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Sepia Ink: An Untouched Molecule from Deep Oceans

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ABSTRACT

Due to ever increasing demand of safer medicine impetus has been on researches in natural products especially marine products as it is still an untouched field. One such product is sepia ink obtained from cuttlefish present in Mediterranean and Atlantic Ocean. It has a very special place in homeopathic medicine and in traditional Chinese medicine along with its culinary uses. It is mainly composed of eumelanin and degradation studies have revealed it is a copolymer of 5, 6-dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid. It has tremendous potential in variety of diseases like uterine dysfunction, anticancer, antimicrobial, anti inflammatory activity along with haemopoetic and hepatoprotective effects. Present review aims to assemble various pharmacological activities of sepia ink although deeper insight in its pharmacological potential is required.

Keywords: sepia, cuttle fish, marine drugs, eumelanin

INTRODUCTION

Natural products particularly marine metabolites are increasingly becoming major players in drug discovery due to their structurally exclusive molecules produced by marine organisms. 1,2. Recent studies on marine drugs have focused their potential applications in the treatment of human diseases and betterment of human health. Several nautical natural products are currently in pre-clinical and medical evaluation, have shown promising results. [(1)] New trends in drug discovery from natural sources emphasize on investigation of the marine ecosystem to explore numerous complex and novel chemical entities. These entities are the sources of new leads for treatment of variety of diseases such as cancer, AIDS, inflammatory conditions including viral, bacterial and fungal infections.[(2)] Sepia ink mainly composed of melanium has proved to be a valuable substitute and has a wide range of therapeutic applications like anti-radiation, antitumor, immunomodulatory, procoagulant function, etc.[(3,4,5)] Present review aims to include various pharmacological, and phytochemical studies so that better insight on this obscure marine product can be obtained.

SOURCE and Chemistry

Sepia ink is a suspension of melanin granules in a viscous colourless medium obtained from common cuttlefish, *Sepia officinalis* L. (family *Sepiidae*) is distributed in the Mediterranean Sea, Eastern Atlantic-ocean and north-western coast of Africa. [(6)] It is produced at the end of the cuttlefish maturation in digestive tract degenerate. Ejection of dark ink from the sac is a defensive mechanism of cuttlefish employed to avoid dangers and risks. Squid ink is a mixture of large amounts of melanin along with proteins, lipids, glycosaminoglycan's and various minerals. [(7)] Degradation studies on sepia melanin proved that it is a copolymer of 5, 6-dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid, which are believed to be main monomeric building blocks of eumelanin. [(8,9)]

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TRADITIONAL/ HOMEOPATHIC USES

Nair et al. in a review has ascribed to sepia ink as a traditional medicine, both in Western (ancient Greece and Rome) and Oriental culture (including China).[10,11] Hahnemann regarded as father of homeopathy reported observations about the cachectic condition of sepia ink which convinced him about its role as antipsoric remedies.[12] In Chinese traditional medicine it had been reported in the treatment of haemostasis for centuries and listed in the Compendium of Material Medica complied by Shizhen Li (of Ming Dynasty) for treatment of heart pain and curative effects in gynaecology, surgery, etc. [11]

PHARMACOLOGICAL ACTIVITIES

Uterine dysfunctioning

In a recent clinical trial conducted by The Institute of Oceanology, China where 400 women with uterine dysfunctional bleeding were given sepia ink capsules has been proved efficient. Improvement has also been seen for the gastrointestinal and chronic tuberculosis bleeding. [13]

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 although the mechanism of action is still not clear. [14,15] A study has shown that purified tyrosine with no added extracted from the melanin-free fraction of ink is toxic to transformed human cell lines. Russo et. al., speculated the cytotoxic effect to the production of dopaquinone, which is interacts with nucleophiles to produce protein-bound DOPA through a 5-S-cysteinyldopa residue and causes cellular damage by oxidation [16]. Peptidoglycans extracted from sepia ink possesses anti-tumour effects as it has been reported that peptidoglycans can affect cell division eukaryotes which include fragmentation of DNA and apoptosis and the reserve of embryonic development. [17,18,19,20,21] Sulphated sepia ink peptidoglycans derivatives has known to suppress invasion and migration of carcinoma cells by inhibiting matrix metalloproteinase-2. [22] They have also known to suppress melanoma metastasis by inhibiting tumour adhesion and angiogenesis mediated by basic fibroblast growth factor. [23, 24, 25] Sepia ink oligopeptide has been reported to inhibit prostate cancer cells by inducing apoptosis via activation of caspase-3 and elevation of the ratio of Bax/Bcl-2. [26, 27, 28]

Hematopoietic Effects

Lie et. al., in 2007 had speculated that cuttlefish ink increases haematopoiesis which results in strengthening of immune responses by it enhancing the proliferation and differentiation of granulocyte-monocyte progenitor cells. [29]

Anti-Hypertensive Actions

A peptide derivative purified from squid ink causes dilation of blood vessels, resulting in lower blood pressure and acts as a potential anti-hypertensive [30].

Anti-Retroviral Activity

Ink from *Loligo duvauceli* and *Sepiella inermis* has been reported to have an anti-retroviral activity. [31]

Anti-ulceration activity

Study conducted in 1982 by Andersen et. al., has concluded that sepia ink possesses marked antiulcer activity by decreasing gastric juice secretion. [32]

Anti-Inflammatory Activity

Mimura et al. [33, 34] reported anti-inflammatory activity for the same fraction of squid ink that inhibits gastric secretion.

Hepatoprotective effects

Studies have shown that sepia ink extract has shown a general decrease in total bilirubin, direct bilirubin and indirect bilirubin in the Bile Duct Ligation (BDL) animal model which is a typical animal model of secondary biliary disease in animals that causes of bile duct epithelial cells proliferation, hepatocellular necrosis, apoptosis, stellate cell activation, and, causes liver fibrosis and cirrhosis and hepatotoxicity.[35]Treatment with sepia ink extract caused a decrease in serum gamma glutamyl transferase in rats models due to the protective effect of sepia extract on hepatic injury during bile constriction.[36]

Antibacterial activity

Ink isolated from *Sepia pharaonis* and purified by column chromatography using diethyl ether showed maximum inhibitory effect against *Pseudomonas aeruginosa, Staphylococcus epidermidis, Escherichia coli* and *Klebsiella pneumoniae*. [37]

Haemostatic effect

Chitin and sepia ink hybrid haemostatic sponge has been proven for hemostasis and stimulation of healing. Several kinds of blood parameters were taken into consideration like thrombin time, prothrombin time, activated partial thromboplatin time, fibrinogen and platelet factor 4; anticoagulation parameter including antithrombin III, fibrinolytic parameters including plasminogen, fibrin degradation product etc. Results proved that Chitin and sepia ink hybrid haemostatic sponge has no significant effect on the blood parameters of mice. [38]

NON PHARMACEUTICAL USE

It is used as food flavouring agent worldwide because of its superior flavour. [39] *Arroz negro* (black rice), baby squid in ink sauce, ikasumi jiru ink soup with pork and squid and Cavianne (an imitation caviar) are some of the dishes and foods that use sepia ink. Processed ink is used as a food colouring. [41] Due to its antimicrobial properties cuttlefish ink is also used to cure and, thus, extend the shelf life of cuttlefish meat. [40,41,42]

CONCLUSION

Sepia ink has acquired unique space in the hoemeopathy although its not is still not prevelant in the evidence based medicine. Recent researches and studies have shown some of its beneficial pharmacological uses like anticancer, haemostatic, hepatoprotective, antimicrobial activity etc. Detailed work and investigation is required on sepia ink and other marine products as this is the need of hour.

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