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(REVIEW ARTICLE)]



Squid ink and its pharmacological activities

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Abstract

With the development of technical instruments the isolation and characterization of many natural products from marine and freshwater organisms, promotes a major advancement of discovery of these aquatic derived compounds. Due to the increasing demand of medicines from natural products, many researches on marine products are going on and is still a undiscovered journey. One such product is squid ink obtained from squid fish which is present in Mediterranean and Atlantic Ocean. It is mainly contained of melanin and many degradation studies have proven and still for the research work. The squid ink has spectacular activities in many ailments like uterine dysfunction, anticancer activity, antimicrobial activity, anti-inflammatory activity along with hypertensive effects. It has a very special place in homeopathic medicine and in traditional Chinese medicine due to its therapeutic uses. Hence it is believed that the squid ink can be used as a better tool against these dysfunctions. The present review aims to assemble various pharmacological activities of squid ink although deeper insight in its pharmacological potential is required.

Keywords: Squid; Squid ink; Pharmacological activities; Traditional/homeopathic uses

1. Introduction

The squid world comprises of around 304 species that belongs to the order Teuthida, in cephalopods. Anatomically it have eight arms and longer, tentacles that helps them to swim. Some of them can even "fly" out of the water for short distance. The identified squids are classified into two categories; either myopsida or oegopsida and it can be found in several sizes. The majority of these species are not more than 60 cm (24 ft) in length. The giant squid have a maximum size of 13 m (43 ft) [1] and a colossal squid can weigh up to 1,000 pounds and grow to a length of 35 feet which is the largest species in the squid world. It tends to stay in cold, deep water. Another type of squid is known as vampire squid that have a capability to jump out of water. It is black in color and has long arms that can move like a black cape. These squid are normally around the size of 1 foot and have small suckers on the arms. In American countries, squid as food is often marketed using the Italian word *calamari* [2]. Table 1 describes about different types of squid discovered in the world including its species name, family, common name and catch tones. The goal of this review is to describe about the squid ink including different types of squid currently available, chemical constituents of squid ink and its pharmacological activities along with the traditional / homeopathic effects affecting human body.

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Figure 1 Squid

Table 1 Types of squids discovered in world

Species	Family	Common Name	Catch Tones
<i>Loligo gahi</i> Or <i>Doryteuthis gahi</i>	Loliginidae	Patagonian Squid	24,976
<i>Loligo pealei</i>	Loliginidae	Longfin Inshore Squid	16,684
Common squid	Loliginidae		22,5958
<i>Ommastrephus bartramii</i>	Ommatrophidae	Neon Flying Squid	22,483
<i>Ilex argentinus</i>	Ommatrophidae	Argentine Shortfin Squid	511,087
<i>Dosidicus gigas</i>	Ommatrophidae	Humboldt Squid	406,356
<i>Todarodes</i>	Ommatrophidae	Japanese Flying Squid	504,438
<i>Nototodarus sloanii</i>	Ommatrophidae	Wellington Flying Squid	62,234
<i>Squid nei</i>	Various		414,990
Total			2,189,206

2. Types of squid

Scientists believe that there are four different types of squid,

- 1) *Squidus squida*: It is the main ingredient in calamari.
- 2) *Squidus blooperus*: It is found in the seas of the Mushroom Kingdom.
- 3) *Squidus flyidae*: It is similar to *Squidus blooperus* in structure, but its habitat is the skies of the Mushroom Kingdom instead of the seas.
- 4) *Jellyfishus squida*: It is a type of jellyfish that many scientists believe may actually be a squid [3].

3. Squid Ink

The ink produced from cephalopod species is a dark cloudy liquid which is released as a defense that helps to escape from predator. Each species in this family can produce slightly different colored inks and it is popular in many names such as squid ink, cuttlefish ink, tintacalamar, nero di seppia, black squid ink, cephalopod ink and octopus ink. Commonly octopuses produce black ink while squid ink is blue-black in colour and cuttlefish ink is like a shade of brown. Squid ink is most popular in Italy and Spain, due to its unique appearance [4]. It contains a large number of important nutrients particularly antioxidants and low in fat and calories. The striking blue – black color of squid ink is due to the presence of large amounts of melanin. The melanin pigment is produced in mature cells of ink gland which is present in the bottom of ink sac. Additionally, it also contains large quantities of proteins, lipids, minerals, taurin and dopamine [5]. The food chemistry studies using ink of the neon flying squid, boreal clubhook and boreo pacific gonate squid reveals that they are also rich in taurin and hydroxyproline. The tyrosinase in the ink is converted to toxic quinines that act as detergent for predator. The morphology of released ink is of two types; pseudo morphs and clouds [6].

Nutritional data per 1/4 cup squid ink [7] is as below:

Calories: 130

Total Fat: 10 g

Carbs: 2 g

Protein: 9 g

4. Pharmacological activities

4.1. Uterine dysfunctioning

A recent clinical trial conducted by the Institute of Oceanology in China. In this clinical study about 400 women with uterine dysfunctional bleeding were given by sepia ink capsules and have been proved efficient. There is an unbelievable improvement for the gastrointestinal and chronic tuberculosis bleeding were also been reported [8].

4.2. Anticancer/Anticytotoxic effect

The carbohydrate part of peptidoglycan extracted from sepia ink has proved antitumor activity as it linearly decreases DU-145 cell growth in a dose dependent manner and the mechanism of action is still unclear [9]. Russo et al, theorise the cytotoxic effect of the production of dopaquinone, which interacts with nucleophiles to produce protein-bound DOPA through a 5-S-cysteinyl-dopa residue and causes cellular damage by oxidation. The study shows that the purified tyrosine from the melanin-free fraction of ink is toxic to transformed human cell lines. Peptidoglycans separated from sepia ink can also affect cell division in eukaryotes which include fragmentation of DNA and apoptosis and the reserve of embryonic development [10-13]. The sulphated sepia ink peptidoglycans derivatives will suppress invasion and migration of carcinoma cells by inhibiting matrix metalloproteinase-2 [14]. It also known to suppress melanoma metastasis by inhibiting tumor adhesion and angiogenesis mediated by basic fibroblast growth factor [15]. The oligopeptide has been accused to inhibit prostate cancer cells by activating apoptosis via induction of caspase-3 and elevation of the ratio of Bax/Bcl-2 [16]. Study on mice reveals that squid ink helps to prevent cancer by promoting the action of killer cells. It also improves WBC production during chemotherapy.

4.3. Antioxidant activity

The squid ink polysaccharide (SIP) is a type of glycosaminoglycan with a unique structure - [3GlcA β 1-4(GalNAc α 1-3)-Fuc α 1]_n- that have antioxidative activities and chemoprotective roles. Nrf2 (NF-E2-related factor 2) is an important transcription factor that binds to AREs that are important gene regulatory elements of many phase II drug-metabolizing/detoxification enzymes and cellular defensive enzymes and regulates anti-oxidative stress and plays a major role in eliminating intracellular superfluous reactive oxygen species (ROS) and improves antioxidant ability. Some bioactive substances have been speculated to induce Nrf2 to relieve or prevent diseases related to oxidative stress. However, it is still unclear whether SIP impairs CP-caused testicular damage [17].

4.4. Anti-hypertensive actions

An angiotensin converting enzyme (ACE) peptide derivative separated and purified from squid ink causes dilation of blood vessels, results in lowering of blood pressure and acts as a potential anti-hypertensive. The filtered ink solution was loaded onto sephadexG-15 (1.5×100cm) that had been equilibrated with a 10 Mm phosphate buffer (pH 7.5). Take the absorbance at 214 nm with the elute. Three fractions were collected from column and the ACE activity was measured by Cushman and cheung method. A reaction is carried out with reaction mixture at 30°C and the assay result shows that F1 fraction had highest inhibitory activity (32%) [18].

4.5. Anti-retroviral activity

Ink from *Loligo duvauceli* (squid fish) and *Sepiella inermis* (cuttle fish) has been reported to have an anti-retroviral activity. The aqueous extract of the cephalopod ink were tested against Molony Murine Leukemia Virus Reverse Transcriptase (MMLVRT) and have exhibited antiretroviral activity. The ink obtained from juveniles of *S. inermis* and *L. duvauceli* showed strong inhibition of MMLVRT [19].

4.6. Anti-ulceration activity

Study conducted in 1982 by Andersen et al, has concluded that squid ink possesses marked antiulcer activity by decreasing gastric juice secretion. The melanin extract from squid ink could inhibit gastric acid secretion in rats [20].

4.7. Anti-Inflammatory Activity

Mimura et al., reported that squid ink could inhibit gastric secretion in rats. The melanin extract which is responsible for the anti-inflammatory activity consists of melanin pigment (90%) protein (5.8%) and carbohydrate (0.8%) [21].

4.8. Hepatoprotective effects

Studies have shown that sepia ink extract has shown a general decrease in total bilirubin, that is direct bilirubin and indirect bilirubin in the Bile Duct Ligation (BDL). An animal model was selected with bile diseases. The various changes such as epithelial cell proliferation, hepato cellular necrosis, apoptosis, stellate cell activation, liver fibrosis and hepatotoxicity were studied [22]. The treatment with sepia ink extract causes a decrease in serum gamma glutamyltransferase in rat due to the protective effect of ink on hepatic injury [23].

4.9. Antimicrobial activity

Squid Ink shows better antimicrobial activity against various microbes. It is also shown to have effective antibacterial properties, making it a great choice of natural antibiotic. Sherif and his coworkers have investigated antimicrobial activity in ripe ANG butanol extract of Indian squid species (*L. duvauceli*) against *E coli*. The unsaturated fatty acids like DHA, oleic acid, arachinoic acid and EPA content in the extract was 1.973mg/g showed antimicrobial activity and immature extracts does not show the activity. The halide dependent peroxidase enzyme present in ANG of squid is responsible for the antimicrobial activity [24].

4.10. Hemostatic effect

Chitin and sepia ink hybrid hemostatic sponge was studied for hemostasis and stimulation of healing. The different blood parameters like thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen and platelet factor 4; were taken into consideration. The anticoagulation parameter including antithrombin III, fibrinolytic parameters such as plasminogen and fibrin degradation product were also observed. The results showed that the Chitin and sepia ink hybrid hemostatic sponge has less effect on the blood parameters on mice [25].

4.11. Hematopoietic Effects

In 2007 Lie and his coworkers had speculated that squid ink slightly increases the haematopoiesis which results in strengthening of immune responses by improving the proliferation and differentiation of granulocyte-monocyte progenitor cells. To investigate the protective effects of squid ink in chemotherapy, BALB/c mice were used as animal models in which injuries in mice is induced by a well-known chemotherapeutic drug cyclophosphamine. In this experiment the mice were randomly divided into five groups with the same number of males and females in each group. The animals were sacrificed to evaluate the organ indexes, antioxidant ability of the spleen, peripheral blood profile, and quantities of bone marrow nucleated cells. The result shows that the hemopoietic function of mice, as indicated by decreases of contents of erythrocytes, leukocytes, hemoglobin and bone marrow nucleated cells while platelets were not affected. But there is a modification in organ indexes and spleen antioxidant ability. The sepia ink extract has markedly increased the levels of erythrocytes, leukocytes, hemoglobin and bone marrow nucleated cells without affecting platelets. There is also a reverse effect by cyclophosphamine on organ indexes and antioxidant ability of spleen. Hence the Squid ink extract did not change bone marrow hemopoiesis but it improves the antioxidant ability of spleen in the animals. This reveals that squid ink extract can protect the hemopoietic system from chemotherapeutic injury [26].

4.12. Traditional/ homeopathic uses

Squid ink has its applications in homeopathic and traditional medicines. Nair et al. explained that sepia ink is used as a traditional medicine, both ancient Greece and Rome and Oriental culture including China. Hahnemann, the father of homeopathy reported about the cachectic condition of sepia ink and its role as antipsoric remedies [27]. It had been reported in the treatment of hemostasis for centuries in Chinese traditional medicine. It is also used in the Compendium of Material Medica compiled by Shizhen Li of Ming Dynasty for treatment of heart pain and curative effects in gynecology, surgery, etc.

5. Conclusion

Squid ink has acquired unique in the homeopathy although it's not is still not prevalent. Recent research studies have shown some of its beneficial pharmacological activities like anticancer, hepatoprotective, antimicrobial activity etc. Detailed work and investigation are conducted to determine the usefulness and benefits to the present world and yet

many researches are going well to implement the advantage of squid ink as food and medicines in modern scenario. So, it is a promising and effective to use in current therapeutical and pharmaceutical areas.

Compliance with Ethical Standards

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