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Review Article

Exploration of the Sea Cucumber, *Holothuria arenicola* Health Benefits *Holothuria arenicola* as Promising Material for Therapeutic Drugs

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Abstract

Marine invertebrates have become attractive as nutraceutical and functional foods and as a source material for the development of therapeutic drugs. The bioactivity of echinoderm, *Holothuria arenicola* extracts and their secondary metabolites has been identified by researchers as a promising potential rich source of natural drugs. *H. arenicola* is rich in several phenolic compounds, amino acids, alkaloids and other important nutraceutical compounds. The health benefits of *H. arenicola* are associated with its antioxidant, antifibrotic and antimicrobial effects. Thus, this review aims to elaborates and analyze the role of *H. arenicola* in the modulation of several organ-specific diseases.

Keywords: *Holothuria arenicola*; Anti-ulcerogenic; Antifibrotic; Anti-microbial; Antioxidants

Introduction

Marine invertebrates constitute one of the major groups of marine organisms from which a wide range of natural products have been devised [1]. However, there is increasing interest in the bioactivity of echinoderms extracts and their secondary metabolites. The consumption of sea cucumbers is thought to boost the immune system and to have aphrodisiac properties. They are gelatinous marine resources that are shaped like a cucumber that feed on microscopic algae, absorbing nutrients from the organic matter [2]. It is considered as "sea ginseng" because of its known medicinal properties aside from its nutritional value. The therapeutic use of the sea cucumbers for healing is established, where they were used for joint pain, tendonitis, and sprains [3]. Sea cucumber extracts usually showed multiple biological activities such as wound healing and antimicrobial, anticancer, and immunomodulatory [4,5]. They are also remarkably rich in vitamins, trace elements, and polysaccharides (chondroitin sulfate), which reduce arthritis pain, inhibit viral activities, and saponin glycosides that inhibit cancer activities [3].

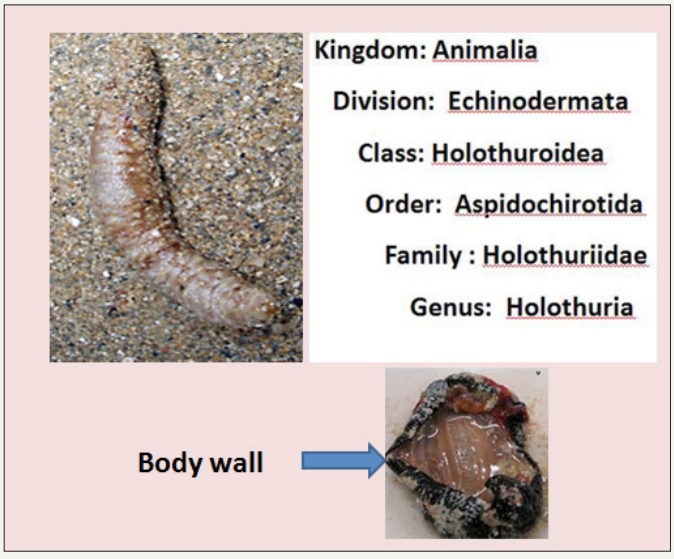

Figure 1: External feature of *Holothuria arenicoloa.*

Holothuria arenicola Semper 1868 (Figure 1) is distinctive burrowing holothurians that are very common throughout the tropical regions of the world and it was one of the best known tropical shallow water species. The specific name arenicola Semper, 1868 is universally accepted, and has been used in a large number of systematic and ecological publications. In Egypt, *Holothuria arenicola* is distributed along the Alexandrian Mediterranean coast [6]. In 1984 *H. arenicola* was recorded for the first time on the Egyptian Mediterranean coast [7]. In 1998, small scale sea cucumber fishery began in Egypt in the southern part of the Red Sea. Later in the year of 2000, the sea cucumber fishery excelled greatly as a result of the high demand for the sea cucumber due to its consumption as a food newly introduced in Egypt and for exportation purposes. During those years Egypt has become one of the most important countries supplying the sea cucumber [8]. Sea cucumbers are well known to exert many beneficial effects on human health.

Nutritional Compounds of *Holothuria arenicoloa*

Sea cucumber is an attractive bioactive source due to the presence of several bioactive compounds with therapeutic properties. Nutrition content of the *H. arenicola* plays an essential function in its medicinal, nutritional, and therapeutic properties. High-performance liquid chromatography analysis of *H. arenicola* revealed the presence of five non-volatile phenolic compounds [9] (Figure 2). Chlorogenic acid was the major component (89.66%), whereas ascorbic acid (0.077%) was the minor component. Other components, such as pyrogallol (1.88%), rutin (1.06%) and coumaric acid (1.23%) were also recorded. Presence of active phenolic compounds in the body wall of the sea cucumbers, *H. arenicola* may be due to phenolic-rich materials such as phytoplankton and particles derived from degrading marine macroalgae which the main sources of food for sea cucumbers are [10]. Phenolic compounds are very important antioxidant compounds [11], due to their redox properties which play an important role as free radical scavengers, reducing agents, quenchers of singlet oxygen and complexes of pro-oxidant metals [12]. Feng et al. [13] has been reported that chlorogenic acid is one of the most abundant polyphenols in the human diet that has been known to decrease the incidence of chemical carcinogenesis in several animal models of cancer. It is an important component of coffee [14]. The major polyphenol in coffee is CGA. CGA is an ester formed from cinnamic acids and quinic acid and is also known as 5-O-caffeoylquinic acid (5-CQA) (IUPAC numbering) or 3-CQA (pre-IUPAC numbering) [15]. It was demonstrated that CGA exert many biological activities such as antibacterial, antioxidant, and anticarcinogenic activities, particularly hypoglycemic and hypolipidemic effects [16-19].

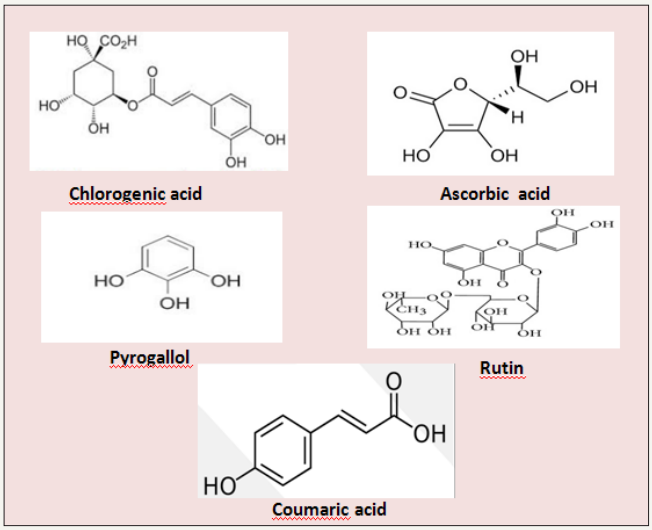

Figure 2: Chemical structure of the *H. arenicoloa* body wall phenolic compounds.

The potential hepatoprotective effect of chlorogenic acid in several animal models of liver injury was reported [9,12]. Chemical screening of the *H. arenicola* body wall and coelomic fluid showed presence of other important bioactive compounds which exhibit numerous medicinal benefits and health functions, especially flavonoids, alkaloids, tannins, quinones, saponins, proteins and amino acids [20]. The use of *H. arenicola* in the traditional medicine may originate from its ability to regenerate body wall after being cut up [21]. In addition, Bordbar et al. [22], reported that the health benefits of sea cucumbers are associated with the presence of bioactive components such as saponins, glycosaminoglycans, sterols, cerebrosides, peptides, sulfated polysaccharides, and essential fatty acids.

Antiulcerogenic effects of *H. arenicola*

Peptic ulcer is the most prevalent disease among the gastrointestinal diseases in most part of the world. Gastric ulcer develops because of several endogenous and exogenous factors [23]. It results as a consequence of impaired balance between gastro-protective factors such as mucus, bicarbonate and prostaglandins, and gastro-destructive substances [24]. The incidence varies with the age, gender, geographical location and is associated with severe complications including hemorrhages, perforations, gastrointestinal obstruction, and penetration [25]. Under normal conditions a large number of defense mechanisms prevent local damage and maintain structural and functional mucosal integrity [26]. Tradi-

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tional medicines have been used to prevent or treat gastric ulcers for a long time. Accordingly, many natural products have been examined for their anti-ulcerogenic effects [27,28].

H. arenicola extract has been shown to produce promising antiulcerogenic efficacy that attributed to its high content of chlorogenic acid (CGA) [29]. Gastric ulcer lesion usually occurred due to increased gastric acidity secretion [30]. Most therapeutic agents exert their actions through inhibition of the gastric acid secretion [31]. *H. arenicola* induced marked improvement in gastric acid volume as compared to ranitidine (RAN) in rat model of gastric ulcer [29]. Gastric acid decimation by ranitidine is attributed to its ability to antagonize the binding of histamine to the H2 receptor on the parietal cells [32]. *H. arenicola* may be interferes with the gastric acid secretion and eliciting gastroprotection via an adaptive mechanism. These findings indicate that the *H. arenicola* probably acts by inhibiting H2-receptor leading to blockade of histamine release whose stimulatory action on gastric acid secretion via H2-receptor, has been well reported [33]. It has been reported that CGA exert inhibitory effect on mast cell activation and subsequently histamine release [34]. Thereby, *H. arenicola* may decrease gastric acid secretion due to inhibition of histamine secretion as a result of its high content of CGA.

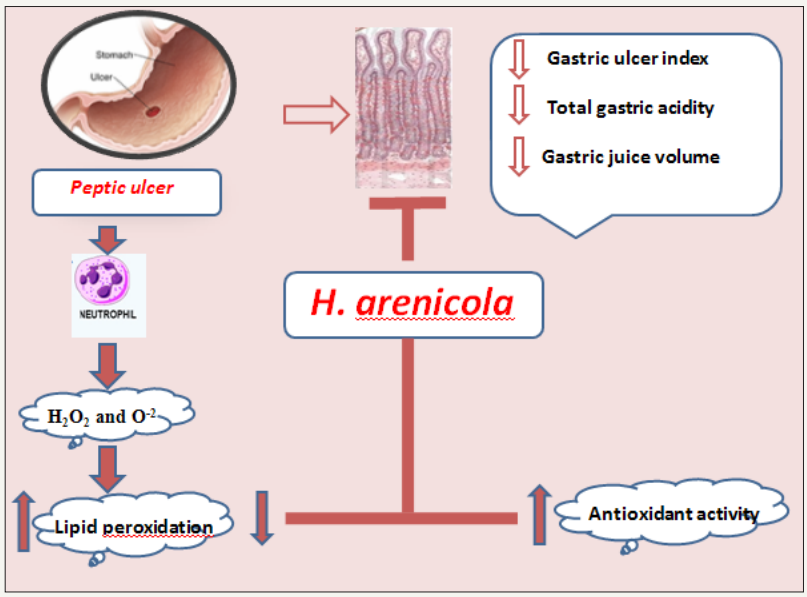

Figure 3: Schematic diagram showing antiulcerogenic mechanism of *H. Arenicola* body wall extract on some gastric indices.

Gastric ulceration is a benign lesion on the mucosal epithelium upon exposure of the stomach to excess acid and aggressive pepsin activity [35]. Fahmy et al. [29] showed that *H. arenicola* exert significant improvement in gastric ulcer index as compared to the standard drug RAN (Figure 3). *H. arenicola* may stimulate gastric mucosal cellular growth and repair by the same mechanism of wound healing. Indeed, the damage of the gastric mucosa is also related to the increase in neutrophil infiltration into ulcerated tissues. These neutrophils inhibit ulcer healing mediated lipid peroxidation through the release of cytotoxic factors such as superoxide and hydrogen peroxide. It was reported that RAN caused significant inhibition of neutrophil activation and gastric acid secretion [36]. *H. arenicola* may stimulate gastric mucosal cellular growth via inhibition of neutrophil activation. This mechanism can be supported by the study of Shimoyama et al. [37] and Zatorski et al. [38], who reported that CGA treatment blocked the influx of neutrophils into the gastric tissue. Other studies have also shown that CGA inhibits neutrophil recruitment into inflammatory tissues [39,40].

Moreover, the anti-ulcerogenic effects of *H. arenicola* may be due to its antioxidant effect [29,41]. *H. arenicola* provided a marked suppression of oxidative damage through excellent radical scavenging activity to DPPH radical. Moreover, many dietary polyphenols are antioxidants, and the possibility exists that they protect against oxidative damage by directly neutralizing reactive oxidants [42]. The body wall of the sea cucumbers contains high amounts of phenolic compounds [43], which may exert scavenging activities by donating a hydrogen atom from their phenolic hydroxyl groups [11]. Thereby, *H. arenicola* may be an effective source of direct precursors for salvage glutathione reduced (GSH) biosynthesis.

The enhancement of the GSH level by the *H. arenicola* could be due to either its effect on the de novo synthesis of glutathione, its regeneration, or both [44]. Moreover, *H. arenicola* may act directly and scavenges the reactive oxygen species (ROS) derived by oxidation-reduction cycle with the cell or it may work in union with the existing antioxidant compounds and helps to prevent their loss during the ulcer oxidative injury. Fahmy et al. [29] also showed that *H. arenicola* induced significant enhancement in the activities of GST, CAT and SOD antioxidant enzymes to prevent the accumulation of excessive free radicals and protect stomach from ulcer formation, suggesting that the anti-ulcerogenic effect of *H. arenicola* against oxidative stress induced injury might be involved in decreasing lipid peroxide generation and stimulating antioxidant

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enzyme. Fahmy et al. [29] proved that *H. arenicola* may overpower gastric ulcer onslaught by suppressing the formation of ROS and protecting the antioxidant machinery. Moreover, the induction of the antioxidant enzymes by the *H. arenicola* represents a promising preventive strategy as a bifunctional inducer, along with the enhancement of antioxidant system enzymes which affords protection against cellular damage and inhibits ulcer promotion.

Antifibrotic effects of *H. arenicola*

Chronic liver disease is an important cause of morbidity and mortality and represents a major health problem worldwide [45]. The high prevalence of chronic liver diseases in Egypt has led to increasing numbers of Egyptian patients suffering from end-stage liver disease [46]. Obstructive jaundice, a frequently observed condition caused by obstruction of the common bile duct or its flow may end up with serious complications like hepatic failures [47]. Cholestatic liver fibrosis, characterized by excessive accumulation of extracellular matrix (ECM) proteins [48]. Cholestasis represents the consequence of impaired bile formation and generally caused by conditions that the enterohepatic circulation is interrupted, and bile acids accumulate within the liver [49]. Mainly inflammatory cell infiltration, hepatocyte necrosis, and liver fibrosis are the main pathological features of cholestasis [50]. Retention of hydrophobic bile salts within the hepatocytes during cholestasis leads to apoptosis and necrosis [51]. Oxidative stress (OXS) and inflammatory injuries are the most important pathogenic events in cholestatic liver injury [9,52].

Liver fibrosis, which etiologically and pathogenetically resembles the biliary fibrosis in the human beings can be induced by bile duct ligation and [53]. Several potential therapies for fibrosis have been identified in previous preclinical studies. These include interruption of matrix deposition and hence inhibition of collagen synthesis [54]. For the therapeutic strategies of liver injury and disease, it is important to find antioxidant compound that are able to block liver injuries through free radicals generated due to toxic chemicals. During the course of evolution, many invertebrates have established as a selective advantage by endogenous production of protective chemicals [55]. It was demonstrated that *H. arenicola* exerted an apparent arrest in the progression of collagen deposition in the cholestatic animals which may be a consequence of the increased mass of regenerated liver cells [9] This give an additional support that *H. arenicola* are able to condition the hepatocytes, accelerate regeneration of parenchyma cells, protect against membrane fragility and hence decrease leakage of the enzymes into circulation.

Acceleration in albumin synthesis may be another mechanism by which *H. arenicola* extract exert its antifibrotic efficacy [9]. Awang [56] has been reported that stimulation of albumin synthesis has been advanced as a contributory hepatoprotective mechanism which accelerates the regeneration process and the production of liver cells [56]. It was reported that oxidative stress occurs during cholestasis plays a role in cholestasis induced liver fibrosis [57]. Tissues and cells would be subjected to oxidative injuries when large quantities of inner free radicals are generated, or the activities of antioxidant system deteriorate. Accordingly, antioxidant therapy represents a potential strategy to prevent liver injury and fibrosis. Treatment with *H. arenicola* normalized the antioxidant levels during cholestasis through its rich of polyphenolic compounds especially chlorogenic acid that has the ability to scavenge free radicals. Wang et al. [58] proved that chlorogenic acid decreased malondialdehyde (MDA) contents in liver while increased activities of antioxidant enzymes (Figure 4).

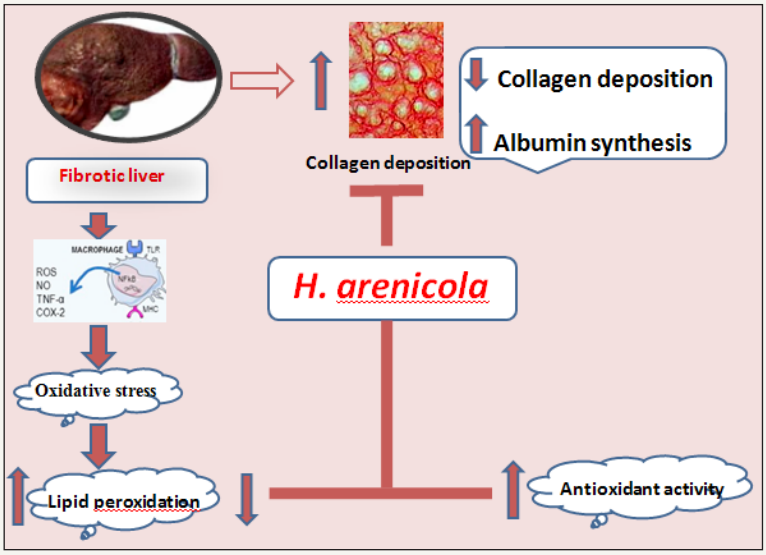

Figure 4: Schematic diagram showing antifibrotic mechanism of *H. Arenicola* body wall extract.

Antimicrobial effects of *H. arenicola*

Several drug discovery projects have screened for echinoderms for antibiotic activities. Moreover, anti-fungal, anti-bacterial, antithrombotic, anti-malarial, anti-protozoa and anti-virus effects have been reported from some sea cucumber isolated compounds [59]. Many investigators reported the *in vitro* antibacterial and antifungal activities of Holothuria leucospilota body wall and coelomic fluid [60,61]. Fahmy et al. [20] proved the Body wall

extract of the *H. arenicola* showed a broad-spectrum antibacterial activity against Staphylococcus aureus and Escherichia coli. The antibacterial potency of the *H. arenicola* may be due to their antimicrobial components, flavonoids, alkaloids, tannins, quinines and saponins. It was reported that these active constituents have antibacterial characteristics [62].

Sepsis, a systemic inflammatory response syndrome (SIRS) induced by infection, is accompanied by the presence of bacteria [63]. Abundant evidence shows that CLP-induced sepsis with acute supportive peritonitis is a typical sepsis model with G-bacteria as the predominant infection source [64]. In a study by Fahmy et al. [20], the antimicrobial effects of *H. arenicola* was examined using rat model for cercal ligation and puncture (CLP) in which 200mg/kgb.wt. of the methanolic extract of *H. arenicola* was used. The results showed that *H. arenicola* body wall extract successfully increased survival rate of septic rats to 66.7% through its antibacterial activity. Procalcitonin (PCT), the precursor for the hormone calcitonin (CT) is a biomarker that exhibits greater specificity than other proinflammatory markers (cytokines) in identifying patients with sepsis and can be used in the diagnosis of bacterial infections [65] (Figure 5). Usually, PCT used to guide antibacterial therapy as a surrogate biomarker [66]. Fahmy et al. [20] showed that treatment of septic rats with *H. arenicola* body wall extract succeed to normalize the PCT level which may be due to their antimicrobial constituents. Accordingly, antibacterial of *H. arenicola* body wall extract may be due to its content of polyphenolic compound especially quinine, saponins and terpenoid that show antibacterial characteristics [20].

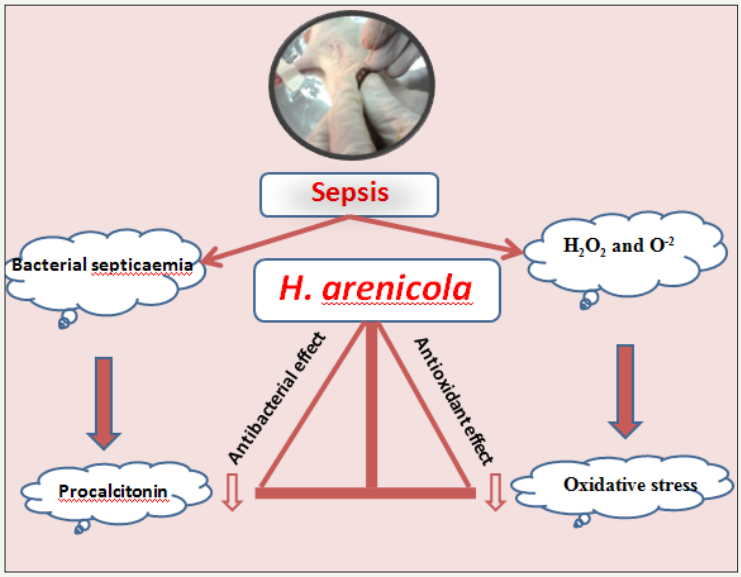

Figure 5: Schematic diagram showing antiseptic mechanism of *H. arenicola* body wall extract.

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