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Calcium Fructoborate: Plant-Based Dietary Boron for Human Nutrition

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ABSTRACT. The main objective of this paper is to evaluate the scientific evidence on the form of organic boron, calcium fructoborate (CF), including health dates, dietary needs, pharmacology, experts opinion, research papers, clinical evidence, and dosing. CF is a natural product with effects in oxidative metabolism and cell apoptosis. We review the biological and biochemical action of chemical natural-identical entity of CF. This mini review provides support for future clinical research.

KEYWORDS. calcium fructoborate, boron, micronutrient, osteoporosis, osteoarthritis, anti-inflammatory, cancer, omega-3, cholesterol

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Journal of Dietary Supplements, Vol. 6(3), 2009
Available online at www.informaworld.com/WJDS

doi: 10.1080/19390210903070772

INTRODUCTION

Boron is an essential nutrient element for the normal growth and development of plants (Warington, 1923). Studies have also shown the necessity of boron in animals (Nielsen, 1996). While the World Health Organization concluded that boron is "probably essential" for humans, no specific biochemical function for boron has been identified in animals or humans (Coughlin & Nielsen, 1999). The average daily intake of boron received by adults from natural sources is estimated to be 1–4 mg, depending on nutritional habits (i.e., vegetarians consume more), geographical location, and other sources of exposure (Hamilton & Minski, 1973; Hunt & Meacham, 2001; Rainey et al., 1999). The richest sources of boron can be found in nuts, dried fruits, and herbs, and in wine, particularly red wine. The vegetarian normal diet (including wine) would provide around 7 mg/day in Europe (Richold, 1998). In some cases the diet can reach to 15 mg/day. Boron levels in water and soil are usually the highest in arid climates, such as the desert regions of the United States and South America, the Red Sea region of the Middle East, and parts of Australia (Richold, 1998). Orally administered boron is easily and completely absorbed; it passes through the body without metabolism, is excreted with a half-life of 21 h, and is mostly eliminated with only a low level of accumulation in bones (Zhao, Unrine, & Dourson, 1999). The interaction between calcium (Ca) and boron (B) has been observed in plants, bacteria, animals, and humans, but the specific nature of the interaction is still under experimental investigation (Bolaños, Lukaszewski, Bonilla, & Blevins, 2004).

Boron natural complexes have been isolated and characterized from the phloem sap of celery and floral nectar of peach as boric acid ester with fructose (fructose-B-fructose), glucose (glucose-B-glucose), and sorbitol (sorbitol-B-sorbitol). These represent the first soluble complexes isolated from higher plants (Hu, Penn, Lebrilla, & Brown, 1997). Traditionally, boric acid and some of the inorganic borate have been used for boron supplementation. Recently, some other boron compounds have been introduced in the market of the pharmaceutical industry with the same purpose (Miljkovic, 1998). Calcium fructoborate (CF) has recently shown to possess an interesting antioxidant effect (Scorei, Cimpoiasu, & Iordachescu, 2005) and anti-inflammatory (Scorei et al., 2007) and anti-tumor activity (Scorei et al., 2008).

In this paper, we review the biological and biochemical action of chemical natural-identical entity of CF, which has a chemical structure similar to the natural one of boron found in edible plants (Miljkovic, 1998; Wagner, Curotto, Diez, & Bara, 2008).

BORON INTAKE AFFECTS PEOPLE'S HEALTH

Extrapolations of data from animals suggest that 1 mg of boron daily for humans would offer optimal nutritional benefits for this element. Data from both animals and humans were used by the World Health Organization to suggest that doses of boron consumption could be 1–13 mg/day (World Health Organization, 1996). Side effects and interactions may occur with boron supplementation. Boron may enhance the effects of estrogen (Sheng et al., 2001) and a diuretic effect of boron was noted during a high-dose administration (Tagawa et al., 2000). The toxic effects to boron supplementation are related to reduced fertility, decreased sperm motility, and testicular toxicity (Devirian & Volpe, 2003).

In boron supplementation the contraindications are related with hormonal treatments because boron supplementation obviously elevates the serum concentrations of 17-β-estradiol and testosterone (Nielsen, Hunt, Mullen, & Hunt, 1987).

Low boron concentrations (1.48 ppm boron versus 4–6 ppm normal level) in hair have been associated with the osteoarticular Kashin–Beck disease (KBD) from China (Fang, Wu, Hu, and Huang, 2003; Peng, Lingxia, Schrauzer, & Xiong, 2000). Occurrence of the KBD is restricted to 13 provinces and 2 autonomous regions in China, but cases have been reported in Siberia and North Korea, where the frequency of disease decreased in correlation with socioeconomic development. Etiology of KBD is controversial. Among the risk factors of KBD are boron and selenium deficiency, inorganic material (e.g., manganese, phosphate) and organic matter (humic acids and fulvic acids) present in drinking water, and grain fungi (Fusarium sp., Alternaria sp.) which are producers of mycotoxins.

Certain studies show that boron affects transportation of signals or regulator ions along cell membranes. The mammalian borate transporter NaBC1, which is essential for cellular boron homeostasis, conducts Na^+ and OH^- across cell membranes in the absence of boron (Park, Li, Shcheynikov, Zeng, & Muallem, 2004). At small concentrations boron activates the MAPK pathway to stimulate growth and proliferation of HEK293 cells in culture. Diadenosine phosphates are present in all cells and function as signal nucleotides associated with neuronal response and have better affinities for boron than any other boron ligand presently recognized in animal tissue (Ralston & Hunt, 2001). A bacterial quorum-sensing signal molecule (auto-inducer AI-2) was characterized as a furanosyl borate ester synthesized from adenosylmethionine (Xu et al., 2002). Another indication that boron has action at the cell membrane level is that dietary magnesium and fatty acids, which affect membrane function, influence the response to boron deprivation (Nielsen, 1996, 2008).

Boron and Calcium Metabolism

The first study implicating boron in calcium metabolism showed that boron deprivation increases the urinary excretion of calcium and magnesium and decreases the levels of 17-β-estradiol and testosterone in women at postmenopause (Nielsen, 2004b). The effects of boron on calcium metabolism, and 25-hydroxycholecalciferol specifically, may have positive implications on bone metabolism including a reduced risk for osteoporosis and perhaps other maladies (Zittermann, 2003). A study conducted on 13 subjects with vitamin D deficiency (less than 12 ng/ml in serum) found that during a 60-day supplementation period with 6 mg boron/day, serum 25-hydroxy vitamin D levels rose by an average of 20% (Miljkovic, Miljkovic, & McCarty, 2004). Before the 60-day supplementation, the study group had a serum level of 8.53 ± 2.74 ng/ml and after supplementation this was 10.26 ± 3.83 ng/ml. In this study, the authors establish only the relation between boron supplement intake and serum 25-hydroxy vitamin D deficiency, without reference to the calcium level. The patients were advised to continue normal life style and were not given any special diet or exercise.

Boron and Arthritis

A reduced boron diet has also been associated with rheumatic arthritis (Havercroft & Ward, 1991). A comparison between countries found that the occurrence of arthritis is negatively correlated with the level of boron in the soil and food supply. The study found that in areas where daily boron intakes are typically 1.0 mg or less, the estimated incidence of arthritis ranges from 20% to 70%, whereas in areas where daily boron intakes are typically 3–10 mg, the estimated incidence of arthritis ranges from 0% to 10% (Newnham, 1991). In further support, a double-blind study involving 20 subjects with osteoarthritis noticed beneficial results in those taking 6.0 mg boron/day. Boron availability in soil is limited in many regions in the world, including Japan, China, United States, and Brazil. The major reason of boron deficiency in these regions is high rainfall. Boron in soil solution is present as boric acid and easily leached out from the soil due to its high solubility (Shorrock, 1997; Yan et al., 2006). After 8 weeks of supplementation, the average condition of all patients' joints was significantly better, and there was significantly less pain at passive movement for those taking boron compared to those on placebo (Newnham, 1994).

Boron and Potential Protective Role against Prostate Cancer

In addition to its role in promoting healthy bones and joints, boron may play an underappreciated role in protecting men against prostate cancer. As men grow older, their risk for prostate cancer skyrockets. Fortunately, in the clinical trial, the study used data from NHANES III conducted between 1988 and 1994 by the National Center for Health Statistics, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services on 9,401 male subjects. The study indicates that boron may help prevent prostate cancer and showed that boron's increased contribution has been associated with a reduced risk of prostate cancer with a doseresponse pattern (Yan et al., 2004). Recent studies suggested that boron has a chemo-preventive role in prostate cancer (Barranco & Eckhert, 2004; Eckhert, Barranco, & Kim, 2007). Another recent study found that boric acid inhibits proliferation of some human cells of prostate cancer (Barranco & Eckhert, 2004).

Boron Effects on Brain Function and Cognitive Performance

A series of studies has constantly shown that boron deprivation in rats and humans leads to undesirable effects on brain electrophysiology (Penland, 1998) and, in humans, results in significantly poorer performance on tasks involving eye–hand coordination, attention, and short-term memory (Penland, 1994, 1998). It has also been shown that boron-depleted diets in humans is associated with the reduction of performance on tasks measuring manual dexterity, perception, and long-term memory (Penland, 1994).

Dietary Boron Enriches Omega-3 Fatty Acids in Animals

In recent research studies, scientists are learning that the bone health benefits of omega-3 fatty acids may be greatly magnified when these essential fats are combined with the critical trace of mineral boron (Nielsen & Stoecker, 2006). Intriguing new research findings suggest that boron's bone-supporting effects may be the greatest when omega-3 fatty acids are also available. For instance, when laboratory animals consumed a diet rich in both omega-3 fatty acids and boron, they demonstrated greater bone mineral density and stronger bones compared to animals fed other dietary fats and boron. These findings suggest that omega-3 fatty acids and boron may work together to support dense, strong bones (Nielsen, Stoecker, & Penland, 2007). While boron has not yet been classified as an essential nutrient, this may soon change. Growing evidence suggest that boron plays many essential roles in maintaining skeletal health. Studies offer powerful support for optimizing intake of boron and omega-3 fatty acids as part of a nutritional strategy for maintaining strong, healthy bones (Gorustovich, Steimetz, Nielsen, & Guglielmotti, 2008a, 2008b).

CALCIUM FRUCTOBORATE AS FOOD SUPPLEMENT

The chemical status of boron in nutrition is very important. In plants, boron is found in the form of sugar esters (Brown & Hu, 1996) and there are studies that show that its assimilation is very much connected to the chemistry of boron sugar esters (Brown & Shelp, 1997; Scorei & Cimpoiasu, 2006). The boron sugar esters are the best chemical form for assimilation into cells (Brown & Hu, 1998).

In researching various boron compounds, scientists discovered a plant form of boron known as CF—that is a complex of calcium, fructose, and boron found naturally in fruits, vegetables, and other food (Hu et al., 1997). This form of boron is not only safe, but also bioavailable compared with other commercial forms of boron (Miljkovic, 1998).

Physicochemical Structure

Calcium fructoborate samples with linear formula $Ca(C_6H_{10}O_6BO)_2 \cdot 3.5H_2O$ were characterized by chemical analysis, infrared and Raman spectroscopy, and thermogravimetric and differential thermal analysis data (Wagner et al., 2008). The neutral trigonal monodentate form of boron organic ester with fructose, under solid form, is modified in solution in the anionic tetrahedral bis-dentate form (Miljkovic, 1998).

Calcium Fructoborate and Osteoporosis

Osteoporosis is a disease that affects a large group of people at different ages, both men and women, and it takes a long treatment, with expensive materials and social costs. Through its complications, the disease produces a great number of patients immobilized in bed and with multiple deficiencies. Treatment of osteoporosis is expensive and very long. CF may influence bone density in vitamin D-deficient animals. Boron has been shown to improve bone strength characteristics in rats (Nielsen, 2004a) and pigs (Amstrong, Spears, Crenshwa, & Nielsen, 2000). Results show a dose-dependent increase in bone density as measured by total ash mass. Three months of treatment with 35 mg of CF resulted in 1.46% increase in total ash. Moreover, 184 μg of CF increased bone ash up to 5.8% in the femurs (Hector de Luca, unpublished, 2002). These results suggest that supplemental boron prevents the severe hypocalcaemia of vitamin D3 deficiency through an alternative metabolic pathway, yet little known, of the assimilation of calcium (Dupre, Keenan, Hegsted, & Brudevold, 1994).

Calcium fructoborate also has been found to counteract the harmful effects of dietary vitamin D deficiency. A study conducted at the Department of Orthopedic Medicine at the University of Novi Sad, Serbia, examined the correlation between intake of CF and serum vitamin D3 levels (N. Miljkovic, D. Miljkovic, & G. Ercegan, unpublished results, 2002). Research has shown improvements in vitamin D3 metabolism after boron supplementation. Study participants took one capsule containing 226 mg of CF per day for 60 days. All participants showed vitamin D3 deficiency (under 12 ng/ml) at the beginning of the study. Out of all study participants, 85% saw an increase in vitamin D3.

Previous results of this study demonstrated a correlation between vitamin D3 deficiency and an increased risk for cardiovascular attacks (Richart, Li, & Staessen, 2007) and influence of vitamin D3 on bone health and articulations (N. Miljkovic, unpublished results, 2002). Recent studies have shown that CF was absorbed from the gastrointestinal tract to the bloodstream in an intact form and time-dependent manner (VDF FutureCeuticals, xxxx). The results of this study show for the first time that CF can be detected intact in blood following oral administration. If this is the case, the biological effects of CF observed so far could be due to its activity in an intact form. A clinical and practical research program of the effects of CF on osteoporosis was initiated in Romania, using this compound as dietary supplement (Ghivercea, Grecu, Lichiardopol, & Maria, 2004). Final conclusions of the study have shown that CF is a good adjuvant in the treatment of osteoporosis, possibly the best in dietetic prevention of osteoporosis based on the large study group (100 subjects, males and females) (Ghivercea et al., 2004). The B/CF is relatively a new supplement approved only on the U.S. market and this is why it is not yet included in the clinical guidelines for the prevention of osteoporosis. The authors do not know existing studies about comparison of B/CF with dietary intake of calcium/vitamin D in prevention of osteoporosis.

Calcium Fructoborate, Arthritis and Pain

Another recently completed clinical study was conducted at the Orthopedic Clinic of the University of Novi Sad, with 20 osteoarthritis patients divided into two groups of cases with mild and medium forms of osteoarthritis on the one hand and those with severe cases on the other hand (N. Miljkovic, unpublished results, 2002). The mild to medium cases received CF in unique dose of 6 mg and the severe cases received 12 mg/day in two doses of 6 mg. The results were quite impressive. For mild and medium osteoarthritis, the average pain reduction was 62.5% in 4 weeks and 70.83% in 8 weeks (Ibuprofen). In the first 4 weeks, 80% of the test subjects reduced or eliminated their use of painkillers. By 8 weeks, 67% gave up using painkillers (Ibuprofen). Joint rigidity disappeared for half the patients in the first 4 weeks and for the remaining half it was decreased on the average of 87.5%. By week 8, the patients were rigidity-free. Mobility and flexibility were enjoyed by 71.43% of the patients at 4 weeks and by 77.77% at 8 weeks.For the severe osteoarthritis group, the average pain reduction was 47.85% at 4 weeks and 64.5% at 8 weeks. In the first 4 weeks, 40% of the test subjects reduced or eliminated their use of painkillers (Ibuprofen). By 8 weeks, 75% had quit using painkillers (Ibuprofen). Joint rigidity disappeared for half the patients in the first 4 weeks, but only later in the day, and for the remaining half was decreased giving an average rigidity reduction of 50%. By week 8, the figures remained the same. Mobility and flexibility were enjoyed by 50% of the patients at 4 weeks and by 62.5% at 8 weeks. One of the most fascinating results of the study was how the CF acted as an efficient painkiller. In mild and medium cases of osteoarthritis, it eliminated the need for other painkillers in 67% of the patients. Even in severe cases, 75% of the patients stopped using painkillers or decreased their number on a daily basis which is statistically significant ($p < .05$). When compared to other studies that treated osteoarthritis using glucosamine and chondoitrin sulfate, CF has been much better than these substances, both as an anti-inflammatory agent and a painkiller. These findings highlight other benefits of boron in biological systems. It serves as an anti-inflammatory substance through inhibition of the oxidative burst by scavenging cells (leukocytes) and excessive activity by neutrophils, white cells that scavenge debris and invaders outside of the circulatory system. CF and boron also improve free radical scavenging by raising the level of

SOD (Scorei et al., 2005) and catalase and glutathione peroxidase in blood and cells (Mohora, Boghianu, Muscurel, Duta, & Dumitrache, 2002). This triumvirate of antioxidant enzymes is the main natural defense against free radicals. And finally, related to arthritis, bone and joint health, CF has been shown to inhibit the activity of collagenase enzymes (N. Miljkovic, unpublished results, 2002). These enzymes are naturally generated in human biochemistry and break down collagen. Their effect for elderly people contributes to wrinkled, flaccid skin, more fragile joints, vascular, and bone deterioration (Bord, Horner, Beeton, Hembry, & Compston, 1999).

CALCIUM FRUCTOBORATE AS A POTENTIAL MEDICINE

Calcium Fructoborate and Anti-inflammatory Processes

A new study called "in vitro effects of CF on fMLP-stimulated human neutrophile granulocytes" is now available (Scorei et al., 2007). This study investigated the effects of CF on the human polymorph nuclear neutrophiles (PMN) that play a central role in the inflammatory response.

Results demonstrated that CF exposure induced a dose-dependent decrease in cell viability. Treatment of PMN cells, for 24 h, with 22,500 μM CF led to a decrease in cell viability by 61.1%, an inhibition of respiratory burst by 92.9% in the case of fMLP-stimulated cells, a diminution of intracellular level of superoxide anion with 59.3%, and a stimulation of superoxide dismutase activity by 72% in unstimulated PMN cells. The researchers concluded, "Altogether, these results suggest the antioxidant and anti-inflammatory properties of CF" (Scorei et al., 2005).

Calcium Fructoborate and Oxidative Stress

In addition to boron's beneficial effects on bone density, joint health, prostate cancer, and cognitive function, researchers have begun to explore its value as an antioxidant. The preliminary results are promising indeed. In a study at the University of Craiova, in Romania, researchers investigated CF application on skin wounds and healing. Specifically, they tested if CF exhibits antioxidant properties in human keratinocyte cultures, which serve as a laboratory model of human skin cells. Cells treated with CF were exposed to exogenous hydrogen peroxide to mimic environmentally induced oxidative stress. The researchers found that CF decreased the production of intracellular reactive oxygen species, leading them to conclude that CF has antioxidant activity that could have clinical significance in protecting skin cells from oxidation-induced injury (Scorei et al., 2005).

Calcium Fructoborate and Breast Cancer

In a recent paper we have investigated the effects of CF and boric acid on the activation of the apoptotic pathway in MDA-MB-231 human breast cancer cells (Scorei et al., 2008). Exposure to boric acid and CF inhibited the proliferation of breast cancer cells in a dose-dependent manner. Treatment with CF but not with boric acid resulted in an increase of p53 and bcl-2 protein levels. Furthermore, following the treatment with CF augmentation of pro-caspase-3 protein expression, cytosolic cytochrome c level and caspase-3 activities were observed, indicating apoptotic cell death induction. This was also demonstrated by TUNEL assay. In conclusion, our data provide arguments to the fact that both boric acid and CF inhibited the growth of breast cancer cells, while only CF induced apoptosis. Additional studies will be needed to identify the underlying mechanism responsible for the observed cellular responses to these compounds and to determine if boric acid and CF may be further evaluated as chemotherapeutic agents for human cancer.

Calcium Fructoborate and Omega-3 Fatty Acids in Human and Animal Physiology

Our studies have suggested that CF has a direct role in lipid metabolism, especially metabolism of omega-3 fatty acids. We published some articles concerning the interaction of CF at cellular level with reactive oxygen species, especially with superoxide (Criste et al., 2005). We consider that it is very important to take into account some correlation of boron deficiency with certain pathologies. For animals, there are studies concerning boron influence and returning to a balanced fatty acids dietary profile (omega-6/omega-3 from 10:1 to 2:1), with important effects for human nourishment. The research wants to summarize the progress made in establishing essential roles for boron and essential omega-3 fatty acids in human and animal physiology and assesses that progress related of criteria for essentiality of boron element (Criste, Grossu, Ciurascu, Scorei, & Mitrut, 2005). The data record suggests that humans and at least some higher animals may use boron to support normal biological functions. However, the nature of boron biochemistry suggests specific lines of investigation. In particular, further characterization of the cell signaling molecules capable of reacting with boron should provide insights into the specific biochemical functions of boron in humans.

Calcium Fructoborate and Its Effect on Lipid Metabolism

Testing the clinical and biological effects of the polyunsaturated acids and CF-enriched functional ecological eggs was recently accomplished especially on dislipidemy disorder patients (Mitrut, Scorei, Badea, & Dumitrescu, 2006). The use of CF and omega-3 fatty acids to enrich forage in the nutrition of animals leads to the improvement of the animals' health condition and thus to the improvement of product quality (Criste et al., 2005; Grossu, Criste, Scorei, Ciurascu, & Duca, 2005). Obtaining ecological eggs from hens raised in special conditions, with CF nutritional supplements which ameliorate the chemical composition, can become an opportunity in the human nutrition for certain categories of patients, for whom this aliment is restricted or even contraindicated. The low-cholesterol and high-polyunsaturated omega-3 fatty acids make these products have major indications on patients with dislipidemy, metabolic disorders, and cardiovascular disorders. The high boron concentration has also benefic effects on the health condition, being the need to identify the patient categories that can benefit by this therapy, giving anti-osteoporosis, anti-inflammatory, and regulation effects of its mineral metabolism. The strong point of a Romanian paper (Mitrut et al., 2006) is represented by the effect of the ecological functional CF-enriched egg diet on the lipidic metabolism. The effect on the total cholesterol was a decrease of the average value of 229.39 mg/dl up to a value of 218.99 mg/dl with a high statistical significance. The influence of the CF-enriched eggs diet on metabolism of the uric acid also presented a high statistical significance: the level of the uric acid on the first and second determination decreased from 5.30 mg/dl to 4.84 mg/dl. This also has a special significance, drawing the attention on the possibility of using these ecological products on patients with severe disorders, as it is the gout or the hyperuricemia of other causes. The study of the C-reactive protein level pointed out a decrease of the average value from 0.54 mg/dl to 0.43 mg/dl during the study. The registered decrease has statistical significance and is extremely interesting. Associated to the decrease in the cholesterol level, the decrease of the C-reactive protein through the CF-enriched eggs diet draws our attention to the opportunity of using these aliments for patients with cardiovascular disorders as adjuvant treatment with benefic effects. The level of the fibrinogen also significantly statistically decreased from the average value of 456.68 mg/dl to the value of 417.29 mg/dl. This fact shows the unspecific anti-inflammatory effect of the fatty polyunsaturated omega-3 fatty acids-enriched ecological eggs. This effect associated to the decrease of the C-reactive protein level and with the diminishing of the articular pains during the study draws our attention on the extremely benefic effects to the patients with osteoarticular pathology, especially to those with osteoarticular pains with inflammatory cause. It is also a new argument for the benefic effect of this diet to patients with cardiovascular pathology. The effect on the lipidic metabolism with the reduction of the total cholesterol and the decrease of the C-reactive protein is an argument for these aliments' intentional indication use in the diet of patients with cardiovascular and dislipidemy disorders. The ecological functional CF-enriched eggs consumption does not present side effects and the digestive tolerability is very good both for patients with different affections and for healthy persons.

A pilot study was realized at University of Craiova, Romania, regarding the CF effect over the lipidic metabolism in humans (R. Scorei & P. Mitrut, unpublished, 2008). The results of the analysis show a constant diminution of the serum level of the cholesterol values between 25% and 10%. The glycemia level was not significantly influenced by medication, the values being normal in all cases. While giving the medication, significant side effects had not been noticed. In 50% cases of patients with articular pains, improvement of symptomatology had been noticed.

CONCLUSIONS

Calcium fructoborate is a natural product that can be very efficiently used as a boron food supplement in prevention and adjuvant treatment of osteoporosis and osteoarthritis. Our opinion is that more boron should be added to multivitamins especially in the organic form of these (CF). The CF form of boron is being found in some vegetables like celery and broccoli and fruits like grapes and plumes (Hu et al., 1997). At the same time, CF may also become a pharmaceutical ingredient with effects in oxidative metabolism and cell apoptosis. CF enters the cell by a "masked" transport, probably using one of sugar transporter, according to our preliminary data.

Calcium fructoborate has a beneficial effect upon the lipid metabolism. The major effect of taking CF has been seen regarding the blood cholesterol levels, where those were lowered in all cases of our study. CF does not show side effects. The improvement of the articular symptomatology is obvious for all patients with this pathology. For cells with great affinity for sugars in physiological pathogenic states, CF could induce cell apoptosis. The prooxidant and antioxidant mechanisms are directly correlated to the molecular structure of CF. Compared to CF, the boric acid is transported into the cells using boron-specific transporter, NaBC1, while CF is transported using probably a sugar transporter. We believe that CF is highly reactive only toward the cells with overexpressed sugar transporters, such as intestinal cells, adipose cells, muscle cells, and some cancerous cells.

ACKNOWLEDGEMENT

R.I. Scorei and V.M. Cimpoiaşu acknowledge the financial support to the Ministry of Education, Research and Innovation, represented by the CNCSIS Council, for the framework "Ideas" 2008 code ID 418.

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doi: 10.1080/19390210903070772