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Boron Compounds in the Breast Cancer Cells Chemoprevention and Chemotherapy

Ion Romulus Scorei
Biochemistry Department, University of Craiova,
Craiova, Dolj,
Romania

1. Introduction

Various biological functions of Boron (B) compounds are known (Blevins & Lukaszewski, 1994; Tariq & Mott, 2007; Nielsen, 2008). Boron is found in nuts, vegetables, dried/fresh fruits and red wine (Brown & Shelp, 1997). Boron is also present in bacterial antibiotics, such as tartrolon, borophycin, boromycin and aplasmomycin (Rezanka & Sigler, 2008); in the bacterial quorum sensing molecule *auto-inducer AI-2* (Bemd et al., 2002); and in vibrioferrin, a B-containing siderophore produced by particular marine bacteria (Shady et al., 2007). In plants, the rigidity of the cell wall depends on the rhamnogalacturonan II complex (RG-II) formation, a pectic polysaccharide covalently linked by cis-diol bonds to apiosil residues of borate-esters (Ishii & Matsunaga, 1996, 2001). Several articles have provided information about transporters responsible for efficient B uptake by roots, xylem loading and B distribution among leaves. The transporters are required under B limitation for efficient acquisition and utilisation of B. Two types of transporters are involved in these processes: NIPs (nodulin-26-like intrinsic proteins) for boric acid channels and boron exporters encoded by BOR1 (Miwa & Fujiwara, 2010). The expression of the genes encoding these transporters has been shown to be finely regulated in the B availability response to ensure tissue B homeostasis. Furthermore, the tolerance of plants to the stress produced by low B or high B in the environment can be generated by altering the expression of these transporters (Tanaka & Fujiwara, 2007). All of these transporters are involved in boron transport regulation in plants. B is an essential element not only for vascular plants but also for diatoms, cyanobacteria and a number of marine algal flagellate species (Rezanka & Sigler, 2008). Recently, ATR1 has been found to be responsible for the high B tolerance in *S. Cerevisiae*. ATR1 encodes a multidrug resistance transporter and it is widely distributed in bacteria, archaea and lower eukaryotes (Miwa & Fujiwara, 2010). Animals such as zebra, fish, trout and frogs also require boron (Rowe & Eckert, 1999; Fort et al., 1999). Borate ions activate the mitogen-activated protein kinases pathway and stimulate the growth and the proliferation of human embryonic kidney 293 cells (Park et al., 2005). The B-transporter, NaBCl, controls plasma borate levels in human kidney cells (Park at al., 2004). The fact that B has such a broad range of physiological functions is not surprising. The electron structure of B and its position in the periodic table (adjacent to carbon) make B-containing molecules electrophilic with the trigonal

planar structures that are isoelectronic neutral relative to carbocations. The additional bond with B allows the formation of anionic tetravalent compounds with tetrahedral structures, which behave as nucleophiles (Petasis, 2007). Various types of B-containing molecules already exist and have been investigated as therapeutic agents. These molecules include B-containing analogues of natural biomolecules (Morin, 1994), the antibacterial and antimalarial agent diazaborine (Baldock et al., 1998), antibacterial oxazaborolidines (Jabbour et al., 2004; Jabbour et al., 2006), antibacterial diphenyl borinic esters (Benkovic et al., 2005), the antifungal agent benzoxaborole AN2690 (Baker et al., 2006) and a B-N bond containing an estrogen receptor modulator (Zhou et al., 2007). Except for the drug Bortezomib, the majority of B compounds currently used in cancer treatment are in the Neutron Capture Therapy (BNCT) class (Beddoe, 1997; Endo et al., 2003). The discovery of many B-containing molecules is predicted, and these molecules will be useful in applications involving cell surface signalling (Bolanos et al. 2004; Redondo-Nieto et al., 2008). The main objective of this review is to reveal other promising research directions for B-based chemicals in chemoprevention and chemotherapy, particularly in breast cancer.

2. Boron compounds in cancer prevention

2.1 Dietary boron and cancer risk

A diet with low B has been found to lead to a number of general health problems and to increase cancer risk. The most common symptoms of B deficiency include arthritis, memory loss, osteoporosis, degenerative and soft cartilage diseases, hormonal disequilibria and a drop in libido (Scorei & Popa, 2010). The daily uptake of B varies as a function of food selection, the use of some specific personal products and the water B content. Reported values for the overall B uptake vary as follows: 0.8-1.9 mg/day in the European Union, 1.7-7 mg/day in the United States, ~0.93 mg/day in Korea, 2.16-2.28 mg/day in Australia, 1.75-2.12 mg/day in Mexico and 1.8-1.95 mg/day in Kenya (Rainey & Nyquist, 1998). These dissimilarities may be correlated with regional differences in the abundance of high-energy food and in food products rich in fibres and plant proteins. The actual B requirements for the human body remain unclear. Thus, more knowledge about the biological functions of B and the regulation of its exchange is required (Nielsen, 2009). The B Tolerable Upper Intake Level (UL) for adults of ~18 years is ~20 mg B per day (Scorei & Rotaru, 2011).

2.1.1 Lung cancer

The mortality due to lung cancer has reached higher values for men than for women (Espey et al., 2007). A negative correlation has been found between the amount of B intake and the incidence of lung cancer, although the underlying mechanism remains unclear (Meacham et al., 2007). Experimental evidence has shown that nutrition with some B-compounds (such as boric acid, borax and calcium fructoborate) has had anti-oxidant or/and anti-inflammatory consequences (Nielsen, 2000; Hunt, 1998; Scorei et al., 2005). Correlations exist between some lung cancers and 17-beta-estradiol, and the treatment includes 17-beta-estradiol-based Hormone Replacement Therapy (HRT) (Schabath et al., 2004). Dietary supplementation with B has been shown to increase the concentration of 17-beta-estradiol (Wang et al., 2008), mimic the HRT effect and, in the case of postmenopausal women, it may be used to decrease the cancer risks associated with low estrogen levels (Devirian & Volpe, 2003). Low dietary B

(alone or together with HRT) has been correlated with an increase in lung cancer risk for women (Mahabir et al., 2008). The reduction of lung cancer risk may involve estrogen receptor binding substrates, other than estrogen, including carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs) from cigarette smoke condensate (Pike et al., 1999). Women with high dietary B intake and HRT users may present higher hormone levels that compete with cigarette smoke carcinogens for estrogen receptors. If this model is correct, increasing the B intake during HRT will also limit the carcinogenic potential of PAHs from cigarette smoke. Recently, the highest quartile of B intake has been confirmed to be associated with the lowest lung cancer risks for smokers, while the highest risk exists in smokers with low dietary B and no HRT (Mahabir et al., 2008).

2.1.2 Prostate cancer

Dietary B is inversely correlated with the occurrence of prostate cancer (Yan et al., 2004), even if the source of this correlation remains unclear. The prostate cancer risk was one third smaller for men ingesting more than 1.8 mg B per day from food, relative to only 0.9 mg B/day. A relatively high correlation (r = 0.63) was found between the B concentration from the subsurface water and the prostate cancer distribution in Texas (Barranco et al., 2007). A broader understanding of the cellular mechanisms that involve B have shown that boric acid (BA) inhibits prostate cancer cell growth by decreasing cyclin A-E expression, though B does not induce cell death (Barranco et al., 2009). Furthermore, cells treated with BA demonstrate diminished adhesion and migration, which indicates a low metastatic potential. B has been hypothesised to have effects on prostate cancers through its influence on steroid hormones (particularly androgens, which are involved in prostate carcinogenesis) (Gann et al., 1996). Three research directions have been followed to study the relationship between B and prostate cancer risk: steroid hormone regulation, anti-cancer metabolites and cell proliferation. Several potential BA binding sites may be involved in prostate cancer. For example, Prostate Serum Antigen (PSA), a serine protease, is a potential site for direct boration (Gallardo-Williams et al., 2003). Boric acid decreases the expression of five major cyclin proteins (A, B_1, C, D_1 and E), which have significant roles in the cell cycle (Barranco & Eckhert, 2006) and inhibit the release of Ca(II) stored by the NAD+cADPR system. This regulation of cyclins could explain the effects of B on prostate cancer cells. When B consumption was ~1.17 mg per day, no correlation with prostate cancer frequency was observed (Gonzalez et al., 2007).

2.1.3 Cervical cancer

Cervical cancer is the second most frequent cancer in women worldwide (Parkin et al., 1993). The cause of this discrepancy is still unclear and can involve a combination of environmental, genetic, social and infectious factors. For example, Human papillomavirus (HPV) is the primary cause of cervical cancer. HPV 16 and HPV 18 are responsible for ~95% of cervical cancers. Many other factors also correlate with the incidence of cervical cancer (Ursin et al., 1996; Ylitalo et al., 1999; Castellsague et al., 2002). According to one hypothesis, the low cervical cancer incidence in Turkey correlates with its B-enriched soil (Sayli et al., 2001; Simsek et al., 2003). Indeed, the ingestion of B via drinking water prevents cervical cancer risk (Korkmaz et al., 2007). This effect has been suggested to be due to the B interference chemistry in the life cycle of HPVs, but no correlation could be found regarding the incidence of oral cancers, which are also induced by HPVs. Serine protease inhibitors

have been found to reduce the immortalisation and transforming capacity of the HPV E7 oncogene (Stoppler et al., 1996). Because B exists in the human body mostly in the form of BA, which is an inhibitor of serine proteases, ingestion of high amounts of B through drinking water has been hypothesised as able to inhibit HPV transformation, thus reducing the incidence of cervical cancer (Korkmaz et al., 2007).

2.2 Dietary boron and breast cancer prevention

Today, breast cancer is the most common cancer type diagnosed in women, excluding non-melanoma skin cancers (Greenlee et al., 2000). Breast cancer is related to endogenous hormones. Many studies have linked breast cancer risk to the age of menarche, menopause and first pregnancy (Harris et al., 1992). Postmenopausal obesity has been observed to increase the risk (Stoll, 1998; Pujol et al., 1997), perhaps due to increased peripheral estrogen production. However, this relationship between weight and risk does not appear in premenopausal women (Kelsey, 1979). In fact, some studies have reported an inverse relationship between weight and risk at a younger age (Holmes et al., 1999). In Japan, breast cancer is a rare disease compared to the Western countries (Tominaga & Kuroishi, 1999). When Japanese women immigrated to the USA, they acquired the same risk for breast cancer as that in the general population of women in the USA (Probst-Hensch et al., 2000). This increased risk occurred due to environmental and dietary factors (Maskarinec et al., 2001; Probst-Hensch et al., 2000). Proliferative breast disease has been observed more frequently in women with a significant family history of breast cancer (Vogel, 2000). A number of environmental factors have also been linked to breast cancer risk. Exposure to ionising radiation, whether after a nuclear explosion or during medical procedures, has clearly been demonstrated to correlate with an increase in the risk of breast cancer (Spiegelman et al., 1994). The risk level varies with the age of the subject. The risk was observed to be lower for exposures in the case of women over 40 years. The role of diet in the aetiology of the breast cancer seems to be extremely important. This importance has been suggested by the international variation in breast cancer incidence rates and by the observation that national per capita fat consumption correlates with breast cancer incidence and mortality (Armstrong & Doll, 1975). However, prospective studies regarding diet and breast cancer risk have failed to identify a relationship between dietary fat intake and breast cancer incidence during 10 years of follow-up (Hunter & Willett, 1996). The absence of a link between dietary fat intake and cancer risk within the context of a Western diet has been confirmed by a pooled analysis of seven cohort studies involving 337,816 women. The analysis has demonstrated no risk differences between women with the lowest and those with the highest quintile of fat intake (Hunter et al., 1996). However, all of these studies have addressed fat intake during adult life and do not exclude the possibility that fat intake during childhood and adolescence could subsequently influence breast cancer risk. Strong evidence exists that supports an association between alcohol and breast cancer. A meta-analysis of 12 cases of control studies has demonstrated a relative risk (RR) of 1.4 for each 24 g of alcohol consumed daily (Longnecker et al., 1988). However, defining a relationship between the age at which alcohol consumption began and breast cancer risk is difficult.

2.2.1 Dietary boron intake, sex steroid hormones and breast cancer

Several reports have indicated that 17-beta-estradiol levels increase with dietary boron supplementation in human subjects (Nielsen et al., 1987; Naghii & Samman, 1997).

Therefore, dietary boron might mimic the actions of Hormone Replacement Therapy (HRT). After one week, supplementation of healthy males with 10 mg B/day resulted in a significant rise in the plasma free testosterone concentration, which is an observation based on recent clinical data (Naghii et al., 2010). According to this recent study, the free testosterone level increases and the estradiol level decreases after short-term boron consumption. Breast cancer patients appear to have relative sex steroid hormone imbalance, in favour of estrogens (McTiernan et al., 2003). High bio-available testosterone counteracts the proliferative effects of estrogens on the mammary tissues and exerts a protective role to the breast, inhibiting cancer development and/or tumour growth (Hofling et al., 2007). However, preclinical studies have suggested that testosterone serves as a natural, endogenous protector of the breast. Worldwide data from prospective studies regarding the connection between the endogenous sex hormones levels and breast cancer risk in postmenopausal women have also shown multiple and complex relationships. Nine prospective studies of women who had not taken exogenous sex hormones when samples from their blood were collected for the determination of hormone levels have shown that the breast cancer risk increases significantly with an increased concentration of all examined sex hormones: total estradiol, free estradiol, non-sex hormone binding globulin (SHBG)–bound estradiol, estrone, estrone sulphate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulphate and testosterone. High SHBG has been associated with a decrease in breast cancer risk (Dimitrakakis et al., 2010). Investigations regarding the association between premenopausal estrogen levels and breast cancer risk are complicated due to the cyclic estrogen variation during the menstrual cycle. The breast cancer risk among premenopausal women is directly related to the circulating levels of testosterone and androstenedione.

In conclusion, daily dietary B intake at a minimum of 10 mg of B per day decreases the estradiol level and increases the testosterone level (Naghii et al., 2010). This regulation assures a true hormone-dependent protection against breast cancer.

2.2.2 Boron, vitamin D and breast cancer

Vitamin D is a steroid hormone that is synthesised in human skin from 7-dehydrocholesterol in the presence of the UV light. Vitamin D is primarily metabolised in the liver and subsequently in the kidney in the form of calcitriol, the most biologically active metabolite of vitamin D (Zehnder et al., 2001; Tangpricha et al., 2001). In addition, epidemiologic, clinical and animal studies have demonstrated that vitamin D is important as a protective agent against the development of breast cancer (Buras et al., 1994; Mehta & Mehta, 2002). Boron has a role in energy substrate metabolism due to its involvement in vitamin D metabolism (Hegsted et al., 1991). Various boron-containing compounds have been discovered to be effective in transiently and acutely raising calcitriol levels to a significant degree in mammalian blood. Indeed, calcitriol levels could be increased almost 80% upon the oral administration of a single dose of a boron-containing complex (15-20 mg boron as calcium fructoborate per day) (Pietrzkowski, 2010). Calcitriol in turn controls calcium and phosphate homeostasis and is essential for the development and maintenance of healthy bones. Calcitriol, or 1,25-DihydroxyvitaminD_3, is the biologically active form of vitamin D and interacts with the Vitamin D Receptor (VDR). Calcitriol is a coordinate regulator of proliferation, differentiation and survival of breast cancer cell (Colston & Hansen, 2002). Therefore, vitamin D compounds that bind and activate VDRs have become

established therapeutic agents for breast cancer treatment. Various *in vitro* and *in vivo* studies have shown that vitamin D inhibits cell proliferation of a wide range of cell types, including carcinomas of the breast, prostate, colon, skin and brain, myeloid leukaemia cells and others (Mehta & Mehta, 2002; Ingraham et al., 2008). However, the processes mediating this inhibition have still not been entirely elucidated. Recently, vitamin D has been demonstrated to induce apoptosis and inhibit angiogenesis, tumour invasion and metastases. These preclinical data suggest that vitamin D (alone or in combination with other agents) has potential applications in cancer prevention and treatment. Low levels of plasma calcitriol have been associated with high rates of colorectal, breast, lung and prostate cancer incidence and mortality in men (Garland et al., 2006). The broad-spectrum anti-tumour effects of calcitriol and its analogues are mostly based on the inhibition of cancer cell proliferation and invasiveness, induction of differentiation and apoptosis and promotion of angiogenesis.

In a NHANES III (National Health and Nutrition Examination Survey III) cohort, Freedman has reported that women with serum calcitriol levels higher than 62 nmol/L present a 75% decrease in breast cancer mortality (Freedman et al., 2007). In two other studies, the authors have concluded that the breast cancer risk for women is 58% lower when vitamin D levels are higher than 95 nmol/L, in comparison with women with a calcitriol level lower than 37.5 nmol/L (Simard et al., 1991; Bemd & Chang, 2002; Gissel et al., 2008). In a dose-response meta-analysis, it has been reported that women with the highest calcitriol levels in their blood have a reduced breast cancer risk (Garland et al., 2006). In another study, 1760 women were divided into 5 groups, from the lowest to the highest calcitriol levels (Garland et al., 2007). A dose-response association was evident. The highest breast cancer rates were found in the group with the lowest calcitriol levels (less than 32 nmol/L). The cancer rates were the lowest in women with serum calcitriol levels higher than 130 nmol/L. If the serum calcitriol levels are high enough, they reduce the breast cancer risk by 35%. Thus, boron could become an effective preventive diet for breast cancer by its action in inhibiting calcitriol degradation (Miljkovic, 2004).

2.2.3 Boron, omega-3 fatty acids and breast cancer

Laboratory animals subjected to a diet rich in both omega-3 fatty acids and boron demonstrate a high bone mineral density and their bones become stronger compared to animals fed with other dietary fats and boron. These findings suggest that omega-3 fatty acids and boron can work together to support dense, strong bones (Nielsen & Penland, 2006). A diet rich in omega-3 α-linolenic acid promotes femur strength, especially when the dietary boron is adequate. In recent research studies, the bone health benefits of omega-3 fatty acids have been discovered to be greatly amplified when these essential fats are combined with the critical trace of mineral boron (Nielsen, 2008). Intriguing new research findings have suggested that bone-supporting effects of boron can be the greatest when omega-3 fatty acids are available. For instance, as mentioned earlier, a diet rich in both omega-3 fatty acids and boron give laboratory animals higher bone mineral density and stronger bones in comparison to animals that are fed other fats.

The association between ω-3 fatty acids and breast cancer risk has been examined in several studies (Rose & Connoly, 1993; Deckere, 1999; Saadatian et al., 2004). The results have demonstrated that this correlation varies according to the study design. A meta-analysis of biomarker studies based on three cohorts and seven case-control studies has found a

significant protective effect of total ω-3 PUFAs (Kim et al., 2009). At the same time, only an inverse association with a borderline significance for α-linolenic acid in case-control studies has been demonstrated (Fritsche & Johnston, 1990). However, according to a recent systematic review, only one study has shown a significantly increased breast cancer risk, three studies have presented a decreased risk and seven other studies have failed to demonstrate a significant relationship with ω-3 fatty acid intake (MacLean et al., 2006). In the UK, fish oil consumption has been associated with protection against breast carcinogenesis (Caygill et al., 1995; Caygill et al., 1996). A postmenopausal study, which took place in the USA, has found a significant inverse correlation between fish intake (canned, fried, fresh and shellfish) and breast cancer risk (Shannon et al., 2003). This investigation identified fish and fish ω-3 fatty acid intake as an important potential protective factor in the nutritional aetiology of breast cancer. Moreover, recent studies have shown that boron protects omega-3 fatty acids (Nielsen, 2004; Nielsen & Penland, 2006) and consequently, a diet rich in boron and omega-3 will ensure a low breast cancer risk for women, especially because boron stimulates calcitriol synthesis, an anti-tumour agent that has been extremely well studied during recent years.

3. Boron-mediated chemoprevention of breast cancer

Cancer chemoprevention uses natural, synthetic or biological chemical agents to reverse, suppress or prevent carcinogenic progression (Sporn & Suh, 2000). Epithelial carcinogenesis is a multi-step process in which an accumulation of genetic events within a single cell line leads to a progressively dysplastic cellular appearance, deregulated cell growth, and, finally, carcinoma. In fact, the initial proposed definition for chemoprevention strictly refers to cancer prevention with pharmacological agents that inhibit or reverse the carcinogenesis process. This concept differs from that of cancer prevention, which refers mostly to removal or avoidance of factors such as fat, tobacco or UV radiation (Malone et al., 1989). According to their mechanisms, chemopreventive agents are classified into two broad categories: effective compounds against complete carcinogens and effective compounds against tumour promoters. Some compounds belong to both categories. The inhibitors of carcinogen-induced tumours are further divided in three major groups according to their different mechanisms of action. The first group includes agents that interfere with the precursor compounds of metabolic reactions, which are converted into carcinogens. The second group comprises agents capable of preventing carcinogens by reaching or reacting with target sites. This mechanism is realised by scavenging the reactive form of carcinogens. The third group includes molecules that have an inhibitory action following the exposure to carcinogenic agents. For this reason, these molecules are called suppressing agents.

3.1 Boric acid

Boric acid (BA) is one of the most studied B-containing chemicals. BA has been demonstrated to control the proliferation of some cancer cell types (Barranco et al., 2009; Barranco & Eckhert, 2006; Acerbo &Miller, 2009; Scorei et al., 2008). BA is an inhibitor of peptidases, proteases, proteasomes, arginase, nitric oxide synthase and transpeptidases (Bradke et al., 2008; Hunt, 1998). Inhibition of serine protease and dehydrogenase activities can be explained by the capacity of BA to bind OH groups from NAD and serine (Gallardo-Williams et al., 2003). The Prostatic Serum Antigen (PSA) is a serine protease and a putative target for BA (Scorei & Popa, 2010). Based on the PSA inhibition, the use of BA in the

chemical therapy of prostate carcinoma has been proposed (Gallardo-Williams et al., 2003). BA inhibitory effects have also been found in androgen-independent cell lines (DU-145 and PC- 3l), suggesting that other (serine protease-independent) mechanisms could also exist (Barranco & Eckhert, 2006). BA inhibits the cell cycle control and proliferation of DU-145, acting against the agonist-stimulated release of Ca^{2+} from ryanodine receptor sensitive cell stores (Henderson et al., 2009). In the case of melanoma cells, BA slows down the proliferation, possibly by inhibiting the second step of pre-mRNA splicing (Shomron & Ast, 2003). A high dose of BA (12.5–50 mM) slows cell replication and induces apoptosis in both melanoma cells and MDA231 breast cancer cells (Acerbo & Miller, 2009; Scorei et al., 2008). Thus, the inhibition of cancer cells by BA involves a diversity of cellular targets, such as direct enzymatic inhibition, apoptosis, receptor binding and mRNA splicing.
Recently, 1 mM of BA has been experimentally demonstrated to inhibit the ZR-75-1 breast cancer cell line, but not the MCF-7 cell line (Meacham et al., 2010; Elegbede, 2007). The lack of BA-mediated inhibition of MCF-7 cellular growth could be due to the presence of the "sodium-boron co-transporter (NaBC1)". This co-transporter exists on the cell surface and can pump out boron molecules from the cell in exchange for Na^+ ions. This co-transporter is not present in ZR-75-1 cells. ZR-75-1 is a non-metastatic epithelial breast cancer cell line, which is estrogen receptor– and progesterone receptor–positive. MCF-7 is metastatic epithelial cell lines of breast cancer. These cells are positive for estrogen receptor and progesterone receptor. If BA becomes an anti-cancer agent for breast cancer, these data will encourage women with increased cancer risk factors to raise their boron intake to reduce their chance of developing this disease.

3.2 Calcium fructoborate

Calcium fructoborate (CF) is a natural product that is extracted from plants, but it can also be produced by chemical synthesis (Scorei & Popa, 2010). CF is efficient in the prevention and treatment (as adjuvant) of osteoporosis and osteoarthritis (Peng et al., 2000; Miljkovic et al., 2009; Scorei & Rotaru, 2011). In addition, CF has shown inhibitory effects on MDA-MB-231 breast cancer cells (Scorei et al., 2008; Scorei & Rotaru, 2011). CF most likely enters the cell through a co-transport mechanism via a sugar transporter (Miljkovic et al., 2009). MBA-MD-231 is a metastatic cancer cell line and is negative for expression of estrogen receptor. Inside cells, CF acts as an antioxidant and induces the over-expression of apoptosis-related proteins and eventually apoptosis. In our recent study, we have demonstrated that CF and BA inhibit the proliferation of MDA-MB-231 breast cancer cells in a dose-dependent manner (Scorei et al., 2008). As revealed by different experiments (TUNEL, Bcl-2 and pro-caspase-3 protein expression and cytochrome c caspase-3 activities), the anti-proliferative effect of CF in MDA-MB-231 breast cancer cells appeared to be mediated by the induction of apoptosis. On the other hand, CF raises the calcitriol level in blood (Pietrzkowski, 2010), which induces apoptosis and inhibits angiogenesis, tumour invasion and metastasis of breast cancer cells.

3.3 Boronic acid and its esters

From the structural point of view, boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent (i.e., a C–B bond) and two hydroxyl groups to fill the remaining valences on the boron atom. Boronic acids are potent and selective inhibitors of cancer cell migration and viability. One potential mechanism of action is the inhibition of proteases. Due to the easy interconversion of boronic acids between the neutral

sp^2 (trigonal planar substituted) and the anionic sp^3 (tetrahedral substituted) hybridisation states, the B-OH unit replaces the C=O bond at a site where an acyl group transfer takes place (Groziak, 2001). Phenylboronic acid (PBA) and diphenylboronic esters (DPBE) are the most efficient types of boronic acid derivatives that act as serine protease inhibitors (Yang et al., 2003). PBA is more efficient than BA and decreases cancer cell viability in eight days. Non-tumorigenic cells are at least five times less sensitive to PBA at the effective dose for cancer cells. These data suggest that PBA could be a promising cancer treatment and could possibly be used prophylactically. Phenylboronic acid has more favourable *in vitro* properties than do other compounds (e.g., migrastatin and carboxyamido-triazole). PBA shows a selective inhibition of breast and prostate cancer migration *in vivo* and of tumour metastasis in mice (Bradke et al., 2008). The properties that phenylboronic acid shares with other anti-cancer drugs highlight the fact that it is more effective than BA for cancer chemoprevention (Groziak, 2001; Yang et al., 2003).

4. Boron chemotherapy of breast cancer

4.1 Bortezomib

The drug Bortezomib (PS-341) (Teicher et al., 1999) is a boronic acid derivative and a proteasome inhibitor, which is a novel target in cancer therapy. This compound disrupts cell cycle regulation and induces apoptosis. Strong cytotoxic effects of PS-341 have been seen in prostate cancer cells and MCF-7 and EMT-6 breast carcinoma cells. In cell cultures, Bortezomib induces apoptosis in both haematologic and solid tumour malignancies, including myeloma, mantle cell lymphoma, cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, breast cancer, and head and neck cancers (Palumbo et al., 2008; Adams et al., 1999; Boccadoro et al., 2005; MacLaren et al., 2001). A good correlation has been observed between the Bortezomib dose, proteasome inhibition and positive modulation of serum PSA. Bortezomib has been approved by the US Food and Drug Administration for the treatment of chemorefractory multiple myeloma patients (Kane et al., 2003) and for some forms of non-Hodgkin's lymphoma (Goy et al., 2005). This inhibitor is still in clinical studies for multiple tumour types, including breast cancer (Boccadoro et al., 2005; Dees et al., 2004; Cardoso et al., 2004; Codony-Servat, 2006). In a phase II trial, the Bortezomib efficacy in patients with metastatic breast cancer was evaluated (Albenell et al., 2003). Although Bortezomib inhibits proteasome activity and reduces the circulating levels of IL6, these biological effects have not been associated with a meaningful clinical activity; no objective clinical response has been observed. Therefore, we do not recommend further investigations for Bortezomib as a single agent in the treatment of metastatic breast cancer (Yang et al., 2006). Until now, clinical experiments with Bortezomib have demonstrated only a limited activity against solid tumours when it is used as a single agent. However, Bortezomib could have a significant anti-tumour activity when it is used in combination with other active conventional agents (Agyin et al., 2009). Numerous trials using Bortezomib combination regimens are currently pending. Regarding breast cancer, the potential efficacy of Bortezomib with taxanes and anthracyclines is of particular interest. In a recent phase I trial that used Bortezomib together with docetaxel in anthracycline-pretreated advanced breast cancer, six of nine patients achieved partial response (Yang et al., 2006). *In vitro* and *in vivo* (murine xenograft) studies have revealed that Bortezomib is active against a variety of malignancies, including haematologic malignancies and solid tumours (i.e., breast, prostate, lung, pancreas, colon, ovarian, and head and neck cancers). Bortezomib has demonstrated

its activity as a single agent and in combination with several other cytotoxic agents, such as 5-fluorouracil, irinotecan, gemcitabine, doxorubicin and docetaxel, and with radiation, enhancing both chemotherapy- and radiation therapy (RT)-induced apoptosis. Bortezomib has also shown activity in some cell lines resistant to standard therapies. Bortezomib has been demonstrated to decrease the survival of cultured MCF-7 cells derived from human breast cancer and of EMT-6 parent mouse mammary carcinoma xenograft tumours in a dose-dependent manner (Teicher et al., 1999). In addition, combinations of Bortezomib with anthracyclines have been investigated, proving the prominent role of these agents in breast cancer therapy. Using a BT-474–based xenograft model of human breast cancer, the researchers found that the combination of Bortezomib with liposomal doxorubicin enhances anti-tumour efficacy and increases apoptosis, compared with the results obtained using each agent alone (Orlowski & Dees, 2003). Recently, a new proteasome inhibitor has been designed and synthesised; this compound, named BU-32, is a bisdipeptidyl boronic acid, a Bortezomib analogue, that contains an additional dipeptide boronic acid moiety on the pyrazine ring to potentially achieve a stronger binding affinity and an increased potency (Agyin et al., 2009). Divalent proteasome inhibitors, either hetero-bivalent or homo-bivalent, have been reported to increase the potency of inhibition by two orders of magnitude compared to the monovalent analogues, although a linker of 18 to 22 carbon atoms typically separates the active moieties in these compounds. A novel diboronated Bortezomib analogue, named BU-32 (NSC D750499-S), has been shown to be a potent and selective inhibitor of the chymotrypsin-like activity of the 20S proteasome. This compound has *in vitro* anti-tumour activity against different breast cancer cells and *in vivo* efficacy in mouse xenograft and metastasis models.

Paclitaxel (PAC), an anticancer drug, is used for the treatment of breast, ovarian, lung and head and neck cancer (Von Hoff, 1997; Rowinsky, 1997). However, this drug is known to cause adverse effects in different organs, such as heart and brain (Lachkar et al., 2006). Recently, results have clearly indicated that boron (as BA) supplementation to lymphocyte cultures ameliorates PAC-induced DNA damage (Turkez et al., 2010). BA plays a similar role in cancer patients after chemotherapy. However, specific protective agents for chemotherapy induce adverse effects after PAC or treatment with other anti-cancer drugs, although they should not interfere with the anti-tumour activity of the drugs (Pisano et al., 2003). The *in vivo* BA and PAC interactions are still unknown. At this point, further *in vivo* investigations are necessary to justify boron daily intake to minimise the adverse effects of anti-cancer drugs.

5. Mechanisms involving the activity of Boron compounds on cancer cells

5.1 Boron cross-talk with calcitriol

Assuming that boron and vitamin D are linked in a metabolic pathway, how does boron increase calcitriol levels? It seems unlikely that boron status would influence endogenous cholecalciferol synthesis, which is a nonenzymatic dermal reaction in which 7-dehydrocholesterol, an intermediate in cholesterol synthesis, is cleaved by ultraviolet light and then undergoes a spontaneous rearrangement. On the contrary, it seems likely that boron either up-regulates the 25-hydroxylation step or suppresses the major pathway of 25-OH-D catabolism, 24-hydroxylation (Miljkovic et al., 2004), giving the hypothesis that boron acts to suppress the latter reaction. Boron readily forms covalent complexes with cis-vicinal dihydroxy compounds. Thus, it is conceivable that boron can form such a complex with

24,25-dihydroxyvitamin D, the final product of the 25-OH-D reaction with 24-hydroxylase. Either this postulated complex acts as a competitive inhibitor for the 24-hydroxylase reaction, or, alternatively, acts to down-regulate the expression of this enzyme. Another possibility is that boron is a direct enzyme inhibitor at very modest concentrations. Indeed, boron can inhibit numerous enzymes, usually at supraphysiological concentrations (Hunt, 1994). Testing these hypotheses *in vitro* are mandatory, using hepatocytes or other cells capable of expressing the 24-hydroxylase activity. Clinically, the testable implication of this hypothesis is that boron supplementation should increase 25-OH-D serum levels, while 24,25-dihydroxyvitamin D serum levels remain constant or decline. This implication would strengthen the interesting possibility by which boron is a potent inhibitor for a range of microsomal enzymes, which catalyse the insertion of the hydroxyl group vicinal to the existing hydroxyl groups in steroids; specific examples of such enzymes are 24-hydroxylase and the estradiol hydroxylases (Miljkovic et al., 2004). Epidemiological studies have shown an inverse relationship between exposure to solar radiation and high breast cancer incidence and mortality (Garland et al., 1990; John et al., 1999). Another plausible link between 1,25-$(OH)_2D_3$ and breast cancer has been uncovered by the observation that the 20q13.2 chromosomal region, which contains 24-hydroxylase (CYP24), is amplified in breast cancer. Because 24-hydroxylase is involved in the degradation of 1,25-$(OH)_2D_3$, its amplification may lead to a decrease in 1,25-$(OH)_2D_3$ serum levels, thus providing a conducive microenvironment for cell growth in the absence of vitamin D-mediated growth control (Guryev et al., 2003). Furthermore, 1,25-$(OH)_2D_3$ serum levels have been found to be reduced to a greater extent in advanced bone metastatic breast cancer patients than in early stage patients (Mawer et al., 1997). The VDR is expressed in most breast cancer cell lines, carcinogen-induced rat mammary tumours, normal breast tissues and primary breast cancer tumours. Furthermore, increased RXR and VDR protein levels have been found in breast cancer tissues, compared with levels in normal breast tissues (Bortman et al., 2002; Friedrich et al., 2002). Several studies have demonstrated that a high proportion of breast cancer biopsy specimens contain vitamin D receptors (VDR) (Freake et al., 1984; Eisman et al., 1986; Berger et al., 1987). Moreover, an association between VDR levels and prognosis appears to exist; tumour receptor status has been positively related to disease-free survival (Colston et al., 1989; Berger et al., 1991).

Several studies have indicated that the activation of the cell death pathway is an important aspect of the anti-tumour effects of vitamin D analogues in breast cancer cells. Further characterisations of the apoptosis-related genes, which are regulated directly or indirectly by vitamin D derivatives, will provide the basis for the design of new compounds able to target these pathways in breast cancer cells. Understanding how the apoptotic pathway, mediated by the vitamin D, can modulate or overlap with more-established pathways leading to cell death is likely to provide clinically useful information. When biologically active vitamin D is needed, 25(OH)D in the kidney is enzymatically converted to its active form, 1,25$(OH)_2D_3$ (calcitriol). This conversion is mediated by the 25(OH) vitamin D 1α-hydroxylase, a cytochrome P450 protein, and 1,25$(OH)_2D_3$ is then conducted to the tissues. The actions of calcitriol in calcium homeostasis control of cell growth and differentiation, cell adhesion and apoptosis (controlled cell death) are mediated by its interaction with the VDR, which is a member of the nuclear receptor super-family (Thorne & Campbel, 2008).

In a recent study (Liu et al., 2006), it was reported that one of the first observed responses upon infection of human monocytes with tuberculosis (*M. tuberculosis*) is the activation of

the cytochrome P450 enzyme encoded by the gene *Cyp27B1,* which converts vitamin D to its active form. When calcitriol is available for the cell, it is able to synthesise cathelicidin, an antimicrobial peptide that can destroy the tuberculosis bacteria. When calcitriol is not available, cathelicidin cannot be synthesised and the defence mechanism fails. The protective effects of calcitriol against the development of cancer are mainly due to its role in regulating the cell cycle (Gombart et al., 2005). Calcitriol and functional VDR are required for normal control of the cell cycle. Normal cell growth is controlled by regulating the levels and activity of cyclins and their dependent kinases. Calcitriol and boron affect the cyclin pathways by regulating gene expression of the proteins p27 and p21; the consequence of this regulation is inhibition of the cyclin dependent kinases (CDKs). Calcitriol and its active complexes interact with cyclin D and have a protective effect by blocking cell proliferation (Holick, 2007; Ingraham et al., 2008).

5.2 Boron and proteasome inhibition

The proteasome inhibitor, Bortezomib, exhibits anti-proliferative, pro-apoptotic, anti-angiogenic and anti-tumour activities in several cancer models (Cardoso et al., 2004). The mechanism of action of Bortezomib involves the stabilisation of NF-κB, p21, p27, p53, Bid and Bax, the inhibition of caveolin-1 activation, the activation of JNK and the endoplasmic reticulum stress response (Boccadoro et al., 2005). These preclinical evaluations have revealed that Bortezomib is well tolerated at doses that demonstrate an anti-tumour activity in xenograft models of multiple myeloma, adult T-cell leukaemia, lung, breast, prostate, pancreas, head and neck, colon cancers and melanoma (Yang et al., 2003). The proteasome is an adenosine triphosphate (ATP)–dependent multi-catalytic protease that is present in the cytoplasm and the nucleus of all eukaryotic cells, from those in yeast to those in humans. The proteasome represents approximately 1% of the cellular proteins and is responsible for the non-lysosomal degradation of most intracellular proteins. The 26S proteasome consists of two functional entities: the 20S core catalytic complex and the 19S regulatory subunits. The proteasome has three catalytic activity types: chymotryptic-like, tryptic-like and caspase-like or postglutamyl cleavage activity. The boronic acid group forms a complex with the threonine hydroxyl group in the chymotrypsin-like active site and acts as a reversible inhibitor of the chymotryptic-like activity of the proteasome, which is sufficient to inhibit proteolysis (Boccadoro et al., 2005). In addition to the removal of damaged or unnecessary proteins, proteasome-mediated proteolysis is also an important mechanism for regulating the levels of some key regulatory proteins and their inhibitors. This regulation is crucial for controlling many cellular processes, including the activation of transcription factors, cell cycle progression, angiogenesis, cell adhesion, cytokine production and apoptosis. Many processes that rely on proteasome function contribute to the growth and survival of cancer cells. Thus, the critical role of the ubiquitin–proteasome pathway has led to the investigation of proteasome inhibition as a potential anti-cancer therapy (D'Alessandro et al., 2009). In cancer, the ubiquitin–proteasome pathway plays a number of important roles, including the regulation of tumour growth through multiple targets influencing cell cycle progression and apoptosis, cell adhesion, invasion and metastasis. The ubiquitin–proteasome pathway is also required for transcriptional regulation. Nuclear factor–κB (NF-κB) is a critical transcription factor involved in immune responses and cellular growth. Constitutive activation of NF-κB has been shown to be involved in the development of many human malignancies, including breast cancer (Cardoso et al., 2004).

NF-κB activation is regulated by the proteasome-mediated degradation of the IκB inhibitor protein. After IκB degradation, NF-κB moves to the nucleus and regulates genes encoding cytokine-like tumour necrosis factor (TNF), interleukin (IL)–1, IL-2, and IL-630, pro-inflammatory enzymes (nitric oxide synthase, cyclooxygenase-2), chemotactic factors (IL-8 and the monocyte chemoattractant protein–1) and cell adhesion molecules, such as E-selectin, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which are involved in tumour metastasis and angiogenesis (Boccadoro et al., 2005). NF-κB also regulates genes involved in the expression of anti-apoptotic proteins, such as members of the Bcl-2 and inhibitors of apoptosis families, which mediate resistance to chemotherapy and radiation therapy (RT) (Dong et al., 2002). Malignancies with high-activated NF-κB levels, such as breast cancer, should be sensitive to the interruption of this pathway. The level of NF-κB in tumour cells is high in the estrogen receptor (ER)–negative human breast cancers. Inhibition of NF-κB activation has been suggested to be a potential therapeutic approach in such tumours (Ling et al., 2003). The ubiquitin–proteasome pathway is also involved in ER turnover and in the regulation of growth factor receptors such as HER2/*neu* and EGFR (Tikhomirov et al., 2000; Mimnaugh et al., 1996; Magnifico et al., 1998) and oncoproteins, such as c-fos/c-jun, c-myc and N-myc. Although proteasome inhibition stabilises or increases the levels of these growth factors, preclinical studies have demonstrated that this stabilisation does not lead to activation of proliferation or increases in tumour growth.

6. Conclusion

Many scientific data exist that have shown that boron is an essential microelement in animal cells. With the knowledge that borate linkages function in cell-to-cell adhesion, it has been hypothesised that boronates target structural glycoproteins located along the cytoskeleton-plasma membrane-cell wall assembly. The latter are normally cross-linked by boron, and results confirm that boronates can indeed disrupt a boron-glycoprotein linkage. Therefore, any biological function of boron represents the result of its role as a cross-linking molecule.
Deficiency of boron in the diet has been linked to several pathological conditions, including some forms of cancer, osteoporosis and osteoarthritis.
Breast cancer affects many women all over the world and has a favourable prognosis when it is discovered in time (in its initial phase). Diets rich in boron could significantly reduce some cancer types, especially breast, prostate, lung and cervical forms of cancer. Discovering the role of boron in animal cell metabolism will have a great significance in the "war" against cancer. Establishing boron as an anti-cancer agent in breast cancer will encourage women with increased risk factors for this disease. Thus, these women will increase their intake of boron-rich food (i.e., avocado, broccoli, raisins and nuts) and dietary boron supplements to reduce their chance of developing this disease.
The present paper highlights the role of boron in the prevention, chemoprevention and chemotherapy of some forms of cancer, including breast cancer.
The major elements in breast cancer prevention, chemoprevention and chemotherapy with boron include:

1. for prevention, keep a diet rich in boron (around 20 mg per day) and an adequate 4:1 balance between omega-6 and omega-3 in nutrition;
2. in chemoprevention, BA and CF are the main "fighters" against breast cancer. Based on experimental evidence, BA induces apoptosis in both melanoma cells and MDA231

breast cancer cells and inhibits growth of breast cancer cell lines, like ZR-75-1 cells. CF has shown inhibitory effects on MDA-MB-231 breast cancer cells. In addition, it raises the calcitriol level in blood, thus increasing the level of protection against the development of breast cancer;

3. in chemotherapy, Bortezomib is a novel target in cancer therapy, being approved by the US Food and Drug Administration. It exhibits anti-proliferative, pro-apoptotic, anti-angiogenic and anti-tumour activities in several cancer models, including breast cancer.

In conclusion, even though the actual B requirements for the human body remain unclear and further researches are necessary, the amount of B in prevention and chemoprevention of breast cancer up to the 'Tolerable Upper Intake Level' (~ 20 mg B per day) is probable the adequate amount of boron in the body that might diminish the incidence of some forms of cancer, including breast cancer. However, it is compulsory to discover and develop new boron-containing compounds with anti-tumour activity.

7. References

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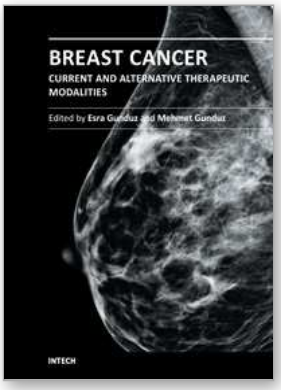

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Cancer is the leading cause of death in most countries and its consequences result in huge economic, social and psychological burden. Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death among females. In this book, we discussed various therapeutic modalities from signaling pathways through various anti-tumor compounds as well as herbal medicine for this deadly cancer. We hope that this book will contribute to the development of novel diagnostic as well as therapeutic approaches.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821