants. They exhibit the capability to reduce DPPH radicals by 36.27%, superoxide radicals by 59.57%, and hydroxyl radicals by 45.86%[25]. Some peptides isolated from cephalopods can share electrons and make bonds with metal associated with oxidative stress, indicating their antioxidant properties. These peptides reduce the negative impacts of free radicals and overcome DNA damage and oxidation of lipids that occur due to oxidative stress. Peroxidase-like nanozyme, a natural melanin nanoparticle from cuttlefish, shows effective antioxidant activity[22]. Detailed information about the antioxidant properties of cephalopods is presented in Table 2.

Anticancer properties

A current trend in biomedical research is the quest to discover potent pharmacological agents for treating tumours. Investigators are generally interested in developing novel potent anticancer agents with minimal side effects because most compounds with anticancer properties possess high aggressiveness and local side effects. Numerous anticancer properties of biologically active metabolites extracted from diverse cephalopod species, including octopus, squid, and cuttlefish, have been documented using a range of assays such as MTT, cell viability assessment with trypan blue, cell proliferation assays (CCK-8), and comet assays, among others[14,15]. The extract from cuttlefish, *S. pharaonis,* at doses of 25 and 75 µg/mL possesses high antiproliferative activity towards fibroblasts of chick-embryo[27]. A peptide isolated from cuttlefish (*S. mendroni*) with amino acids (glutamic acid, serine, aspartic acid, threonine, and alanine) possesses pro-apoptotic activity towards prostate cancer cell lines PC-3, DU-145, and LNCap in a time and dose-dependent manner[28]. A dose-dependent administration of cuttlefish polypeptide (5, 10, 15 mg/mL concentration) with 24-hour exposure shows apoptosis from 11.84 to 38.26% for DU-145, from 22.27 to 39.96 % for PC-3 and from 5.05 to 16.11 % for LNcap prostate cancer cell lines respectively[29,32].

Table 2 — Antioxidant activities of Cephalopods

Name of Cephalopod species	Mode of by-product used	Method of determining antioxidant activity	Antioxidant activity	References
Cuttlefish (*S. officinalis*)	Aqueous extract of crude ink)	Lipid peroxide level determination, DPPH radical scavenging activity, GSH-Px activity, total SOD activity, FRAP assay	Significant reduction of oxidative stress	42
Spendid Squid (*L. formosana*)	Melanin free ink	Chelating activity towards Fe 2+, DPPH radical scavenging activity, ABTS radical scavenging activity	Good antioxidant activity found in vitro assays	43
Squid (*Ommastrephes bartrami*)	Ink	Total SOD activity determination, MDA (malonidialdehyde)content determination, Glutathione peroxidase(GSH-Px) activity determination	SOD and GSH-Px activity increased, and MDA content decreased	44

In vitro studies have supplied evidence supporting the anticancer activities of cuttlefish and squid ink[30]. The anticancer effects of these inks have been shown to occur through the apoptosis process, as substantiated by the isolation of various apoptosis-inducing compounds from the ink[28]. The investigation into cephalopod-derived compounds for their anticancer properties represents an exciting area of biomedical research with potential implications for cancer treatment and therapy development. The detailed information is presented in Table 3.

Innate and adaptive immunity

Biologically active metabolites derived from cephalopods have received significant interest in the area of immunology due to their potential influence on the immune system. Peptides derived from cephalopods have been found to activate components of both the innate and acquired immune systems[30]. They induce cellular and humoral immunity, enhance the phagocytic activity of macrophages and neutrophils, and promote the activation of natural killer (NK) cells. Moreover, these peptides can modulate both pro-inflammatory and anti-inflammatory effects[31]. Squid ink has been observed to boost the immune function of broiler chickens. When incorporated into their diet, squid ink was found to increase the relative weight of essential immune organs such as the thymus, spleen, and bursa of Fabricius[30].

Additionally, it promoted the proliferation of lymphocytes in the spleen, indicating a positive impact on the chickens' immune response. Polysaccharides extracted from sepia ink have demonstrated the ability to increase the presence of goblet cells in mice, leading to increased expression of mucins such as Cyto18. This effect serves as a protective barrier against the penetration or colonisation of pathogens in the intestinal mucosa. Furthermore, it aids in the restoration of mucosal immunity in mice subjected to cyclophosphamide treatment. In their research, Zuo *et al.* revealed that sepia ink polysaccharides significantly enhance the expression of genes such as occludin, zonula occludens, claudin, cingulin, and Ecadherin[29]. This effect stabilises tight and adherent junctions, which in turn, play a important role in safeguarding the immune role of the intestinal mucosa in mice subjected to chemotherapy[29]. Polysaccharides derived from squid ink have been observed to stimulate the production of secretory IgA by plasma cells in mice that were immunosuppressed with cyclophosphamide[30]. Cuttlefish ink also boosts the humoral immune response to the MethA antigen of sarcoma, enhances macrophage phagocytosis, and elevates the levels of TNF-α and IL-2 in both immunocompromised and intact mice[30].

Lipid metabolism

Dyslipidemia is a primary contributor to cardiovascular diseases, atherosclerosis, and other infectious processes. To mitigate the undesirable side effects associated with statins, which are commonly used for dyslipidemia management, there is a growing need for a novel and safe alternative agent. Many studies reported that BASs derived from cephalopods have lipid-lowering capacity. A study shows that rats with experimental hyperlipidemia, when administered doses of 50 and 200 mg/kg of squid ink, decrease triglycerides, total cholesterol, and low-density lipoproteins level and improve high-density lipoproteins level in the blood serum[33]. Nagata *et al.* observed potential cholesterol-lowering (hypolipidemic) effects resulting from the consumption of squid tissue from the species *T. pacificus* when administered to laboratory rats[33].

Table 3 — Anticancer properties of Cephalopods

Name of Cephalopod species	Mode of by-product used	Active against cancer cell lines	References
Indian squid (*L. duvauceli*)	Fridge dried ink, crude ink, melanin-free ink, partially purified ink by ammonium sulphate	HepG2	37
Cuttlefish (*S. pharaonis*)	Crude ink	Cervical cell lines (HeLa and Caski)	38
Cuttlefish (*S. officinalis*)	Crude ink	HepG2, Human glioblastoma cells U87	39
Cuttlefish (*S. inermis*)	Crude ink	Chick embryo fibroblast cells	38
Cuttlefish (*S. mendroni*)	Oligopeptide isolated from cuttlefish extract	Human prostate carcinoma cells (DU-145, PC-3 and LNCaP cells), Human ovarian carcinoma cell line (SKOV3)	32,40
Cuttlefish (*S. esculenta*)	Oligopeptide isolated from cuttlefish extract	Prostate carcinoma cell (DU-145)	41

Angiotensin-converting enzyme (ACE) as a target for bioactive metabolites from cephalopods

Angiotensin-converting enzyme (ACE) is essential for maintaining water and electrolyte balance, regulating blood pressure, and managing renal hemodynamics. BASs derived from cephalopods have been identified as ACE inhibitors. These BASs effectively inhibit the angiotensin-converting enzyme, thereby influencing the activity of both the kallikrein-kinin and renin-angiotensin systems. This inhibition disrupts the formation of angiotensin-1 and ultimately deactivates the renin-angiotensin system, decreasing blood pressure and arterial vasoconstriction[31]. As reported by Cian *et al.*, ACE inhibitors primarily consist of peptide compounds[34].

An example of this is the gelatin found in the skin of the *Dosidicus eschrichtii* squid, which contains peptides with inhibitory effects on ACE. The effectiveness of ACE inhibitors hinges on the precise sequence of amino acids. In the cuttlefish species *S. officinalis*, nine peptides with precisely defined amino acid sequences were successfully extracted from the hydrolysate of its muscle tissue. In an *in vivo* study, the administration of a 10 mg/kg dose of the peptide resulted in a noteworthy reduction in systolic blood pressure in rats with spontaneous hypertension[34].

Wound healing effects of biologically active metabolites

Healing of wounds is a complex system that involves the inflammatory signal to injury, cell migration to the damaged area, proliferation, and blood vessel formation and remodelling. BASs from cephalopods increase the migration of cells involved in inflammation and promote the activity of many factors of inflammation[30]. In Raw 264.7 cells, chitin from squid extract induced the formation of Nitric Oxide (NO), an inflammatory mediator in macrophages. It also induced the synthesis of pro-inflammatory cytokines like IL-1, TNF-α, and IL-6[30]. Cuttlefish extract increases the production of IL-8 in mice and enhances the invasion and migration of fibroblasts into the wound. It has been reported that cuttlefish extract increases the proliferation of murine fibroblasts and promotes angiogenesis and activation of fibroblasts by increasing the synthesis of VEGF and TGF-β[30,35]. It synthesised a larger quantity of metalloproteinase-1 (MMP1) under the influence of bioactive metabolites, indicating that cuttlefish extract acts as an agent for the healing of skin injuries, lesions and burns[30,35].

Other properties

Research studies have documented that cuttlefish ink exhibits potential radio-protective properties by enhancing the production of granulocytes and monocytes in the bone marrow, while concurrently reducing lipid peroxidation in various tissues[14]. This protective effect is attributed to the melanin in ink, which inhibits the chain reactions of free radicals, thereby mitigating radiation-induced damage. Notably, many endometrial cancer patients undergoing radiation therapy often experience complications such as proctitis, cystitis, colitis, and diarrhoea as side effects[14,15]. However, the utilisation of squid body tissues has shown promise in reducing the severity of these complications. This suggests that squid-derived metabolites may hold potential for ameliorating the adverse effects of radiation therapy in cancer patients, thereby improving their overall quality of life during treatment. Several studies have highlighted various uses of cephalopods in areas such as food, nutrition, pharmacology, economic utilisation, and industrial applications[36]. The conservation status and management of various cephalopod species have been studied to utilise these marine resources sustainably.

Current status and future perspective

Cephalopods represent a valuable source of novel bioactive metabolites with the potential to be harnessed for the development of new drugs[14]. Recent scientific research efforts have been particularly concentrated on a few selected species, including *Sepioteuthis lessoniana*, *Octopus maya*, *L. duvauceli*, *S. officinalis*, and *O. vulgaris*. However, it's important to note that there is critical knowledge gap persists in the medicinal properties of various other cephalopod species. There is a scarcity of scientific publications and clinical studies that explore the full spectrum of medicinal values across different cephalopod species. To further enhance our understanding in this area, it is essential to conduct more comprehensive clinical analyses that focus on the medicinal properties of cephalopods. Future research should focus on to bridge the gap between controlled laboratory experiments and practical applications in real-world scenarios. This holistic approach will enable a more comprehensive understanding of the potential medicinal benefits offered by cephalopods and pave the way for their responsible utilisation in drug development and healthcare.

Conclusion

This review provides a comprehensive overview existing information and research on cephalopod skin, ink, and cuttlebone focousing on their production, chemical composition, biological properties, and significant biomedical relevance for drug design and therapeutic innovation. However, informations on the bioactive compounds in cephalopod by- products remains limited. It is anticipated that review encourages further investigation into cephalopod biology and applications. Emerging advancements in marine biotechnology, genomics, and high-throughput screening technologies are accelerating the discovery and functional characterisation of novel bioactive compounds. Prioritising sustainable harvesting and conservation-driven strategies will help maintain resource availability while safeguarding marine biodiversity. With marine bioactives gaining global attention, cephalopods may serve as key resources for future drug discovery and functional therapeutics.

Conflict of interest

Author(s) declared no conflict of interest.

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