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Mini review

Bioactive compounds from brown seaweeds: Phloroglucinol, fucoxanthin and fucoidan as promising therapeutic agents against breast cancer

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ABSTRACT

Breast cancer is one of the most common cancers among women and its incidence tends to increase year by year. Chemotherapy is an effective treatment for many types of cancer, however its toxicity in normal cells and acquired tumor resistance to the drug used are considered as the main barriers. New strategies have been proposed to increase the success of anticancer drugs namely it combination with natural dietary compounds, decreasing drug dose administered and reducing its toxicity to normal cells. Seaweeds are rich in bioactive compounds and, in Traditional Chinese Medicine and Japanese folk medicine are used to "treat" tumors. Attending to the attractive biological effects of some seaweed several efforts have been made to isolate the bioactive compounds and explore its action mechanisms. Phloroglucinol, fucoxanthin and fucoidan are bioactive compounds present in brown seaweed showing chemopreventive and chemotherapeutic effects against cancer. Several mechanisms namely antioxidant, cell cycle arrest, induction of cell death and inhibition of metastasis and angiogenesis have been mentioned as responsible for it anticancer activity. Beside the promising biological effects of these compounds, synergistic effects with cytotoxic drugs have been less explored. This review focuses on the potential protective and therapeutic effect – mainly against breast cancer – of the bioactive compounds phloroglucinol, fucoxanthin and fucoidan present in the brown seaweeds. Current knowledge about interaction between each of these compounds and the conventional anticancer drugs and the further research opportunities are discussed.

Contents

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1. Introduction

Breast cancer is the most diagnosed cancer in women and its incidence tends to rise year by year (Jemal et al., 2011). Several risk factors have been identified, such as age, reproductive events, hormonal replacement therapy, lifestyle, familial history of breast cancer, previous benign breast disease, ionizing radiations exposure, high mammographic breast density, geographic location, mutations in BRCA1 and BRCA2 genes and in other high-penetrance genes such as p53 (Dumitrescu and Cotarla, 2005; Jemal et al., 2011). Additionally, breast cancer has a large molecular heterogeneity and is histologically diverse. For that reason, accomplishing an effective therapy is difficult (Florea and Busselberg, 2013; Gottesman, 2002).

Breast cancer treatment depends on the pathological stage at the time of detection and diagnosis. The treatment includes surgery, radiotherapy and chemotherapy (Maughan et al., 2010). Chemotherapy is the option for cancers in advanced stages and nowadays, several drugs are available (e.g., cisplatin, tamoxifen, paclitaxel and doxorubicin) with different mechanisms of action (Dasari and Tchounwou, 2014; Mayer and Burstein, 2007; Osborne, 1998; Perez, 1998; Silver et al., 2010; Thorn et al., 2011). Beside the development of increasingly more specific and effective drugs, genetic and epigenetic changes contributed for drug resistance which represent the main reason of chemotherapy failure in cancer treatment (Florea and Busselberg, 2013).

The medical and scientific communities are well aware of the problems associated with current therapeutics and therefore have continually sought new solutions. The search of new compounds and possible combination with conventional anticancer drugs seems to be crucial strategies to reduce mortality and improve life quality in breast cancer patients. Recent reports have been showed that the success of anticancer drugs can be increased in tumors with the combination of natural dietary compounds and that may allow lower doses of the drug administered, reducing its toxicity to normal cells (Kapadia et al., 2013; Kim et al., 2014; Saldanha and Tollefsbol, 2012; Wang et al., 2012a).

Chemopreventive and/or chemotherapeutic effects of several natural products has been reported, namely from plants, fruits and vegetables (Kalimuthu and Se-Kwon, 2013). In the last decades the attention has turned to the sea, mainly due to the large surface of the marine environment (about 70% of the word surface), high biodiversity (95% of the world biodiversity), and the specific conditions where some species live (e.g. salinity, pressure, temperature) (Appeltans et al., 2012; Dalmaso et al., 2015). This makes the sea a relevant source of bioactive compounds, some of them present in our food chain from many centuries ago.

Marine macroalgae (seaweeds) are rich in unique bioactive compounds that are used for human consumption for a long time (mainly in Asian countries). In Traditional Chinese Medicine and Japanese Folk Medicine, seaweeds are used to “treat” tumors. Epidemiologic studies have shown that people that consume seaweed daily, mainly Asiatic women, have lower rates of breast cancer than in the western world, however the mechanisms involved remain unclear (Moussavou et al., 2014; Smit, 2004; Teas et al., 2013).

The potential protective and therapeutic effect of bioactive compounds such as phloroglucinol, fucoidan and fucoxanthin present in the brown seaweeds mainly in breast cancer will be explored in this review. In view of the latest advances and current knowledge gaps, interactions of bioactive compounds from seaweeds with conventional anticancer drugs in breast cancer will be revised and future paths will be discussed.

2. Bioactive compounds in brown seaweed

Generally, seaweeds have high concentration in polysaccharides, minerals, polyunsaturated fatty acids and vitamins and low content in lipids as well as high content in bioactive molecules that make the seaweed a good source of healthy food (Gupta and Abu-Ghannam, 2011; Holdt and Kraan, 2011). Apart from food uses, seaweeds are also used in the pharmaceutical and cosmeceutical industry (Ahmed et al., 2014; Martins et al., 2014). According to their composition of pigments, seaweeds are classified into three divisions: Clorophyta (green seaweed), Phaeophyta (brown seaweed), and Rhodophyta (red seaweed). Among all the three types, the highest phytochemical content (such as terpenes, carotenoids and phenolic compounds) have been reported from brown seaweeds (Gupta and Abu-Ghannam, 2011).

2.1. Phlorotannins (seaweed phenols)

Brown seaweed accumulates a variety of phloroglucinol-based polyphenols (phlorotannins), formed from polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units resulting in compounds with different molecular weight (Gupta and Abu-Ghannam, 2011; Li et al., 2011; Wijesekara et al., 2010). Based on the monomers linkage, phlorotannins can be classified into four subclasses: fuhalols and phlorethols (ether linkage), fucols (phenyl linkage), fucophlorethols (ether and phenyl linkage), and eckols and carmalols (dibenzodioxin linkage). Phlorotannins are present in many marine organisms, especially in brown seaweed, where it concentration is highly variable depending on the species and the geographic area (Gupta and Abu-Ghannam, 2011; Li et al., 2011; Pal Singh and Bharate, 2006; Vinayak et al., 2011). It was found that *Ecklonia cava* is a particularly rich source of phlorotannins compared to other brown algae (Heo et al., 2005). Phlorotannins are stored in special vesicles (physodes) and are presumed to be the defense compounds involved in protection against stress conditions and herbivores (Gupta and Abu-Ghannam, 2011; Li et al., 2011). Nowadays, several biological activities have been attributed to the phlorotannins, such as, antioxidant, antibacterial, anti-inflammatory and anti-allergic, contributing for the reputation of brown seaweed as a source of healthy food (Eom et al., 2013; Kim et al., 2009; Sugiura et al., 2006).

2.1.1. Phloroglucinol

Phloroglucinol is a polyphenolic compound that chemical structure includes an aromatic phenyl ring with three hydroxyl