REVIEW

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Boron-containing compounds in Dentistry: a narrative review

IOANA MITRUŢ[1)], ION ROMULUS SCOREI[2)], HORIA OCTAVIAN MANOLEA[1)], ANDREI BIŢĂ[2,3)], LAURENŢIU MOGOANTĂ[4)], JOHNY NEAMŢU[2,5)], LUDOVIC EVERARD BEJENARU[3)], MARIA VIORICA CIOCÎLTEU[2,6)], CORNELIA BEJENARU[7)], GABRIELA RĂU[2,8)], GEORGE DAN MOGOŞANU[2,3)]

[1)]*Department of Dental Materials, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Biochemistry, BioBoron Research Institute, S.C. Natural Research S.R.L., Podari, Dolj County, Romania*

[3)]*Department of Pharmacognosy & Phytotherapy, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania*

[4)]*Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania*

[5)]*Department of Physics, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania*

[6)]*Department of Analytical Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania*

[7)]*Department of Pharmaceutical Botany, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania*

[8)]*Department of Organic Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

Research on the use of boron (B) in the field of oral health has gained momentum in recent years, with various studies on the possibilities of using various B-containing compounds (BCCs). A multitude of applications have been discovered, from cariostatic activity to anti-inflammatory and antifungal activity, paving the way for other new research directions. B is a microelement that is commonly found in the human diet, and present throughout the body, with the highest concentration in the structure of bones, teeth, and gastrointestinal mucus gel layer. Multiple studies have demonstrated that B plays some important roles, especially in bone development and recently has been proposed to have an essential role in the healthy symbiosis. In addition, B has also attracted the interest of researchers, as various studies used BCCs in conventional or modern biomaterials. In this review, we have brought together the information we have found about B updates in the dental field and analyzing its future perspectives and potential for further studies.

Keywords: boron-containing compounds, oral microbiome, oral health, tooth structure, dental materials.

Introduction

In science, boron (B) is appreciated as an element with two roles: on the one hand, B is important in the life emergency and evolution, and on the other hand, it is a micronutrient with a beneficial role in animal and human nutrition. Thus, B falls in both directions of the definition of prebiotic, as necessary mineral in the appearance and evolution of life and as micronutrient with an important role in nutrition in plants, bacteria, fungi, animals, and humans [1–5].

B is also considered to be a key element in the symbiosis progress between legumes and a group of bacteria named nitrogen-fixing bacteria (*Azorhizobium*, *Bradyrhizobium* and *Rhizobium*). B was claimed as an essential micronutrient (mineral) for the symbiotic interaction and development of bacterial nodules in vegetables, although these bacteria have not shown that B is essential for them [6].

B organic species are present in plants in a large range of essential primary metabolites as B–carbohydrate complexes, B amino acids and secondary metabolites as organic acids and recently *in vivo* discovered as B–phenol complexes [6]. Although B is essential for plants, some bacteria, fungi, and algae, in terms of human health, its role is not yet defined in human and animal metabolism, as no biochemical molecule with B or any metabolic pathway using B has been discovered [7].

Currently, there are also B organic compounds found on the market as dietary supplements: B aspartate, calcium fructoborate (CaFB), B gluconate chelates, B citrate, B ascorbate, B glycinate and inorganic compounds, such as boric acid (BA), sodium borate or sodium tetraborate decahydrate. All known forms of B easily hydrolyzed in the intestine to BA. BA is reactive and tends to accumulate in tissues. BA is not metabolized by humans or animals and is excreted unchanged. Studies in both humans and other animals have shown that the absorption of BA is rapid following oral exposure, with 81–95% of the BA absorbed within 24–96 hours of ingestion. More than 98% of all forms of ingested B (BA, sodium tetraborate) are absorbed as undissociated BA. B citrate, B aspartate, B ascorbate and B glycinate are digestible (having low association constants), are being degraded in the stomach and absorbed in the small intestine. Only a small amount of about 2–5% reaches the colon. It is well known that B forms very stable complexes with sugars, especially with fructose. CaFB is transformed

in BA and fructose in the superior gastric system similar B citrate, B ascorbate, B aspartate, B glycinate. Other old studies show that fructoborate (FB) is being identified in blood of rats fed by CaFB gavage [8, 9].

New insights into natural organic B (NOB) species essentiality to animals and humans were reported by us recently. All the known effects of B on animal and human health can be explained by the essentiality of B on healthy symbiosis. Recently, B was claimed to have as its mechanism of action the presence of the B signaling molecule [auto-inducer-2 borate (AI-2B)], and also its presence in the colonic mucus gel layer fortification with B from B-rich diet. Thereby, B can be a micronutrient essential for symbiotic interaction between microbiota and a mammalian host for healthy humans and animals. The consequences of insufficient B levels in the intestine microbiota may be: (*i*) dysbiosis due to the deficiency of the AI-2B signaling molecule; and (*ii*) increased intestinal translocation and permeability of the intestinal microbiota from lumen to the systemic circulation, due to B deficiency in the mucin gel structure, which dictate the direct interaction of the host cell membranes with bacteria biofilm, and therefore their direct infection. Consequently, the microbiota needs B to achieve: (*i*) biosynthesis of a furanosyl borate diester (AI-2B), a member of a signaling molecules family used in quorum detection; and (*ii*) prevents direct contact between bacteria and the host organism, thus preventing the occurrence of direct infectious effects [6].

Current studies proved that the oral cavity microbiome is the main source in the cause of many systemic and oral diseases [10]. The oral cavity environment is home to over 700 species of bacteria that have the purpose of maintaining its health and normal physiological state. The colonizing bacteria can be located on the teeth hard surfaces or on the oral mucosa soft tissues. Mouth diseases, such as periodontal disease and dental caries, have one of the highest prevalence among worldwide diseases. Dental caries represents the leading cause of tooth and loss oral pain and could begin as small surface changes and continue until dentin is getting damaged. The accumulation of subgingival plaque leads to periodontal disease thus producing changes in the microbiota from a health to a disease [11–14].

Today, the treatment of periodontal disease consists in the reduction of the number of local pathogens to maintain disease control. The use of antibiotics helps with the reduction of the bacterial communities, but they cannot be distributed freely. Oral cancer is a third mouth disease that requires a real amount of consideration. Oral cancer is one of the most common cancers; there is a relation between the function and structure of the oral microbiota and oral cancer. In general, several studies have proved that tooth loss and deficient mouth health rise the risk of pancreatic, gastric, and other cancers. One of the first symptoms of compromised mouth health is usually inflammation and it is getting worse as health deteriorates. The relationships between oral disease, the oral microbiome, and systemic disease are increasingly the focus of current research. Pathogens can enter the bloodstream, alter the appropriate immune responses, or can determine an excessive and dysregulated quantity of inflammatory mediators and produce diseases in various areas of the body [15].

Aim

Our work reviews the latest research on the relationship between the health of the oral microbiota and the potential of B-containing compounds (BCCs) in promoting oral health.

Oral microbiome in mouth and systemic diseases

Composition of the oral microbiota

Archaea, bacteria, viruses, protozoa, and fungi are oral microorganisms and are associated with multiple oral pathologies [16]. In the oral cavity, there are almost 1000 species of bacteria, which include, *e.g.*, *Actinobacteria*, *Bacteroidetes*, *Chlamydia*, *Euryarchaeota*, *Fusobacteria*, *Firmicutes*, *Proteobacteria*, *Spirochaetes* and *Tenericutes*, and also some less known ones, such as *Chloroflexi*, *Chlorobi*, *Synergistetes*, SR1, TM7, GN02, and WPS-2. In the oral cavity, there are also about 100 species of fungi including *Aureobasidium*, *Aspergillus*, *Cladosporium*, *Candida*, *Cryptococcus*, *Gibberella*, *Fusarium*, *Rhodotorula*, *Penicillium*, *Saccharomycetales*, *Schizophyllum* and *Malassezia* [17]. The domain *Archaea*, a special phylogenetic lineage in the life tree, is perceived as part of the human microbiota but its function in mouth sites is little understood. However, certain clinical experiments suggest potential activities in oral diseases [18]. As for the protozoan population, it appears mainly saprophytic, and the most frequently reported members were *Entamoeba gingivalis* and *Trichomonas tenax*. Besides that, *E. gingivalis* has been reported to appear in excess in periodontal disease [19]. Out of the virome components, meaning eukaryotic viruses (*Anelloviridae*, *Herpesviridae* and *Papillomaviridae*) and phages, only the phages have the ability to lyse bacteria and can be used as a treatment in bacterial infections [20].

The oral dysbiosis in dental caries, periodontal disease, oral candidiasis, oral cancer, and systemic diseases

In systemic diseases, the dysbiosis of the oral microbiota reduces microbial diversity and increases the number of pathogenic bacteria at the expense of commensal bacteria with effects on oral infections and diseases, such as periodontitis, gingivitis, oral ulcers, dental caries, and oral candidiasis [16]. It is known that the salivary microbiota is found in specific niches in the mouth cavity, is representative of the oral microbiota and reflects the oral and systemic health of people. Thus, the changes in the structure of the salivary microbiota could be biomarkers for the monitoring of pathologies, such as periodontal disease, caries, and oral cancer. Saliva defense proteins, such as antimicrobial peptides, immunoglobulins, lysozyme alpha-amylase, mucins, peroxidases and statherins, are being involved in oral immunity [21].

Quite recently, the appearance and progress of caries are shown to be associated with several bacteria, fungi, and viruses, such as: *Lactobacillus*, *Actinomyces*, *Prevotella*, *Neisseria*, *Scardovia*, *Propionibacterium*, the Epstein–Barr virus (EBV) and the fungus *C. albicans* and there is more and more research demonstrating the link between oral dysbiosis and caries progression [22, 23].

The development and formation of oral biofilms are related with bacterial quorum sensing (QS) and quorum quenching (QQ). As communication mechanisms, QS and QQ interfere with microbial community, becoming an alternative treatment for oral infections. Without killing any mouth bacteria, QQ keeps the balance of the mouth microbiota and hinders the development of biofilms, thus preventing the overgrowth of *Staphylococcus epidermidis* and *C. albicans* [17, 24–26]. Dysbiosis of the oral microbiota investigated in systemic diseases decreases microbial variety and alters the structure of the microbial flora by rising pathogenic bacteria and reducing commensal bacteria. The results of oral dysbiosis are mouth infections and diseases, such as gingivitis, periodontitis, mouth ulcers, dental caries, and oral candidiasis. Most microbial pathogens increase proinflammatory cytokines, leading to gingivitis and periodontitis. The pathogenesis of multiple diseases due to microbial flora could be better described as atopobiosis, which is defined as the appearance of microorganisms that are specific to a certain microenvironment in the "wrong" place. Atopobiosis is one of the most common mechanisms of participation of the oral microbiome in numerous conditions and diseases [27].

Recently, periodontal disease is a changed concept, no longer linked to a certain bacterium, but more to poly-microbial groups, these causing dysbiosis and modifying normal immune responses. It has been demonstrated that *Porphyromonas gingivalis* (a pathogen found in humans in the oral cavity), in small numbers (<1%) determines and modulates the virulence of the entire community [11–14, 28].

Moreover, dysbiosis causes periodontitis and thus the subgingival microbiome is important in the pathogenesis of the disease and has been associated with systemic diseases, such as oral, esophageal, gastric, lung, pancreatic, prostate and breast cancer. Also, other systemic diseases are related to periodontitis, such as cardiovascular diseases/atherosclerosis, rheumatoid arthritis (RA), neurological and endocrine system disorders, inflammatory bowel disease, Alzheimer's disease, diabetes. Consequently, the oral microbiota can be a marker of human health and reflect the state of the disease in real time, an important tool in the early warning of the risk of disease. The metabolites of the oral microbiota enter the blood and produce inflammation in the human body promoting the development of chronic inflammatory diseases in the digestive system [10]. For example, *P. gingivalis* and *Fusobacterium nucleatum* are the most well-known pathogens of periodontal disease that influence and disturb the structure of the intestinal microbiota community, actively participate in the destruction of the intestinal barrier by increasing the permeability of the intestinal mucus and implicitly in the systemic inflammatory response [29]. Recent studies have shown that dysbiosis in periodontal disease was directly correlated in the long term with RA and when RA was properly treated, oral microbiota dysbiosis was restored [30].

Recently, a significant number of studies have demonstrated a strong correlation between the oral and intestinal microbiota and osteoarthritis (OA), but many clinical researches are still necessary to prove the precise mechanism of action that affects the composition and behavior of the intestinal microbes. Characteristics of the microbiome and its metabolites have already been shown to be applied in the future to diagnose and treat OA or other bone-related diseases. It is known that the current treatment of OA only relieves the pain. In the future, diet, fecal transplantation, and future therapies targeting the microbiota are estimated to be approached in all diagnostic and therapeutic protocols. Consequently, diet control (especially foods with low gluten content and enriched in indigestible B) could open new scientific horizons in the occurrence and monitoring of OA pathology [6, 31–34].

More and more studies have shown that the reduced buffering capacity of saliva is related to periodontal disease and caries. Oral probiotics and prebiotics are a method of direct introduction of certain species of bacteria and prebiotics into the oral microbiota and can determine a rapid and effective physiological and biochemical response in oral health. There are many anti-aging pre- and probiotic formulations, but mainly it is the utilization of the alkalogenicity of some species to fight the demineralization of tooth by pathogenic bacteria. Thus, a main source of alkalinity in the mouth is arginine, which has been proved to effectively inhibit the dental caries and has recently been considered as an ingredient in certain toothpastes. Furthermore, natural indigestible B compounds, which are found in many fruits and vegetables, have recently been shown to have significant effects on the buffering capacity of saliva and on periodontal disease [35, 36].

Boron in dental medicine

Boron in tooth structure

B-rich diet influences tooth mineral composition, tooth strength, density and micro-hardness, alveolar bone mineral density in rabbits nurtured with a high-energy diet. Thus, the B content in the diet had a beneficial effect on the teeth mineral composition and on the surrounding alveolar bone [37, 38].

Several researches have been found that fluorine (F) and B are mainly concentrated in the teeth and bones of the human body (B accumulated between 0.001 ppm and 5.88 ppm, while F accumulated between 21.24 ppm and 449.22 ppm). The level of B and F of non-carious teeth was higher than that of carious teeth in human tests and a negative correlation between F and B was detected which was significant in the group. The negative correlation found between B and F in all groups was significant. The results once again demonstrated the importance of F and B as a protective factor for dental caries [39–41].

B element is found throughout the human body with a high level in bones, teeth, and nails. Surprisingly, B was detected in the teeth in the range of 25–85 ppm. Recently data indicated that the $^{10}B/^{11}B$ ratio in the enamel of carious and healthy teeth according to age and sex varied from 0.2007 to 0.2574 [42]. Also, some studies have shown that other microelements such as F, aluminum, strontium (Sr), iron, selenium, manganese, cadmium, and copper are directly related to the existence of dental caries in humans and animals, more precisely some prevent caries and others amplify it.

We have found some studies that demonstrated the presence of B in the tooth structures and its influence on the cariogenic activity.

In a specific study, the levels of B in non-carious teeth were demonstrated to be higher than those of carious teeth, thus proving that the B-rich diet can have a cariostatic effect [41]. Furthermore, B was showed to have an osteogenic effect and can influence trabecular and alveolar bone [43]. It was also proved that increasing the level of B in the diet increased the concentration of B in the mineral composition of the teeth and had positive effects on the alveolar bone around the teeth [43]. Moreover, B was showed to have an important role in the growth and development of teeth after eruption [44].

Boron in dental materials

Recently, important progress has been presented in the introduction of new catalysts and methods for incorporating B into organic molecules [45]. Biomaterials containing B can be the new generation of biomaterials, with a role in bone regeneration, because B demonstrated an increased ability to adhere to these dental materials and to stimulate the bone-derived cells' development and osteogenic differentiation [46, 47].

Recently, changes in the mechanical properties of polymethyl methacrylate (PMMA) were investigated when B was part of the acrylic mass in different proportions. It was observed that the mechanical properties of PMMA were favorably modified both by adding borax and colemanite, the resistance tests to bending and impact and surface hardness being superior to the form without added B [48]. The incorporation of B in dental materials was demonstrated to limit the progression of dental caries, more precisely, a level of B in dental composites, namely concentrations of 1%, 5% and 10% (*w/w*) as sodium pentaborate pentahydrate has an antibacterial effect on *S. mutans* [49, 50].

An intensively studied synthetic organic compound of the boronic acid class is AN0128, a B-containing synthetic compound. This has antibacterial and anti-inflammatory properties *in vitro* against the bacteria *Prevotella intermedia*, *P. gingivalis*, *Eubacterium nodatum* and *Treponema denticola* that are associated with periodontal disease [51].

The cariopreventive effects of dental materials that release ions, for example, F and B, have recently been demonstrated *in vitro* [52], this being an area of interest scientifically supported in recent years. Moreover, dental materials that release ions, such as Sr and B, have antimicrobial, remineralizing and acid-resistant properties [53, 54]. Innovative applications in dentistry have claimed that nanomaterials reinforced with adhesives possess beneficial biological properties and improve mechanical and physical properties to help maintain adhesion for a long time [55]. For example, B nitride nanotubes (BNNTs) have recently been used for dental adhesives and have shown much improved bioactivity and physicochemical properties [56]. Furthermore, researchers studied the effect of adding B (as an additive) on the density and biocompatibility of sintered implants [57].

A classic example of the use of BA in cosmetic formulations, as an antiseptic and antiviral agent, such as in mouthwash, eye drops, skin lotions and other cosmetic products have been synthesized and tested for antimicrobial activity. BA forms tetrahedral anionic complexes with polyhydroxy compounds in aqueous solution [49, 58]. Recently, the biocompatibility and antimicrobial activity of borate dendrimers of poly(glycerol-chitosan) (PGLD-Ch)B were investigated and the sorption properties, cytotoxicity, antimicrobial activities and *in vivo* behavior of these macromolecules in rats were determined [59]. Recently, irrigation with 0.75% BA was demonstrated to be a possible adjuvant in the treatment of moderate gingivitis and therefore it can be a therapeutic tool in the management of periodontal disease and a treatment choice for periodontitis and gingivitis [51, 60–63].

Recent results regarding the clinical response of the periodontal material to CaFB and BA hydrogels showed a significant decrease in the inflammatory response related to classical procedures. The CaFB hydrogel showed a superior anti-inflammatory reaction to the BA hydrogel [36]. Moreover, CaFB being proven as a peroxide scavenger positively influences calcium metabolism, the development of bones and their growth, soft tissues and collagen can be an adhesive for many classes of dental materials in the future [5, 64–66].

Conclusions and future perspectives

BCCs are still proving their capacity as additives for dental materials as they continuously prove their anti-inflammatory and antibacterial properties. In addition to that, one of the most important aspects to be taken into consideration is the further testing for biocompatibility of the other oral structures, such as periodontal ligaments, dental follicle cells, and gingival fibroblasts. Over times, BCCs have demonstrated their usefulness in dentistry.

The new perspectives regarding the B essentiality for the healthy symbiosis will determine new directions for the use of B compounds, which are not digestible. An example is the recently discovered diester chlorogenoborate (DCB) complex [67, 68] that will guide the natural B-based nutraceuticals to be used to target the human microbiome (gut, which is the most important for human health, oral cavity, vagina, skin, and scalp microbiome). In the future, we believe that indigestible B species will become essential prebiotic candidates and will ensure both the oral cavity and the colon health, as new functional foods. In fact, indigestible B, in nutrition, will target the colon and the oral cavity, and last but not least, the vagina, the skin and the scalp.

Recently, B is proposed as an essential element for AI-2 synthesis of the QS system, which affects bacterial collective behavior, population density detection, virulence, biofilm production [68]. Recent studies have shown that the addition of B species to an AI-2 precursor (which is synthesized by bacteria intracellularly) generates AI-2B in the extracellular environment of the bacteria [67].

New insights into B species essentiality to animals and humans were reported by us. All the known actions of B on human health can be explained by the essentiality of B on healthy symbiosis. The action mechanism of B species

(*e.g.*, DCB complex, CaFB, etc.) is actually the participation in the metabolism of the signaling molecule B (AI-2B), as well as the inclusion of B in the mucus gel layer. Both the microbiome and the mucus gel layer may become B targets. Thereby, B can be an essential micronutrient for symbiotic interaction between microbiota and a mammalian host for healthy humans and animals.

B deficiency in the microbiota can cause: (*i*) dysbiosis, and (*ii*) mucus degradation, with consequences on symbiosis [6, 67, 68], which produces the direct interaction of host cell membranes with bacterial biofilm, and therefore their direct infection. Consequently, the microbiota needs B to achieve: (*i*) biosynthesis of a furanosyl borate diester (AI-2B), a part of signaling molecules family used in quorum detection; and (*ii*) a protective barrier that separates the microbiota from the host (B prevents direct contact between bacteria and the host organism, thus preventing the occurrence of direct infectious effects).

The human body health depends on the microbiome health, and B as a nutrient element becomes radical for the human health. Moreover, the microbiome interacts with the entire human body through the well-known axes: gut–immunity axis, gut–bone axis, gut–brain axis, gut–heart axis, gut–cartilage axis, gut–thyroid axis, gut–lung axis. Subsequently, if B is essential for the symbiosis, then B has a beneficial role in hindering some diseases, such as osteoporosis (OP), OA, RA, cardiovascular inflammation, depression, obesity, diabetes, viral, bacterial, and parasitic infections, thyroid disease [6, 69–71].

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author

Ion Romulus Scorei, Professor, PhD, Department of Biochemistry, BioBoron Research Institute, S.C. Natural Research S.R.L., 31B Dunării Street, 207465 Podari, Dolj County, Romania; Phone/Fax +40351–407 543, e-mail: romulus_ion@yahoo.com

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