Mini review

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

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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 its 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.

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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-penetration 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; Cottessman, 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; Dalmasso 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 Asian 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 beexplored 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: Chlorophyta (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), fucools (phenyl linkage), fucophoreths (ether and phenyl linkage), and eckols and carmalols (dibenzoxydlinkage). 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; Sugiiura et al., 2006).

2.1.1. Phloroglucinol

Phloroglucinol is a polyphenolic compound that chemical structure includes an aromatic phenyl ring with three hydroxyl
groups (Fig. 1a). Like other phenolic compounds, phloroglucinol shows a variety of biological activities such as antioxidant, anti-inflammatory, anti-diabetic antimicrobial, anti-allergic, and anti-HIV, by which has attracted attention for the development of new drugs (Crockett et al., 2008; Daikonya et al., 2002; Kim and Kim, 2010; Sithranga Boopathy and Kathiresan, 2010; Vo and Kim, 2010; Wang et al., 2012b). The eventual toxicity of phloroglucinol in normal cells has not been reported yet. Rather, it has been shown cytotoxic effects on oxidative stress induced cell damage in several models (Kang et al., 2006; Kang et al., 2010; Kim et al., 2015). Beside the extensively interest in medicine, phloroglucinol has been used also in cosmetics, textiles, pesticides, paints and cements (Kim et al., 2015; Singh et al., 2010).

2.2. Carotenoids

Carotenoids are tetraterpenoids with a specific linear C40 molecular backbone and are represented by more than 600 known natural structural variants (Mikami and Hosokawa, 2013; Pizarro and Stange, 2009; Tapiero et al., 2004). They are colorful pigments synthesized in plants, seaweeds and other photosynthetic organisms as well as in some non-photosynthetic bacteria and are involved in photosynthesis, hormonal synthesis, photoprotection and photomorphogenesis (Balboa et al., 2013a; Stahl and Sies, 2005; Tapiero et al., 2004). Carotenoids are usually divided in two general classes: carotenes (containing only carbon and hydrogen atoms) and xanthophylls (which have at least one oxygen atom) (Krinsky and Johnson, 2005; Tapiero et al., 2004). β-carotene is the most common carotene, while lutein, fucoxanthin and violaxanthin belong to the xanthophylls class (Das et al., 2005 Zorofchian Moghadamtousi et al., 2014). In seaweed, carotenoids profiles are used to classify seaweed into green, brown and red (Takaichi, 2011).

The structure of carotenoids strongly affects their activity (e.g., presence of functional groups in the terminal rings increase the antioxidant potential). The antioxidant activity of carotenoids is mainly due to its ability to quench singlet oxygen and scavenging free radicals. Their antioxidant property is one of the main mechanisms by which they prevent oxidative stress-related diseases, namely cancer, cardiovascular and neurodegenerative diseases (Mayne, 1996; Miyashita et al., 2011; Sachindra et al., 2007; Stahl and Sies, 2005; Terao et al., 2011).

In vitro and in vivo studies have shown that carotenoids may protect against several types of cancer. These studies are consistent with data from epidemiological studies that showed an inverse correlation between consumption of a carotenoids rich diet and the risk of developing cancer (Krinsky and Johnson, 2005; Mayne, 1996; Stahl and Sies, 2005).

2.2.1. Fucoxanthin

Fucoxanthin is a carotenoid with a unique structure including an allenic bond and oxygenic functional groups, such as epoxy, hydroxyl, carbonyl and carboxyl groups in the polyene hydrocarbon chain (Fig. 1b) (Mikami and Hosokawa, 2013; Zheng et al., 2013). Fucoxanthin is found in microalgae and macroalgae such as brown seaweeds and has protective and photosynthetic functions (Peng et al., 2011). It is the most abundant of all carotenoids found in brown seaweed, despite its content varies during season and life cycle of seaweed (Balboa et al., 2013a).

Recently, several studies have been demonstrated the anti-inflammatory, antioxidant and anticancer activity of fucoxanthin (Fung et al., 2013; Gammone and D’Orazio, 2015; Heo et al., 2012; Kumar et al., 2013; Yan et al., 1999). The antioxidant activity of fucoxanthin involves free radical scavenging and is one of the main mechanisms underlying its anticancer effect (Zheng et al., 2013; Zorofchian Moghadamtousi et al., 2014).

Fig. 1. Chemical structure of (A) phloroglucinol; (B) fucoxanthin and (C) fucoidan.
2.3. Polysaccharides

Polysaccharides are polymers of monosaccharides linked by glycosidic bonds resulting in complex molecular structures. Large amounts of polysaccharides are present in the seaweed cell walls conferring strength and flexibility. It composition differs according to several intrinsic and extrinsic factors, namely seaweed specie, geographic area, season, age and parts of the seaweed collected. (Gupta and Abu-Ghannam, 2011; O’Sullivan et al., 2010). The interest in polysaccharides have been increase due to their biological activities such as immunomodulatory and anticancer effects that are structural-dependent (Sun et al., 2012; Wijesinghe and Jeon, 2012; Wong et al., 1994).

Different polysaccharides have been found in brown seaweeds, like alginates, fucoids, and laminarans (An et al., 2013; Rioux et al., 2010). The latter two types are water-soluble polysaccharides present in brown seaweed while algic acids are alkali-soluble. The algic acid and sulfated fucans constitute the two types of acid polysaccharides present in the extracellular matrix of brown seaweed. In the case of fucans, they can be classified into three groups: fucoids, glycorunogalactofucans and xylofucoglycuronans (Gupta and Abu-Ghannam, 2011; Wang et al., 2012b).

2.3.1. Fucoidan

Fucoidan consist mostly of sulfated -fucose and small proportions of galactose, mannose, xylose, glucose, and uronic acids (Balboa et al., 2013b; Li et al., 2008). Chemical structure of this compound is complex and different structures appears depending on the seaweed specie from which it is isolated (Zorofchian Moghadam et al., 2014). Actually, fucoidan has been found in all the brown seaweed examined until now (mainly in the orders Fucales and Laminariiales), but was not detected in green and red seaweed species analyzed (Gupta and Abu-Ghannam, 2011; Jiang et al., 2010). Several biological activities including antiproliferative, antiangiogenic, antioxidant, anti-inflammatory, antiviral, antilipidemic, anticoagulant and immunomodulatory have been, recently, attributed to the fucoidans (Cumashi et al., 2007; Elizondo-Gonzalez et al., 2012). Nowadays, some applications have been emerged and fucoidan is used as additive to drinks, health foods, and cosmetics (Kwak, 2014; Zorofchian Moghadam et al., 2014).

3. Anticancer activity of brown seaweed against breast cancer

Carcinogenesis is a multistep process characterized by several hallmarks such as sustentation of proliferative signaling, evasion of growth suppressors, resistance to cell death, activation of invasion and metastasis and induction of angiogenesis (Hanahan and Weinberg, 2011). The huge variety of molecular targets and mechanisms involved in the carcinogenesis opens a wide range of opportunities for the action of the natural anticancer agents. However, undesirable side effects (toxicity in normal cells) and drug-resistance is a very frequent and complex problem that is necessary to solve urgently. Alteration in cell cycle checkpoints, resistance to apoptosis, increase of DNA repair, scavenging enzymes, and drug efflux are the main pathways involved in drug resistance (Abu-Hammad and Zilhif, 2013; Shi et al., 2007; Teas et al., 2013; Tegze et al., 2012; Tsuru et al., 2003). In fact, compounds that may act in one or more of these pathways, without cytotoxic effects in normal cells, show a potential anticancer activity alone or in combination with other cytotoxic drugs.

Another important mechanism by which the compounds may act is through it antioxidant activity. Oxidative stress may act in cancer initiation, promotion and progression (Hussain et al., 2003). Therefore, antioxidant compounds can indirectly reduce cancer development. Numerous seaweed species have been reported to prevent oxidative damage by scavenging free radicals (Yuan and Walsh, 2006). However, brown seaweed have been indicated to contain higher antioxidant potential than red and green seaweed (Balboa et al., 2013a).

In vivo studies and in vitro examinations with cell lines of effects of crude extracts of brown seaweed collected from diverse marine

![Anticancer Activity in Breast Cancer](image)

**Fig. 2.** Molecular mechanisms and targets of phloroglucinol, fucoxanthin and fucoidan mediating the anticancer activity in breast cancer.
environments showed a promising anticancer potential (Yuan and Walsh, 2006; Zorofchian Moghadamtousi et al., 2014). Due to the high potentiality revealed by many brown seaweed several bioactive compounds have been isolated and identified (Zorofchian Moghadamtousi et al., 2014). The knowledge about the molecular mechanisms involved in the anticancer activity of phloroglucinol, fucoxanthin and fucoidan against breast cancer (Fig. 2) are in the beginning but reveal promising results.

3.1. Phloroglucinol

Phlorotannins such as phloroglucinol and its derivatives isolated from brown seaweed showed antioxidant activity acting as chemopreventive agent in the inhibition of carcinogenic process (Balboa et al., 2013a; Kim et al., 2009; Li et al., 2011; Wijesekara et al., 2010). The antioxidant activity seems to be related with free radical-scavenging and metal chelation properties. However, in breast cancer cells the majority of the noted effects of phloroglucinol are related with its cytotoxicity.

Dryofragin, a phloroglucinol derivative, isolated from Dryopteris fragrans (L.) Schott exhibited potential anticancer activity in human breast cancer cells. Zhang et al. (2012), showed that dryofragin inhibited the growth of MCF-7 cells inducing apoptosis through mitochondrion-dependent pathway with the involvement of reactive oxygen species (ROS) production. Another phloroglucinol derivative isolated from E. cava, dioxinodehydroeckol, has a potential inhibitory effect on proliferation of MCF-7 and MDA-MB231 cells. The antiproliferative effect of dioxinodehydroeckol was more effective in MCF-7 cells by induction of apoptosis, that was mechanistically confirmed to be made via up-regulation of p53, activation of Bax, inhibition of Bcl-2, increase in caspases 3 and 9 activity, and, at last, via cleavage of PARP (DNA repair Poly ADP ribose polymerase enzyme). It was also suggested that the inhibition of cell proliferation and induction of apoptosis by dioxinodehydroeckol in MCF-7 cells might be associated with down regulation of NF-κB family and NF-κB dependent pathway (Kong et al., 2009).

Metastatic spread of breast cancer cells is the main leading of death in breast cancer patients (Weigelt et al., 2005). On cancer metastasis, epithelial–mesenchymal cell transition (EMT) involves complex morphological and cellular changes that are regulated by a large number of molecular signaling pathways (Scheel and Weinberg, 2012). Recently, it was demonstrated that phloroglucinol suppresses metastatic ability of breast cancer cells in vitro through inhibition of EMT process. Phloroglucinol decreased the expression of SNAIL-related zinc-finger transcription factors through inhibition of PI3K/AKT and Ras/Raf-1/ERK signaling pathways in breast cancer cells. In the same study phloroglucinol also decreased primary tumor formation and inhibit EMT in vivo. A reduction of breast cancer infiltration in 3D-culture system was also reported (Kim et al., 2015).

Despite the few studies performed until now, phloroglucinol showed promising biological activities in breast cancer models that need to be explored in future research, with the aim to develop new therapeutic agent in breast cancer therapy.

3.2. Fucoxanthin

Attending to the mechanisms of anticancer activity of fucoxanthin, its antioxidant properties have an important role in cancer chemoprevention. The antioxidant action of fucoxanthin is attributed mainly to their ability to quench singlet oxygen and scavenge free radicals avoiding the harmful damage induced by oxidative stress (D’Orazio et al., 2012; Sachindra et al., 2007). Beside the antioxidant activity, some studies have reported a prooxidant effect of fucoxanthin on cancer cells, leading to increases of ROS. This could be a possible strategy to induce cell death in cancer cells (Kumar et al., 2013). However, other mechanisms have been described and are based on the regulatory effect of fucoxanthin on biomolecules related to cell death, cell cycle arrest and metastasis (Kumar et al., 2013; Miyashita et al., 2011). Studies have shown that fucoxanthin exhibits antiproliferative potential in different types of carcinomas including breast cancer (MCF-7) cells (Konishi et al., 2006; Kumar et al., 2013; Rengarajan et al., 2013). Apoptosis induction has been suggested one of the mechanisms by which fucoxanthin inhibit proliferation of cancer cells (Konishi et al., 2006; Kotake-Nara et al., 2005; Nakazawa et al., 2009; Peng et al., 2011). Rwigemera et al. showed that fucoidan and its main metabolite, fucoxanthinol, inhibited the viability of MCF-7 and MDA-MB-231 cells with induction of apoptosis. In MDA-MB-231 cells, anticancer effect of fucoxanthin and fucoxanthinol seems to be mediated by inhibition of NF-κB pathway (Rwigemera et al., 2014; Rwigemera et al., 2015).

Although the anticancer activity of fucoxanthin is reasonably known for several types of cancers, in breast cancer the data available are very limited. Consequently, further investigations are needed to assess the details of the effect and the underlying molecular mechanisms of fucoxanthin against breast cancer cells.

3.3. Fucoidan

Several studies show that fucoidan is an exceptional natural antioxidant and has great potential for preventing free radical-mediated diseases such as cancer (Kwak, 2014; Li et al., 2008; Mak et al., 2013). Anticancer effects of fucoidan in breast cancer cells have been reported both in vitro and in vivo studies, affecting several cell signaling pathways. Fucoidan isolated from Cladosiphon okamuranus inhibited the proliferation of MCF-7 cells in a time and dose dependent manner, and induced apoptosis through a caspase-8-dependent pathway, without any effect on the viability of normal human mammary epithelial cells (Yamasaki-Miyamoto et al., 2009).

Fucoidans from Saccharina japonica and Undaria pinnatifida inhibited both proliferation and colony formation in T-47D breast cancer cells (Vishchuk et al., 2011). Zhang et al. (2011), reported that fucoidan extract decreased cell proliferation and induced apoptosis in MCF-7 cells, through regulation of the Bcl-2 family proteins and depolarization of mitochondrial membranes with phosphorylation of JNK, p38 and extracellular signal-regulated kinase (ERK1/2). The involvement of MAP kinases, AKT signaling and inhibition of angiogenesis on the fucoidan-anticancer activity has been reported in other cancer cell lines (Aisa et al., 2005; Hyun et al., 2009; Koyanagi et al., 2003).

Xue et al. (2012), showed that crude fucoidan extracted from Fucus vesiculosus decreased proliferation of 4T1 breast cancer cells, without causing cytotoxic effects in normal cells. Decrease of cell proliferation was accomplished by apoptosis induction through mitochondrial pathway. Fucoidan was also able to decrease VEGF expression in 4T1 cells, showing antiangiogenic activity. It was also demonstrated that intraperitoneal injection of fucoidan extract in 4T1 xenograft female Balb/c mice, inhibited tumor growth, angiogenesis and suppressed lung metastasis of breast cancer. Beside inhibition of cell growth, increase of cell death, fucoidan also induced cell cycle arrest through down-regulation of Wnt/β-catenin pathway in breast cancer 4T1 cells in vitro and in vivo (Xue et al., 2013).

Fucoidan was able to block MDA-MB-231 breast carcinoma cells’ adhesion to platelets, contributing to tumor metastasis suppression (Cumashi et al., 2007). In those cells fucoidan also induced apoptosis trough activation of caspases and mitochondrial dysfunction, with cytochrome c release, and decreased of antiapoptotic proteins (Chen et al., 2014; Zhang et al., 2013a).
Hsu et al. (2013), showed that fucoidan inhibits migration and invasion during the EMT in MDA-MB-231 and 4T1 breast cancer cells through modulation of TGFβ/Smad-dependent signaling, in vitro and in vivo.

Attending the current findings fucoidan has potential as an anticancer agent against breast cancer. However further studies are needed to consolidate the data gained so far.

4. Anticancer activity of phloroglucinol, fucoxanthin and fucoidan in combination with conventional drugs against breast cancer

In the last decade several reports have been showed the additive or synergistic effects of natural compounds when in combination with conventional anticancer drugs (Fujiki and Suganuma, 2012; Kapadia et al., 2013; Wu et al., 2013). The promising results in this field showed that the application of combination approaches involving chemotherapeutic agents could improve drug absorption and activate different mechanisms enhancing the clinical response. Some marine compounds are able to enhance the antitumor activity of cytotoxic drugs both in vitro and in vivo (Alekseyenko et al., 2007; Eid et al., 2012; Kumar et al., 2013). An example is fucoxanthin that improved the chemotherapeutic effect of cisplatin in human hepatoma cells, through modulation of NFκB and DNA repair pathways (Liu et al., 2013). Recently was demonstrated that patients with colorectal cancer under chemotherapeutic treatment with oxaliplatin/5-fluorouracil/leucovorin or irinotecan/ fluorouracil/leucovorin may benefit from a co-treatment with fucoxanthin. Decrease of some adverse effects, such as general fatigue, and a tendency to increase survival rate was reported in the group of patients that received fucoidan (Ikeguchi et al., 2011).

In breast cancer, a recent report showed that fucoidan extract are able to enhanced the antiproliferative effect induced by cisplatin, tamoxifen and paclitaxel in MCF-7 and MDA-MB-231 cells through induction of apoptosis and cell cycle arrest. Regulation of Bcl-2 family proteins, ERK and AKT signaling, estrogen receptors and production of oxidative stress has been proposed as possible mechanisms (Zhang et al., 2013b).

Since phloroglucinol, fucoidan and fucoxanthin have anticancer activities against breast cancer, it combination with conventional anticancer drugs may reveal surprising data. However, information about the possible interaction between them in breast cancer is clearly missing and more data are urgently needed, viz. to back up clinical trials that allow bench-to-bed translation; recent benefits in other illnesses are encouraging (Boubaker et al., 2010; Fu et al., 2014).

5. Conclusion and future perspective

More effective drugs to treat breast cancer are necessary, and the development of natural therapeutics into potential anticancer agents are possible. Within the wide number and variety of bioactive compounds present in brown seaweed, phloroglucinol fucoxanthin and fucoidan are among the most abundant and with promising anticancer activity. Antioxidant activity, inhibition of cell proliferation, induction of cell death, and suppression both of metastasis and angiogenesis are some of the anticancer mechanisms those three compounds possess and that do modulate breast cancer. However further investigations are needed to appropriately clarify the in vitro and in vivo mechanisms and the molecular targets underlying their chemopreventive/chemotherapeutic effects.

Attending the so promising beneficial impacts of phloroglucinol, fucoxanthin and fucoidan as anticancer agents, it not only makes scientific sense but we defend that it is urgent to assess their effects in combination with conventional anticancer drugs.

Experimental and clinical data obtained with other types of cancer, show that the bioactive compounds present in seaweed are able to potentiate the activity of cytotoxic drugs. However, in breast cancer, the combination of bioactive compounds with anticancer drugs is until now few explored. Potentiation of anticancer activity with reduction of administered doses (decrease cases of resistance) and reduction of undesirable effects can contribute for the increase of life expectancy and improving life quality of breast cancer patients; a major contemporary concern (Hong-li et al., 2014). Hopes are emerging from the sea as well as in the past the life as emerged.

Conflict of interest
The authors declare that they have no conflict of interest.

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References


