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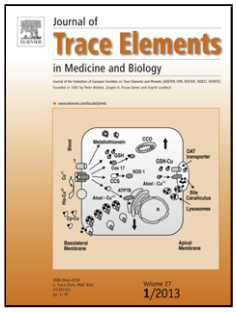

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Effects of Boron-Containing Compounds on Cardiovascular Disease Risk Factors – A Review

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Short title: Boron On Heart Disease Risk Factors

ABSTRACT

Boron is considered to be a biological trace element but there is substantial and growing support for it to be classified as an essential nutrient for animals and humans, depending on its speciation. Boron-containing compounds have been reported to play an important role in biological systems. Although the exact biochemical functions of boron-containing compounds have not yet been fully elucidated, previous studies suggest an active involvement of these molecules in the mediation of inflammation and oxidative stress. Chronic inflammation and oxidative stress are known to amplify the effects of the main cardiovascular risk factors: smoking, diet, obesity, arterial hypertension, dyslipidemia, type 2 diabetes (as modifiable risk factors), and hyperhomocysteinemia and age (as independent risk factors). However, the role of boron-containing compounds in cardiovascular systems and disease prevention has yet to be established.

This paper is a review of boron-containing compounds' existence in nature and their possible functions in living organisms, with a special focus on certain cardiovascular risk factors that may be diminished by intake of these compounds, leading to a reduction of cardiovascular morbidity and/or mortality.

Keywords: boron-containing compounds; inflammation; stress-oxidative; cardiovascular risk factors; speciation; essentiality.

1. INTRODUCTION

It has been hypothesized that boron (B) is an essential element for the origin and evolution of life on Earth [1–5]. Similar to other elements, however, boron should not be considered to act on its own but, rather, should be more accurately viewed as a contributory participant to certain bioactivities relative to its inclusion and chemical positioning within various molecules. After carbon, boron (B) has the most interesting speciation of any bioelement [6], being extremely widespread in the three kingdoms of life (Archaea, Bacteria and Eucaria) [6-9]. Boron's organic speciation results from the biochemical evolution of the inorganic boron species [2,4,7]. The involvement of boron's biochemical speciation is crucial for its essentiality in plants [8,9] and more recently, in animals [10–15]. The boron organic speciation is also essential for the human health [16–19], being involved in the cellular metabolism [11,12,20,21]. Within the 3 kingdoms of life there are numerous active natural organic boron-containing compounds (BCCs), meaning esters of boric acid/borates presented as *cis*-diol biological molecules, such as: plant-based organic BCCs, a few polyketide antibiotics (borophycin, boromycin, aplasmomycin, tartrolon B, C, and E), boron siderophore complexes (of vibrioferrin, rhizoferrin, petrobactin, aerobactin) and the bacteria signaling molecule AI-2 (furanosyl borate diester) [22–26] Out of all these, plant-based organic BCCs, such as sugars and polyalcohol borate esters (fructose borate and glucose borate esters, *bis*-sucrose borate esters, sorbitol borate esters, mannitol borate esters), pectic polysaccharide borate esters (rhamnogalacturonan II – RG-II), organic acid-borate esters (malic acid neutral borate ester, mono-malic acid borate ester, bis-malic acid borate ester), aminoacid-borate esters (bis-N-acetyl-serine borate ester), are very important in the animal/human nutrition [14].

Hence, our discussion will be involved less about the arguably inaccurate terminology "forms of boron" and will be focused more on the "boron-containing compounds". Boric acid (BA)/borates (BX) are inorganic BCCs found in soils and employed by plants and bacteria for the manufacture of all known B organic natural compounds [15–17]. In humans, the natural organic BCCs can be used in cell metabolism during which they are at least partially transformed into BA that will subsequently be eliminated as waste [27]. It is important to point out that inorganic BCCs have distinctly different chemical and biochemical properties as compared to the natural organic BCCs [28–30]. The biochemical activities of the natural organic BCCs are especially differentiated depending upon the various organic ligands involved, as well as the binding constant of B relative to any specific molecule [29,31,32].

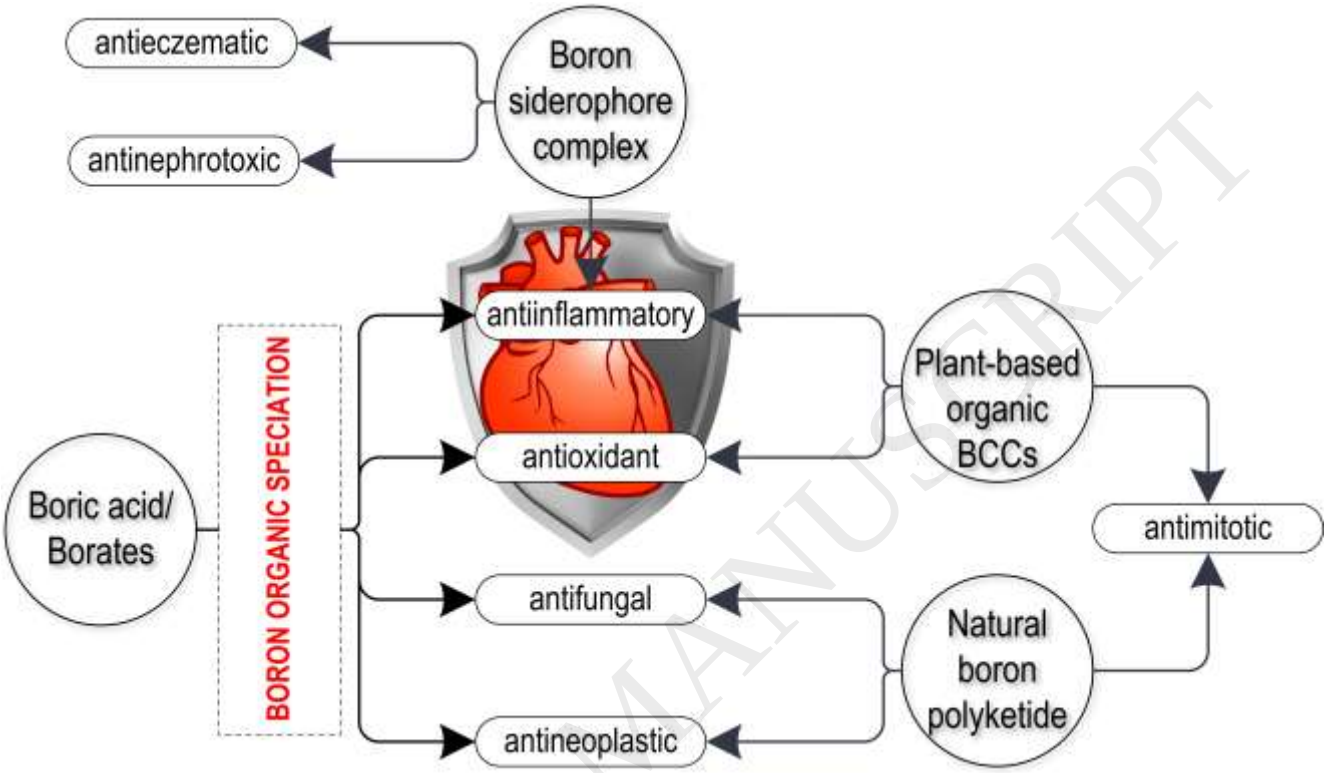
Currently the role of BCCs in cellular enzymatic and non-enzymatic metabolism is not precisely known, although several hypotheses are being tested. These hypotheses are based on the interaction between BCCs and the ribose-containing biomolecules (NAD^+, SAM, riboflavin, adenosine, diadenosine phosphates, cyclic ADP-ribose) [33], or proteins (cytokines, enzymes, membrane receptors) [12,34].

The strength of such interactions is determined by the various chemical structures of specific types of BCCs. Different BCCs, as distinct entities, may elicit different bioactivities and potencies (**Figure 1**). This is an important distinction that should be considered in order to avoid a generalized view that all boron-containing compounds are equally potent, or exert the same or similar bioactivities, related to modulation of enzymatic activity or/and interactions with the proteins or ribose-containing molecules mentioned above. Interestingly, several types of cytokines and enzymes contribute to the processes of development of cardiovascular malfunctions. All of these biomolecules are involved in certain chronic inflammations and oxidative imbalances, and said inflammations and imbalances are important pathologies triggered by the main cardiovascular risk factors [35], although the role of inflammation in the development of heart diseases has been recently emphasized [36,37].

It has been known for a long time that B deficiency in soils, leads to depletion of BCCs in fruits and vegetables in the food supply, was correlated with a high incidence of arthritis [38–40], an inflammatory disease also related to cardiovascular health [41,42]. The term "cardioprotection" embraces all of the ways in which the cardiovascular health may be preserved. Perhaps nutrition is the most important of these [43]. The everyday Mediterranean diet, including staple foods rich in BCCs, ensures a total BCC intake that delivers more than 13 mg B/day/person [44], although as little as 1 mg B/day/person is currently claimed to provide health benefits [12]. We again hypothesize here that the cardiovascular protection from the Mediterranean diets may be driven more by the types and varieties of BCCs providing specific biochemical functions related to cardiovascular health rather than being due to the simple total content of elemental boron.

Our review aims to suggest the importance of BCCs-based nutrition as a possible means to better ensure cardiovascular protection and to provide science-based evidence in support of the hypothesis that BCCs' cellular mechanisms may diminish the effects of risk factors and could in fact reduce cardiovascular morbidity and/or mortality.

Figure 1. Confirmed biological activities of the natural (inorganic and organic) boron containing compounds.



2. THE MECHANISM OF ACTION OF BORON-CONTAINING COMPOUNDS

2.1. Cellular transport mechanisms

Until recently, conventional thought held that in humans all the BCCs are absorbed and then rapidly eliminated through urine, being present mostly as boric acid in biofluids and tissues. A new school of thought, however, suggests that natural BCCs from dietary sources (fruits, legumes, leafy vegetables and nuts) may be absorbed differently, and may be present in body tissues and fluids as borate ester anions [25]. In plants, B transport is accomplished by passive diffusion across membranes, influx by channel-mediated facilitated diffusion (NIPs protein) and efflux by energy-dependent active transport (BORs protein) [45,46]. To date, regarding animals, no specific boron transporter has been definitively identified, although such a transporter was previously claimed [47,48]. Later, the previously claimed boron transporter (NaBC1) was shown to actually transport NH_3 and not B [49]. There is a high probability that BCCs' transportation through the cell membrane may be accomplished by free diffusion, and for boric acid by an aquaporin-like protein transporter [50–52]. However, as of now, the actual BA and organic natural BCCs transportation mechanisms in animal and human cells are still undiscovered [53]. Fructoborates and glucoborates (FGBs), unique plant organic natural BCC complexes, may be transported via active sugar transporters since these transporters have decreased the permeability relative to unchelated borate [11,54]. However, the question of whether FGBs are bioavailable as intact molecules or in parts, (e.g. whether as sugar-borate, or boric acid and sugar) is to date unanswered.

2.2. BCCs catalyzed CO_2 hydration

Boron is a contributor to the buffer capacity of the ocean [55], and there are some similarities between ocean alkalinity, cellular evolution and the emergence of life on earth [7,56]. The CO_2/HCO_3^- equilibrium is the most important pH buffering system of our bodies [57]. Bicarbonate (HCO_3^-) has a central position in mammalian physiology [58]. The ability of boron compounds to stimulate the reactive absorption of CO_2 into aqueous media is acknowledged. Several studies

recorded that BCCs are catalysts for the CO_2 hydration ensuring the bicarbonate ion development. The process has been proposed to be similar to the enzymatic carbonic anhydrase action [59,60]. More importantly, the buffer capacity of the borate anion coupling with cis-diol esters is higher than the buffer capacity of the bicarbonate to pH 7.4 due to the complexes formed with cis-diol organic acids, polyalcohols and sugars (pKa between 5-7.4) [61]. The BCCs' ability to catalyze the CO_2 hydration in the blood could determine a new research angle for the essentiality of B. The blood pH is reliant on the ratio of plasma CO_2 concentration (metabolic factor) to pCO_2 (respiratory factor) [62,63]. Hence, if the pCO_2 increases without an equivalent rise in bicarbonate, the pH falls. Oppositely, if pCO_2 lowers without an equivalent decrease in bicarbonate, the pH rises. So, the bicarbonate is mandatory for the optimal contractility in the isolated cardiac myocytes [64]. The intracellular pH (pH_i) is an essential regulator of the myocardium contraction [64], and a powerful trigger for the electrical arrhythmia [65].

2.3. BCCs as Pleiotropic Modulators of Cell Signaling Pathways

BCCs as modulators of the cell signaling pathways interfere in the enzymatic and non-enzymatic reactions, depending on their speciation. It can be generally considered that through the assistance in biochemical reactions BCCs can be viewed as super-switches for the production of energy, development, reproduction, survival, and life extension. Overall, BCCs have an impact on signaling pathways implicated in many cell functions [12,13,21].

It is well-reported in animal physiology that low BCC concentrations induce the mitogen-activated protein kinase (MAPK) pathway and stops cellular proliferation [47,48]. Since organic BCCs in bacteria are signaling molecules [22] then it logically follows that BCCs also act through the interaction with transcription factors [10], resulting in a large alteration of gene expression [66]. Some exciting reports have suggested that boron-mineral salts could have played a critical role in the 'RNA world' stage of life origin by ribose stabilization; this is why the stabilization of microRNAs by borates is a possibility that is worth investigating further [1,3,4,7]. Additionally, potential targets of BCCs such as adenylates and inositides [8,67] may be included in a group of signaling pathways influenced by B deficiencies.

Thus, it has been demonstrated that BCCs (as BA) prevent the proliferation of certain tumor cells by affecting the release of Ca^{2+} by cyclic ADP ribose (cADRP ribose) [69], which may be justified by the ability of the BA to bind NAD^+ [69]. In animals, cADPR is a cellular messenger for calcium signaling and a modulator for many cellular functions [68]. In pathophysiological states, the level of NAD^+ is low. Furthermore, the experimental results show that BA suppresses the release of Ca^{2+} deposits through the NAD^+/cADPR mechanism, thereby explaining the BCCs effectiveness on the prostate as well as on other biological structures [69]. On the other hand, BCCs (as borate) have been demonstrated to increase NAD^+/NADH ratio in animals [70]. The low level of NAD^+ also suggests that SIRT3 activity is decreased. Collectively, this data shows that BCCs elevate the NAD^+ levels which has the ability to trigger SIRT3 in the heart and to enhance the cardiac activity. The sirtuins activation, particularly SIRT3, by means of NAD^+, enhances cellular bioenergetics, mitochondrial function, and stress resistance [71]. Increasing the NAD^+ level may reduce the damage caused by the hyperactive ARTDs and ADPR cyclases. Subsequently, NAD^+ deficiency is emerging as an essential factor for cardiac and renal disorders [71].

However, it is important to study all BCCs at biologically relevant concentrations. Furthermore, aside from exploring BCCs' primary interaction with signaling and regulatory molecules and transcription factors, it may be important to further establish the relationship between borate anion/sugar-borate anion/B deficiencies and the influx of calcium [72], and to identify those calcium-releasing mechanisms dependent upon inositides or adenylates. The results from studies of this kind may determine the relationship between borate anion/sugar-borate anion/B and calcium on the regulation of the expression of certain genes. Also, the plant's natural organic BCCs complexes (fructose and/or glucose borates) have been hypothesized to be involved in cellular signaling mechanisms of reactive oxygen species (ROS) [73,74] (**Table 1**). Obviously, ROS are a known cause of progression of the cardiovascular diseases [75].

Table 1. Confirmed and predicted activities of boron sugar complexes.

Calcium fructoborate applications	Beneficial health effects	Mechanism of action
Bone health	Reduced OA[a]-associated pain [76,77]	Modulation of leukotriene synthesis
	Bone mineralization [61,77]	Improvement of vitamin D_3 metabolism
	Increased bone density [61,77]	Modulation of microsomal enzymes (24-hydroxylase and estradiol hydroxylases)
Immune health	Exacerbated cellular immune responses [73,78]	Modulation of IL-6[b], IL-1β[c], NO[d], TNF-α[e]
Joint health	Reduced pain and stiffness [79]	Modulation of collagens synthesis
	Increased joint function [79]	
Skin health	Antioxidant properties in human keratinocyte culture [73,78,80]	Superoxide scavenger
Prostate health	Induces apoptosis [54,78]	Proteasome inhibition
		Borate/phosphate similarities
Breast health	Apoptotic cell death induction [40,81]	Augmentation of pro-caspase-3 activity
		Increase of cytochrome c cytosolic level and caspase-3 activity
Ca and Mg metabolism	Improvement of assimilation of calcium and magnesium [77]	Inhibition of vitamin D_3 degradation
Heart health	Significant reduction of LDL[f], TG[g], TC[h], IL-1β, IL-6, MCP-1[i] and CRP[j] [82,83]	Cytokines modulation

[a]OA: Osteoarthritis; [b]IL-6: Interleukin-6; [c]IL-1β: Interleukin-1beta; [d]NO: Nitric oxide; [e]TNF-α: Tumor necrosis factor-alpha; [f]LDL: Low-density lipoproteins; [g]TG: Total glucose; [h]TC: total cholesterol; [i]MCP-1: Monocyte chemoattractant protein-1; [j]CRP: C-reactive protein.

2.4. Borate - Phosphate Similarities

There have been scientific findings related to the presence of a contradictory interaction between the level of B and phosphates in many plants [84] and also in osteoporotic bones [85]. It is known that B anions enhance phosphorylation by the TNF-alpha mediator, which is involved in a cascade of phosphorylations [86]. Albeit boron and phosphorus (as anions) have similarities regarding activity and structure, actual and specific differences between the effects of the substitution of borate and phosphate are still unknown. The literature suggests that since borate establishes ester connections non-enzymatically, it can theoretically simulate phosphate ester complexes. The small size of the boron core prevents the formation of pentacoordinated structures that would mimic presumed associative transition state phosphate geometry [87]. Mainly, the formation of borate esters can provide insight into the structural and activation aspects of homologous phosphate-esters. By complexing the 2'- and 3'-oxygens, borate evidently directs the phosphorylation reaction to the 5'-hydroxy group [4]. The similarity of borate and phosphate together with borate's skill to esterify the cis-diol groups suggests that phosphate may be non-enzymatically replaced by borate anion of BCCs. Practically speaking, borate from BCCs cannot replace phosphate in healthy cells due to the fact that B concentrations are thousands of times lower than phosphorus amounts; hence, these molecules are in fact dissimilar [54]. Recent studies showed that phosphorus depletion increased borate-phosphate similarity in the enzymatic catalysis of RNAse [88]. Recent chemical evidences show that the ribonucleoside is stabilized by borate and is region-specifically phosphorylated in non-enzymatic ways, probably by some mechanism similar to the beginning of life [4]. Enzymatic and non-enzymatic B metabolism is essential for the normal physiology of health [89,90]. In our opinion, BCCs are an important factor of the non-enzymatic phosphorylation mechanism, being involved in the phosphorous balance [4].

2.5. Modulation of enzymatic activity

Various enzymes from microorganisms, plants, animals and humans react with BCCs resulting in stimulation, stabilization and/or inhibition. BCCs' activity in human cells is based on certain enzymes' inhibition (such as serine proteases,

dehydrogenase of xanthine oxidase, CYT B5 reductase, alcohol NAD-dehydrogenases, glutamyl transpeptidase), on the binding of some specific receptors, and on mRNA splicing and on the induction of apoptosis [78]. Moreover, B by some reaction stabilizes the phosphatase alkaline enzyme, thereby preventing oxidative stress [7]. Additionally, B-containing molecules increase the resistance of hemeproteins (such as metmyoglobin and CYT C) to denaturation [7] with possible cardioprotective effects due to their stabilization induced by B-containing molecules against peroxides [11]. Recently, the fructoborate complex [28] was been found to be a strong catalyst in different biological reactions in plants and possibly might perform as a coenzyme [61,74].

2.6. Modulation of inflammation

Inflammation is considered to be a major element in the development of atherosclerotic lesions and is involved in all stages of the disease initiation, progression, destabilization and rupture of atherosclerotic plaques. Atherosclerosis is thought to be a complex inflammatory process triggered by the presence of lipids in the vessel wall. It involves interactions between the components of the vessel wall, inflammatory cells and lipoproteins mediated by several adhesion molecules and cytokines [91]. Atherosclerosis is a primary etiology for the development of subsequent cardiovascular disease. Subclinical atherosclerosis is a common pathology in the middle-aged population. It has been proposed that BCCs help preserve the structures of numerous macromolecular compounds as well as the membrane and protein complexes [20,92]. Hunt implies that B could react with up to four OH groups or, also, with a nitrogen element on distinct biological ligands, like the serine proteases and flavin/pyridine nucleotides. Furthermore, B is able to bind with the ribosyl group of the nucleotide by means of the cis-OH or, in the instance of serine proteases, the imidazole group of histidine by the means of an OH group or nitrogen from serine [20,91]. BCCs may be critical to these processes. Recent studies on mice highlight the interaction of BCCs with T and B cell receptors resulting in the proliferation of lymphocytes and the growing of the macrophages to release inflammatory mediators as a primary mechanism. In this study, mice were stimulated with lipopolysaccharide [93] and the administration of BX (sodium tetraborate decahydrate − $Na_2B_4O_7{\cdot}10H_2O$ – non-plant, inorganic BCC) induced an increase in lymphocyte proliferation and cytokines synthesis (TNF-α, nitric oxide, interleukins 6 and 1β), and also an overexpression of iNOS [94]. However, in the real world, animals and humans do not naturally ingest BX but rather obtain daily boron-containing molecules via consumption of plant materials.

Other clinical studies have showed the ability of calcium fructoborate, a sugar-borate ester originally postulated by Miljkovic and later discovered in plants [28,95,96], to modulate molecular markers of inflammation, mainly C-reactive protein. Rogoveanu et al. [83] showed that calcium fructoborate at 112 mg/day compared to placebo for 30 days produced a significant decrease of interleukins 6 and 1β, C-reactive protein and monocyte chemoattractant protein-1 (MCP-1). There was also a positive effect on lipid profiles, suggesting that this organic natural BCC could be beneficial for cardiovascular system. The two most significant risk factors for cardiovascular disease are the chronic low-grade inflammation and the oxidative stress. Numerous studies have shown that BCCs can modulate the response to the inflammatory and oxidative stress through the binding of NAD^+ and/or cyclic ADP ribose (cADPR) [12,13].

2.7. Oxidative Stress Modulation

In addition to BCC's reported favorable effects on joint health, bone density, cognitive function, and prostate health, researchers have begun to investigate its value as an antioxidant [11,12,78]. In one study, researchers examined the administration of a BCC, such as calcium fructoborate (CFB), on skin wounds. Particularly, they tested whether CFB exhibited antioxidant features on cultures of human keratinocyte (human skin cells). The cells treated with CFB were subjected to exogenous hydrogen peroxide in order to replicate environmentally induced oxidative stress. The results revealed that CFB reduced the production of intracellular reactive oxygen species, suggesting that CFB may possess superoxide dismutase (SOD)-like activity which could be clinically significant in defending the cells from oxidation-induced damage [73]. Furthermore, previous studies showed that boron based diet might increase the enzymes activity by SOD pathway [13,21,97]. It is also known that extracellular SOD has protective activity against atherosclerosis, hypertension, heart failure and diabetes mellitus [98]. All of these, support the role of oxidative stress in the development of cardiovascular damage.

3. EFFECTS OF BCCS RELATED TO CARDIOVASCULAR RISK FACTORS

3.1. BCCs and dyslipidemia

Positive effects of BCCs supplementation on plasma lipids have been mostly seen in studies on animals (cattle or rabbits), wherein sodium borate administered orally induced a significant decrease of total cholesterol, of lipoprotein fractions (low-density LDL and very low density VLDL, and of triglyceride (TG) levels) [16,99,100]. Other authors, however, were unable to confirm these effects, and furthermore an undesirable HDL-cholesterol lowering effect was observed [101]. They

studied the effect of a 4-week BA supplementation on steroid hormones and plasma lipids on rats. BCCs supplementation (administered with drinking water as boric acid) induced a decrease in plasma TG ($p < 0.05$) and the concentrations of total HDL-cholesterol ($p < 0.05$) after 2 weeks, but after a month HDL-cholesterol was the only significantly lowered parameter ($p < 0.002$). This negative or neutral effect was also reported in other animal studies [102]. There are studies reporting that total plasma lipids, cholesterol and LDL can be significantly decreased ($p<0.01$) and at the same time increasing HDL (compared to the control value) by adding boron to layer diets [103]. The lowest total lipids, cholesterol and LDL were recorded for hens which were fed a basal diet with an addition of 200 mg boron/kg. After sodium tetraborate administration, the concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), glucose, insulin, and non-esterified fatty acids diminished [104–106]. The conflicting results could be the evidence of boron speciation in the animal metabolism as BCCs can have a different speciation depending on chemical structure, animal physiology and species.

Studies on the effect of BCCs supplementation on lipids in humans are scarce. Naghii et al. [107] included eight male volunteers in a single-blind cross-over trial lasting 8 weeks. The subjects took 5 mg of sodium tetraborate for one month, followed by a month of placebo intake, or vice versa. This inorganic BCC supplementation had no effect on plasma total cholesterol (LDL and HDL) and on triglyceride. Also, the oxidizability of low-density lipoprotein was unaffected. Caglar et al. [108] studied serum B and lipids levels (total cholesterol, HDL, LDL, TG, lipoprotein-A, apolipoprotein-A-I and apolipoprotein-B) in pregnant women divided into two groups (19 with gestational diabetes mellitus and 15 without). The median measured B concentration was 15.2 μg/L (0.0152 ppm; range, 8.4 - 25.4 μg/L) and the differences between the two groups of women were not significant. A 60-day randomized clinical trial was conducted by Militaru [82] on patients with stable angina pectoris. The study revealed a small (< 10%) but significant improvement of the lipid profile in all of the active treatment groups.

Previously, omega-3 polyunsaturated fatty acids (PUFAs) from dietary sources or fish oil capsules demonstrated beneficial effects on cardiovascular disease outcomes, including all-cause mortality and sudden cardiac death [109]. The European Society of Cardiology recommends omega-3 polyunsaturated fatty acid preparations for lowering triglycerides [110] and as an adjunctive therapy in patients with symptomatic heart failure [111]. An interaction between BCCs and omega-3 fatty acids was demonstrated in animal studies of brain function [112] and bone structure [113]. It has been suggested that CFB may have some direct function in metabolism of omega-3 fatty acids [40].

3.2. BCCs and type 2 diabetes

Glucose metabolism disorders and especially diabetes mellitus are important risk factors for cardiovascular diseases. Bakken and Hunt [20] designed an experiment to determine the effect of BCC as BA on insulin secretion. In rats deprived of B they found significantly higher plasma insulin concentrations, but without a change in plasma glucose levels. This effect was independent of dietary magnesium or vitamin D. Also, significantly higher peak insulin values were recorded in boron-deprived chicks compared to those fed physiologic amounts, and B, as a direct secretagogue, did not affect peak insulin release or pancreatic weight. These findings suggest that BCCs could reduce the quantity of insulin needed to preserve glucose homeostasis, and that B in some form may reduce plasma insulin concentrations with no apparent relationship to the dietary status of vitamin D or magnesium. In another experiment [92] on 30 Sprague-Dawley rats fed with a BA and borax-supplemented diet, with a dosage of 100 mg B/kg, (an unnaturally high concentration and therefore not physiologically relevant to actual use), the authors found a decrease of leptin, insulin, and glucose levels; body weight decreased, probably linked to an increase in T3 thyroid hormone level. Between the two compounds used, borax had the better effect.

3.3. BCCs and smoking risk factor

WHO considers tobacco an epidemic and a leading public health threat [114], smoking being one of the major risk factors for cardiovascular disease.

The basic components released through smoking are nicotine and CO, elements which enhance oxidative stress, endothelial damage and dysfunction. It also leads to high serum concentrations of total cholesterol and triglycerides, reduces the cardioprotective HDL, and promotes intravascular inflammation representing a serious risk factor for the development of atherosclerosis and cardiovascular diseases [115].

Tobacco products contain a plethora of potential toxic molecules, amongst the most cytotoxic of them being nicotine. Diets enriched in BCCs exhibited a notable risk reduction for cervical cancer, prostate cancer, and also in lung cancer for women who were heavy smokers [116]. Moreover, the superior natural BCCs intake has been correlated with the most reduced

lung cancer risks in smoking persons, while the most advanced risk is found in smoking persons with concurrent lack of hormone replacement therapy (HRT) and low B intake [116].

Recent evidences prove that the BA antioxidant properties prevent DNA damage and reduce nicotine induced cytotoxicity *in vitro* cells [117]. These observations open possibilities that natural BCCs may also show potency to counteract the detrimental effect of smoking.

3.4. BCCs and obesity

At present, one of the worldwide major health concerns, especially in developed countries, is obesity and its related comorbidities (cancer, type 2 diabetes, metabolic syndrome, cardiovascular disease).

First studies about inorganic BCCs as BA and body weight [118–120] proved an overexpression of thermogenic proteins in the adipose and skeletal muscle tissues and a 28.1% body weight loss in mice due to the BA intake as a dietary supplement.

Another *in vitro* study [121] showed the inhibitory activities of BA and sodium pentaborate pentahydrate (1 mg/mL) on adipogenesis. The same study also claimed that boron-based nutrition may be effectively used in the obesity and associated diseases prevention. However interesting, *in vitro* studies do not always translate into clinical activity; therefore, more clinical research is necessary to further investigate these findings.

A recent study [122], carried out on healthy obese and non-obese subjects, showed the inverse correlation between natural BCCs intake and body weight relative to body mass index (BMI), but the mechanism is not identified. The same study also claimed that age is an essential issue in terms of physiology and metabolic effects of dietary BCCs. Although there are very few studies on obesity and dietary BCCs relationship, we nonetheless suggest that antiinflammatory and antioxidant effects of natural BCCs may be connected with the management of body weight [11,123]. Boron diet supplementation (100 mg/kg) lowers the body weight, leptin, insulin and also increases T_3 levels in plasma, thus improving the metabolic activity of rats. It was found that borax had a greater hormonal effect than boric acid [92]. Consequently, boron might not be used as a treatment for obesity but as a prevention agent, nevertheless many studies are required in order to unquestionably prove it [121,124,125].

3.5. BCCs and ageing risk factor

There are several mechanisms involved in the processes of aging and BCCs can potentially make some major contributions to regulation of same. According to the oxidative stress theory, a lack of balance between the production and removal of ROS is the major cause of aging. Recently, it was showed that low doses of various BCCs increased the antioxidant capacity by increasing the enzymatic activities [126]. Also, BCCs may inhibit Maillard reactions, by forming stable borate esters with cis-diol on furanose rings, thus making possible the chemical evolution in aqueous media of sugar and aminoacids, simultaneously, at temperatures of 80–100 degrees C [127]. As a result, borate/borate ester anions in living systems may inhibit glycation. Glycation refers to non-enzymatic reactions between the carbonyl groups of sugars (e.g. glucose) and the amino groups of macromolecules (e.g., proteins, DNA) to form advanced glycation end products (AGEs) [128,129]. Human degenerative diseases with a proposed involvement of AGEs include dementias, blindness, diabetes, cardiovascular disease, osteoarthritis and renal failure [130,131].

Earlier data showed that BCCs as BA are involved in the regeneration of NAD^+ in the mitochondria [70], and in protecting DNA against damage [132]. NAD^+/NADH ratio is very important for increasing the activity of mitochondria in reparation of the nucleic acid, and borate has been demonstrated to increase NAD^+/NADH ratio in animals [70]. Sugars are scavengers of BA with major effects in reducing mitochondrial toxicity [54]. This scavenging attribute of sugars suggests that natural dietary BCCs are participating in some yet unclear process related with senescence. A low boron diet prompts an accelerated rate of ageing but also a high boron diet can likewise extraordinarily hasten it [133]. There is a huge connection between the spatial distribution of longevous communities and soil series and their elemental available forms, showing a natural linkage between the human wellbeing or life span and environment to a specific degree. Furthermore, human wellbeing and life span do not seem to be identified with a solitary component, yet rather a multitude or a relationship of components that are found in soils and the environment. We may extrapolate that the particular relationship of the components in the earth (e.g. the relationship of Se, B, Ni, and Mo for our situation), has a close connection to human wellbeing and life span [134].

This fact could imply that the biological importance of BCCs may be connected to some protective function of protein turnover [12,135,136]. This function could be related to increased resistance to the aging process [135,137,138] via protection of the organism from an excessive accumulation of altered proteins that involve proteolytic degradation and subsequent biosynthetic replacement protein turnover. The rate of total body protein turnover in humans decreases with

age. Also, from another vantage point, in a paper that specifically examined boron toxicity on the population, the birth rate in communities with a high concentration of boron in the potable water was greater than that of the general population of France, as a reference zone ($p < 10\text{-}4$). The rate of mortality in the communities with a high concentration of B in the potable water was less than that of the general population of France, as a reference zone ($p < 10\text{-}3$). No statistical difference was observed between the female-male sex ratios in the different communities ($p = 0.45$) [139].

In conclusion, dietary intake of plant-based boron-containing molecules could have an important role in the life extension of humans. As such, more research is needed, especially because cancer and aging are two facets of the same mechanism [140].

3.6. BCCs and metabolism of homocysteine

Hyperhomocysteinemia has long been recognized as an independent cardiovascular risk factor for both women and men [141]. Homocysteine is an intermediate amino acid synthesized in the methylation cycle of methionine metabolism [142]. Numerous studies have shown that hyperhomocysteinemia is correlated with a high risk of atherosclerosis, venous thromboembolism, of neural tube defects in fetus and other pregnancy-related complications [44]. There are many theories about the mechanisms of the deleterious effects of hyperhomocysteinemia, but it seems likely that the sulfhydryl group of the molecule is involved.

In an experimental study on rats, BCCs deprivation increased plasma homocysteine and cysteine concentrations by affecting the formation or utilization of S-adenosylmethionine [33]. S-adenosylmethionine is a universal methyl donor and is involved in numerous reactions affecting DNA, RNA, histones, phospholipids, and other proteins [143].

The impact of the BCC calcium fructoborate on homocysteine levels was investigated in a broader in-human trial [83]. In this randomized trial, 78 healthy subjects were divided in 3 groups: group B received placebo, groups A and C received CFB (at a dose of 112 mg/day for group A and a dose of 56 mg/day for group C) during one month. In the group A, there was a significant decrease in homocysteine level (around 5%) (change from baseline mean 94.5 ± 54.1%, median 81.1%, range 55.1–334.1%, $p = 0.004$); in the other groups the change was not significant. Further randomized and more extensive studies are needed to confirm this marginal effect.

4. DISCUSSION AND CONCLUSIONS

In this review we mainly addressed the biological importance of BCCs as modulators of the cell signaling pathways. Although certain BCCs may perform other biological functions, we have found the concept of BCCs which are involved in the regulation of signaling pathways such as inflammation, oxidative stress or lipid metabolism to be the most interesting and promising. The potential cardioprotective effects of BCCs represent new and exciting opportunities to use these compounds in dietary supplements and perhaps even in medicines. Positive outcomes from studies related to the signaling modulation will extend the use of BCCs beyond providing basic nutritional effects.

Given the body of direct and indirect evidence, a diet rich in BCCs, whether taken from foodstuffs or from dietary supplements, combined with the current recommendations of professional societies, may be considered an option for preservation of a healthy cardiovascular system. However, science still needs to prove the essential role(s) of BCCs in human nutrition as well as to further identify the exact natural organic BCCs and their respective physiological and molecular mechanisms that may be associated with cardio protection. Subsequently, the identification and research of new natural organic BCCs and the study of their biological activity represents an ongoing but exciting challenge for scientists.

When we discuss about essentiality, we must put the spotlight on the molecular species and not on the element itself, in our case boron. Some essential boron species have been identified in plants and bacteria (autoinductor 2, apiose borate ester). The essentiality issue must be associated with a certain type of speciation of the same element. For example, nitrogen as nitric acid and carbon as carbon disulfide are not essential, but nitrogen and carbon species, like aminoacids, proteins, nucelotides, organic acids, are essential for the living organisms. The level of boron in the living world as well as the ability of some species (sugar borate esters) to intervene in metabolic processes (as modulator of signaling molecules or cofactors) [13,20,73,144] are strong reasons in order to consider that some boron species are essential or conditional-essential for humans [145,146]. Nevertheless, in the future, robust evidence of boron's essentiality in humans and animals will have to include the identification of BCCs (biomolecules) in these species. It is anticipated that some biomolecules awaiting to be discovered derive from ribose, fructose, glucose and function as modulators of cell signaling molecules that interact with the cell surface [7,13,69].

It has been reported that in certain pathologies (arthritis, osteoporosis, prostate and lung cancer) the level of B in blood, tissues and organs is very low when compared to those of healthy persons. Our opinion is that the use of organic natural B

compounds (such as hydrolyzed rhamnogalacturonan II, sugar alcohol borate complex, bis-sucrose borate complexes, poyhydroxi organic acid borate esters, amino acid borate esters) [12,14,19,66,147] may be more promising than BA/BX nutrition supplementation. Presently, there are "organic" compounds of boron which are sold as supplements: calcium fructoborate, boron gluconate, boron aspartate, boron citrate, boron ascorbate, boron glycinate chelates [148]. This is because BA/BX compounds are used by plants as precursors (input sources to produce natural plant-based BCCs) or these compounds are turned into waste products after their ingestion and subsequent metabolism [30,149]. The best known biogenic organic boron species are the naturally-occurring sugar-borate complexes from plants [25,54,95,96,150]. Generally, organic boron insoluble and soluble species decompose, in the acidic environment of the stomach, in B diesters and B monoesters. Since the organic B diesters and B monoesters (polyalchools, sugars, organic acid) have a pKa between 2.5 and 5 [151,152], a big amount of them does not decompose and thus they mostly remain in B organic form. Also, due to the fact that boric acid can be easily coupled with *cis*-diol sugars (ribose, fructose, glucose), it is probable that in the blood the organic B species (sugar borate esters) be reconstructed at the physiological pH. Subsequently the BA/BX might have a beneficial action in the human health as an organic species (Figure 1).

The potential cardioprotective effects of natural organic BCCs represent a forward-looking, optimistic topic and hopefully in the future more studies with good design and sufficient strength will be carried out to endorse this hypothesis.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests or financial benefits from specifying the names of the companies or the trademarks.

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AUTHOR CONTRIBUTION

All the authors contributed equally to the manuscript.

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