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Review

Effects of Boron-Containing Compounds on Liposoluble Hormone Functions

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Abstract: Boron-containing compounds (BCC), particularly boronic acids and derivatives, are being increasingly tested as diagnostic and therapeutic agents. Some effects of BCC involve phenomena linked to the action of steroid or thyroid hormones; among these, are the effects on muscle mass or basal metabolism. Additionally, some toxicology reports on mammals, including humans, sound an alert concerning damage to several systems, among which are the negative effects on the induction of male infertility. Systemic and local mechanisms to explain changes in metabolism and impaired fertility were collected and presented. Then, we presented the putative pharmacodynamic and pharmacokinetic mechanisms involved and demonstrated in these events. In addition, it is proposed that there are adducts of some oxygenated BCC with cis-diols in fructose, an essential source of energy for sperm–cell motility, an uncoupling of sex hormone-binding globulin (SHBG) and its ligands, and the modulation of the DNA synthetic rate. These effects share the reactivity of boron-containing compounds on the cis-diols of key molecules. Moreover, data reporting no DNA damage after BCC administration are included. Further studies are required to support the clear role of BCC through these events to disrupt metabolism or fertility in mammals. If such phenomena are confirmed and elucidated, an advance could be useful to design strategies for avoiding BCC toxicity after BCC administration, and possibly for designing metabolism regulators and contraceptive drugs, among other purposes. Boronic derivatives and carboranes have been proposed and studied in this field.

Keywords: boron; medicinal chemistry; sex hormones; SHGB; thyroid hormones; vitamin D

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1. Introduction

Hormones are molecules used as messengers and modulators of multiple functions in pluricellular organisms. Hormones can be classified according to their structure and behavior in water, or their fat solubility; thus, they are denominated water-soluble and liposoluble (or fat-soluble) hormones [1]. Among the liposoluble hormones, there are many subgroups; those with the most identified actions include thyroid hormones, vitamin D (VitD), and steroid hormones. Belonging to the latter, we find progestogens, androgens, and estrogens [2]. There has been less exploration regarding other types of liposoluble hormones, i.e., those derived from fatty acids, such as eicosanoids [1–4].

On the other hand, the use of natural and synthetic boron-containing compounds (BCC) is expanding in biomedical applications [5], especially, but not limited to, boronic acids [6], complexes borates [7], and boron polyhedral boranes (including carboranes) [8–10]. In fact, some of the effects induced by the administration of natural BCC are clearly linked to action in liposoluble hormones, albeit the mechanisms of action are unclear. As examples, we find the pre- and postnatal effects of BCC administration on bone formation and strength [11,12]; the increasing effect on steroid, VitD, and thyroid plasma levels [13–16]; as

well as those effects related to gestation, morphology, and fertility, reported in animals or humans with extraordinary exposure to BCC [17–19].

Here, we compiled information related to prove or suggest BCC effects linked to the actions of liposoluble hormones, updating information related to possible mechanisms of action. Thus, data were collected and reviewed from the National Center of Biotechnology Information, PubMed, Global Health, Embase, the Web of Science, Google Scholar, and Clinical Trials databases. Additionally, we translated the potential involvement into some pathophysiological processes, and into the inferred medical applications pertaining to the therapeutic field.

2. The Effect on Sex Hormones and Their Receptors

2.1. Changes in Sex Hormones' Plasma Level

The relationship between changes in the plasma levels of sex hormones and boron (B) intake has been repeatedly reported, albeit no one clear mechanism has been established (Figure 1). In fact, there are potential effects of BCC in steroid–hormone synthesis, pharmacokinetics, and pharmacodynamics linked to changes in plasma concentration observed after B supplementation. BCC can disrupt steroid synthesis and decrease globulin synthesis for transportation in blood, but can also disrupt the coupling between steroids and globulins. Other proposed mechanisms for BCC actions involve the disruption of action in targeted cells or in the metabolism and excretion processes, as mentioned in this section.

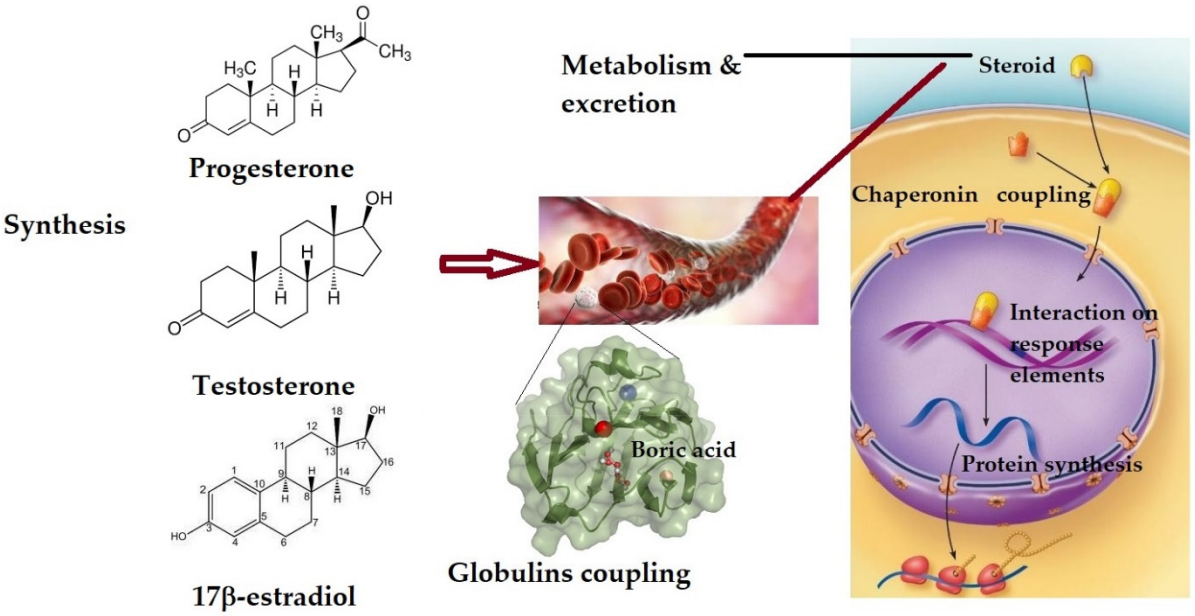

Figure 1. The potential effects of BCC in steroid–hormone synthesis, pharmacokinetics, and pharmacodynamics linked to the observation of changes in plasma concentration after B supplementation.

Thus, the administration of B has been reported as a modulator of the plasma concentration of both estrogens and androgens, with greater evidence with respect to the latter.

Changes often include the increase of the concentration of testosterone in plasma from animals [14]. A study was conducted by Ghanizadeh et al. in which 34 male rats were divided into five groups, including the control group. Four different intervention groups were supplemented with fluoride, boron, calcium, and VitD. After 8 weeks of treatment, the animals' blood concentrations of calcium were significantly higher in those supplemented with fluoride and boron, while higher levels of free testosterone and estradiol (E2) were found in all of the intervention groups [20]. Samman et al. [21,22] reported that B intake exerts a marked effect on the plasma–testosterone concentration; thus, it was theorized that it has implications in the synthesis of those steroid hormones [22,23]. For their part, Lee, Siierind, and Dixon conducted a study in 1978 in which they placed male rats in

an environment exposed to B and demonstrated germinal aplasia and an elevation of follicle-stimulating hormone (FSH) and luteinizing hormone, while the testosterone was not affected [24]. Naghii and Samman replicated the experiment, but with B oral intake, and found that increasing the intake from 2 mg to 12.5 mg and 25 mg resulted in lower plasma–testosterone concentrations, which increased after 6 weeks of treatment [22]. Recently, Naghii et al. showed in an experiment that B supplementation has a direct influence on increasing the plasma levels of various hormones, such as those of E2 and free testosterone, but also VitD and some cytokines, such as IL-6 [14].

In 1992, Nielsen et al. carried out an experiment with dietary B intake and women with estrogen intake; the authors showed that the women with increased B intake, and the women with estrogen intake, exhibited increased plasma levels of 17β-E2 and copper [25].

Further, a decreased quantity was reported of sex hormone-binding globulin (SHBG) [14]; additionally, some data supported the disruption of BCC in sex hormones and SHBG [26]. Moreover, some researchers have presented several hypotheses, such as that BCC can displace steroid hormones from their binding globulins, which could render, in different experimental studies, that the response increases steroid–hormone-free–plasma level. In this way, it has also been suggested that BCC can induce the uncoupling of estrogen and testosterone interactions from the SHBG [26]. In fact, the steroid-binding site of SHBG is particularly attractive for suggesting BCC interaction, in that it is constituted of a cluster of residues close to the center of the N-terminal laminin domain of SHBG, and that it intercalates into the hydrophobic core formed between two β-sheets. The SHBG fold bears no resemblance to other steroid carriers, such as corticosteroid-binding globulin (CBG) [26]. Further, there are two additional sites next to the steroid-binding site, denominated a calcium-binding site (site I) and a second metal-binding site (site II), coordinated by the side chains of histidine 83 and histidine 136, and the carboxylate group of aspartate 65. Site II is located at the entrance of the steroid-binding site and is occupied by Zn^{+2}, which impacts the binding affinity of SHBG to E2 [27]; it could be a site capable of coupling boric acid and other BCC.

Certainly, SHGB is the main transporter of androgen and estrogen in the blood; it is a homodimeric glycoprotein produced and secreted by the liver, placenta, and testes [28,29]. Consequently, it plays a key role in the equilibrium between unbound and bound sex steroids [30]. In this regard, SHBG and CBG are structurally unrelated glycoproteins and they function in different ways; extending beyond their transportation or buffering functions in the blood, they bind steroids with high affinity and specificity [28,31,32]. SHBG binds androgen and estrogen, while CBG binds glucocorticoid and progesterone [19,28]. Specifically, SHBG is able to bind other ligands, and the disruption of steroid coupling has led to damaging results for the steroid target organs [31,33].

In contrast, other studies have provided no clear effect of B supplementation in testosterone in humans [34,35]. Nevertheless, the majority of studies support BCC administration as a strategy to increase the plasma level of androgen hormones in age-related decreased testosterone in men [36], which is poorly explored, probably due to the fact that andropausia is linked to late adulthood. However, B administration has been suggested in young males to increase the effect of testosterone on metabolism and muscle strength [15].

The role of BCC has often been explored in postmenopausal human females. A study of 12 postmenopausal women, with a diet low in B, supports that it is able to reduce the urinary excretion of calcium, magnesium, testosterone, and E2 [37]. Conversely, a diet low in B may increase urinary calcium excretion, as reported in a study by Beattie and Peace, conducted on six postmenopausal women [38]. Additionally, Boyacioglu et al. carried out a study on 53 postmenopausal women aged between 50 and 60 years; these authors elucidated the relationship between B intake and the blood level of osteocalcin, and the genes coding for it [39,40]. With all of these studies together, one is led to assume that B plays a favorable role in calcium metabolism and may entertain enormous importance in the treatment and prevention of osteoporosis and bone loss in postmenopausal women, presumably by action on the steroids modulating these processes [39,41,42]. In addition,

Hunt et al. performed a study in which the authors included dietary modification of different micronutrients for a period of time in postmenopausal women; the authors observed that there is a modification in calcium excretion, but the latter does not cause any kidney damage [43].

2.2. The Effect on Sex Hormone Receptors

It is known that BCC are crucial for numerous biological mechanisms. In humans, some BCC can affect the functionality of hormones, such as estrogen and testosterone, by interacting with their receptors; this can elicit various responses [19,44].

The action of BCC directly on sex hormone receptors is poorly reported; however, some boronic acids have been proposed or proven as ligands in these receptors (Figure 2) [45–47]. In this respect, Raghava et al. proposed BCC with high structural similarity to estrogen as neuroprotective agents by direct action on estrogen receptors. Nevertheless, Liu et al. previously demonstrated the ability of BCC to act as ligand in estrogen receptor α (ERa) competitively (IC_{50} = 4.1 nM) and to effectively downregulate its expression in breast cancer cells [45]. Moreover, the compound GLL398 strongly binds to ERα (IC_{50} = 1.14 nM) and potently degrades it in MCF-7 breast cancer cells (IC_{50} = 0.21 μM) (Table 1).

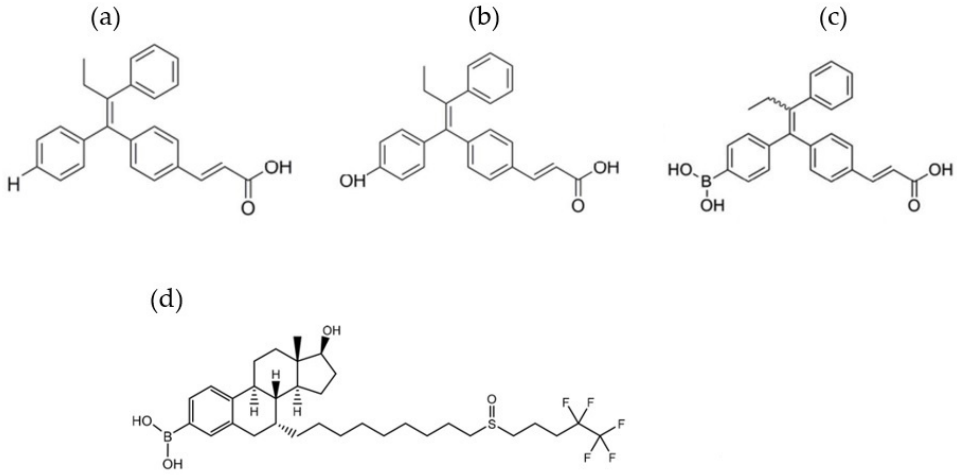

Figure 2. The chemical structure of: (**a**) GW5638; (**b**) GW7604; (**c**) GLL398; and (**d**) ZB716.

Table 1. The binding affinity of boronic-derivative SERD candidates.

Compound	IC_{50} (μM) [1]
GW5638	0.39
GW7604	0.0017
GLL398	1.14
ZB716	4.1

[1] Values were obtained after evaluating competitive binding curves including concentration (M) and the percentage of displacement (%).

In fact, it is proposed that the introduction of the boronic acid group confers 10-fold superior oral bioavailability in rats, as compared to its boron-free analogue GW7604, and other attractive pharmacokinetic values, in terms of its oral administration (Table 2) [46].

Table 2. The oral pharmacokinetic parameters of GLL398 and ZB716.

Compound	$t\frac{1}{2}$ (h)	C_{max} (μg/mL)	AUC (μg·h/mL)
GLL398	3.9	3.51	36.9
ZB716	23.5	0.16	2.5

GLL398 parameters were evaluated after having administered a single dose of 10 mg/kg in rats. ZB716 values were obtained after its oral administration of a single dose of 8.3 mg/kg in mice. Both profiles were assessed at 1, 3, 6, and 24 h post drug administration.

Notably, in 2016, the authors succeeded in developing two oral SERD (these are the BCC GLL398 and ZB716) with selectivity for ERα and remarkably beneficial effects on tamixofen-sensitive and tamixofen-resistant cancer cells [45,46].

However, among BCC, there are carboranes (CB), which are polyhedral clusters obtained by binding B and carbon atoms [48–50]. These have achieved vast popularity due to their multiple applications in the biomedical field, particularly in cancer therapy [19,51]. These compounds possess phenomenal hydrophobicity and thermal stability, which has led to the development of multiple derivatives, among these some that share their shape or that resemble steroidal ligand molecules (Figure 3) [51].

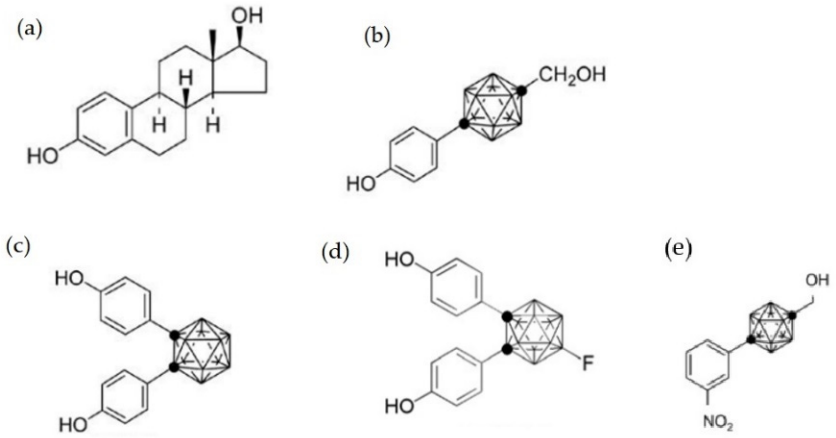

Figure 3. The chemical structure of: (**a**) 17β-E2; (**b**) BE120; (**c**) BE360; (**d**) BE310; and (**e**) BA321.

Some CB derivatives that are structurally related to cholesterol have been evaluated as components of liposomes and have been suggested as bioactives, modifying the uptake of liposomes and probably modulating cytotoxicity [52]. Additionally, CB have been designed to enhance binding to steroidal receptors. In fact, some of these have even stronger interactions with estrogen receptors (ER) than their natural ligand, 17β-E2 (E2) [53].

It is known that CB can produce mixed responses by activating the two subtypes of estrogen receptors, that is, ERα and ERβ, whose function is to act as transcription factors. Although these might be expressed in similar tissues, their distribution pattern is not uniform; the onset of their effects differs, and even their final physiological effect might be distinctive [54,55]. Moreover, GPR30, a G-coupled receptor, is thought to join estrogen signaling pathways and it is extensively abundant in cardiac tissue [55].

Further, CB are thought to regulate the activity of ER regardless of their different affinity to them. In addition, these scaffolds might also function as agonists, antagonists, or modulators, depending on their chemical properties, which highlights the complexity of the signaling involved in these processes [53]. Achieving the selective agonism of ER has been a major challenge over the years, and aiming to model the geometry of E2 is the typical course of action; thus, the incorporation of certain compounds into CB could provide different interactions with those receptors [54]. Alkyl-derived and propyl-derived CB cages revealed an increase in selectivity for ERα. This is particularly useful because menopause decreases the production of E2 and induces the deactivation of ERα. Utilizing these molecules as ligands may be a logical decision in the development of novel drugs for the treatment of this condition; unfortunately, it was reported that this interaction might result in the proliferation of neoplastic breast cells [56].

It is known that CB are reported to play an important role in female health. In 2001, Endo et al. synthetized a globular carborane analog, BE120 (Figure 3), which appeared to entertain a 10-fold increase in potency as compared to E2. The authors evaluated its effect on ovariectomized mice in order to recreate the typical estrogen-depleted environment present in menopausal women. These conditions predispose bone to demineralization and the uterus to atrophy. Interestingly, BE120 significantly alleviated bone loss in the mice and

contributed to the recovery of uterine weight [57]. Furthermore, evidence has previously increased in favor of the bone-related benefits of B by decreasing the excretion of urinary calcium, promoting osteoblastic activity, and optimizing hormonal bioavailability [44,58,59].

In 2009, Hirata et al. designed a new molecule, BE360, and tested it on a group of mice with the same features (Table 3). This novel structure apparently diminished the risk of uterine cancer by limiting estrogenic effects on the uterus [60]. Interestingly, the fluorination of BE360 produces a derivative known as BE310, which also interferes with ER subtype selectivity equilibrium. In 2012, Ohta et al. proved that BE310 (Figure 3) possesses an Erβ affinity that is four times stronger than BE360 [61]; the authors identified some other fluorinated carboranyl phenols as candidate ERβ-selective ligands [62]. Furthermore, in the same year, the authors developed another molecule, which supposedly owns selectivity for ERβ, but its agonistic activity is 40 times weaker [61]. This selectivity disbalance might offer some alternatives for tackling menopausal symptoms such as hot flashes, urogenital atrophy, and osteoporosis, without women experiencing the innumerable adverse effects associated with estrogen therapy [63]. The pharmacokinetic profile of these CB derivatives has not been reported.

Table 3. The binding affinity of carborane derivatives for human recombinant ER and their effect on MCF-7 regarding cell proliferation.

Compound	RBA		Selectivity ERβ/ERα	IC_{50} (μM)	EC_{50} (μM)
	ERα	ERβ			
17β-E2	100	100	1.0	1.0	1.0
BE360	68	46	0.68	0.58	0.024
BE310	15	16	1.1	0.63	0.85

Relative binding affinity (RBA) values were estimated by measuring the inhibition of (6,7-3H)17L-E2 (4 nM) to human recombinant estrogen receptors with each compound at 4 nM. The binding affinity of 17β-E2 was established as 100. An inhibitory concentration of 50% (IC_{50}) and an effective concentration of 50% (EC_{50}) were obtained from the sigmoidal dose-response curves using the GraphPad Prism version 4 software.

As has been described, sensitive changes in the arrangement of CB adjust the affinity for a certain subtype of ER, and this could modulate the overall physiological functions of steroidal compounds [63]. In the mammary gland, ERα is said to regulate estrogen-driven pathways, resulting in the proliferation of both normal and aberrant breast cells, while antiproliferative and anti-invasive properties have been attributed to ERβ [64,65]. The perturbation of CB selectivity might become a new strategy for the development of novel agonists or antagonists that target specific ER and that limit the progression of hormone-related cancers. Anti-breast cancer therapy involves B neutron capture therapy, nicotinamide phosphoribosyltransferase utilization, and so on [53,66]. However, these strategies have resulted as being either insufficient, inespecific, or aggressive, which has motivated some researchers to focus their attention on the effect of BCC on ER [65]. Liu et al. have engaged in efforts to describe the potential applications of selective estrogen receptor downregulators (SERD), which are CB aimed at modulating estrogen actions on neoplastic cells [45]. In a complementary manner, Watanabe et al. presented BA321 as a selective agent on the androgen receptors in mouse bones [67].

Finally, it has been described that CB can alter the normal immune response. ER are thought to participate in the regulation of the spleen's immunological activity [68]. Exposure to CB is mentioned as perturbing lymphocyte proliferation, inflammatory cytokine profiles, and protein expression in spleen tissue in a dose-dependent manner [69].

On the other hand, Mori et al. have designed CB that antagonize progesterone (PR) receptors without interacting with ER or with androgen receptors (AR) [70]. The synthesis of these molecules entails multiple implications for female reproductive health, in that it may modify physiological responses, including uterine-cell differentiation and the ovulation cycle, among others [70,71]. This sort of nonsteroidal PR antagonist could eventually become a key point in the production of abortifacients, and in the treatment of endometriosis, leiomyoma, and even breast cancer [72].

Regarding male reproductive health, CB have been constructed in order to evaluate their effect on AR (mainly having antiandrogenic effects as their objective) [73]. Some CB are of interest because they proved to antagonize AR with stronger affinity than regular antiandrogens, such as hydroxyflutamide [67]. Conventional antiandrogens are typically employed in the treatment of prostate cancer; therefore, CB that bind this receptor might benefit patients suffering from this condition. Additionally, antiandrogen withdrawal syndrome could be managed utilizing these novel compounds [74]. Additionally, it has been demonstrated that nonselective steroidal CB are able to deter bone loss in orchidectomized mice [67], supporting the idea of incorporating CB into bone-deteriorating disease therapy in male and female individuals.

2.3. The Effect on Sex Hormone-Dependent Human Metabolism

Some data related to sex hormones are linked to human metabolism. For example, an imbalance in sex hormones exerts an important impact on metabolism disturbation, as in type 2 diabetes (T2D), mainly through the involvement of visceral adipose tissue [75,76]. Androgens have an interesting sex-dimorphic association with T2D, in that hyperandrogenism in females and hypogonadism in males comprise risk factors for T2D [75,77]. Additionally, estrogen has been linked to disruption in the metabolism of carbohydrates [78].

In this regard, the actions of BCC are attractive because they exert diverse effects on the metabolism of living organisms. Some of these effects are carried out by means of action on the enzymes and the transporters of the membrane. The BCC are able to modify carbohydrate metabolism linked to certain pathologies and other effects that involve their action on a specific enzyme in a metabolic pathway [5,19,79].

Although no clear relationship between the BCC-induced effects on metabolism and on plasma–steroid levels have been established, this relationship could be inferred. In fact, the actions of BCC can also be through influencing the metabolism of steroid hormones [14,19,80]. Steroids are clearly linked to basal metabolism, and B supplementation induced higher sex- steroid–plasma levels in both men and women than in non-supplemented individuals [19,58]. Whatever the mechanism of action of BCC in the disruption of steroid–hormone levels, it is important to analyze the impact of the source of the B, the dose, the time of B supplementation, and the effect. This is because the modified interactions of sexual steroid hormones induces certain alterations that can be observed as effects after the administration of boric acid [26].

For example, dietary B consumed for several weeks induced multiple changes in the metabolism of steroid hormones. In fact, a significant decrease in men's plasma–E2 levels suggests a higher rate of conversion of total testosterone into free testosterone in the testosterone–metabolic pathway, where approximately 98% of testosterone molecules are bound to proteins in the blood [5,14,80]. Additionally, the levels of E2 and calcium absorption in peri- and postmenopausal women suggest effects on the metabolism of steroids [19,38,58,81]. On the other hand, when there is a deprivation of B, there are adverse defects, such as reduced serum–steroid–hormone concentrations and other functions [82–84], which is notably reverted after B supplementation [11,26,85]. In this manner, evidence hints at a role for B in regulating the production of steroid hormones, but also the half-life of the different metabolites of plasma hormones. It could be that the regulator of the formation of steroid hormones from precursors involves one or more hydroxylations [86,87], the latter exerting changes on estrogen and VitD [24,86]. This could be explained as being due to BCC acting as Lewis acids or reducing agents, and participating in hydroboration reactions, in that it is well-known that BCC exert effects on the cis-addition of hydroxyls in some molecules [86,88]. Several studies suggest that these hydroxylation changes modify the estrogen/androgen balance [89]. Therefore, it has been proposed that B could reduce the rate of E2 catabolism by inhibiting the methylation of 2-hydroxyl estrone in 2-methoxyestrone [90]; however, the hydroxylation reaction theory and the 17β-E2 synthesis from testosterone as the precursor appears to be more available [87,91].

2.4. Regarding Fertility

Multiple facts support that BCC with different chemical structures possess different beneficial effects on living things, when taken in appropriate doses; moreover, some BCC are of vital importance for living organisms. The benefits of natural BCC for living things include the alleviation of arthritis or its risk reduction, bone growth and maintenance, central nervous system function, cancer-risk reduction, hormone facilitation and immune response, inflammation, and the oxidative-stress effect [92].

However, it is thought that there may be some side effects if they are taken in high doses. In the case of doses higher than those required to induce the desirable biological effect of some BCC, it is stated that they exert negative effects on the male and female fertility systems due to atrophy in the seminiferous tubules, the loss of germ cells, deterioration in sperm motility, changes in follicle-stimulating hormone and testosterone, and/or the reduction of ovulation processes [44]. Several boron-containing moieties in some BCC, which can transform these from electron-deficient trigonal planar sp^2 hybrid orbitals in electron-rich tetrahedral sp^3 orbitals under certain physiological conditions (Figure 4), have been avoided due to their suggested toxicity, high-toxicity, or instability. However, these moieties are not toxic [5,93]; contrariwise, they have a versatile atom and play an active role in the design of drugs with several medical purposes [94–96].

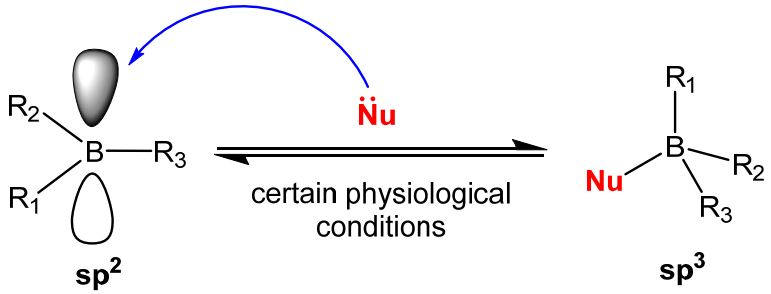

Figure 4. The transition of boron-containing moieties from trigonal planar geometry into tetrahedral geometry under some physiological conditions.

In addition to many application areas of BCC, after the US Federal Drug Administration (FDA) approval of bortezomib (Velcade), ixazomib (Ninlaro), tavaborole (Kerydin), crisaborole (Eucrisa) and vaborbactam as synthetic boron-containing drugs, the fertility effect of such compounds has recently begun. Fertility toxicity has been the focus of many scientific studies and treatments. In scientific studies to date, it has been determined that natural and synthetic BCC, including multiple boronic acids, do not exert a negative effect on fertility over three generations [97,98].

In Turkey, the country with the richest B reserves, Sayli and colleagues interviewed 927 subjects (230 women, 697 men), from six different regions, who were randomly exposed to BCC, either environmentally, occupationally, or both. As a result of this study, the authors explained that there is no evidence that different BCC have a negative effect on human fertility and reproduction [98].

However, the treatment of rats, mice, and dogs with BCC is reported to be dose-dependently associated with testicular toxicity, with inhibited spermiation at low dose levels and decreased epididymal sperm counts at higher dose levels (Bolt et al.) [99] For these effects, a NOAEL (non-observed-adverse-effect level) of 17.5 mg B/kg-bw/day has been identified by official bodies for the (male) reproductive effect of boric acid and borates in a multigenerational study of rats (as the most susceptible species), and a NOAEL for the developmental effect in rats was identified at 9.6 mgB/kg-bw/day [100]. According to the studies presented previously, it is observed that more detailed in vivo and in vitro studies are needed to reveal the negative effect of BCC on fertility and reproduction. As a result, although it is reported that BCC may exert a toxic effect on reproduction only in cases of exposure to high doses, definitive scientific data on this have not yet been fully revealed.

There are various epidemiological studies on whether BCC have an effect on the fertility of workers laboring in the B industry, in addition to the normal population [101–103]. As a result of these scientific studies, the Scientific Committee on Consumer Safety (SCCS) concluded that such studies are insufficient to demonstrate the presence of an effect, or an absence of effect, on fertility or reproduction [104]. However, it is thought that the negative or positive effect of BCC on fertility or reproduction may be related to the dose taken, maternal age, race, and parity. The effect of BCC on fertility was investigated in a study conducted on 753 miners working at U.S. Borax. In this study, interviews with workers were conducted entirely in the form of questionnaires or telephone interviews. The U.S. population-based standard birth rate (SBR), adjusted for maternal age, race, parity, and calendar year, was used in this study to assess the biological fertility of male workers. Excessive numbers of male and female births were reported by the male B-exposed workers in this study. As a result of this study, it was observed that there was no dose relationship between high birth rate and exposure to B compounds, and the highest birth rate was in the category with the highest B exposure. Additionally, the number of excessive births was statistically significant, indicating that fertility rates among U.S. Boron mine workers were not adversely effected [103,105]. Arstan and co-workers suggested that when BCC are employed at certain doses, this is a promising tool to prevent and correct chromium-related effects in plant workers engaged in chromium production and persons living in ecologically unfavorable areas, and that BCC may also exert a positive effect on fertility in the future [106].

The European Medicines Agency (EMA) has established guidelines requiring a warning with respect to fertility concerns associated with boron-containing excipients and a contraindication for children under 2 years of age if the medicine exceeds a threshold of 1 mg B/day. The EMA is asked to advise whether the data sheets for any of these medicines should be changed to reflect fertility concerns due to boron-containing excipients, or whether these should be changed in any other respect to mitigate this concern. In particular, there is a question whether warnings/contraindications regarding B content and fertility concerns in children should be included on the datasheets for any of the drugs discussed in this report [107].

However, in this study, only the effect of boric acid and borates on human fertility was considered; the study was only carried out on male and female rats, and no conclusions have yet been drawn about phase studies. In addition, many natural and synthetic BCC are known today, and it is not known how they will affect fertility. Therefore, it is not clear whether all BCC will exert a negative effect on fertility. Perhaps, as a result of detailed scientific studies, it will be possible that newly synthesized or naturally obtained organic B compounds will have a positive instead of a negative effect on fertility [5].

Some of those effects of BCC on the fertility and biased reproduction of mammals is generally explained by the ratio of X and Y chromosomes, or by the decrease in sperm cells carrying the Y vs. the X chromosome. In a study, it was observed that the relationship between B exposure in semen and Y:X sperm ratios was not statistically significant. In addition, at the end of this study, it was determined that there was no boron-related shift toward female offspring in the sex ratio at birth. According to the scientific data obtained in this study, it has been revealed that there is no relationship between B exposure and a decreased Y:X sperm ratio in male individuals exposed to excessively high doses of B compounds; but an association between pesticide application an Y:X sperm ratio [108,109].

El-Dakdoky and Abd El-Wahab approached the testicular DNA level and quality of male rats by exposing them to three different boron-containing acids in terms of reproductive fertility and progeny results. According to the results obtained from this study, these explained that exposure to different boronic acids at 125 mg/kg body weight had no negative effect on fertility, sperm characteristics, or the prenatal development of pregnant females. When the dose of boronic acids used was increased to 250 mg, it significantly increased serum nitric oxide, testosterone, E2 levels, testicular B and calcium levels, and also significantly decreased serum–arginase activity, sperm quality, and testicular DNA

content with minor DNA fragmentation. The authors explained that when male rats were exposed to different boronic acids at 250 mg doses, there was an effect on fertility including preimplantation loss, resulting in a reduction in viable fetus/seed number. The authors also explained that when these rats were exposed to 500 mg of different boronic acids, the latter caused testicular atrophy, severe spermatogenesis damage, spermiation failure, and a significant reduction in testicular levels of Mg and Zn (Table 4). Thus, the authors explained that the use of different boronic acids only in high doses impairs fertility by targeting highly proliferating cells (germ cells) by reducing the rate of DNA synthesis, instead of inducing DNA damage [110].

Table 4. Control and rats treated with boric acid at different dose levels (125, 250, and 500 mg/kg of body weight), modified from [110].

	Control	B-125	B-250	B-500
Final body weight (g)	299.6 ± 5.36	300.5 ± 7.86	281.3 ± 8.90	267.7 ± 3.88 [a,b]
Body weight gain (g)	120.5 ± 3.63	123.0 ± 6.56	102.3 ± 7.43 [a,b]	96.3 ± 5.48 [a,b]
R. testis weight (g)	1.57 ± 0.03	1.49 ± 0.04	1.38 ± 0.10 [a]	0.46 ± 0.02 [a,b,c]
R. epididymis weight (g)	0.58 ± 0.02	0.57 ± 0.02	0.52 ± 0.04	0.35 ± 0.02 [a,b,c]

Values are mean ± Standard error (SE). [a] Different from the control group, $p < 0.05$. [b] Different from the B-125 group at $p < 0.05$. [c] Different from B-250 group, $p < 0.05$ in all cases.

In another study by Wang et al., male rats were exposed to different concentrations of borax by oral gavage ($Na_2B_4O_7{\cdot}10H_2O$, 99.5% purity), the most popular commercial BCC. The rats, which were then exposed to borax, were mated with female rats. It was observed that, at higher exposure levels (100 mg B/kg/day), fetal viability decreased, and at higher concentrations, fetal malformations increased. In addition, testicular enzyme levels and FSH levels were also found to change in the rats. It has been reported that these changes may be related to changes in the lipid metabolism, which play a key role in hormone and enzyme activities through metabolomic tests (Figure 5). According to the results of this study, an idea is provided about the mechanisms underlying the negative effect of BCC utilized at high doses on fertility and reproduction [18]. However, in this study, only borax was investigated. It has not been clearly revealed what the results will be if this is conducted on other BCC.

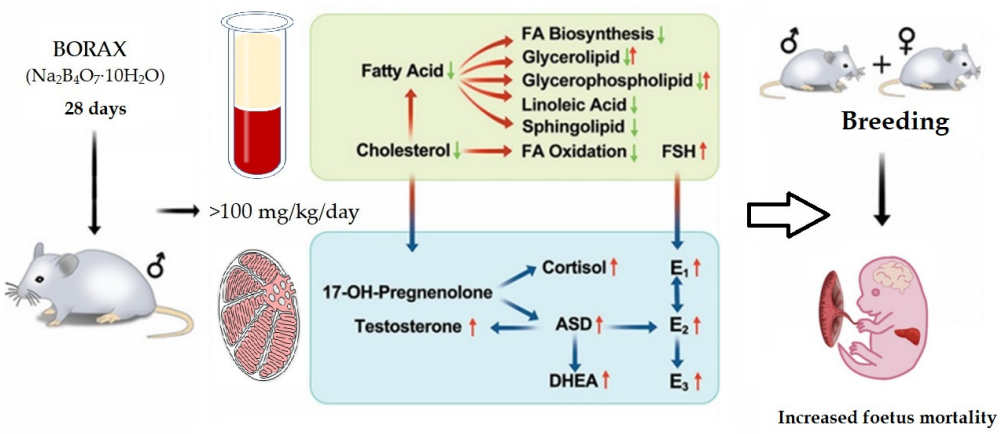

Figure 5. Reproductive toxicity and metabolic perturbations in male rats exposed to boron (as borax). Modified from [18]. FA: fatty acids, FSH: folicule stimulant hormone, DHEA: dehydroepiandrosterone, ASD: androstenedione, E1: estrone, E2: E2, E3: estriol.

3. The Effect in Vitamin D Plasma Levels and Actions

Interestingly, B has been proven to be an important trace mineral because it is essential for its beneficial impact on the body's use of sexual steroids and VitD [19,111,112]. Evidence shows that BCC may possess anti-inflammatory and antioxidant properties that affect the

metabolism of hormones such as E2, calcitonin, and 25-hydroxy-cholecalciferol [19,113]. In fact, B is suggested as being involved with VitD and serum levels by acting as a helper, backup agent, and facilitator for maintaining bone integrity [114,115]. Moreover, some interactions on diverse cholesterol-derived hormonal actions could be complementary in the regulation of minerals, in that the combination of B and E2 may improve the absorption of calcium, phosphorus, magnesium, and other minerals [116]. In this respect, B increases the biological half-life and bioavailability of E2 and VitD, an affect that may exert its hormonal effect [19]. These reported effects could comprise an opportunity for preventing chronic diseases such as osteoporosis, arthritis, and other steroid–hormone–dependent diseases [58,86].

In fact, B (as boric acid or fructoborate) gives rise to significant improvement in bone development by increasing the integration of calcium effectively into bone, joints, and cartilage. Despite it being an unclear mechanism, it appears to reduce the urinary excretion of calcium and magnesium and raises ionized calcium levels [114].

Physiologically, parathormone and VitD act together to increase plasma–calcium levels (protecting the entire organism from hypocalcemia). The parathormone induces the expression and activity of hydroxylases, key for the biotransformation of VitD into the most active calciferols, such as calcitriol. For its part, calcitriol increases the intestinal absorption of calcium, increases the resorption of calcium from bone, and limits calcium excretion from the kidney. Further, B administration induces changes mostly related to the increase of calcitriol in mammals [14,58,117]; however, it limits bone resorption (Figure 6), apparently by means of unknown multiple mechanisms, but it is probably related to the increase of E2, androgens, and progestogen in plasma [26,118–121]. Among these mechanisms, we find the modulation of proteins in osteoblasts. The BCC regulate the messenger RNA (mRNA) expression of extracellular-matrix proteins, such as mineralized tissue-associated proteins, collagen type I, osteoporin, bone sialoprotein, and osteocalcin [19,81]. Additionally, it is probable that some regulator signals, such as RANK or macrophage-stimulating factors, could be involved. B was determined to induce the mineralization of osteoblasts by regulating the expression of genes related to tissue mineralization and the actions of E2, testosterone, and VitD, involved in bone growth and turnover [19,81,122]. Specifically, calcium fructoborate has been related to VitD function by stimulating growth in VitD-deficient animals. Thus, B is involved with VitD and calcium by acting as a helper, backup agent, and facilitator for maintaining bone integrity [19,122–124]. Hence, it appears that B is helpful for the metabolism of bone in terms of proliferation, cell survival, and the mRNA expression of osteoblast proteins and mineralization [19].

These phenomena might play a role in some disorders, such as osteoporosis in postmenopausal women who exhibit disturbed major mineral metabolism under the influence of hormonal variations [86,125]. The evidence reveals that in postmenopausal women, the increase of E2 and plasma copper induced by estrogen therapy was significantly higher when the women consumed 3.25 mg/day of B [25,123], with an increased level of estrogen in postmenopausal women receiving hormone replacement therapy, reducing E2 catabolism [19].

Although the increase of VitD3 in humans administered with BCC is common, extensive studies are required, in that certain data in humans suggest changes related to age, geography, or limited exposure to ultraviolet-B radiation. A clinical trial [126] demonstrated that in 15 men and women with a low B diet for 63 days (0.23 mg B/2000 kcal), D3 increased significantly (a mean of 39%) after B supplementation (3 mg as sodium borate) for another 49 days [19,126,127]. In a study conducted in Serbia on middle-aged women deficient in VitD, with the following supplementation of B at 6 mg/day for 60 days, a 20% increased level of VitD was generated, but there were no other changes in calcium levels or kinetics [128]. This suggests that B may be beneficial to persons with a marginal VitD status, for example, those living in areas where winter provides minimal amounts of ultraviolet light for the synthesis of VitD in the skin [98]. Additionally, it was found that B deprivation exacerbated marginal VitD deficiency and induced a decreased balance

in calcium and phosphorus absorption [129], which at the same time increased plasma glucose and triglycerides [92,130].

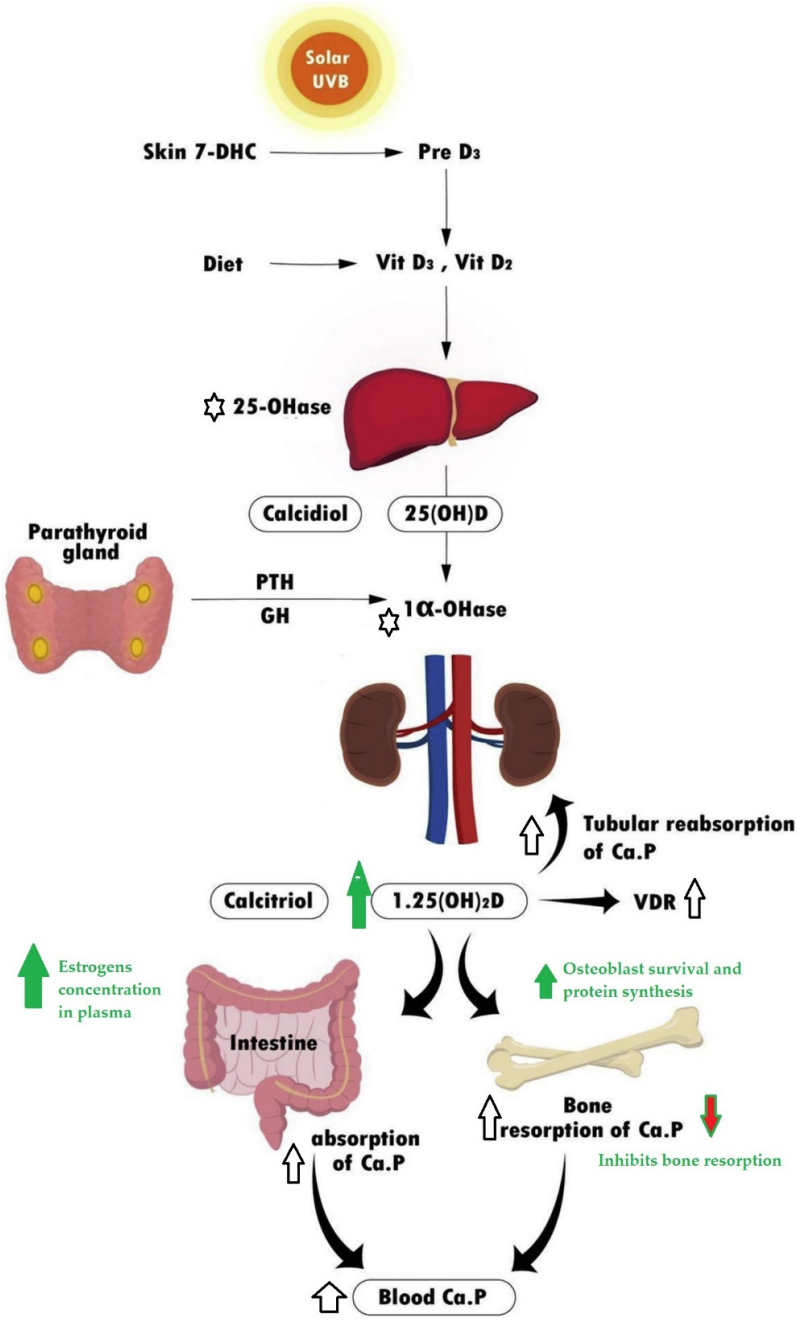

Figure 6. Some actions of BCC in VitD and its effects. The administration of boric acid, borax, or fructoborates increases calcitriol in plasma as well as some of its effects. However, these compounds inhibit bone resorption, which could be related with the increased levels of other steroid hormones. 7-DHC: 7-dehydrocholesterol, Ca.P: calcium and phosphorous, 25-OHase: 25 hydroxylase, 1α-OHase: 1-alfa-hydroxylase, PTH: parathormone, GH: growth hormone.

Similar results are reported when calcium fructoborate (a BCC contained in fruits) was employed as supplementation (6 mg/day); in 13 middle-aged individuals, predetermined to be VitD deficient (serum 25 [OH] D3 < 12 ng/mL), with treatment during 60 days raising D3 levels by 20% [19,127,131]. Additionally, B supplementation reduces urinary calcium

and magnesium excretion and increases the serum level of E2 and calcium absorption in peri- and postmenopausal women [19,59].

Several benefits of B supplementation in an approach such as hormone replacement therapy are supported by studies in postmenopausal women, with a calcium and VitD intervention of 1100 IU/day for at least 12 months, where the levels of deoxyribonucleic acid (DNA) methylation were compared. Interestingly, B supplementation induced a higher production of 25-hydroxylase, and greater potential for VitD activation [19]. However, the results also describe that mean plasma–17β-E2 concentrations, in terms of total testosterone concentrations, increased after supplementation, probably by means of the action in the synthesis pathways [86].

4. Effects in Thyroid Hormones

Interestingly, BCC have been explored regarding their ability to induce effects on thyroid hormones (triiodothyronine or T3, and thyroxine or T4). Nonetheless, such effects are not well established, in that several authors have obtained diverse or contradictory results. Nor has any effect, to our knowledge, on the synthesis of catabolism of thyroid hormones been reported in humans or animals. However, herein we present some considerations and experimental findings on the subject. Notably, the majority of data from humans suggest an inverse relationship between B and thyroid hormones in plasma, while the supplementation of B to other mammals induces rising levels of T3 and/or T4.

In humans, a comparative study on the morphology and physiology of the thyroid revealed a change in the level of serum–thyroid hormones due to the use of boron-containing water. It has been established that the intake of water identical in B concentrations (250 mg/L), but different in terms of an ionic salt base, leads to various structural changes of the thyroid at the tissue, cellular, and subcellular levels. In that study, it was observed that water containing added B induces more pronounced changes that correlate with the blood concentration of T3 and T4; however, the mechanism remains unclear [132]. Moreover, some researchers hypothesize that with respect to overexposure, B may serve as a potential goiterogen or limit data on hyperthyroidism. In particular, B overload may induce thyroid hypo-functioning and goiter formation, which is supported due to the fact that serum and urinary B levels are characterized by a negative association with thyroid hormone levels in exposed subjects. The chemical properties of iodine and direct boron B accumulation and actions in the thyroid suggest that the thyroid gland is the target for B activity [133].

Despite this inverse relationship, systematic reviews have investigated the toxicity of BCC in some organs or cells, including effects on the thyroid gland. To address this, the toxicological literature related to inhalation and dermal exposure has been reviewed, in addition to the literature on its oral exposure, because these studies contribute to the understanding of the toxicity endpoints potentially caused by the previously mentioned pathways. The genotoxic and carcinogenic potential of B compounds was also reviewed, for all exposure routes, as well as in vitro. The inclusion of the latter group of experiments is justified by the notion that genotoxic events, including mutagenicity, generally occur within the cells. In reference to a prior work, it is mentioned that the majority of toxicity data on B refer to boric acid, and isolated reports include certain other BCC. Although some reports suggest certain boronic acids, such as mutagenic, these compounds did not present data on genotoxicity, carcinogenicity, or direct thyroid involvement [109]. In fact, some complementary studies are required to know the effect of B depletion, supplementation, and overdose on the human body, as well as the effect on cells producing thyroid hormones on proteins transporting or metabolizing such hormones, and the possible effect on hormonal feedback systems.

From animal experiments through the utilization of diverse species, certain facts have been proposed in humans. Thus, Kucukkurt et al. studied 30 male Sprague–Dawley rats with boric acid or borax in the diet as a source of B on the serum of some hormones (leptin, insulin, triiodothyronine, and thyroxine) levels. Rats supplemented with B (100 mg B/kg)

in the diet decreased in body weight, related to an increased basal metabolism rate, as well as decreased leptin and insulin levels, while increasing plasma T3 and carnitine levels [134].

In a recent study conducted on propylthiouracil-induced hypothyroid male Wistar albino rats, the administration of B (10 mg/kg or 20 mg/kg) was evaluated. In fact, thyroid hormone analysis and serum biochemical measurements were performed, and the thyroid gland tissue was examined. According to the findings, the level of T3 was increased by B administration; however, some hepatic enzymes (that were at a higher concentration in hypothyroid groups) were also decreased after B administration to values near those of the control group. Therefore, it is suggested that BCC activity in the thyroid hormone could benefit patients or subjects with hypothyroidism on reaching adequate levels of T3; however, additional approaches are required to understand the role of BCC in the thyroid function of rats [16].

Other nonrodent animal species have been explored to identify a specific role for B in thyroid functions. The long-term effect of B supplementation on growth and immune response were evaluated in female piglets. The B supplementation (5 mg/kg) had no effect on growth ($p < 0.58$) during the transition phase, but sows receiving B showed superior growth ($p < 0.05$) throughout the growth phases and during the final stage. However, interesting data revealed that the concentration of thyroid hormones (T3 and T4, and particularly T3), was reduced during some phases of the study by the addition of B [135].

Additionally, dietary B supplementation on thyroid activity in male goats was investigated. The B-supplemented group was fed the baseline diet containing 70 mg B/kg diet for 6 months. Serum samples were collected, and testicular biopsies were obtained at the end of the experiment. The results of 6 months of dietary B supplementation resulted in a significant increase in serum–B concentration, and also in serum–testosterone levels over time. However, in relation to the mean body weight of the animals and serum–T3 and –T4 levels, these remained comparable with those of the control. In conclusion, B does not give rise to negative or harmful effects on the thyroid. Notably, B supplementation significantly increased the mRNA expression of the CYP17A1, which is essential for steroidogenesis, and it also exerted a positive effect on testicular tissue. As a result, B might be considered an excellent food supplement to improve the animals' reproductive capacity [136].

With respect to B supplementation in rams, its addition in the diet (400 mg/kg) significantly increased serum levels of testosterone (T) ($p < 0.05$) when compared with those of the control group. Serum levels of T3 were elevated significantly ($p < 0.05$) with the advancement of age in both groups. The percentage of increase of the T3 level at the end of the experiment (after 17 weeks) was observed to be higher in B-treated rams than in control rams. Additionally, B induced a significant improvement of semen quality compared with the control group ($p < 0.05$). Thus, B is considered a potential and useful supplement in the food ration of rams to improve their testicular and thyroid activities [137].

Another field relevant for the application of BCC is in therapies against thyroid cancer. There is now evidence that the delivery of B and compounds (including BCC) can be combined with drug-delivery system strategies such as polymeric particles, liposomes, and monoclonal antibodies (mAb), to enhance B delivery to malignant tissues and cancer cells, particularly when combined with targeted agents. In addition, researchers in B neutron capture therapy (BNCT) have reported recent findings on boron's radiobiological application, clinical outcome, and critical issues, which need to be addressed in order to increase the efficiency of this treatment modality, as well as its relationship to the treatment of certain cancer diseases, including thyroid cancer [138].

Thus, in a study on cancer treatment by BNCT (a binary approach to cancer therapy that requires the accumulation of B atoms preferentially in tumor cells; and then, localized irradiation would induce a biased damage in neoplastic cells), its application to undifferentiated thyroid carcinoma revealed that B causes tumor destruction in the thyroid. Previous studies had shown that the human undifferentiated thyroid cancer cell line possesses a selective uptake of borophenylalanine (^{10}BPA) both in vitro and after implantation in mice. It was also mentioned that animals injected with borophenylalanine and irradiated

with a thermal neutron with beam, entertain 100% control over tumor growth and a 50% histological cure [139].

Although these suggestions highlight the mechanism(s), another study provides evidence that the slightly increased environmental concentrations of B, cadmium, and molybdenum can accelerate the appearance of transformation markers in the thyroid gland of hypothyroid rats [140]. These findings are consistent with an activation of a homologous recombination–repair mechanism in thyroid cells, while other cell lines demonstrated a different DNA–damage pattern and the activation of both repair pathways after BPA exposure [141]. Therefore, the results of BNCT in some cases of thyroid carcinoma are attractive [142]. Diverse BCC should be explored in this manner, in that the differences are related to some BNCT agents; for example, the intraperitoneal (i.p.) administration of NaB increased B uptake, while oral administration for a longer period of time induced tumor-growth delay prior to BPA administration. The use of NaB i.p. would optimize the irradiation results [143].

A combination of BNCT and the boron-containing carrying system is suggested. In this respect, some nanoparticles (NP), such as the B carrier, confer enhanced permeability and retention effects. Recently, shape-tuned gold NP (AuNP) stabilized with polyethylene glycol (PEG) and functionalized with the boron-rich anion cobalt bis (dicarbollide), evaluated as similar systems, were active against tumors in vitro. The resulting AuNP were evaluated in vivo in a mouse model of human fibrosarcoma (HT1080 cells) using positron emission tomography (PET). Among attractive results, we find that accumulation in the thyroid gland appears to occur faster for core-labeled particles, although those values are subjected to a significant error. Low tumor accumulation in the animal model revealed that the modification of the size and geometry of AuNP is required for future studies [144].

On the other hand, boron-nitride nanotubes have also been suggested as carriers for drug-delivery purposes to transport anticancer drugs into biological systems. In this respect, theoretical assays suggest differences in the dependence of solvents, which could be applied to optimize proposed carrier systems; a recent study approached the interaction of propylthiouracil (a drug employed in some thyroid maladies) [145]. Taken together, it could be observed that although this is an incipient advance, the possibility is clear that the implementation of B in therapies against thyroid cancer could be beneficial to health.

Finally, it should be mentioned that borophenes have been proposed as efficient drug-delivery systems in other biomedical applications (in particular interacting with liposoluble compounds, such as the hormones revised in this manuscript), due to certain shared properties, such as poor water solubility and a predilection for reaching some fat-rich environment, such as that in the central nervous system [146,147].

5. Conclusions

The boron atom appears to have no notable action on human hormones. The latter is supported due to the fact that the current pharmacovigilance reports of some BCC used in humans lack shared effects in the modification of the action of liposoluble hormones. However, some BCC, such as boric acid, borax, and boronic acids, have exerted biological effects presumably through pathways related to the action of liposoluble hormones, but the mechanism of action is incipient.

Moreover, no doubt exists regarding the role of some BCC, particularly synthetic BCC, including polycyclic and cluster compounds in phenomena disrupting processes with liposoluble hormones. The mechanisms of action are suggested by means of enzymes involved in their synthesis or their receptors, due to their structural relationship to endogen steroid hormones.

Knowledge of BCC acting in different liposoluble hormone systems suggest that the advances are biased in terms of their application in the control of steroid action. This could be by means of their action in synthesis, the plasma concentration of these hormones, and/or directly on their receptors. However, other advances (such as those suggesting the beneficial effect of boric acid or fructoborates) support their direct action in bone or

through the modification of VitD and parathormone–plasma levels and activities. Other studies suggest BCC action in thyroid hormones. Notwithstanding this, hormones are often reported as being increased after B supplementation in animals, while in humans, BCC are linked to thyroid hypofunction.

The ability of BCC for modulating the serum levels and actions of liposoluble hormones possesses potential multiple applications in medicine. To mention only some examples, BCC could be used for the following: to regulate fertility; to modulate the signs and symptoms of hormone depletion (including an increased risk for some chronic diseases); in the development of contraceptive agents; in enhancing muscle strength; in the treatment of osteoporosis; and in the treatment of certain thyroid maladies.

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