Journal of Functional Foods 49 (2018) 73–84

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Bioactive compounds and biological functions of sea cucumbers as potential functional foods

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ARTICLE INFO

Keywords:
Sea cucumbers
Biological function
Bioactive compounds
Nutraceuticals
Markets

ABSTRACT

Sea cucumbers are a group of economically important invertebrate marine animals that have been widely used as tonic foods in Asia countries. Various bioactive compounds in sea cucumbers including peptides, triterpene glycosides, polysaccharides, phenols, and lipids have been reported. These compounds demonstrate a myriad of salubrious biological functions such as anti-oxidant, anticancer, anti-inflammation, anti-thrombus, anti-microbes, anti-diabetes, anti-obesity, and learning and memory improvement. This review is to provide a comprehensive and most recent update of these biological functions and their associated bioactive compounds. The management practice to keep sustainable sea cucumbers including natural stock fishery and aquaculture were discussed. The extraction and purification of the bioactive compounds were also summarized, providing a perspective of preparing sea cucumber derived nutraceuticals. It is expected that this review can provide academia and industry an insight of sea cucumbers and their potentials in the development of high value nutraceutical products.

1. Introduction

Sea cucumbers are cucumber-shaped marine invertebrates in the class Holothuroidea. There are more than 1,100 varieties of sea cucumbers in the world, among which about 40 species are available in commercial markets (Conand, 2006). Sea cucumbers are popular tonic foods in many Asian countries. Increasing demand has led to an over exploitation and depletion of the natural stock of sea cucumbers (Purcell et al., 2013). Improved aquaculture production and appropriate natural stock management practices are needed to maintain a sustainable supply of sea cucumbers.

Sea cucumbers are commonly characterized by high protein and low lipid contents (Wen, Hu, & Fan, 2010), with a diverse other compounds such as peptides (Zhou, Wang, & Jiang, 2012), triterpene glycosides (Silchenko et al., 2017), fucoidan (Hu et al., 2015), fucosylated chondroitin sulfate (Myron, Siddiquee, & Azad, 2014), cerebrosides (Xu et al., 2011), sphingoid (Tian, et al., 2016) and phenols (Esmat, Said, Soliman, El-Masry, & Badiea, 2013). As a result, sea cucumbers have been reported to possess various biological functions such as anti-oxidative activity (Wang et al., 2012), anticancer (Tian et al., 2005), anti-inflammation (Song, Park, Cho, & Park, 2013), antithrombotic activity (Matsuhiro, Osorio-Román, & Torres, 2012), anti-diabetes (Barky et al., 2016), anti-obesity (Tian et al., 2016), and antimicrobial activity (Pringgenies, 2013).

Many reviews have been published on specific biological functions and related bioactive compounds in sea cucumbers. For example, Xue

Abbreviations: 8-OHdG, 8-oxo-7,8-dihydro-20-deoxyguanosine; 8-oxo-G, 8-hydroxy-20-deoxyguanosine; AAPH, 2,2′-azobis-2-methyl-propanimidamide, dihydrochloride; Ach, Acetyl choline; AchE, Acetylcholinesterase; CAT, Catalase; C/EBPα, CCAAT/enhancer binding protein-α; CNS, Central nervous system; DAPCI-MS, Desorption Atmospheric Pressure Chemical Ionization Mass Spectrometry; DHA, Docosahexaenoic acid; DNA, Deoxyribonucleic acid; DPPH, 1,1-diphenyl-2-picrylhydrazyl; DRIFTS, Diffuse Reflectance mid-Infrared Fourier Transform Spectroscopy; EPA, Eicosapentaenoic acid; FAS, Fatty acid synthase; GPAT, glycerol-3-phosphate acyltransferase; GR, Glutathione reductase; GSH-px, Glutathione peroxidase; iNOS, Inducible nitric oxide synthase; MAPKs, Mitogen-activated protein kinase; MDA, Malondialdehyde; MMP-2, Matrix metalloproteinase-2; MMP-9, Matrix metalloproteinase-9; NADPH, Nicotinamide adenine dinucleotide phosphate; NO, Nitric oxide; p85-PI3K, p85- phosphoinositide 3-kinase; p-ERKs, p-Extracellular signal–regulated kinases; p-JNKs, p-Jun N-terminal kinases; PI3K/PKB, phosphoinositide 3-kinase/ protein kinase B; PPARγ, Peroxisome proliferator-activated receptor-γ; ROS, Radical oxygen species; Ser473-PKB, Ser473-protein kinase B; SIFA, Stable Isotope and Fatty Acid; SOD, Superoxide Dismutase; SREBP-1c, Sterol regulatory element-binding protein1c; Thr308-PKB, Thr308- protein kinase B; TNF-α, Tumor necrosis factor alpha; UV, Ultraviolet

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https://doi.org/10.1016/j.jff.2018.08.009
Received 3 May 2018; Received in revised form 3 August 2018; Accepted 6 August 2018
1756-4646/

et al. (2015) reported the functional characterization and mechanism of the immune-related molecules. Triterpene glycosides have been widely studied for their anticancer characteristics (Adrian & Collin, 2018; Aminin et al., 2015; Janakiram, Mohammed, & Rao, 2015; Wargasetia & Widodo, 2017) and other broader biological activities (Bahrami & Franco, 2016). The biological and taxonomic perspectives (Honey-Escandón, Arreguín-Espinosa, Solís-Marín, & Samyn, 2015) and structure and function relationships (Park, Bae, Kim, Stonik, & Kwak, 2014) of these special group of compounds were also reported. Another important compound in sea cucumbers, polysaccharide fucosylated chondroitin sulfate, was also reviewed (Myron, Siddiquee, & Al Azad, 2014; Pomin, 2014).

Although many reviews about sea cucumbers have been reported, most reviews were focusing on specific groups of compounds and their associated biological functions. From an application point of view, reports on the use of sea cucumbers as functional foods and drug products are still limited. There is also a lack of summary of the most recent discoveries of sea cucumbers biological functions such as anti-diabetes, anti-obesity and improvement of learning and memory (Bordbar, Anwar, & Saari, 2011, Kiew & Don, 2012). Reviews of the extraction and purification of active compounds from sea cucumbers have been scarce. Additionally, reviews of the management practices to maintain a sustainable sea cucumber supply have been largely neglected.

The aim of this review is to address the above shortcomings by providing an update of the most recent discoveries of sea cucumber biological functions and the associated bioactive compounds. Considering the potential of developing sea cucumber-based nutraceuticals and pharmaceuticals, the practices of preparing pure bioactive compounds and maintaining a sustainable sea cucumber sources were discussed. The information will provide a comprehensive perspective on developing sea cucumber based nutraceuticals.

2. Classification and identification of sea cucumbers

Sea cucumbers are soft-bodied marine animals that can be found on the seabed all around the world (Conand, 2006). More than 1,100 sea cucumber varieties have been reported among which the families *Holothuridae*, *Stichopodidae*, and *Cucumariidae* are most valuable for commercial markets. Sea cucumbers originated from different locations may differ in their food and medical values, it is therefore important to specify their origins.

Sea cucumber species can be identified through their genetic characteristics such as microsatellite (Kang et al., 2011; Kanno, Suyama, Li, & Kijima, 2006; Kim, Choi, & An, 2008). Microsatellite analysis is based on the fact that polymorphic DNA loci (microsatellite markers) contain repeated nucleotide sequences and do not change among the same species. Once the microsatellite-based markers are developed, the gene differentiation between sea cucumber populations can be verified, which can be further used to identify the species.

Characterization of special compounds can also be used to identify sea cucumbers. For example, triterpenoid glycosides were commonly used to identify species based on their species-specific structures (Honey-Escandón et al., 2015). With the advancement of chemical analytical methods, more and more special compounds in sea cucumbers can be characterized to identify the geographical locations and origins of sea cucumbers. For example, special pigments and proteins located on sea cucumber body surface can be determined through Desorption Atmospheric Pressure Chemical Ionization Mass Spectrometry (DAPCI-MS) (Wu, et al., 2009). The unique mid-infrared spectroscopy fingerprints of sea cucumbers can be analyzed through Diffuse Reflectance mid-Infrared Fourier Transform Spectroscopy (DRIFTS) (Wu, et al., 2010). Stable Isotope and Fatty Acid (SI-FA) analysis accesses sea cucumbers based on their δ^{13}C and δ^{15}N and fatty acid profiles (Zhang, Liu, Li, & Zhao, 2017). Multi-elements analysis was used to analyze sea cucumber elements profiles (Liu, Xue, et al., 2012). With the appropriate data analyses such as principal components analysis, cluster analysis, and discriminant analysis, these chemical analytical methods proved high differentiating accuracy.

3. Active compounds in sea cucumbers

3.1. Overall chemical compositions of sea cucumbers

Sea cucumbers have long been regarded as a tonic food in Asian countries. Proteins are the most abundant chemical components and can account 40 ~ 60 wt% of sea cucumber dry matter (Wen et al., 2010). Most sea cucumber proteins are in the form of collagen with up to 70 wt% of body wall proteins being insoluble collagen fiber (Saito, Kunisaki, Urano, & Kimura, 2002). Glutamic acid (Bechtel, Oliveira, Demir, & Smiley, 2013; Roggatz et al., 2017; Zhong, Khan, & Shahidi, 2007) and glycine (Saito et al., 2002; Wen et al., 2010) are two dominant amino acids in sea cucumber proteins.

Fatty acids in sea cucumbers exist at a relatively small amount. Total fatty acids account for 2 ~ 8 wt% in sea cucumber dry matter, among which unsaturated fatty acids can account for up to 70%. Eicosapentaenoic acid (EPA, C20:5, n-3) in total fatty acids can be up to 56.7%, while the content docosahexaenoic acid (DHA, C22:6, n-3) was much lower (up to 5.8% of total fatty acids) (Bechtel et al., 2013; Gao et al., 2016; Salarzadeh et al., 2012; Zhong et al., 2007). Sea cucumbers contain around 15 wt% carbohydrate in body wall and 8 wt% in muscle bands (Bechtel et al., 2013). In addition to these three major components, sea cucumbers are also rich in elements such as Ca, Mg, Fe, with contents varying among different species (Barzkar, Fariman, & Taheri, 2017; Lee et al., 2014; Wen & Hu, 2010).

3.2. Collagens

Collagens as main structural proteins build sea cucumber body tissues and contribute sea cucumbers' palatable tastes (Liu, Zamora, Jeffs, & Quek, 2017). Collagens in sea cucumbers commonly consist of three polypeptide chains, each of which contains a repeating Glycine-X-Y motif where X and Y represent any amino acids (Hulmes, 2008). As a result, glycine is the most abundant amino acid in sea cucumber collagen (Abedin et al., 2014; Adibzadeh, Aminzadeh, Jamili, Karkhane, & Farrokhi, 2014; Lin et al., 2017; Liu et al., 2017; Zhong, Chen, Hu, & Ren, 2015).

Collagen fibers are formed by covalent cross-links between collagens. Electrophoretic assay revealed that sea cucumber fiber tissues are thin, uniform and densely interwoven collagenous fibrils (Liu et al., 2017). External factors such as temperature, salt concentration, sunlight exposure, and nutrient deficiency can induce autolysis of sea cucumber body walls, and drastically change of the tissues mechanical properties such as contraction, relaxation and mucoid degeneration (Liu et al., 2018).

3.3. Glycosides

Glycosides are molecules in which a sugar is bound to another functional group via a glycosidic bond. Sea cucumbers contain triterpene glycosides as abundant secondary metabolites. The unique structure of triterpene glycosides contribute to their biological activity and can be used as taxonomic markers (Honey-Escandón et al., 2015; Kalinin, Avilov, Silchenko, & Stonik, 2015). The carbohydrate chains of triterpene glycosides commonly contain xylose, glucose, quinovose, 3-O-methylglucose, and in rare cases, 3-O-methylxylose, 3-O-methylglucuronic acid, 3-O-methylquinovose, and 6-O-acetyl-glucose (Kalinin et al., 2015; Kalinin, Silchenko, Avilov, Stonik, & Smirnov, 2005). Holostane type triterpene glycosides (lanostane derivatives with an 18(20)-lactone) is the most common triterpene glycosides found in sea cucumbers.