Biological Trace Element Research (2018) 186:31–51
https://doi.org/10.1007/s12011-018-1284-3

The Physiological Role of Boron on Health

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Received: 5 September 2017 / Accepted: 21 February 2018 / Published online: 15 March 2018

Abstract
Boron is an essential mineral that plays an important role in several biological processes. Boron is required for growth of plants, animals, and humans. There are increasing evidences of this nutrient showing a variety of pleiotropic effects, ranging from anti-inflammatory and antioxidant effects to the modulation of different body systems. In the past few years, the trials showed disease-related polymorphisms of boron in different species, which has drawn attention of scientists to the significance of boron to health. Low boron profile has been related with poor immune function, increased risk of mortality, osteoporosis, and cognitive deterioration. High boron status revealed injury to cell and toxicity in different animals and humans. Some studies have shown some benefits of higher boron status, but findings have been generally mixed, which perhaps accentuates the fact that dietary intake will benefit only if supplemental amount is appropriate. The health benefits of boron are numerous in animals and humans; for instance, it affects the growth at safe intake. Central nervous system shows improvement and immune organs exhibit enhanced immunity with boron supplementation. Hepatic metabolism also shows positive changes in response to dietary boron intake. Furthermore, animals and human fed diets supplemented with boron reveal improved bone density and other benefits including embryonic development, wound healing, and cancer therapy. It has also been reported that boron affects the metabolism of several enzymes and minerals. In the background of these health benefits, low or high boron status is giving cause for concern. Additionally, researches are needed to further elucidate the mechanisms of boron effects, and determine the requirements in different species.

Keywords Boron · Dietary nutrient · Safe intake · Physiological benefits

Introduction

The trace element boron is a dynamic nutrient of essential importance to animal and human biology. This has turn into progressively obvious as latest researches have revealed a hitherto surprise actions for this minerals in areas significant to animal and human health. Boron occurs mainly in the form of inorganic borates in oceans and soils [1] and stabilizes ribose, a major constituent of the self-assembling molecule RNA which might have preceded DNA [2]. The physiological quantities of boron can alter the metabolism and consumption of various substances involved in growth and development [3]. Boron, therefore, usually affects several organs and body systems, including the skin, brain, digestive, skeletal, and immune organs and systems. In vertebrates, the borates are essential for their unique bonding and structural characteristics [4]. This function serves to ease certain conditions in animals, such as arthritis, osteoporosis, and coronary heart disease [5, 6]. Boron also alters different metabolic parameters in animals, such as swine, chicken, cattle, ostrich, and some other tested species [6–9]. Furthermore, it is beneficial for different organs, because of its interactions with calcium, vitamin D, and magnesium [10–12]. That is why borates are being used on industrial scale in different diet supplements and medicines.

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Occurrence, Source, and History of Boron

The trace nutrient boron belongs to the family of metalloid, having an atomic number of 5 and a molecular weight of 10.81 g/mol. Boron has two abundant isotopes, ^{10}B and ^{11}B. Due to large capture cross-section, ^{10}B is an exceptional

neutron absorber [13, 4]. Boron does not occur as an elemental form in nature, and its chemistry is complex and forms compound (borates) with other elements [4]. The most widely used borates having boron minerals are listed in Table 1 [14, 15]. The nutrient boron is present mostly in soil and water. The earth crust mainly contains boron, having an average concentration of 10–20 ppm in soil [16]. The large parts of the world has less boron, while a high amount is also present, for example, in parts of the western USA, Turkey, Brazil, Russia, and China [4, 17]. The world's largest deposits of boron are found in a topographical constituency that is from the Mediterranean nations inland to Kazakhstan [17, 18].

The average of 4.6 ppm boron with range of 0.5–9.6 ppm is present in seawater. The range of boron in fresh water varies from 0.01 to 1.5 ppm, with more concentrations in areas having high concentrations in soil [19]. Boron is the most energetic nutrient that makes their approach into the food and can be derived from soil minerals directly. The dietary sources of boron are of plant-based (vegetables, fruits, and nuts). It is also obvious that a considerable amount of boron is found in all main types of feed, which is equivalent to the amount of essential trace minerals such as zinc and copper [20]. Mostly, rich boron concentration is found in fruits except for pineapple, berries, and citrus fruit [21]. Moreover, leafy plants, dry fruits, and nuts contain a high amount of boron [21–24] (Table 2).

The history of boron is very old and credit was dated back over 4000 years ago by Babylonians who used borax as a flux in gold industry. The ancient Egyptians are well known for the use of boron in mummification, metallurgic, and medicinal purposes. These very old evidences has not been verified, but the most verified evidence of boron usage in old ages was the trade of borate "tinkar" from China to Mecca and Medina in the eighth century by Arab traders [25]. Another proved evidence of borax flux usage by goldsmiths of Europe dated back in twelfth century. The most primordial source of borates is considered as Tibetan lakes and transported from Himalayas region to India [26, 19]. The borate manufacturing in Turkey started with calcium borate mining in 1865. At about the similar period, some borate reserves were discovered in Death Valley in Nevada and California. The borax deposit in Mojave Desert in California was found in 1913 [27, 26]. Sodium borates were found in 1960 at Kirka and Anatolia. Turkey has delivered borates for many years to European boric acid manufacturers [26, 28, 29]. As a consequence, today, Turkey is well known for being the largest boron products supplier in the world (Table 3).

Requirement of Boron in Microorganisms and Plants

Boron is constituent in all phyla of living organisms performing several biological functions. Boron is a component of microbial antibiotics, such as borophycin, aplasmomycin, tartrolon, and boromycin [30], present in bacterial quorum sensing signal molecule, auto-inducer (AI-2) [31], and in the vibrioferrin. Some marine bacteria produced siderophore containing boron [32]. Besides, boron is an important element for algal flagellate and marine cyanobacteria species [30, 33]. Recently, a special group of boron compounds containing borolithochromes has been found in well-preserved Jurassic red algae *Solenopora jurassica*, which is responsible for their unique coloration. Borolithochromes are the complex spiroborates (esters of boric acid) having phenolic moieties, and they are representing a distinctive class of fossil organic pigments [34]. Moreover, high boron endurance of *Saccharomyces cerevisiae*, due to multidrug resistance transporter encoded by ATR1, makes it the most beneficial species of yeast, involved in baking and fermenting. This gene is also distributed in some bacteria, fungi, and lower eukaryotes and activated on boron exposure [35]. *Bacillus boroniphilus* needs boron for its growth and can endure more than 450 mM of boron [36]. The *Azotobacter*, which is involved in nitrogen fixation, also needs boron for this activity. Blue-green algae and microorganisms of genus *Frankia* also need boron for their growth. Furthermore, boron was reported to interact and stabilize the glycolipids of the heterocyst's [37–40].

Table 1 The most commonly used boron-containing compounds around the world

Compound	Color	Boron percentage	Water solubility
Anhydrous borax	White	21.49	2.5556 g/100 g at 25 °C
Borax	Colorless	11.34	5.92 g/100 g at 25 °C
Borax penta-hydrate	White	14.85	3.6 g/100 g at 20 °C
Boric acid	White	17.48	63.5 g/L at 30 °C
Boron oxide	Colorless	31.06	Slightly soluble
Colemanite	White	15.78	Slightly soluble
Sodium perborate mono-hydrate	White	10.83	15 g/L at 20 °C
Sodium perborate tetra-hydrate	White	7.03	23 g/L at 20 °C
Ulexite	White	13.33	Slightly soluble

References: Muetterties [14]; Windholz et al. [15]

Table 2 The amount of boron in some edible items

Source	Boron content/100 g	Source	Boron content/100 g
Almonds	2.82	Grapes	2.72
Apples	2.73	Hazelnuts	2.77
Apricots	2.11	Honey	0.72
Avocado	1.66	Lentils	0.74
Bananas	2.06	Milk	0.23
Beans	1.56	Onion	0.20
Bread	0.48	Orange	0.25
Broccoli	2.19	Peaches	0.52
Carrots	1.39	Peanuts	1.92
Cashew nuts	1.15	Peanuts	1.80
Catsup	1.39	Pear	0.32
Celery	2.47	Potato	0.18
Cheese	0.19	Prunes	1.18
Cherries	1.47	Raisins	4.51
Chickpeas	0.71	Soy meal	2.80
Dates	1.08	Tomato	2.72
Egg	0.37	Walnuts	1.63
Flour	0.28	Wheat	2.41

References: Hunt et al. [21]; Vanderpool and Johnson [22]; Nielson [23]; Anderson et al. [24]

Boron is also necessary for plants growth and development, and its availability in water and soil is a key factor of the agricultural production [41]. Some scientists assessed that about 90% of boron is present in the plant cell walls [42]. Boron can form complexes with cell wall ingredients such as polyhydroxyl polymers, pectins, and polyols [41, 43]. That is why boron is associated in stability and synthesis of cell wall by making esters with the *cis*-diol components of cell wall [42]. This helps in provision of shape, strength, and rigidity to the cell. Borates are also able to form linkage with biological compounds having hydroxyl groups. One of the main functions of boron in plants has been described due to its capability to make esters with rhamnogalacturonan II (RG-II) [44]. The establishment of this borate ester is necessary for cell wall function and structure [45], as it plays a role in the control of tensile strength and cell wall permeability [46]. For instance, decreased RG-II dimer formation and abnormally swollen cell walls have been revealed by deficiency of boron [47]. Furthermore, the importance of the RGII-borate complex has been shown in the Arabidopsis *mur1-1* and *mur1-2* mutant plants [48]. Meanwhile, Noguchi et al. have also described less cross-linking actions in the cell walls of Arabidopsis *bor1-1* mutant compared to wild-type plants under boron deficiency [49].

Table 3 Reserves of boron (million tons) around the world

Country	Total reserves (million tons)	Percentage share of world
Argentina	09	01
Bolivia	19	02
Chile	41	05
China	36	04
Kazakhstan	15	02
Peru	22	02
Russia	100	11
Turkey	563	64
USA	80	09

Reference: Sirin [29]

Numerous studies have also pointed out the importance of boron for nitrogen-fixation, as in the vesicles of actinomycetes of the genus *Frankia* [37]. This microorganism needs boron for the solidity of the envelopes that shelter nitrogenase by oxygen from inactivation. Boron is also required for the regulation of glycoproteins that are essential as indicators for differentiation of bacteroid into a nitrogen-fixing form [38]. It is well established that boron is involved in various processes in plants such as oxidase activity, root elongation, sugar translocation, pollen tube growth, carbohydrate metabolism, and nucleic acid synthesis [42]. Boron is an important nutrient, required for flowering, seed setting, pollination, and fruit quality. Adequate boron uptake will assist in the increased fertilization and fruit set, because it is involved in pollen tube formation and pollen germination [42]. Therefore, if the supply of boron is insufficient, flower will blossom poorly, the rate of fruit setting is low, and the yield is affected. There is also increasing data that boron is obligatory for the

preservation of the functions and structure of plasma membrane [50, 44]. It has been proposed that few membrane molecules having hydroxylated ions such as glycolipids and glycoproteins are good contenders for a probable boron action in the plasma membranes [42]. However, the mechanism of these borate complexes has not been cleared yet. Thus, it is essential to note that boron might put forth its potential in plasma membranes not only by alleviating of membrane molecules having *cis*-diol groups but also by modulating the genes expression interwoven in membrane function and structure.

Role of Boron in Animals and Humans

Recently, boron is considered to be possibly essential for animals and humans health. Boron appears to participate in hydroxylation reactions, which plays a role in the synthesis and metabolisms of diverse reactions [8]. Boron is an effective treatment choice for arthritis and cause significant improvement in bone development seen in 95% of cases by increasing calcium integration effectively into bone, joints, and cartilage. Moreover, it affects several hormones, comprising testosterone and estrogen [1]. The cancer therapy can be ensured by boron neutron capture agents. The boric acid is very useful to overcome breast cancer cells in vitro [51]. It is supposed that boron can affect some of the blood clotting factors in the body. Boron can expressively ease the problems produced by congestive heart failure conditions. Boron assists to lessen lipid accumulation and allows the cholesterol removal through various ways, therefore minimizing the risks of developing situations like blood clots and atherosclerosis, and defending the body against heart attacks and strokes [52]. But further research is required to validate this result, which would lead to a main confederate in the battle against heart disease. Due to complex structure and bonding characteristics, borates have shown inhibitory action on enzymes like aldehydes dehydrogenase, nitric oxide synthase, peptidase, xanthine oxidase, and proteases [53]. Boron affects the metabolism of testosterone, estrogen, glucose, and insulin. Glycoproteins, glycolipids, and other molecules having hydroxyl group may form complex with boric acid and modify the integrity of membrane [54, 55]. Borates also revealed the actions as an anti-inflammatory and antioxidant agent in cancer, wound healing, diseases control, reducing genotoxicity, and modulating mitochondrial membrane activity [56–58]. Additionally, boric acid has overhauled the job of the acetylcholinesterase which is repressed by the pesticides [59] and also prevented the body from the oxidative stress induced by CCL_4 and other agents [60–62]. The required boron quantities are species-specific and also highly variable. In most species, including humans, the exact required amount of boron is still being determined.

Boron and Growth Performance

Boron is essential for growth, due to its role in strengthening the cell membrane [63]. The concentration of boron varies from species to species [64, 65] and low boron status inhibits growth [66]. As boron deficiency leads to poor growth, for that reason, it should be available in suitable concentration for body growth and development. In the previous study, ostrich chicks supplemented with 160 mg/L of boron exhibited a positive effect on the final body weight. Similarly, the average daily gain and acid detergent fiber also significantly increased [64]. In another study, broilers were given free access to water and feed, and different groups were treated with various doses of boron. The body weight of female birds was not influenced by dietary boron; however, it was significantly increased in male birds [67]. Fassani et al. showed that providing boron at 30, 60, 90, and 120 ppm caused linear growths in the body weight at the age of 21–42 days in birds. Birds fed 30 ppm of boron consumed 140 g of less feed compared to control, and showed better feed conversion and less mortality [68]. Similarly, boron was added to boron-deficient diet, and an improved feed intake and growth rate was observed in pigs [6, 69]. Goihl described that low amount of boron supplemented to the swine feed (5–10 ppm) were favorable, causing better weight gain, feed efficiency, and phosphorus and calcium maintenance in the body [70]. Though the findings are revealing a positive boron function in the animal's growth, it is recommended that the ultimate concentration should be found based on further studies.

Boron and Meat Quality

According to several researches, the ultimate pH, ash contents, and meat color are the most significant indicators of meat quality [71, 72]. The pH of meat depends on the lactic acid content in muscle tissue, and glycolysis is the main producer of lactic acid after slaughter, while a close correlation between muscle pH and glycogen levels has been widely accepted [73, 74]. The alteration in pH of meat significantly affects its quality and is a direct result of changes in muscle glycogen stores prior to slaughter [75]. It has been reported that meat with a higher pH has a higher water holding capacity and lower levels of moisture loss [71]. At a higher pH, protein can bind more strongly with water, resulting in less free water and a darker meat color [76]. Meanwhile, at a high pH, the tenderness of the meat also increases and the flavor becomes less attractive [75]. Boron, with the aid of oxidoreductases, plays a basic role in controlling the processes associated with specific metabolic pathways [77]. Oxidoreductases need pyridine to promote enzyme activity. Boron reversibly reduces the activity of these enzymes by making transition state analogs, or by competing for nicotinamide adenine dinucleotide (NAD) or flavin adenine dinucleotide (FAD) [77, 78], which

are the important substrates of glycolysis. Boron inhibits the glycolytic pathway by acting on NAD, thereby reducing the lactic acid content of muscle and affecting the pH value of meat. Boron has also been reported to regulate the pH concentration of muscle by acting on metabolite concentration [64]. Since supplemental boron is beneficial in controlling pH, therefore suitable for improving the quality of the meat [77, 64].

The ash content of the muscle is also an important index, as it is representative of the minerals and trace elements in the meat [79]. Boron regulates the metabolism of minerals like Mg, P, Mo, and Ca [80]. The addition of boron to the drinking water of the chickens also showed the improvement of Fe and Zn levels in the meat [81]. Therefore, boron supplementation modulates the contents of ash in meat [82]. The ash content showed a gradual increase, as boron effectively increased the mineral content of the muscle; however, further research is needed to quantify this factor. Supplementation of boron also inhibits the activity of serine proteases. Serine proteases comprise one of the most abundant groups of proteolytic enzymes that are involved in several physiological processes, through the activation of precursor proteins [83]. In one study, different doses of boron were administered in the drinking water of ostriches to evaluate physical and chemical properties of ostrich meat [64]. The meat physical properties (pH, drip loss, cooking loss) showed significant result following boron administration. The data revealed that the cooking loss and drip loss were decreased, while the result of meat color was non-significant by boron supplementation. The results of meat chemical properties (moisture, fat, protein, ash, and cholesterol levels) were also significant in boron-treated groups as compared to non-boron-treated group. And, the doses of boron up to 160 mg/L were desirable in both physical and chemical properties of meat in ostrich chicks [64]. Meanwhile, the previous study on rat showed that boron supplementation at 8 mg/kg caused a reduction in triglycerides (TG) and cholesterol levels [84]. Also, boron showed positive effects on visceral fat by reducing oxidative stress [85]. Furthermore, the administration of boron reduced levels of TG, cholesterol, and non-esterified fatty acids in the blood [8], thus modulates muscle profile. So far, the studies have been carried out mainly in serum. Data on changes in the lipid profile in the muscle after boron administration are necessary, thus more studies are needed to elucidate the effect on the lipid profile.

Boron and Bone Development

Boron plays an important role in the development of bones [86], as it is beneficial in metabolism [87] and regeneration [86] of bones. Boron also plays a role in the proliferation and mineralization of bones [88]. It is well known that boron affects a variety of metabolic activities in bones. It interacts with magnesium, vitamin D, and calcium, all of which play an important role in the metabolism of bone [1]. This synergistic association with Ca and Mg homeostasis aids its role in bone strength [10]. The increment of age may cause bone weakness with porous bone, and boron is helpful to overcome this deterioration by certifying that the level of calcium and magnesium is working effectively [89, 90, 10]. Boron appears to accelerate the osteoblastic cell activity through calcium flux [91]. Calcium fructoborate significantly reduces serum levels of the C-reactive protein levels in serum, signifying that this distinctive plant–mineral borate formulation may stimulate the bone health and strength by controlling inflammation related with the loss of bone mineral density [92]. Furthermore, boron was reported to be helpful for the metabolism of bone in terms of proliferation, cell survival, and mRNA expression of osteoblast proteins (MC3T3-E1) and mineralization [88].

The concentration of boron in bone depends on the amount of element consumed that could be favorable for bone metabolism, mineralization, and regeneration [93]. Boron deprivation in animals leads to impaired growth and abnormal bone development [1]. Rats that had been deprived of boron showed increased trabecular separation and reduced bone volume. Furthermore, boron deficiency resulted in reduced strength of the femur [94]. Boron deficiency is associated with mineral changes, suggesting that boron plays a role in promoting bone growth and maintenance in osteoblast activity [95]. Some researchers recommend only an optimal dosage of boron for proper bone development in the animals and humans [88, 96]. Earlier studies have shown that suitable doses could have desirable effects on bone strength and development. A low supply of boron accelerates the differentiation and proliferation of osteoblasts [91]. Histopathological and microbiological evaluation indicated that local or systematic application of boric acid was effective to treat bone disorders [97]. An experimental study showed that boron was helpful in improving the ash content of the femur [94]. Cheng et al. supplemented the drinking water of ostrich chicks with boron at 0, 100, 200, and 400 mg/L, to investigate the effects of those doses on the tibia. Various parameters, such as bone mineral density, tibial length, ash content, weight, perimeter, and thickness of cortical bone, were examined. A significant increase was noted among most parameters, and 200 mg/L was shown to be an effective dose for enhancing bone strength [96]. Appropriate boron supplementation caused significant improvement in bone strength because it affects leptin which is essential for bone [96, 98]. Rats that are deficient in leptin exhibit lower bone density in the femur and lower levels of bone minerals [99].

Recently, bioactive glass technology has also shown that boron aids in bone formation. When bioactive glass contains boron, bone formation was enhanced [100]. This enhancement occurs because of the effects of bioactive glass on angiogenesis, a process that is important for tissue engineering and wound repair. Experimentally, animal showed increased

angiogenesis with the use of boron-containing bioactive glass [101]. Furthermore, the comparison of boron supplementation at doses of 1.0 and 0 ng/mL was conducted following cell culture study, and displayed positive effects with boron [88]. In addition, boron increases the levels of bone morphogenetic proteins, and its deficiency could lead to osteoporosis [102]. These studies show that boron is an important and effective therapy for weak bones, thus, essential for the formation and maintenance of bone. More studies in different animals are needed to determine optimum level of boron.

Boron and Liver Functions

The liver is known as the largest body gland [103] and the first organ receiving nutrients from food. That is why the liver is more prone to the risk of toxic substances exposure. As liver develops, the liver cells gradually attain the ability to perform the functions, for instance the detoxification of toxic ingredients such as pesticides, drugs, etc. [104]. Boron has reported to show positive effects in the development and protection of liver. Significant reductions in very low-density lipoprotein (VLDL) and serum TG levels were reported in animals treated with boron via oral administration [105]. In one study, boron was orally administered to 12 pregnant cattle at 30 g/day for 28 days. In that study, the effects of hormones and serum metabolites were evaluated and blood samples were collected on a weekly basis. Boron showed positive effects in the modulation of serum metabolites, which are necessary for liver. The overall liver metabolism was enhanced by boron, and the incidence of liver damage during early lactation was reduced [8, 105]. Although the precise mechanisms remain unknown, boron obviously counteracts the adverse effects of liver disease, by modulating the effects of oxidative stress and restoring normal liver function [106].

In another study, the effects of boron on the liver were examined in New Zealand white rabbits. Rabbits were supplemented with oral doses of boron at 10, 30, and 50 mg/kg BW for 96 h. These levels did not affect any hematological parameters, and the report suggested that boron showed positive effects on fatty liver and visceral fat, by reducing oxidative stress [107]. Boron appears to inhibit liver damage by acting on the mitochondria. It reportedly affects the Krebs cycle, the glucose-alanine cycle, and methionine metabolism, thereby reducing oxidative stress and positively affecting the lipid profile of the liver [107]. The administration of boron at 4 g/day has been effective in maintaining relatively low lipid levels in the plasma of dogs. One week after oral administration of boron, lower levels of insulin, glucose, and apolipoprotein B-100 was detected in boron-treated dogs, in comparison to the non-boron-treated group. During the second week of boron supplementation, lower levels of TG and VLDL were also observed [108]. These results support the assumption that boron effectively reduces lipid levels in the liver. Boron might also affect other hepatocyte functions, including the storage and metabolism of glycogen at optimal supplementation. So, it is necessary to evaluate this mechanism.

Boron and Embryonic Development

The fetus depends entirely on maternal nutrition, comprising trace minerals. Insufficient transmission of these nutrients can lead to fetal mineral dearth, resulting in fetal dysplasia and other abnormalities. In addition, newborns with inadequate maternal nutrients intake in the course of gestation or pregnancy have less body assets and are prone to mineral paucity in the early life [109]. Some researchers have studied the significance of boron in animals and human nourishment. Nielsen's "stressor model" is an extensively used proposal. In this project, the lack of one or more nutrients in diet, such as potassium, copper, calcium, magnesium, or vitamin D, is used as dietary stress to increase the chance of observing boron reactions [110]. Moreover, Nielsen et al. executed many studies to assess the supplemental boron effects on diets having marginal concentration of copper or magnesium in the body [111]. Under these circumstances, boron positively altered the biochemistry of numerous nutritional indicators, including hemoglobin, blood glucose, platelet, and hormonal levels. In addition, boron supplements were found to reduce the severity of birds and rats lacking calcium and vitamin D [112, 113].

The data regarding the role of boron nutrient in embryonic development is not sufficient, and only a few species have been described so far. Previously, it was shown that the growth of the trout embryo and the survival of the zebrafish embryo were impaired by a deficiency of boron [114, 115]. Moreover, low boron profile adversely affected the embryonic development of rats [116] and frogs [117]. And, boron deficiency also restricts the maturation events of oocytes in *Xenopus laevis* [66]. The mechanism underlying the enhancement of fetal development and survival by boron has not been studied. In the past, nutrition and embryology was mostly considered as a distinct field. More recently, researchers have focused more on the cellular mechanisms that affect fetal development. Though most of work is done with rat models, it is required to persuade the results to the practice of human and animal nutrition. Some controlled nutritional trials must be piloted to determine whether animals and humans have the same effect. With latest technologies and sensitive assays available, effects of boron nutrition and embryonic development can be studied more easily together. The recent results presented that boron treatment upregulated myogenic gene expression including desmin, myosin heavy chain, myogenin, and MyoD [118]. These outcomes offer an opportunity for the development of scaffolds for the embryonic muscle growth.

Boron and Brain Activity

Boron is essential for the activity of brain functioning, as its deficiency possibly has unfavorable effects on the central nervous system [119]. The study of brain activity in humans and animals have displayed that boron deprivation in diet caused a decline in the electrical activity of the brain [120]. Under controlled feeding conditions, boron supplementation (3 mg/day) in subjects who consumed a diet that provided approximately 0.25 mg boron/2000 kcal for about 63 days altered the electroencephalogram, with a trend toward less activity at lower frequencies and greater activity at higher frequencies of the dominant frequency spectrum [121]. Meanwhile, supplemental boron has led to improved psychomotor skills, less drowsiness, short-term memory improvement, mental alertness, and improved attention in older men and women. Similar effects have been observed in the rat. Increased activity at low frequency is characteristic of the relaxed state, and behavioral activation is associated with reduced performance of psychomotor tasks. Reductions in high-frequency activity have been associated with memory impairment in boron-deficient subjects [120–122]. Boron supplementation, following a state of boron deficiency, leads to improved psychomotor speed and dexterity, and the enhanced short-term cognitive processes of attention and memory [120]. Boron deficiency also showed reduction in the amount of cerebellum P, indicating the modulation of brain activity in response to boron deficiency [119]. Furthermore, boron-deficient rats (0.1 mg/kg) were less active than boron-sufficient rats (3.0 mg/kg). This is because boron deficiency reduces the number, distance, and time of horizontal movements; front entries; distance from the margin; and vertical breaks and jumps [123]. In the ostrich, boron has a positive effect on the brain and an effective dose aids in brain development. The histological structure of the brain in the ostrich showed an enhanced development of neural cells when 160 mg/L boron is added to the drinking water. Furthermore, inhibition of apoptosis in the brain has also been observed at this dosage [124]. It has been hypothesized that effects of boron on brain function and brain behavior are due to membrane changes that affect the transmission of nerve impulses [125, 123].

Boron and Hormonal Effects

Boron influences the metabolism of steroid hormones and in particular of sex hormones. It upsurges low testosterone levels in men and estrogen levels in menopausal women [126, 127]. The results showed that heavy body exercise for 2 months could disturb the testosterone level of non-professional bodybuilders, but the supplementation of boron regulates the level of this hormone [128]. Boron can increase the estrogen production in menopausal females, and can take back their sex energy within a few days of treatment. It raises the natural sex hormones level in the body, therefore reducing the need for pharmaceutical solutions or hormone replacement therapy. Boron can affluence the signs such as night sweats and hot flashes that are usually related with menopause, and it confirms that the level of minerals is appropriate, as postmenopausal females often suffer from hormonal imbalances that can skew many of the body's most important systems [126, 129, 130]. Furthermore, progesterone hormone therapy successfully prompted germinal vesicle breakdown in the oocytes from females nourished a boron-supplemented food [131]. Boron nutrition intake has reduced the adverse effects of vitamin D shortage in rodent model [132]. The mechanism may be arbitrated by increasing level of 25-hydroxyvitamin D in serum. The boron supplement can also enhance the level 17β-estradiol in postmenopausal females getting hormone replacement therapy [132]. In the diet of ovariectomized rat, the 5 mg/kg supplemental boron significantly improved the beneficial actions of 17β-estradiol hormone therapy on bone growth density, bone trabecular volume, and trabecular separation [133]. The formulation of 17β-estradiol with boron significantly enhanced the absorption and retention of calcium and magnesium [129]. Limited data recommends that boron can promote the role of insulin. In feed of rat containing 0.2 mg/kg boron, 2 mg/kg of boron supplementation reduced the plasma insulin level, but did not alter the concentration of blood glucose [131, 134]. It was reported that pancreatic insulin level released from boron-deficient chicks was nearly 75% more than boron-sufficient chicks [134]. Furthermore, boron is obligatory for salvation of testosterone and estrogen levels in blood [111]. Therefore, boron supplementation in animals and humans has positive effects on estrogen, testosterone, and estradiol, while boron deficiency is associated with the negative effect on these hormones [130, 131].

Boron and Wound Healing

Boron is known as wound healer, because 3% boric acid solution was reported to cure deep wounds. In the past, boric water (pharmacopeia) was known as antimicrobial agent [135]. In recent days, borates are also used as treatment of different wounds in very low concentrations. The mode of action of boron in healing of wound is unclear, but some trials have revealed that it is engaged in protein, collagen, and proteoglycan synthesis [136, 137]. It was examined that boron regulates the production of the extracellular matrix, which shows a significant role in the wound healing course by enhancing the release of proteins, collagen, and proteoglycans. Boron also encourages the release and synthesis of tumor necrosis factor [136, 138]. Furthermore, incubation with 10 mg/L of boron for 6 h induces the expression of intracellular matrix metalloproteinase-9 in keratinocytes [139]. Gelatinase zymography increased the secretion of gelatinase in keratinocytes supernatant after incubation with boron for

24 h. This may indicate that boron is one of the trace minerals necessary for wound healing. An in vitro trial verified quicker wound healing using boron compared with control [140]. Boron may play a role in wound healing by increasing keratinocytes migration. Boric acid is also reported to accelerate the wound healing by affecting the DNA double-strand breaks formation. The DNA damage and wound induced in experimental subjects with etoposide, irinotecan, doxorubicin, and hydrogen peroxide was measured through phosphorylation of $pATM^{(Ser1981)}$ and $H2AX^{(Ser139)}$ by the immunofluorescence method in the control and boron-treated groups. It was shown that foci numbers of $H2AX^{(Ser139)}$ were decreased significantly in the boric acid-treated groups and process of wound healing accelerated [141]. The results also indicate that boron hydrogel formulation can heal burn wounds successfully. This borate formulation may encourage burn wound healing process through complicated mechanisms of cell migration stimulation, vascularization, inflammatory response, and expression of growth factor [142]. The radiological, clinical, and histological investigation also shows that local boric acid administration may stimulate the fractures healing process [143]. In light of all this, there is a need for additional studies to further elucidate the mechanism of action of boron in wound healing, and controlled studies must be performed to investigate the role of boron in the treatment of wounds.

Boron and Oxidative Stress

Organophosphate (OP) compounds cause oxidative stress and changes in the antioxidant status in organisms. OP is often used as an insecticide in the food supply, so both humans and animals are routinely exposed to them [144]. OP compounds have produced toxic effects, particularly in the generation of ROS, by damaging numerous cell membrane components [145]. Recent work showed that the animal having sufficient amount of boron were protected from the OP insecticides [59]. Administration of boron resulted in reversal of OP-induced oxidative stress and enzyme activity. In addition, boron improved antioxidant mechanism of defense and restored different body organs in the mice [59]. The oxidative stress induced via endotoxin also reversed by boron administration. Endotoxin affects the organs by generating free radicals, and boron may protect the organs from the oxidation by causing functional and structural changes in the proteins [146]. The results in rodent model indicated that 40 mg/L of boron could increase antioxidant capacity of spleens and improve the spleen tissue structure [147]. In a recent study, boron-supplemented subjects who were exposed to chronic alcohol consumption revealed low level of oxidative stress [53].

Boron administration has been thought to reduce oxidative stress by increasing the glutathione reserves that neutralize the oxidants [148]. Additionally, the administration of boron increases the levels of GSH, thereby maintaining the toxic effects of malathion [59]. In the neonatal necrotizing enterocolitis rat model, boron supplementation increased the level of antioxidant to prevent the GSH reserves deletion [149]. Boron is also thought to increase the level of antioxidant capacity by reducing the intracellular ROS and Ca^{+2} ion levels, ultimately averting apoptosis [53, 57]. In addition, the biochemical activity of hepatocyte injury and oxidative stress in hepatocellular carcinoma may also be reversed by boron induction [150]. The effectiveness of some borates on the oxidative stress and genotoxicity induced by heavy metals was assessed in human blood cultures. The micronuclei (MN) assays and sister chromatid exchange (SCE) were executed to check the lymphocyte DNA impairment. The oxidative stress in the RBC was calculated by assessing the changes in the oxidant/antioxidants and enzyme activity [62, 151]. The SCE, MN, malondialdehyde, and glutathione frequency was reportedly increased by heavy metals induction, but the borates successfully minimize this genotoxic and oxidative effects of heavy metals.

Boron and Anti-inflammatory or Immune Response

The additional boron intake has obvious immuno-stimulant effects, comprising the enhancement of natural killer (NK) cell activity and T cells proliferation. A recent study showed that boron plays an important role in the organs of the immune system [152]. Experimental animals have shown pronounced signs of enhanced immunity following administration of boron [152, 9]. The thymus and spleen are important immune organs in vertebrates. The thymus mediates cellular immunity and supports the maturation of T lymphocytes. The spleen produces antibodies and is actively involved in the immune response. An appropriate level of boron supplementation can promote thymic development in rats, the expression of the macrophage Fc receptor, and IL-6 secretion, as well as enhance cellular immune function and increase the number of circulating NK cells [153]. Meanwhile, the development of spleen was seen in ostrich chicks following low dose of boron supplementation. The area of white pulp and red pulp was increased at the dose of 160 mg/L boron in ostrich chicks [9]. Additionally, boron regulates enzymatic activity associated with the immune system [1]. The growth and development of immune organs in broilers becomes slightly modulated in 2-week-old chicks, following boron supplementation at 100 mg/L. Differentiation and proliferation of T cells and B cells are also affected during early growth but show significant results in mature birds [154]. In addition, 20–40 mg/L of boron in the drinking water of rat model significantly improved IgG concentrations, IL-4, IFN-γ expression, as well as proliferating cell nuclear antigen cells and $CD3^+$, $CD4^+$ number in the spleen. The administration of boron at low amount also significantly increased IL-2 expression and the $CD4^+/CD8^+$ cell ratio [155].

Several research laboratories have declared that boron also affects the response to infection or injury. When inoculated with an antigen (*Mycobacterium butyricum*) to prompt arthritis, boron-supplemented (2.0 mg/kg diet) rats had less paw swelling and lower circulating concentrations of NK cells and $CD8^{+}/CD4^{-}$ cells than did boron-deficient (0.1 mg/kg diet) rats [156]. Meanwhile, when low boron diet (0.2 mg/kg) rats were fed with dietary boron (20 mg/kg), there was seen delayed arthritis [156]. The diet supplemented with low boron (1.2 mg/kg) showed expressively more skinfold thickness response to an intradermal inoculation of phytohemagglutinin compared with high boron (5 mg/kg) offering in gilts [69]. When rats were offered with two different levels of boron supplementation in two groups, one with low boron diet (0.2 mg/kg) and one with high boron diet (3 mg/kg), enhancement in immune response were seen in low-dose groups [157]. The suggestion that boron has played a regulatory role in immune or inflammatory response can be further reinforced by an examination of mice infested with the *Heligmosomoides bakeri*, a nematode. Boron deficiency downregulated 30 of 31 chemokines or cytokines related with the inflammatory or immune response 6 days prior to primary infection. A contradictory pattern was found, especially after 21 days of boron exposure; mice were shown an increase in 23 of 31 cytokines [158]. These results are consistent with lower serum INF-γ and TNF-α in pigs after LPS injection nourished a boron-deficient diet (0.2 mg/kg) than in pigs augmented with a high boron (5 mg/kg) diet [159].

Boron may also make changes in immune cell populations prompted by other dietary factors, including dietary fatty acids. Supplementation of healthy young men with polyunsaturated fatty acid n-3 (PUFA-3) 6 g/day for 12 weeks reduced the number of white blood cells, mainly due to a reduced number of granulocytes; the reduced number of granulocytes led to an increase in the percentage of lymphocytes in white blood cells [160]. In contrast, 1.5 g of fatty acid caused granulocyte count increment [161]. Compared to safflower oil (mainly PUFA-6), fish oil (high PUFA-3) increased the white blood cell count, with most of the increase in lymphocyte fraction, in boron-sufficient diet (3 mg/kg) instead of boron-deficient diet [162]. Fish oil (high PUFA-3) instead of safflower oil (high PUFA-6) amplified basophil and monocyte number in boron-deficient rats but not in boron-sufficient rats. Similarly, canola oil (high PUFA-3) improved the proportions of white blood cell that were monocytes and basophils in boron-deficient rats, instead of boron-sufficient rats [163]. The consequence on the inflammatory or immune response could be the reason that boron was estimated favorable in an experiment on 20 patients having osteoarthritis disease. The proper amount of boron in these patients results in recovery from bone disorders for a trial of 8 weeks [164]. Arthritic individuals supplemented with boron self-reported considerable progresses in personal measures of restricted motion, fewer analgesics for pain relief and joint swelling. The anti-inflammatory or immune response of boron has been ascribed to the various mechanisms. These include inhibition of serine proteases released by white blood cells, suppression of leukotriene production, reduction of oxidative stress, and regulation of activity of T cell and the antibody concentrations [78]. Affecting the immune response could be the reason that intake of boron has been associated with cancer therapy.

Boron and Cancer Treatment

The experimental and epidemiological studies have shown that boric acid has a positive effect on human prostate cancer cells [165, 166]. These anti-carcinogenic effects of boron may be associated with its action on NAD and calcium channel. NAD is needed for cholesterol and fat production for the cells [167, 168]. The cell survival also depends upon the movement of Ca^{++} into and out of the cells. The cell working affects when the production of NAD/NADP is interrupted. It has been found that boric acid alters the NAD production and Ca^{++} release in the cancer cells depending upon concentration. The proliferation of cancer cell was reported to be impeded by 30–97% by borates [165]. The results also show that borates showed dose-dependent effects and can bind to ADP ribose which is an agonist of ryanodine receptor. It was suggested that boric acid binds to a site on the ryanodine receptor so that it can keep Ca^{++} channel inactive in the cancer cell lines [169]. When Ca^{++} levels decline due to the inactivation of calcium channel, cytoplasmic stress granules production and eIF2α/ATF4 pathway are prompted subsequently in DU-145 prostate cells supplemented with the physiological quantities of boric acid [170]. The scientists found that boric acid was also required to enhance the anti-proliferative action of chemopreventive agents, selenomethionine and genistein, while improving the rate of cell removal by radiation treatment [171]. Boric acid can hinder the cADPR Ca^{2+} channel pathway which stimulates cell proliferation and prevents differentiation and triggers TIA-1 which inhibit tumor invasion and progression. The treatment of boric acid amplified GRP78 which disturb the tumor cell migration and calreticulin which minimize prostate cancer lines by inhibiting metastasis and growth. Calreticulin is also required for p53 tumor suppressor [172].

A lab experiment established that borates exposure was beneficial for cancer treatment because it caused cells to stop their growth and flatten these prostate cancer cells. Borates also showed the reduction of cyto-chemicals, MAPK, and A-E cyclines, which subsidize growth of cells. So, cells revealed reduced adhesion, F-actin modifications, invasive activity, and migration [166]. Boric acid suppressed the proliferation of tumor cell lines LNCaP and DU-145 in a dose-dependent manner, and had a good inhibitory effect on tumor cell growth. Also, PC-3 tumor cell line was inhibited in cancer

patients [51]. The rodents were inoculated with LNCaP cell line and fed boric acid orally and compared with non-boron-treated group. Tumor size was measured for 2 months. Tumor volume was significantly reduced in mice by 25–38%, while serum PSA levels decreased by 86–88% compared with controls [173]. In addition, boron significantly reduced the insulin growth factor-1 in the tumor [173], which is required for the growth of prostate cancer [174, 175]. When boric acid was added to the diet of the immune system damaged mice, the human prostate cancer tumor that was transplanted into the mice showed a downward trend [173]. Studies also reveal that boric acid and phenylboronic acid alter the actin arrangement and thus reduce the cell migration in the prostate cancer cells. Phenylboronic acid was reported to be a more effective inhibitor of the tumor cell migration [176]. It was also observed that dietary intake of boron can reduce the risk of lung cancer and breast cancer in women [177].

Furthermore, boron neutron capture therapy (BNCT) that utilizes the nuclear capture reaction of epithermal neutrons by boron-10 resulting in a localized nuclear fission reaction and subsequent cell death emerged as a technique for cancer therapy [178]. As the destruction of cells is limited to the diameter of individual cells, so only the cells that contain a large amount of boron accumulation in the neutron field are destroyed [179]. But, the development in BNCT as a comprehensive cancer treatment in large part has been hindered by a scarcity of tumor-selective boron containing agents [180, 179]. Due to these strict necessities, only L-boronophenylalanine (BPA) and sodium borocaptate (BSH) are used clinically [181]. Many scientists have carried out a large number of efficacious clinical trials in BNCT by using these two borates as boron agents. Because of the selectivity of the tumor, new agents are urgently needed [181]. Recently, many boron agents have been tried in rodent model, including boron-containing liposomes, boronated porphyrins, boronated DNA intercalators, boronated epidermal growth factor, transferrin-polyethylene glycol liposomes, antiepidermal growth factor receptor, BSH fused cell-penetrating peptide, and vascular endothelial growth factor. But no agents have outdone BPA and BSH [178, 179, 181]. So, for a boron agent to be considered best, it will require decisive improvement in the success of cancer treatment. For enhancing tumor selectivity in BCNT, we must look for an ideal boron agent that is more efficient than BPA and BSH in the upcoming years.

Applications of Boron in Food and Medicinal Sectors

Boron compounds are used commercially, and almost all of them are involved in boron-oxygen compounds. The formation of ester bonds has led to commercial applications and provides a basis for the biological interaction of boron. The borates commonly used as food supplements in capsules, effervescent powders, chewable tablets, and different liquids are borax and boric acid. The formulations of these products vary in different products. Moreover, these borates may also be used as preservative in different food products at 4 g/kg dose [182]. The most commonly available products in the market are boron aspartate, boron ascorbate, boron chelates, boron citrate, sodium borate, and calcium fructoborate [183]. Among all borates, the most widely studied nutraceutical is calcium fructoborate. The calcium fructoborate is basically a sugar borate ester (SBE) [102, 184], and produced from different sugars by esterification of boric acid and other borates [185, 102]. These SBEs are of plant origin, easily absorbed by cells of living beings, and occur mostly in vegetables and fruits [186, 187]. The great advantage of SBE is that of less toxicity than other borates. That is why calcium fructoborate is used commercially as supplement in the cure of osteoarthritis and osteoporosis [187, 188]. Meanwhile, calcium fructoborate due to having anti-inflammatory properties was reported to use for patients suffering from angina pectoris [189, 102]. So, calcium fructoborate dietary supplements may improve the quality of life [186–189]. Recently, some borate products are also most commonly applied in boron neutron capture therapy for cancer treatment [190, 191].

The previous data showed the medicinal uses of borates, for instance, boric acid is used in contraceptives and vaginal products [192]. The tetra-borates are reported to be used in wave setting and bath products in concentration of 8 and 18% respectively. Also, boric acid and tetra-borates are used as oral hygiene and used in different products with low concentration. They are also used in some cleaning products having higher concentrations [192, 193]. The usage of borates in the manufacture of glass and other vitric products accounts for nearly half of all boron use. Agriculture and timber protection are also important areas of application. New techniques are being developed for the use of borates in the paper, pulp, ceramics, and other industries [194]. Borax (sodium borate) is commonly used in household products such as laundry and cleaning products, fertilizers, and in pesticides [195]. Boric acid and disodium octaborate tetrahydrate showed the antibacterial effects and antibiofilm capacities on selected bacterial strains. This effect of boron is worth noting in order to find new methods for the use of different functional microorganisms tests in the medicine and industry [196]. Borax is used as an ingredient in vaccines [197]. The U.S. Centers for Disease Control and Prevention (CDC) Vaccine Excipient and Media Summary lists four vaccines that contain sodium borate: Hep A (Vaqta); Hib/Hep B (Comvax); HPV (Gardasil); HPV (Gardasil 9) [197]. The role of borax in the vaccines is very limited and unclear. According to the Immunization Advisory Centre based at the School of Population Health at The University of Auckland in New Zealand, sodium borate is identified as a buffer in vaccine composition and

manufacturing [198]. They describe buffers as substances that "serve to resist changes in pH, regulate tonicity, and control osmolarity" [198].

The awareness of the important role of boron in biological systems has emerged in recent years. Many countries have authorized the borates usage in food products [199]. Boron is commonly used as a texturing agent to promote elasticity and crispiness in certain foods such as in shrimp, prawns, noodles, rice, and starch jelly. Therapeutic Goods Administration (TGA) has issued a license to 14 oral borates dietary supplements in Australia. TGA has insured that concentration of supplements must be less than 3 mg/day. These supplements are mostly used in combination of vitamin D, magnesium, and calcium. Interestingly, TGA has issued borates supplements specific to the mineralization of bone, and labeling was not showing any warning except indicating usage for only adults [200]. The borates usage is also common in the UK and European nations as mineral and multivitamin supplements, not in licensed pharmaceuticals [201]. The only limitation of borates on commercial scale is concentration, which must be in safe amount. In 2004, the "European Food Safety Authority" set the upper level (UL) tolerable amount for boron consumption from 3 to 10 mg/day, based on age groups [201]. The WHO recommended a UL for boron to 28 mg for adult weighing 70 kg [202]. The US Institute of Medicine Food and Nutrition Board set a UL of 20 mg/day [203]. Therefore, borates (especially sodium borate and boric acid) are appropriate for supplementation in foodstuffs and diets for specific nutritional purposes, if the aforesaid UL is not surpassed.

Interaction of Boron with Other Nutrients

The numerous biological effects of boron which are described above may be associated with its interaction with different minerals. For instance, it binds with diverse organic compounds to affect various biological functions [78]. Several studies have demonstrated that chicks deficient in vitamin D show increased levels of plasma glucose on exposure to boron [204, 205]. Furthermore, chicks deficient in vitamin D show higher plasma concentrations of pyruvate and triglycerides (TG); however, administration of dietary boron alleviated these effects [206]. Boron deficiency in rats leads to vitamin D deficiency and ultimately raised plasma pyruvate and reduced plasma TG concentrations [207]. Conversely, no such effects had been reported, when the diet had enough levels of boron [206, 65]. Boron deficiency also promotes hyperinsulinemia [207], when dietary levels of either vitamin D or Mg are altered in chicks and rats [134], and influences on growth. A study was conducted to determine the dietary levels of Mg and Ca that are required for effective interaction with boron, and it was reported that boron was necessary for growth, and Mg deficiency might represent a source of stress in boron metabolism [208].

Furthermore, boron supplementation reduced the abnormalities level induced by Mg deficiency in chicks. Boron supplementation also enhanced plasma concentration of Ca and Mg, which ultimately lead to inhibition of calcification and other complications [209]. Because of this ability, it has been reported that boron is used to treat and prevent hypomagnesemia, hypocalcemia (milk fever), and fatty liver in lactating dairy cows [8]. It was also reported that low calcium diet in lambs caused oxidative stress, reduced immune response, less growth rate, and alteration in kidney/liver tissues, but supplementation of boron to this diet restored normal functions along with ameliorated effects on morphology of organs [210]. In another study, when boron was supplemented in the diet of chickens, Ca and P deficiency was reduced and growth was enhanced [65]. Furthermore, while boron was supplemented in the diets of rats with severe K deficiency, a supportive effect was evident through the maintenance of body fat and enhancement of glycogen deposition in the liver [211, 212]. It has previously been reported that boron has an antidotal effect in the control of fluorosis in buffalo due to its interaction with various minerals. The high intake of fluoride in the body caused serious complications in the body as it caused an improvement in the activity of ALP and phosphorus, while causing the decrease in calcium levels. However, boron supplementation caused ameliorated effect on serum mineral profile against fluoride toxicity [213]. Recently, it was demonstrated that supplemental boron can be used for the cure of acute cadmium toxicity. The results showed that boron reversed the toxicity induced by cadmium and protect the liver and kidney from severe damage [214]. Boron may also alter biological systems because of its affinity for *cis*-hydroxyl groups of the cell membrane and interfere with manganese-dependent enzymatic reactions [6, 215].

Metabolic Effects of Boron

The biological effects of boron can also be attributed to the metabolic actions of boron on biological systems of living organisms. It is well known that boron contributes to the metabolism of animals and humans. In living organisms, boron affects numerous mechanisms which comprise regulation and metabolism of carbohydrate, minerals, enzymes, and hematological indices [216]. Kabu et al. performed a study showing the effects of boron (30 g/day) on metabolites (calcium, magnesium, phosphorus) of serum in the dairy cattle during peripartum period. Serum calcium and magnesium levels improved with boron supplementation, while the parameter of phosphorous metabolite was not significant in all groups. The results indicate that sodium borate can be suitable for maintaining the metabolic balance and maybe averting metabolic

syndromes such as hypocalcemia and hypomagnesaemia in the dairy cattle during the calving period [217]. Furthermore, it was documented the positive metabolic effects of boron on plasma calcium and phosphorus [119, 113], and plasma magnesium levels [119] in rats. In addition, boron also had certain metabolic effects in broilers [112]. And, slight increases in serum metabolites were perceived by low dose of boron supplementation in the layers [205]. In a study executed by Hall et al., LDL, TG, and cholesterol levels in rats declined after addition of boron [84]. This decrease level repressed the bonding and entrance of LDL into liver and aorta cells. This phenomenon was claimed to be helpful for the atherosclerosis patients as it may lead to the removal of cholesterol from the tissues and a reduction in the lipids accumulation [1]. In the study carried out by Naghii and Samman, boric acid was also reported to decrease total cholesterol and lipoprotein when it was given to rats for 2 weeks at a dose of 2 mg/day [127].

Another study showed that supplementation of boron in the form of boric acid in the broiler significantly affected the serum alanine aminotransferase, aspartate aminotransferase, creatine kinase, gamma-glutamyltransferase, lactate dehydrogenase, aspartate aminotransferase enzyme activities and calcium, magnesium, phosphors, LDL, HDL, total cholesterol, total protein, total bilirubin, albumin, globulin, glucose, and creatinine metabolite activity [218]. Furthermore, boron increased insulin and lipase activities and decreased glucose and LDL levels significantly in the diabetes group. So, boron may have favorable effects on metabolic indexes changes in the experimental diabetes [219]. Boron also appears to be suitable in reducing negative energy balance and enhancing health status of postpartum cows by regulating the metabolites comprising β-hydroxybutyrate, postpartum valine, polyunsaturated fatty acid, propionate, citrate, choline, isobutyrate, cholesterol, and fatty acids [220].

The effects of sodium borate on selected hormone and serum metabolites in pregnant cows were also supportive. The results showed that the concentrations of glucose were higher during pre-partum period, and the amount of postpartum β-hydroxybutyric acid and glucagon serum levels were higher in the un-supplemented boron group. After sodium borate administration, concentrations of total cholesterol, triglyceride, HDL, LDL, VLDL, glucose, insulin, and non-esterified fatty acids in the blood were decreased [8]. Borax administration also increased serum total protein and decreased the serum uric acid concentration in Simmental cows at week 4, and decreased serum HDL concentration at week 3 of the experiment. Serum total cholesterol, beta-hydroxybutyric acid, and blood urea nitrogen concentrations increased significantly, while non-esterified fatty acids decreased significantly after parturition. The beta-hydroxybutyric acid concentration was more in the control group, but began to decrease in the borax group during the final week of the experiment. The results show that sodium borate supplementation have positive effect on the metabolic profile of Austrian Simmental cows during early lactation [221].

Furthermore, a very few scientific data also indicated the effects of boron on hematological indexes. It was reported that borax significantly regulates the hemoglobin, white blood cell, hematocrit, platelet, and red blood cell count in rats. Similarly, number of lymphocyte, monocyte, neutrophil, and basophil were also affected [222]. Kabu et al. also tried to assess actions of boron (30 g/day) along with propylene glycol and methionine on hematological parameters in the dairy cattle during the calving. There were no alterations seen in the number of monocytes, white blood cells, red blood cells, lymphocytes, granulocytes, and platelets after the supplementation of this combination. A significant difference was perceived in the levels of mean cell volume and hematocrit on the calving [8]. This study suggests the positive effects of boron on some of the hematological parameters of bovines in the periparturient period.

Pharmacokinetics of Boron

Boron is absorbed easily through the intestinal epithelia in animals and humans, and across mucous tissues, such as the eyes, mouth, and urinary system [223]. Hunt stated that animals and humans absorb around 100% of dietary inorganic boron [78]. Some organic compounds of supplemental boron may be not accessible to animals as plants absorb only organic compounds in the soils after the mineralization process. Boron is mainly defecated in the urine, with a loss of 2% in the feces, and smaller quantities lost in sweat, breath, and bile [130]. Boron concentrations in tissues are usually retained stable by a homeostatic mechanism, principally through renal secretion, and higher boron intakes do not dramatically enhance plasma levels [224]. Boron seems to be completely and readily absorbed by the human body after oral dose [225]. After absorption, boron appears to be more concentrated in the bone than in the blood; however, the stoppage of dietary boron intake leads to a rapid decrease in bone boron content [226]. At normal diet or supplemental levels, there is no evidence that boron is accumulated over time in the tissue. Tissue homeostasis is maintained through rapid elimination of excess boron [130, 225]. As the intake of boron in the diet increased, the amount of urine excretion and fecal excretion also increased. The rate of urinary boron excretion varies rapidly with the change of boron intake, suggesting that the kidney is the main place for boron regulation in the body. At a dosage of 10 g/day, 84% of supplemented boron is reported to recover in urine [224]. The half-life of boron elimination is about 21 h, whether it is administered orally or intravenously in a healthy body and boron in urine is a more sensitive indicator in the range of 0.3–10 mg boron intake [224, 225].

Previous metabolic study on 11 postmenopausal females for 167 days revealed a swift surge in urinary boron when intake of boron increased from 0.36 to 3.22 mg/day [227]. Naghii and Samman deliberated the effect of dietary boron on urinary excretion in healthy male animals. When 18 healthy animals offered regular diet, the amount of boron excretion in urine was 0.3–3.53 mg/day on two different occasions. The boron value difference from urine collection after 24 h from these two values were not statistically significant, but slight difference were seen within and between some animals, suggesting differences in term of boron consumption among tested subjects. In a second study, when animals were administered 10 mg/day of dietary boron for 4 weeks, the amount of urinary boron increased from 1.64 ± 0.3 to 10.16 ± 0.92 mg/day. This urinary excretion increment was significant in each tested animal [228]. These results offer evidence that urinary boron excretion reflects boron ingestion. Furthermore, pharmacokinetics and bio-distribution of boron was determined by administrating boronated porphyrin (BOPP), 35 mg/kg intravenously in the dogs. The concentrations of boron were measured in all of tissues and plasma, and mixed modeling effects were applied to determine the pharmacokinetic parameters. The levels of boron in plasma demonstrated triexponential kinetics having small amount of biodistribution and long terminal half-life [223]. Among tissues, lymph node, liver, kidney, and adrenal tissues hoarded the highest amounts of boron, while least levels accumulated in the brain. These findings showed that BOPP has tissue pharmacokinetic and bio-distribution capabilities, suggesting that it might be an appropriate borate for practice in the cancer therapy.

Mechanism of Action for the Bioactivity of Boron

A plausible mechanism of boron action may be clarified by the boron biochemistry. Boric acid along with hydroxyl groups of organic compounds forms ester complexes. This characteristic mostly results in the complex formation with numerous biologically essential sugars [229]. These sugars comprise ribose, which is a part of adenosine. Recent studies suggest that the versatile favorable effects of boron happen through distressing the presence of biomolecules containing adenosine. The most important biomolecules that have more boron affinities include adenosine phosphates (ADP) and S-adenosylmethionine (SAM-e) in animal tissues [229]. ADP are occurred in all animal cells and serve as signal nucleotides in neuronal response. SAM-e is one of the utmost often used enzyme substrate in the body [230]. About 95% of SAM-e is involved in methylation responses, which affect the RNA, DNA, phospholipids, proteins, and hormonal activities. These methylation reactions end in the formation of SAM-e, which further hydrolyzed into homocysteine. The boron-deficient rats showed increased plasma homocysteine and decreased SAM-e which support the hypothesis that boron bioactivity is through an effect on SAM-e formation [231]. Furthermore, depleted SAM-e has been found in disorders like osteoporosis, arthritis, diabetes, and urolithiasis which are affected by nutritional intake of boron [208].

The hypothesis is further supported by bacterium quorum sensing signal molecule, AI-2, a furanosyl borate diester synthesized from SAM-e. AI-2 plays an important role and incorporates boron. AI-2 signaling is produced by the reaction of 1-deoxy-3-dehydro-D-ribulose, which is raised enzymatically, with boric acid [31]. Bacterium quorum sensing is the cell-to-cell communication accomplished through the exchange of extracellular signaling molecules. Furthermore, boron binds strongly to the oxidized form of NAD^+ [229], thus influencing those reactions in which it is participating. One of the roles of NAD^+ is binding on plasma membrane with CD38 receptor which is ADP ribosyl cyclase and converting NAD^+ into cyclic ADP-ribose sugar. This cyclic ADP binds to ryanodine receptor in the endoplasmic reticulum and encourages calcium ion release [56]. Boron is a reversible inhibitor of cyclic ADP-ribose and its concentration decreased calcium ion release from ryanodine receptor [56]. Therefore, it can be hypothesized that bioactivity of boron is through binding cyclic ADP ribose and NAD^+ and inhibiting calcium ion release, which is helpful in many processes including bone formation, brain activity, liver function, and immune response. Studies with plants proposed another possible mechanism of action for boron bioactivity. Boron might also showed bioactivity through forming ester borate complexes with glycoproteins, glycolipids, and phosphoinositides, in cellular membranes. These ester complexes may act as redox modifiers and calcium chelators [63] that affect the membrane function and integrity [232]. This modifying action could affect the transduction of regulatory or signaling ions across the membranes. The effects of this mechanism in animals and human are still to be determined.

Toxic Effects of Boron

Current data regarding the lethal level of boron is limited, so it needs to be improved. Boron is an essential element for life and intake via different sources into the body. The toxic effects of boron and compounds on the body has not been studied enough especially in tissue level. There have been some reports of congestion, inflammation, exfoliative dermatitis, renal epithelial cells degeneration, swelling, and edema. Risk assessments data regarding diet or water level showed that sodium borate and boric acid at high level in diet and water caused toxicity. They are not causing skin burning, but caused irritation in eyes [233, 234]. The compounds of boron are

lethal at high doses tested in some species, but are not carcinogenic. In the high boron-supplement group, the size of the normal fetus was greatly squeezed in a dose-dependent manner [235, 236]. The major toxicities are reproductive and developmental [235]. Experimentally, the toxicity in fetus was detected in rabbits, rats, and mice [236–238]. The developmental toxicities reported after boron contact comprise decreased fetal size, prenatal mortality, central nervous system abnormality, eyes irritation, effect on cardiovascular system, effect on immune organs, and intestinal apoptosis [9, 124, 236–239].

In order to check the effect of high boron status in the growth of birds, some scientists supplemented high amount of boron to Japanese quails, and revealed that high levels of boron supplementation effectively reduced weight gain, feed consumption, and feed efficiency in the birds. Percentages of fat in the carcass were also increased [82]. Kabu et al. executed the study to assess the effects of borax the most intaken form of boron compound on different intraabdominal organs histologically and also clinically. Forty-two male rats divided into 7 equal groups and different toxicological doses consistent with its LD50 dose (5000 mg/kg/day) were administered by gavage except control and sham groups. In the study, two different kinds of borax one of which was produced for research and the other for agriculture but the same formulation were used and their effects were also compared [240]. As a result, it was found that borax did not cause any histological changes in the kidney, large intestine, liver, and stomach in lower doses. But if doses were increased, a slightly inflammatory cell migration was detected without clinical signs in the liver and large intestine. However, when a single very high dose of borax was administered, very high edema, inflammatory cell migration, and neovascularization was observed and clinically two out of six rats died within 5 h. İt was suggested that very high dose intake of borax may cause sudden death and also during long periods and higher dose intake may pave the way of inflammatory bowel diseases. At the same time, in boron-related studies, they advice that the kind of boron and also their source should be evaluated carefully and the most suitable compound should be chosen in case of faulty results [240].

In vertebrates, the basic toxic consequence related with boron includes reproductive system [235, 241–244]. For instance, boron initiated unfriendly effects in reproduction of dogs, mice, and rats, including degeneration, germ cells loss, seminiferous tubules atrophy, and inhibition of spermiation. Additionally, ovulation reduction and lesions in mice were also observed [235]. Ku et al. administered orally 0, 26, 38, 52, and 68 mg boron/kg/day for 63 days in rats to associate the link between lesions development and boron levels. They found that doses of 52 and 68 mg caused atrophy. Meanwhile, it was reported that 52–68 mg boron amount in testis reduced the production of sperm. While this study also showed that low boron doses may reversed these negative effects on reproduction [243]. Subsequent to this finding, the same scientists exposed the testis with 11.9 μg B/g in vitro, and found that boron affected negatively the maturation and production of germ cells at high dose [244]. Overall, the data regarding boron toxicity are supported by toxicity studies in different animals (Table 4), which used higher levels of boron.

Conclusion

Recent findings have reinforced the significance to health of adequate boron status. The effects of boron are multiple and

Table 4 Toxic effects of boron in different species

Species	Dose (mg/kg)	Adverse effects
Mouse	79	Effects on development
Rat	26	Sperm inhibition
	52	Testicular atrophy
Rat	50	Germinal aplasia
Rat	13.3	Decreased fetus body size
Rat	25	Developmental problems
Rabbit	43.8	Fetal deformities
Rat	58.5	Testicular atrophy, weight of testis decreased, increased thyroid/brain weight
Dog	29.0	Testicular atrophy
Ostrich	640 mg/L	Increased intestinal apoptosis
	320–640 mg/L	Spleen structural changes/toxicity
	320–640 mg/L	Brain structure impairment
	400 mg/L	Negative effect on bone

References: Heindel et al. [236]; Ku et al. [243]; Lee et al. [241]; Price et al. [237]; Price et al. [238]; Weir and Fisher[242]; Sun et al. [239]; Haseeb et al. [9]; Tang et al. [124]; Cheng et al. [96]

versatile, demanding further studies to elevate the benefits and lessen the hazards of this influential trace mineral. When administered at an effective dose, boron shows remarkable properties, and its nutritional value cannot be underestimated. Experimental boron administration in animals and humans has resulted in marked improvement in immunity, antioxidative effects, growth, and embryonic development. Boron also facilitates improvements in brain function, hepatic development, osteoporosis, cancer therapy, and wound healing. Conversely, high dose of boron showed opposite effects; that is why usage of boron is still limited on commercial scale. Although numerous trials on boron have been executed over the previous decade, additional data is required to illuminate its mechanism of actions. The new methods should also be developed to estimate the requirement of boron in each species, which may have encouraged the therapeutic aspects and field applications.

Acknowledgements This work was supported by the National Natural Science Foundation of China, No. 31272517, 31672504.

Compliance with ethical standards

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

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