REVIEW

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

A comprehensive review of the pharmacological, therapeutic, and toxicological properties of boric acid and other boron-containing compounds: current landscape and future perspectives

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Received 05 Jan 2025 After peer review 17 July 2025 Accepted 19 July 2024

The aim. In this review, information obtained through a comprehensive scan of scientific resources on recent developments in the field of health regarding boric acids and BCCs is brought together, and current and future perspectives are presented.
Matherial and methods. The literature studies on boron were collected using multiple databases (WOS, PubMed, Scopus, Science Direct, SciVerse, SciELO, Cochrane Library, Embase and Google Scholar). The health effects of boric acids and BCCs used in preclinical and clinical studies were systematically compiled.
Results and conclusion. Different natural and synthetic boron-containing compounds (BCCs) are increasingly used in the healthcare sector. To date, five BCCs drugs (bortezomib, crisaborole, ixazomib, tavaborole and vaborbactam) have been approved by the Food and Drug Administration, for diverse clinical applications. It is also understood that more than ten boron-based compounds (alabostat, sodium borocaptate, voromycin, TOL-463 and others) are being investigated in different clinical trial phases. In addition, it is seen that clinical studies are continuing for combinations of various drugs with BCCs for use in new indications. In addition, it is observed that boron and boron-containing compounds are widely used as supplements. This review also provides an overview of recent advances in the pharmacological activities of boric acids and BCCs, including antioxidant, anti-inflammatory, anti-atherosclerotic, anticancer, antimicrobial, antiparasitic, antiviral, antiprotozoal, cardioprotective, hepatoprotective, neuroprotective, osteoprotective, antidiabetic, anti-apoptotic, anti-obesity, ferroptosis properties, effects on immune system, antiepileptic, anti-Parkinson, and anti-Alzheimer's activities and the mechanisms of action involved, obtained from both *in vitro* and *in vivo* studies.

Keywords: boron-containing compounds; pharmacological profile; boron containing drugs; medical applications

Abbreviations: 4-OHFBA — 4-hydroxyphenylboronic acid; AD — Alzheimer's disease; ALT — alanine transaminase; APAP — acetaminophen; AST — aspartate transaminase; Aβ — Amyloid beta; BA — boric acid; BAD — BCL-2 associated agonist of cell death; BCCs — boron-containing compounds; BCL-2 — B-cell lymphoma 2; BIRC-2 — Baculoviral IAP repeat Containing-2; BNCT — boron neutron capture therapy; BODIPY — boron–dipyrrin; BPH — borax pentahydrate; cAMP — cyclic adenosine monophosphates; CAT — catalase; CD — cardiovascular diseases; CP — cyclophosphamide; DPPs — dipeptidyl peptidases; EMA — European Medicines Agency; FAP — fibroblast activation protein; FAS — fetal alcohol syndrome; FDA — U.S. Food and Drug Administration; GI — gastrointestinal; GPX4 — glutathione peroxidase 4; GSH — glutathione; hBNs — hexagonal boron nitride nanoparticles; HCV — hepatitis C virus; HDL-C — high-density lipoprotein cholesterol; HF — heart failure; HIV — human immunodeficiency virus; HUVEC — human umbilical vein endothelial cells; I/R — ischemia and reperfusion; IFN-γ — interferon-gamma; IL — interleukin; iNOS — inducible nitric oxide synthase; LDL — low-density lipoprotein; LPS — lipopolysaccharide; LxR-α — liver X receptor alpha; MDA — malondialdehyde; MF — myocardial fibrosis; MI — myocardial infarction; MPP+ — 1-methyl-4-phenylpyridinium; MRSA — methicillin-resistant *Staphylococcus aureus*; NaB — sodium pentaborate pentahydrate; NAD^+ — nicotinamide adenine dinucleotide; NF-κB — nuclear factor kappa B; NO — nitric oxide; OEA — oleoylethanolamide; PBCT — proton boron capture therapy; PD — Parkinson's disease; PPARγ — peroxisome proliferator-activated receptor gamma; QCT — quercetin; ROS — reactive oxygen species; SOD — superoxide dismutase; SREBP-1c — sterol regulatory element-binding protein 1c; TAC — total antioxidant capacity; TNF-α — tumor necrosis factor-alpha; OC — total oxidative status; WHO — World Health Organization.

For citation: O. Yunusoglu, I. Kalfa, M.E. Demirel, M.A. Binzet, U.Z. Sevinc, I. Turel, A.H. Kurt. A Comprehensive Review of the Pharmacological, Therapeutic, and Toxicological Properties of Boric Acid and Other Boron-Containing Compounds: Current Landscape and Future Perspectives. *Pharmacy & Pharmacology.* 2025;13(3):202-238. **DOI:** 10.19163/2307-9266-2025-13-3-202-238

Для цитирования: О. Юнусоглу, И. Калфа, М.Э. Демирель, М.А. Бинзет, У.З. Севинч, И. Тюрель, А.Х. Курт. Комплексный обзор фармакологических, терапевтических и токсикологических свойств борной кислоты и других борсодержащих соединений: текущее состояние и будущие перспективы. *Фармация и фармакология.* 2025;13(3):202-238. **DOI:** 10.19163/2307-9266-2025-13-3-202-238

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОБЗОР
DOI: 10.19163/2307-9266-2025-13-3-202-238

Комплексный обзор фармакологических, терапевтических и токсикологических свойств борной кислоты и других борсодержащих соединений: текущее состояние и будущие перспективы

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Получена 05.01.2025 После рецензирования 17.07.2025 Принята к печати 19.07.2025

Цель. В этом обзоре собрана информация, полученная в результате комплексного изучения научных ресурсов о последних достижениях в области здравоохранения, касающихся борных кислот и БСС, а также представлены текущие и будущие перспективы.
Материалы и методы. Источники литературы были собраны с использованием нескольких баз данных (WOS, PubMed, Scopus, Science Direct, SciVerse, SciELO, Cochrane Library, Embase и Академия Google). Были систематизированы данные о воздействии на здоровье борных кислот и БСС, используемых в доклинических и клинических исследованиях.
Результаты и заключение. Различные природные и синтетические борсодержащие соединения (БСС) все чаще используются в здравоохранении. На сегодняшний день 5 препаратов БСС (бортезомиб, крисаборол, иксазомиб, тавaборол и ваборбактам) одобрены Управление по контролю качества пищевых продуктов и лекарственных средств США (FDA) для различных клинических целей. Также известно, что более 10 соединений на основе бора (алабостат, борокаптат натрия, воромицин, TOL-463 и другие) исследуются на различных этапах клинических испытаний. Кроме того, как видно, продолжаются клинические исследования комбинаций различных лекарственных средств с БСС для применения по новым показаниям. Кроме того, отмечается, что бор и борсодержащие соединения широко используются в качестве пищевых добавок. В этом обзоре также представлен анализ последних достижений в области фармакологической активности борных кислот и БСС, включая антиоксидантные, противовоспалительные, антиатеросклеротические, противоопухолевые, антимикробные, противопаразитарные, противовирусные, противопротозойные, кардиопротекторные, гепатопротекторные, нейропротекторные, остеопротекторные, противодиабетические, антиапоптотические, против ожирения, ферроптоз, влияние на иммунную систему, противоэпилептическую, антипаркинсоническую и альцгеймеровскую активность и соответствующие механизмы действия, полученные в ходе исследований как *in vitro*, так и *in vivo*.
Ключевые слова: борсодержащие соединения; фармакологический профиль; борсодержащие лекарственные средства; медицинское применение
Список сокращений: 4-OHFBA — 4-гидроксифенилбороновая кислота; АД — Болезнь Альцгеймера; АЛТ — аланинаминотрансфераза; APAP — ацетаминофен; АСТ — аспартаттрансаминаза; Aβ — бета-амилоид; БК — борная кислота; BAD — связанный с BCL2 агонист белка клеточной гибели; БСС — борсодержащие соединения; BCL-2 — белок, регулирующий уровень апоптоза в клетках; BIRC-2 — белок 2, содержащий бакуловирусный IAP; БНЗТ — бор-нейтронозахватная терапия; BODIPY — дипиррометен бора; BPH — тетраборат натрия пентагидрат; цАМФ — циклическиq аденозинмонофосфат; CAT — каталаза; ССЗ — сердечно-сосудистые заболевания; ЦФА — циклофосфамид; ДПП — дипептидилпептидаза; EMA — Европейское агентство лекарственных средств; FAP — белок активации фибробластов; ФАС — фетальный алкогольный синдром; FDA — Управление по контролю за продуктами и лекарствами США; ЖКТ — желудочно-кишечный тракт; GPx4 — глутатионпероксидаза 4; GSH — глутатион; hBN — гексагональный нитрид бора; HCV — вирус гепатита С; ЛПВП — липопротеины высокой плотности; СН — сердечная недостаточность; ВИЧ — вирус иммунодефицита человека; HUVEC — эндотелиальные клетки пупочной вены человека; I/R — ишемия и реперфузия; ИФН-γ — гамма-интерферон; ИЛ — интерлейкин; iNOS — индуцируемая синтаза оксида азота; ЛПНП — липопротеины низкой плотности; ЛПС — липополисахарид; LxR-α — альфа-Х-рецептора печени; МДА — малоновый диальдегид; МФ — фиброз миокарда; ИМ — инфаркт миокарда; $МФП^+$ — 1-метил-4-фенилпиридиний; MP3C — метициллинрезистентный золотистый стафилококк; $НАД^+$ — никотинамидадениндинуклеотид; NF-κB — ядерный фактор каппа B; NO — оксид азота; OEA — олеоилэтаноламид; ПБНЗТ — протонно-бор-нейтронозахватная терапия; БП — болезнь Паркинсона; PPARγ — рецептор, активируемый пероксисомным пролифератором гамма; QCT — кверцетин; АФК — активные формы кислорода; СОД — супероксиддисмутаза; SREBP-1c — белок, связывающий регуляторный элемент стерола 1; ТАС — общий антиоксидантный статус; TNF-α — фактор некроза опухоли альфа; ОС — общий окислительный статус; ВОЗ — Всемирная организация здравоохранения.

INTRODUCTION

Boron is a naturally occurring trace element found in both the environment and living systems, where it plays diverse roles in numerous biological processes [1]. It is distributed in the Earth's crust, soil, and oceans, existing at specific concentrations. The average boron concentration in soil is 10–20 ppm [2]. Boron is found in various regions of the world, particularly in countries like the United States, Turkey, Brazil, Russia, and China, which have substantial boron reserves [3, 4]. By taking part in hydroxylation processes, boron plays a crucial function in the production and metabolism

of several reactions [5, 6]. Primarily, at the neutral pH levels present in most biological fluids, boron exists as boric acid (BA; H_3BO_3) and a small amount of borate anion ($B(OH)_4^-$). Both BA and borate tend to form complexes with sugars and other compounds containing trans-hydroxyl groups [7]. Boron compounds are known to be water-soluble. Both borax and BA are soluble in water, and it is well-known that the solubility of BA in water increases with rising temperatures [8].

Organoboron compounds are one of the most versatile classes of heteroatom-containing organic molecules [9]. This versatility is due to the unique chemical properties of boron. In analytical chemistry, the slightly Lewis acidic character of the boron atom is particularly valued in areas such as carbohydrate and fluoride determination [9]. This property plays an important role in analytical processes thanks to its ability to form tetracoordinate borates with fluoride anions and polyols [10, 11]. Boron is more electropositive than carbon, and this fundamental property is most efficiently utilized in organic synthesis, which has become one of the most important application areas of organoboron compounds [9]. This property of boron allows catalytic effects and selective reactions in various organic transformations. Given the covalent binding capacity of boron to biological targets, it can be assumed that organoboron compounds are simple electrophiles, similar to acrylates, epoxides and aldehydes, which are known electrophilic agents of chemical biology [12]. However, the behaviour of boron in biological systems is more complex, making it a unique chemical tool. According to studies, boron has the ability to form multiple covalent bonds with a protein, although boronic acids hydrate in aqueous solution and in some examples, boron was observed to interact indirectly with histidine via a bridging water molecule [13]. This feature enables boron to offer a unique binding mechanism in biological systems. Boron and its compounds are also used to develop methods for drug analysis [14–16] and to modulate different chemical reactions [17–19]. The role of boron compounds in chemical biology and drug discovery is increasing. The unique chemical properties, selective binding mechanisms and low toxicity of boron make it a valuable element in the development of therapeutic agents.

Boron concentrations vary between species, and low boron levels inhibit growth [20–22]. Recognized as a trace element, boron has low toxicity in mammals and is essential for the development of animals and human bodies [23, 24]. Additionally, optimal boron intake is suggested to positively influence bone growth and development [25, 26], the proliferation and differentiation of blood cells, and brain functions [27–29]. However, it has also been reported that excessive intake of boron can be harmful [30, 31]. Experimental boron applications in animals and humans have been shown to result in significant improvements in immunity, antioxidant effects, growth, and embryonic development [1]. Natural boron compounds possess antibacterial, antiviral, and anticancer properties [32, 33]. Boron is necessary for a wide range of metabolic processes in microorganisms, including antibiotic action, nitrogen fixation, and quorum sensing [34]. Furthermore, thanks to their anti-inflammatory properties, these compounds are used as dietary supplements for the treatment of neuroinflammation and neurodegeneration [35]. Approximately 80% of the global population use conventional medicine for healthcare [36]. In individuals with boron deficiency, reductions in high-frequency brain activity have been associated with memory impairment [37–39]. Borax, one of the boron compounds, exhibits antiseptic, antifungal, and antiviral effects, as well as anti-osteoporotic, anti-inflammatory, hypoglycemic, and anticoagulant properties [40, 41]. Because of its ability to scavenge free radicals, it has also been reported to have antioxidant qualities. It inhibits proliferation in tumor cells and shows anticancer effects by inducing apoptosis [42–44]. BA has also been reported in numerous studies to have antioxidant [45], anti-genotoxic [46], anti-carcinogenic [47], non-cytotoxic [48], and metal-chelating properties [49, 50]. Boron-containing compounds (BCCs) have a wide range of pharmacological activities (Fig. 1).

Currently, medicinal chemists are investigating boron-based small compounds due to the Lewis acid characteristics of boron, which render it reactive towards the nucleophiles found in enzymes, nucleic acids, and carbohydrates [51]. Recently, the U.S. Food and Drug Administration (FDA) sanctioned three BCCs: two from the BA category and one from the

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DOI: 10.19163/2307-9266-2025-13-3-202-238

benzoxazole category [51, 52]. Boronic acids serve as transition state analogs for enzymes such as proteases and lactamases, so efficiently suppressing their function. Boron has garnered considerable interest owing to the FDA approval of multiple boron-containing pharmaceuticals and the existence of additional related pharmacological compounds undergoing clinical testing [6, 51]. It has received significant attention due to FDA approval of multiple boron-containing drugs and the existence of additional related pharmacological compounds undergoing clinical testing [51, 52]. Information was obtained from the European Medicines Agency (EMA), the FDA website, the DrugBank database and various scientific sources. Boron-containing drugs that have received FDA approval to date are shown in Table 1.

In addition to the above drugs that have received FDA approval, various boron and its compounds are being investigated in clinical studies (phases 1 to 3). Among the molecules that have received FDA approval, clinical phase studies continue for GSK8175/GSK2878175 molecule in hepatitis C virus (HCV) clinical research, ganfeborole hydrochloride/(GSK656) molecule in tuberculosis research, xeruborbactam/(QPX7728) molecule as an antibacterial, and AN-2898 molecule in topical dermatitis. Several BCCs are currently undergoing clinical trials, exploring their potential therapeutic applications across various medical fields. Table 2 below provides a detailed summary of these compounds.

Numerous BCCs have been studied, acknowledged for their advantageous qualities, and distributed internationally [1, 69, 70]. BA, borinic acids, and their derivatives, such as borinates, oxoboranes, and boronic acid derivatives, serve as enzyme inhibitors and regulate the opening and closing of membrane ion channels [71]. Research demonstrates that boron, alongside oxygen, was essential in the first synthesis of RNA molecules on Earth [72]. Due to its pronounced electrophilic characteristics, boron and its derivatives have been incorporated into various therapeutic candidates, leading to considerable study in recent years on the synthesis of innovative boron-based structures [73–75]. Historically, the pharmaceutical use of boron was primarily limited to antiseptics; however, its therapeutic range has broadened in recent decades to encompass antibiotics and anticancer drugs [76–78]. A notable characteristic of the boron atom is its ability to absorb neutrons, which has facilitated the advancement of many drug discovery platforms [79]. Furthermore, the documentation of newly synthesized boron-based chemicals affecting metabolic processes in both animals and humans is increasing [80]. The chemical structures of some boron compounds are presented in Table 3.

Boron is known to play a role in growth due to its ability to strengthen cell membranes [81]. It is essential for plant growth and development, contributing to healthy growth and productivity in plants [82]. Approximately 90% of boron in plant cells has been estimated to reside in the cell walls [81]. Boron can form complexes with compounds such as polyhydroxyl polymers, pectins, and polyols, which are components of the cell wall [82, 83]. Thus, by forming esters with cis-diol components of the cell wall, boron aids in stabilizing and synthesizing the cell wall, providing shape, strength, and rigidity to the cell [1, 81]. Plants are also known to be impacted by BA, which is usually found in their cell walls [7, 84–86]. To fully grasp the potential of boron in medicinal chemistry, more research is necessary, as demonstrated by the drug analogs that exhibit a range of biological activities with a single boron atom or boron cluster molecules. This study will highlight many of the uses of boron chemistry in the medical profession, however there have been other reviews and books recently that demonstrate the advancements in boron chemistry and its applications.

THE AIM. This review aims to provide a comprehensive overview of the expanding role of BA and BCCs in the healthcare field. In recent years, both natural and synthetic BCCs have garnered significant attention due to their diverse pharmacological properties and growing clinical relevance. Several BCCs have already received regulatory approval for medical use, while many others are currently undergoing various phases of clinical evaluation. In addition, new therapeutic strategies involving the combination of BCCs with other pharmaceutical agents are being actively explored. This review focuses on the broad spectrum of biological activities exhibited by BA and BCCs, including antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral, antiparasitic, neuroprotective, cardioprotective, hepatoprotective, osteoprotective,

and antidiabetic effects. The mechanisms of action underlying these activities, as demonstrated in both *in vitro* and *in vivo* studies, are discussed in detail. Furthermore, the review highlights the use of boron-based compounds as dietary supplements and examines their potential contributions to human health. Scientific data were systematically collected from multiple reputable databases, including Web of Science, PubMed, Scopus, ScienceDirect, SciVerse, SciELO, Cochrane Library, Embase and Google Scholar. Overall, this review aims to synthesize recent advancements, evaluate current applications, and provide insights into future directions for the use of BA and BCCs in medical and therapeutic contexts.

MATERIALS AND METHODS

This systematic review was conducted in accordance with PRISMA guidelines and was registered in the International Prospective Register of Systematic Reviews. A literature search was carried out across multiple electronic databases PubMed, Web of Science, Scopus, Google Scholar, Cochrane Library, and Embase to identify relevant studies published in English, with no time restrictions. The search terms were designed to align with the research objectives, using Boolean combinations such as: “pharmacokinetics,” “pharmacodynamics,” “bioavailability,” “therapeutic potential,” “biological activity,” “pharmacological activity,” “antimicrobial activity,” “clinical trial,” “toxicity,” and other terms related to “boric acid” or “boron-containing compounds/BCCs”. A systematic search conducted across multiple scientific databases yielded a total of 312 eligible studies (n = 312), comprising both original research articles and review papers, which were subsequently included in the present analysis.

RESULTS AND DISCUSSION

The pharmacokinetic properties of boric acid and boron-containing compounds

Absorption of boric acid and boron-containing compounds

Humans have good absorption of boron from the gastrointestinal (GI) tract [87]. Research has indicated that around 90% of boron ingested orally is absorbed by both humans and animals [87]. According to the World Health Organization (WHO), humans absorb 0.44 μg of boron per day through their inhaled air, 1.2 mg per day on average through their diet, and 0.1–0.3 mg per liter of boron through their drinking water [88]. Vanderpool et al (1994), the GI tract absorbs more than 90% of boron taken orally in 3 hours, and the absorption is finished in 24 hours [89]. Furthermore, absorption through the skin is one of the ways BA enters the body. Although studies have shown that the passage through intact skin is low, it is stated that absorption may increase in the presence of damaged skin [90].

Distribution of boric acid and boron-containing compounds

BA is found in large quantities in bodily water in humans (98.4% as BA and 1.6% as the, $B(OH)_4$) [91]. The distribution of BA in humans and animals is comparable. Not all BCCs can reach the entire organism, even those with a significant volume of dissemination [92]. This implies that certain barriers contain transporters. Additionally, following BA treatment, bone boron levels seem to be higher than those in plasma or soft tissues, while boron levels in soft tissues are equal to those in plasma [93]. Furthermore, it has also been shown that some boron-containing nanoparticles and BCCs tend to preferentially accumulate in specific organs, such as the brain or heart [94].

Metabolism of and biotransformation of boric acid and boron-containing compounds

In both humans and animals, BA is not metabolized. Because breaking the B-O bond requires a lot of energy (523 kJ/mol), biological systems are unable to metabolize BA. Many inorganic borates are metabolized at low concentrations, despite the fact that BA is not. And also, they produce BA as the primary metabolite at physiological pH on mucosal surfaces prior to absorption [93]. Additionally, it is known that BCCs can undergo biotransformation, and that this biotransformation frequently involves boron-free bonds, even though there are no known enzyme processes that break boron-containing bonds [95].

Elimination and excretion of boric acid and boron-containing compounds

According to the statistics, hepatic and renal clearance are the main factors influencing boron

ОБЗОР
DOI: 10.19163/2307-9266-2025-13-3-202-238

excretion [95]. Boron is mostly expelled through urine, with only trace amounts seen in perspiration, breath, and bile, and to a lesser degree through stool (2%) [96]. Studies show that the amount of fecal and urine excretion increased along with the dietary intake of boron [1]. Despite having fairly similar renal clearance values (39 and 55 mL/min/1.73 m^2 in humans; 40 mL/min/1.73 m^2 in mice), rats and mice typically have higher rates of renal clearance than humans, which suggests the possibility of different mechanisms at play [97]. Six volunteers were given roughly 131 mg of BA in water (750 mg) and water-emulsifying ointment (740–1473 mg, or roughly 130–258 mg BA) by WHO (2009) and they discovered that, on average, 92–94% of the BA that was given was eliminated in the urine after 96 hours [98].

Therapeutic potential and biological activities of boric acid and boron-containing compounds

Anti-inflammatory activity of boric acid and boron-containing compounds

Inflammation serves as an initial defense mechanism against harming agents, notably toxins, pathogens, and allergens [99]. When the acute inflammatory response persists, the immune system engages in a more intricate, prolonged reaction. The chronic inflammatory response is typically of low intensity and encompasses numerous proinflammatory cellular elements, including leukocytes predominantly consisting of macrophages and lymphocytes. Due to their effectiveness in alleviating pain and inflammation, nonsteroidal anti-inflammatory drugs rank among the most utilized medications, solidifying their status in the WHO Model List of Essential Medicines [100]. Non-steroidal anti-inflammatory medicines account for 30% of hospital admissions due to preventable adverse drug reactions, primarily resulting in bleeding, myocardial infarction (MI), cerebrovascular accident, and renal impairment [101]. According to the research, it investigated the potential of BA as a novel anti-inflammatory medication [102–105]. Anti-inflammatory effects of BA have been demonstrated *in vitro* [106–109] and *in vivo* [110–112]. The effects of BA on anti-inflammatory parameters are presented schematically in Figure 2. A study by Gundogdu et al (2024), BA has shown potential effectiveness in decreasing inflammation in a rat model of knee osteoarthritis [113]. Tekeli et al (2022) study that supplementing with BA regulates the inflammatory alterations associated with ovariectomy [114]. Moreover, Cao et al (2008) demonstrated that BA was proven to possess strong anti-inflammatory action through the inhibition of the nuclear factor kappa B (NF-κB) signaling pathway and possesses therapeutic potential, especially in chronic inflammatory diseases such as rheumatoid arthritis [102]. In that study, it was shown that the BA significantly decreased the expression of pro-inflammatory cytokines, suppressed inflammatory cell infiltration and that its effect on tumor necrosis factor-alpha (TNF-α) secretion could be induced via thiol-dependent mechanism [102].

Anticancer activity of boric acid and boron-containing compounds

Anticancer activity denotes the capacity of chemicals to impede the growth and multiplication of cancer cells or to trigger their apoptosis [115, 116]. Numerous epidemiological and experimental investigations have shown that BA may have anti-cancer effects on a range of cancer types. Given the lack of definitive treatment for all the different types of cancers, these studies looked into the potential of this substance as a novel therapeutic option for alleviating symptoms and slowing disease progression. Series of recent studies showed effect of BA on hepatocellular carcinoma, endometrial and ovarian cancer, colon cancer, lung cancer, prostate cancer, breast cancer, glioblastoma and thyroid cancer [117–120]. The cytotoxic role of BA application on glioblastoma treatment was investigated by Aydin et al (2021). It was observed that high-dose BA applications had a fatal effect on glioblastoma cells, but non-toxic dosages of BA application did not inhibit proliferation of these cells. As a result of their study, high dosage of BA solution application has been found to be a promising strategy for treating glioblastoma [121]. Furthermore, Lin et al (2013) demonstrated that rats with hepatocellular carcinoma treated with boron neutron capture treatment seemed to have smaller tumors on ultrasound images and clearly had less blood flow to the tumor. On the 80th day following boron neutron capture treatment, the liver lesion had vanished;

a recovery of values to normal levels was also observed [122].

BA and borax dramatically decreased U-87MG cell viability in a concentration-dependent manner, according to Turkez et al (2021). Moreover, they discovered that whereas boron compounds improved the activities of the superoxide dismutase (SOD) and catalase (CAT) enzymes and raised malondialdehyde (MDA) levels and total oxidative status (TOS), they simultaneously decreased glutathione (GSH) levels and total antioxidant capacity (TAC) [123]. In studies examining the effects of BA on breast cancer cell lines (MCF-7 and MDA-MB-231), BA was found to inhibit the growth of breast cancer cells in both 2D and 3D culture media [120]. Furthermore, BA and calcium fructoborate were reported to inhibit cell proliferation in MDA-MB-231 cancer cell lines [124]. BA is also thought to exert a mechanism of action by partially influencing the DNA damage response in breast cancer cells [125]. Based on these findings, studies on breast cancer and BA suggest that BA could be proposed as a chemical protective agent [126, 127]. Besides, the mechanisms of induction of apoptosis by boron against cancer cells are multilevel. Boron induces mitochondrial membrane permeability due to DNA damage, which triggers apoptosis [112, 115, 117, 128]. During the process, the pro-apoptotic proteins BAX, BAK, CASP-3, and B-cell lymphoma 2 (BCL-2) associated agonist of cell death (BAD) were upregulated, and anti-apoptotic genes like baculoviral IAP repeat containing-2 (BIRC-2), BIRC-5, and BCL-2 were downregulated. Additionally, cell cycle arrest was induced by boron in the G2/M and Sub-G1 phases, inhibiting the proliferation of cancer cells [112, 115, 117, 128]. These findings were further supported by detection methods such as ELISA, western blot, and flow cytometry, hence positioning boron as one of the promising candidates in cancer therapies. Further studies are needed to confirm the selectivity of the anticancer effects of boron (Fig. 3).

Activity of boric acid
and boron-containing compounds on apoptosis

Apoptosis functions as a critical physiological mechanism that controls cell population expansion, either to preserve tissue homeostasis or to clear potentially hazardous cells, such as those that suffered DNA damage. In cancer, cell-autonomous apoptosis is a prevalent tumor suppressor mechanism, which is utilized in cancer therapy [129]. Currently, research is investigating the potential of boron compounds as a new anti-apoptotic drug. A study by Hilal et al (2024) has provided evidence for BA induced apoptosis by downregulation of anti-apoptotic genes and upregulation of pro-apoptotic genes [130]. In their study, Cengiz et al (2019) investigated the toxicity induced by cyclophosphamide (CP) exposure in rat livers and the potential protective effects of BA. In contrast to the CP group, TAC marker levels increased while alanine transaminase (ALT), aspartate transaminase (AST), alkalen phosphatase (ALP), TOS, oxidative stress markers, and caspase-3 levels reduced in the BA and CP group. These results demonstrated that BA effectively shielded the liver against CP-induced apoptosis and histological alterations [131].

Boron neutron captures therapy on cancer activity

Boron neutron capture therapy (BNCT), a new treatment approach intended to improve the therapeutic ratio for malignancies that have historically been difficult to cure, is the main biological use of boron-based compounds [132–134]. By carefully concentrating boron compounds within tumor cells and then exposing them to epithermal neutron beam radiation, which specifically kills the tumor cells, BNCT is showing promise as a cancer treatment method. The ability of BNCT to deposit a significant dosage gradient between tumor cells and healthy cells is one of its special qualities. The most advantageous characteristics of boron compounds are there is minimal systemic toxicity, strong tumor absorption in normal tissues, significant tumor/brain and tumor/blood concentration ratios (>3–4:1), tumor concentrations of 20–35 mg ^{10}B/g tumor, quick removal from blood and normal tissues, and tumor persistence during BNCT [135, 136]. The most common methods for delivering boron are boronophenylalanine and sodium borocaptate [137]. The basis for BNCT treatment is nuclear capture and fission when nonradioactive boron-10 is irradiated with low thermal neutrons (<0.025 eV), which produces a recoiling lithium-7 ($^{10}B_5 + {}^1n_{0(th)} \rightarrow [{}^{11}B_5]^* \rightarrow {}^4He_2(\alpha) + {}^7Li_3 + 2.38$ MeV) and an alpha particle. A type of high linear energy transfer particle known as an alpha particle deposits energy over a distance of less than 10 μm, or around one cell›s diameter [135, 137, 138]. The mechanism of BNCT in the tumor cell is shown in Figure 4.

Head and neck cancer, Glioblastoma multiforme,

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recurrent lung cancer, squamous cell carcinomas, salivary gland carcinomas, sarcomas, recurrent malignant meningioma, multifocal hepatocellular carcinoma and extramammary Paget's disease are among the cancers that BNCT has been used to treat thus far [139–141].

Proton boron capture therapy on cancer activity

Proton boron capture therapy (PBCT) is a new treatment strategy that uses protons to create a physical-driven radiosensitization. By taking use of a nuclear fusion reaction between low-energy protons and ^{11}B atoms, $p + {}^{11}B \rightarrow 3\alpha$ (p-B), it increases the biological efficacy of protons by releasing α-particles that are thought to cause double-strand breaks in DNA across Spread-Out Bragg Peak [142]. This method makes it possible to limit the radiosensitization to the object that the proton beam strikes [143]. Alpha particles with energies between 2 and 5 MeV release almost all of the energy of the nuclear process. These alpha particles harm cells close to the reaction site because of their short linear travel and strong linear energy transfer inside the tissue. By selecting the boron compounds that are preferentially deposited inside the tumor, it is possible to optimize the dosage in the tumor location and limit it outside [144]. There are *in-vitro* studies to evaluate the effectiveness of PBCT on cancer. For this, the inclusion of boron in the U-87 MG glioblastoma cell line and the DU145 prostate cancer cell line is known to decrease cell survival by a factor of 2 following proton irradiation in the PBCT experiments [143, 145–147].

Anticancer activity of boron-dipyrromethene

Thanks to their special photophysical characteristics and functionalization potential, near-infrared boron–dipyrrin (BODIPY) and their analogs have been the subject of much research [148]. BODIPY derivatives are widely used in the biomedical field, especially in biological imaging and photodynamic therapy applications due to their high photostability, strong fluorescence properties and wide absorption-emission ranges [149–152]. In recent years, the importance of fluorescent dyes in biological imaging and sensor applications has been increasing [151]. In this case, BODIPYs stand out with their superior photophysical properties compared to other fluorescent dyes, such as narrow absorption and emission bands, high fluorescence intensity and simple signal modulation for practical applications [152]. Owing to these properties, BODIPYs are widely used in areas such as cell imaging, biosensor design and photodynamic therapy [153]. These compounds, whose photophysical properties can be optimised by structural modifications, can be used as targeted diagnostic agents and offer significant advantages especially in the specific detection of cancer cells [151, 152]. Jang et al (2019) developed a BODIPY platform activated by 365 nm UV light. This system shows promise for targeted therapy and imaging by simultaneously providing both anticancer drug release and 'lighten-up' FLI [154]. In another study, Wang et al (2019) developed an innovative therapeutic and diagnostic platform comprising an H_2S-sensitive NIR probe (NIR-BSO) and a potent photosensitiser (3I-BODIPY) for accurate cancer imaging and on-demand image-guided photodynamic therapy [155].

BODIPY-based theranostic agents have a wide range of uses in the biomedical field for both diagnostic and therapeutic purposes. It allows deep tissue analysis with photoacoustic imaging, monitoring of cellular biomarkers with fluorescence imaging, and can target cancer cells by activating with light through photothermal and photodynamic therapies [156]. It can also be used as a drug carrier in chemotherapy, providing controlled release and monitoring tissue temperature with photothermal imaging. Thanks to these versatile properties, BODIPY derivatives are promising agents for advanced biomedical research and cancer treatments.

Effect of boric acid and boron-containing compounds on cell death via ferroptosis

Ferroptosis is a non-apoptotic iron-dependent form of programmed cell death. It is morphologically, biochemically and genetically different from other types of programmed cell death such as apoptosis, necrosis and autophagy. The effects of boron on ferroptosis have recently attracted attention. Ferroptosis leads to damage to the mitochondrial membrane and destruction of mitochondrion crystals. This disrupts the energy production of the cell and triggers cell death [157]. However, iron is involved in the process of lipid peroxidation, which leads to oxidation of intracellular lipids and cell death [158]. In addition, proteins that regulate iron metabolism (e.g. IRP [Iron Regulatory Protein] и IRE [Iron Response Element]) may cause a disturbance of iron balance, which may contribute to the occurrence of ferroptosis [159].

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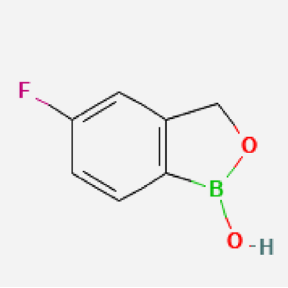
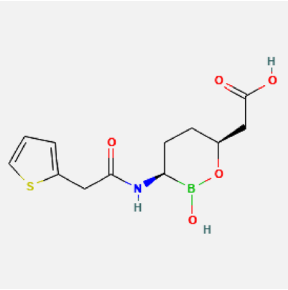
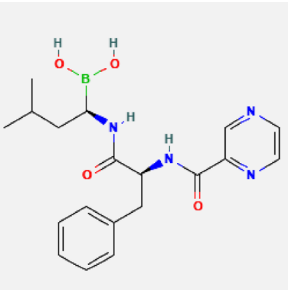
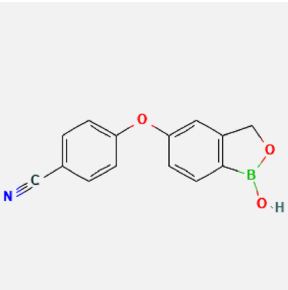
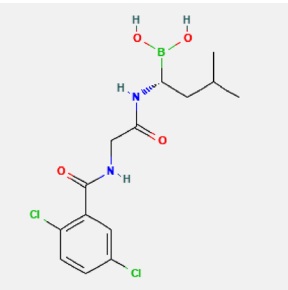
Table 1 – Molecular Architectures and clinical applications of FDA-approved boron-containing drugs

Drug Name / FDA Approed Date	Indications	Mechanism of action	Chemical structure	References
Tavaborole / July 7, 2014	Fungal or yeast infections of the toenails	It inhibits cytosolic leucyl-transfer RNA synthetase which plays a key role in fungal essential protein synthesis		[53]
Vaborbactam / August 29, 2017	Urinary tract infections	Non-β-lactam β-lactamase inhibitor		[54]
Bortezomib / May 13, 2003	Multiple myeloma	Reversibly binds to the chymotrypsin-like subunit of the 26S proteasome, resulting in its inhibition and preventing the degradation of various pro-apoptotic factors		[55]
Crisaborole / December 14, 2016	Atopic dermatitis (eczema)	Broad-spectrum anti-inflammatory activity by mainly targeting PDE4 enzyme that is a key regulator of inflammatory cytokine production		[56]
Ixazomib (Citrate) / November 20, 2015	Multiple myeloma	Blocks protein degradation by inhibiting the 20S catalytic subunit of the 26S proteasome		[57]

Note: The images of the chemical structures are taken from PubChem. PDE4 — phosphodiesterase 4.

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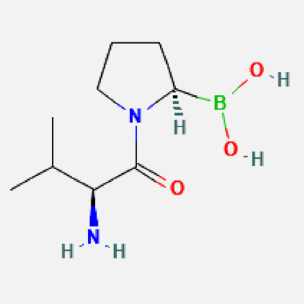
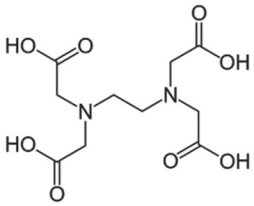
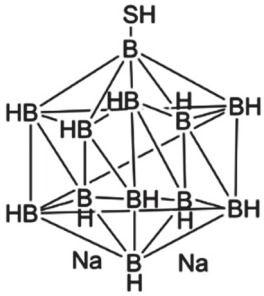
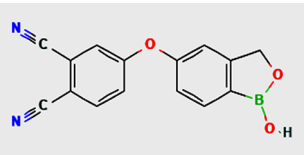
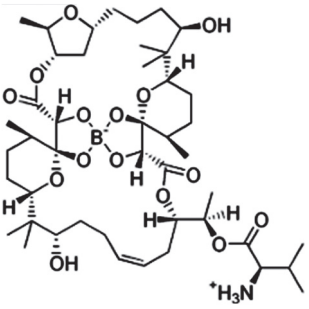
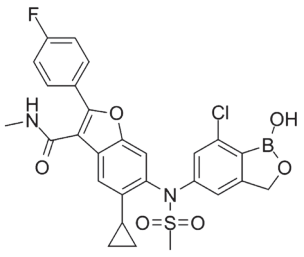
Table 2 – Boron-containing compounds evaluated in clinical trials (phases I–III)

Chemical Name	Indications	Mechanism of Action	Chemical Structure	References
Talabostat (PT-100)	Non-small-cell lung cancer and malignant melanoma	Inhibits tumor-associated FAP and DPPs		[58]
TOL-463	Bacterial Vaginosis and Vulvovaginal Candidiasis	Targeting vaginal bacterial and fungal biofilms		[59]
Sodium Borocaptate	Glioblastoma multiforme	When the blood-brain barrier is disrupted, it penetrates into the brain and affects the cells.		[60]
AN-2898	Atopic dermatitis	3',5'-cyclic-AMP phosphodiesterase (4A-4B-4D) inhibitor		[61]
Boromycin	Gram-positive bacterial infections, coccidiosis, and protozoal infections	Negatively affecting the cytoplasmic membrane, resulting in the loss of potassium ions from the cell		[62]
GSK8175/ GSK2878175	Anti-hepatitis C virus	NS5B inhibitor		[63]

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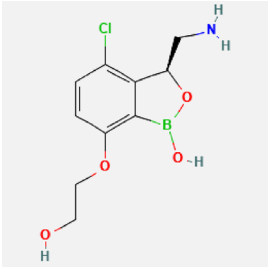
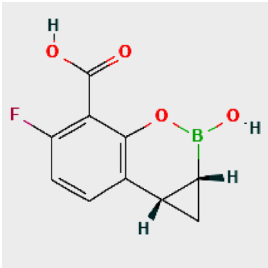
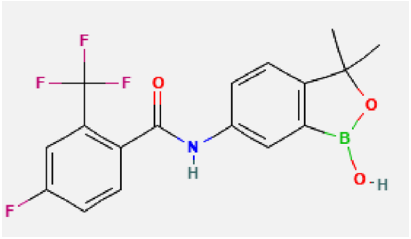
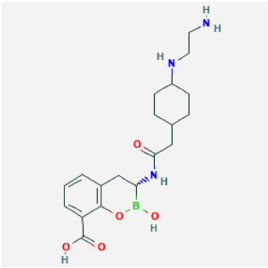
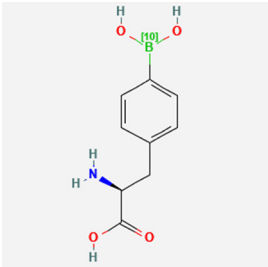
Chemical Name	Indications	Mechanism of Action	Chemical Structure	References
Ganfeborole/ (GSK656)	Anti Tuberculosis agent	Ganfeborole is a first-in-class benzoxaborole inhibiting the Mycobacterium tuberculosis leucyl-tRNA synthetase.		[64]
Xeruborbactam/ (QPX7728)	Ultra-broad-antibacterial spectrum	Beta-lactamase inhibitor		[65]
Acoziborole	African trypanosomiasis	Specifically block the active site and mRNA processing by parasite, but not host CPSF3		[66]
Taniborbactam	Acute pyelonephritis	Reversible, covalent inhibitor of serine β-lactamases and as a competitive inhibitor of metallo-β-lactamase		[67]
Borofalan	Malignant Glioma	Molecular selectivity towards the targeted tumor cell, the nucleus or DNA is targeted		[68]

Note: The images of the chemical structures are taken from PubChem. FAP — fibroblast activation protein-α; DPPs — dipeptidyl peptidases; NS5B — non-nucleoside polymerase.

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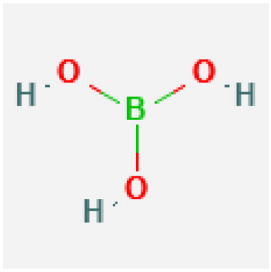
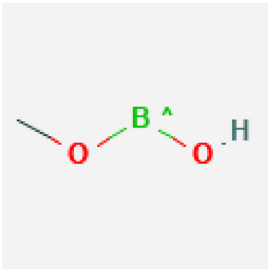
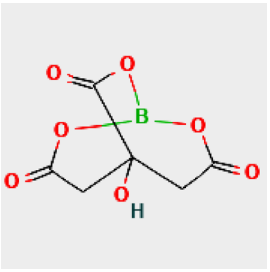
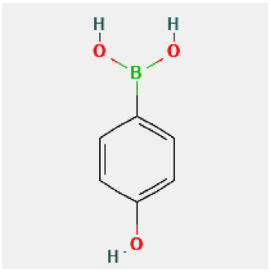
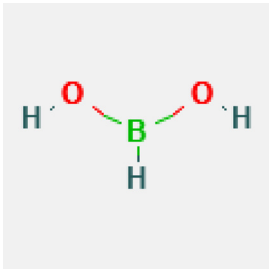
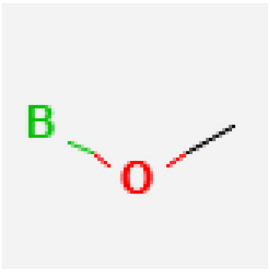
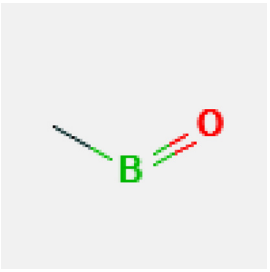
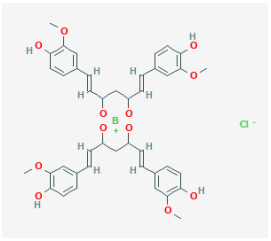
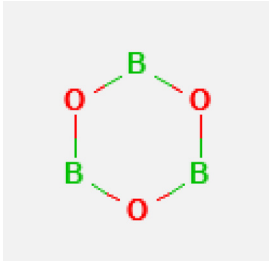
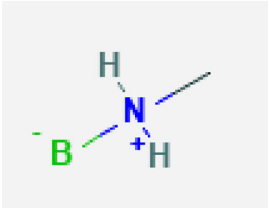
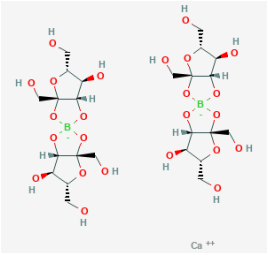
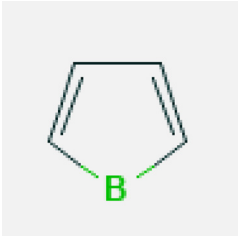
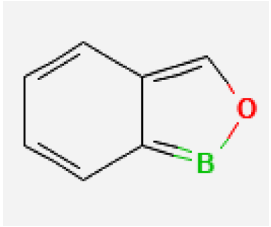
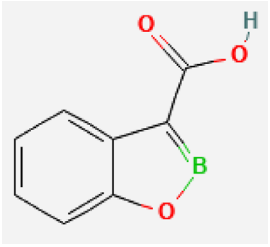
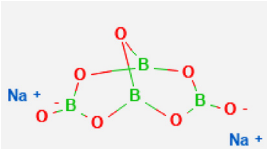
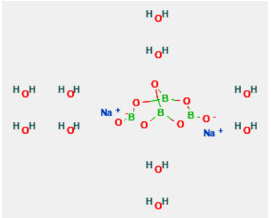
Table 3 – The chemical structure of some boron compounds

 Boric Acid	 Boronic Acid Methyl Ester	 Boron Citrate	 4-Hydroxyphenylboronic acid (4-OHFBA)
 Boronic Acid	 Borinic acid, methyl ester	 (Methyl)oxoborane	 Rosocyanine
 Boroxine	 (Methyl)amine borane	 Calcium Fructoborate	 Borole
 Benzoboroxole	 Carboxy-benzoxaborole	 Borax	 Sodium Tetraborate Decahydrate

Note: The images of the chemical structures are taken from PubChem.

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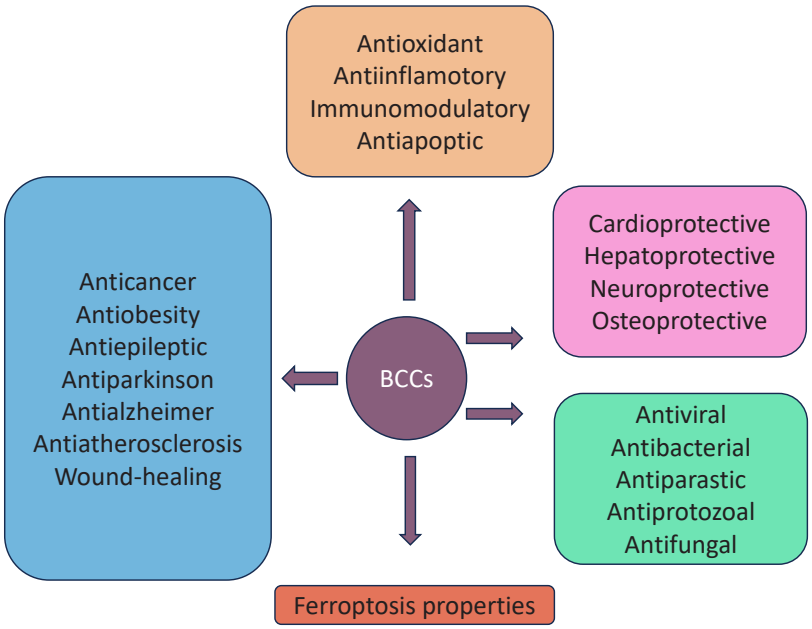

Figure 1 – Pharmacological and therapeutic potential of boron-containing compounds.
Note: The figure was created using Microsoft Office software. BCCs — boron-containing compounds.

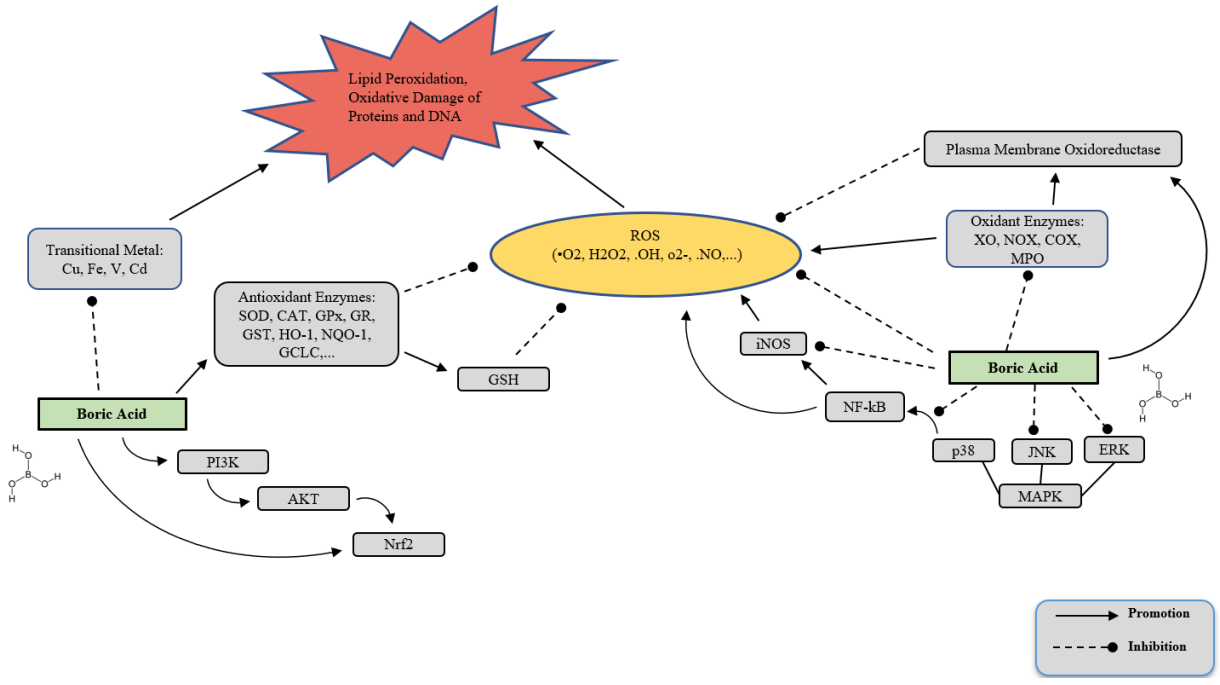

Figure 2 – Effects of boric acid on various anti-inflammatory parameters.
Note: The figure was created using Microsoft Office software. Akt — Protein Kinase B; CAT — Catalase; COX — Cytochrome c Oxidase; CLC — Glutamate Cysteine Ligase ERK — Extracellular Signal-Regulated Kinases; GSH — Reduced Glutathione; GPx — Glutathione Peroxidase; GR — Glutathione Reductase; GST — Glutathione S-Transferases; HO-1 — Heme oxygenase 1; iNOS — Inducible Nitric Oxide Synthase; JNK — c-Jun N-terminal kinase. MAPK — Mitogen-Activated Protein Kinase; PI3K — phosphatidylinositol-3-kinase; MPO — Myeloperoxidase; NF-κB — Nuclear Factor kappa B; Nrf2 — Nuclear Erythroid 2-related Factor 2; NOX — oxidase; NQO-1 — Quinone Oxidoreductase; ROS — reactive oxygen species; XO — xanthine oxidase; SOD — superoxide dismutase.

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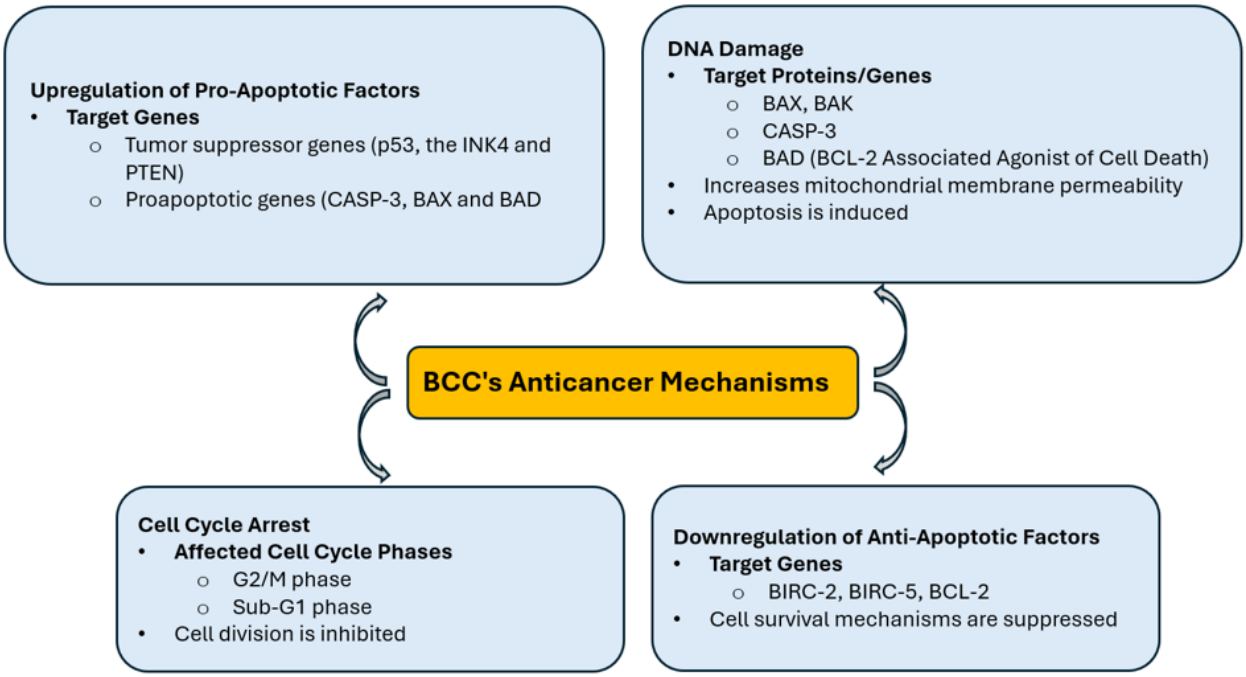

Figure 3 – Molecular base anticancer mechanism of boron-containing compounds.
Note: The figure was created using Microsoft Office software.

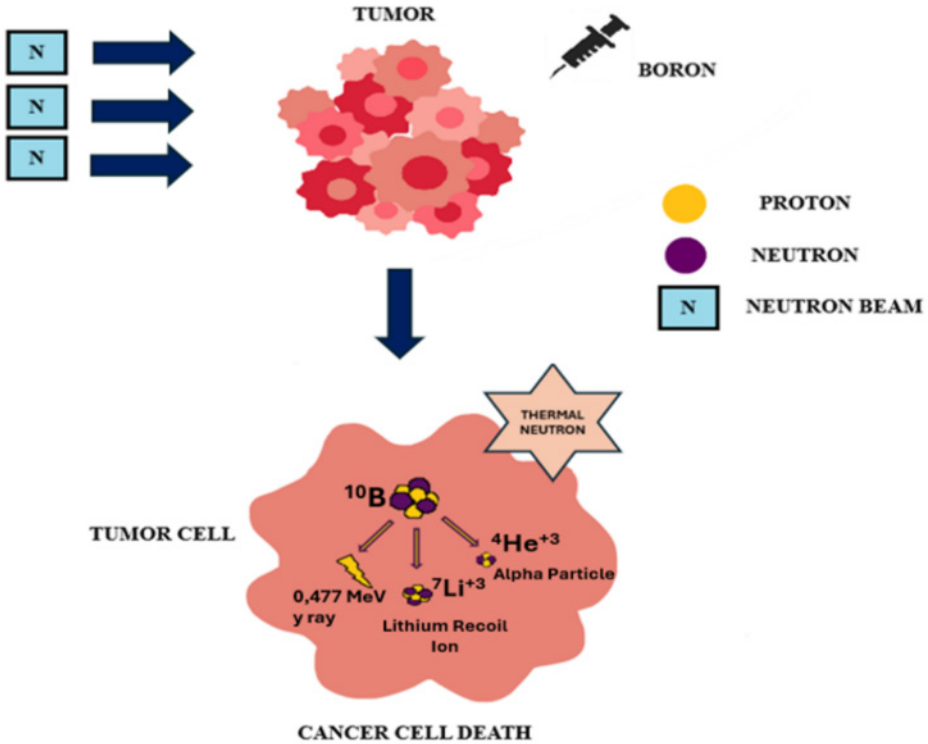

Figure 4 – Tumor cells that are treated with thermal neutrons preferentially contain injected boron compounds.
Note: After that, the boron reacts to producing an inert lithium ion and an alpha particle. The tumor cell is then harmed by the alpha particle within a limited range. The figure was created using Microsoft Office software.

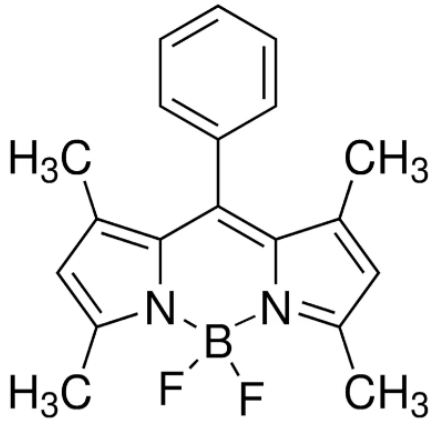

Figure 5 – Near-infrared boron–dipyrrin (BODIPY)

Although data on the effects of boron on ferroptosis are limited, the antioxidant properties of boron and its potential regulatory effects on iron metabolism suggest that these two processes may be related [157, 158, 160]. Boron, especially in the form of BA, has been shown to affect ferroptosis pathways. BA is the predominant form of boron in plasma. Boron has been identified as a potential modulator of ferroptosis, a regulated form of cell death characterized by iron-dependent lipid peroxidation [161]. The effects of boron on ferroptosis are particularly important in the context of cancer therapy, where induction of ferroptosis may overcome resistance to conventional therapies, suggesting its potential as a therapeutic agent in cancer treatment [162, 163]. BA has been shown to induce ferroptosis in glioblastoma cells by affecting the semaphorin-neuropilin signaling pathway [163]. This induction is dose-dependent and is associated with increased levels of total oxidant molecules and caspase proteins, which are markers of cell death. BA disrupts the SEMA3F pathway, leading to decreased cell proliferation and increased apoptosis in tumour cells [163]. Induction of ferroptosis by boron is mediated by modulation of key ferroptosis markers such as glutathione peroxidase 4 (GPx4) and ACSL4. These markers are very important in maintaining the redox balance in cells and their disruption leads to increased lipid peroxidation and cell death [161, 163].

The use of boron in combination with other ferroptosis inducers such as nanoparticles may further increase therapeutic efficacy. Nanoparticles can increase their concentrations in tumor tissues and reduce systemic toxicity at lower doses in the administration of ferroptosis-inducing agents [164–166]. Considering that cancer cells may be more vulnerable to agents that disrupt redox balance and increase oxidative stress, high concentrations of BA may be more harmful to tumor cells through modulation of energy production [167, 168]. In this perspective, BA and boronates can be used as chemosensitising agents to induce/enhance ferroptosis [169]. However, boron may also play a role in the regulation of ferroptosis by cross-linking with other ions such as iron ions. This cross interaction may further contribute to the induction of ferroptosis in cancer cells by affecting oxidative stress and lipid peroxidation [170]. It has also been shown that boron dissociates phosphorus in iron alloys. This suggests that boron may modulate iron metabolism, an important component of ferroptosis, and cell death by altering the availability and distribution of iron within cells [166, 168]. In conclusion, while boron shows promise in modulating ferroptosis and improving cancer therapy, it is important to consider ferroptosis in a broader context. The balance between oxidative stress and antioxidant defenses is crucial in determining cell fate and the role of boron should be understood within this framework. Furthermore, the potential side effects and optimal dosage of boron in clinical settings need to be further investigated to ensure its safe and effective use in cancer therapy.

Antioxidant activity of boric acid and boron-containing compounds

Oxidative stress has been linked to a variety of diseases, including chronic obstructive pulmonary disease, atherosclerosis, cancer and Alzheimer's disease (AD),

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revealing the numerous routes via which oxidants cause cellular damage [171–174]. However, the degree to which oxidative stress participates in the pathogenesis of diseases is quite diverse, therefore the effectiveness of strengthening antioxidant defense may be limited with regard to some diseases [171–173]. Oxidative stress is characterized by a disrupted balance between reactive oxygen species (ROS) generation and antioxidant effectiveness [172]. A compromised antioxidant system could contribute as well to disease pathogenesis [173, 175].

Boron can act as an indirect proton donor, influencing the structure and function of cell membranes [176]. Therefore, it has been proposed that cyclic adenosine monophosphates (cAMP), whose concentrations rise as a result of boron's effects, may disrupt the metabolism of mitochondrial oxidative phosphorylation and inhibits the activities of hydrolytic enzymes [177]. The antioxidative properties of boron compounds such as BA, borax, colemanite, and ulexite in neuronal cells are thought to be linked to their roles in mitochondrial dynamics [178].

The investigations looked into BA as a potential novel antioxidant medication. BA therapy reduced lipid peroxidation, decreased the expression of proinflammatory cytokines, and enhanced the function of the antioxidant defense system in the cell line. Also, the findings revealed that BA effectively lowered formaldehyde-induced oxidative stress and inflammation by blocking lipid peroxidation and preventing the depletion of antioxidant enzymes [179]. Gündoğdu et al (2024) established in their studies that BA protects gastric mucosa from ethanol-induced injury by modifying the oxidative and inflammatory responses [106]. By analyzing prenatal alcohol-induced oxidative stress in the cerebral cortex of newborn rat pups and assessing the protective and advantageous effects of BA supplementation in rats with fetal alcohol syndrome (FAS), Sogut et al (2015) examined the impact of BA administration on FAS. The findings showed that alcohol may harm rat pups' cerebral cortex and that BA may be useful in antioxidant defenses against oxidative stress brought on by prenatal alcohol exposure [180]. Moreover, different compounds have been shown to enhance antioxidant enzyme activities at low supplementation levels without causing oxidative stress in blood cells [181]. Ince et al (2014) found that 20 mg/kg BA treatment alleviated focal gliosis and neuronal degeneration in the brains of rats treated with CP [182]. Another study reported that 100 mg/kg BA partially reduced the effects of arsenic-induced oxidative stress [183]. In conclusion, these findings suggest that BA at various doses may reduce the effects of oxidative stress in tissues by supporting antioxidant enzymes. Additionally, it has been proposed that BA could protect nerve morphology by influencing cellular antioxidant mechanisms and safeguarding axons from the destructive effects of oxidative stress [184].

Antimicrobial activities of boric acid and boron-containing compounds

Recent years included an enormous rise in the literature of boron and its anti-microbial traits. The emergence of FDA-approved boron-based pharmaceuticals has altered the view of boron as an injurious agent [79]. Boron and metals are being researched as potential treatments for microbial resistance and as competitors to antibiotics [185]. The current scientific literature substantially supports boron's antibacterial, antifungal and antiviral traits. However, future research might focus on gauging their mechanisms of action to try to clarify the possible uses in medical use.

Antibacterial activity of boric acid and boron-containing compounds

Modern pharmacology places a strong emphasis on the creation of antimicrobial agents that are both safe and effective [186]. Based on existing experiments obtained from scientific literature, it has been discovered that boron and its compounds possess antibacterial properties. Sayin and Ucan (2016) showed that BA has demonstrated antibacterial and anti-biofilm effects on specific bacterial strains. This capability suggests that new methods could be developed for the use of various functional microorganism tests in medical and industrial applications [187]. Celebi et al (2024) studied the antibacterial activity of nine boron derivatives against biofilm-forming pathogenic bacteria [188]. They found that sodium metaborate tetrahydrate is effective against all pathogens and identified methicillin-resistant *Staphylococcus aureus* (MRSA) as the bacterium with

the strongest biofilm-forming ability. Additionally, boron derivatives were determined to be non-toxic to fibroblast cells (L929) at low concentrations (1 µg/L) and exhibited significant inhibitory activity against biofilm-forming pathogens during short treatment periods [188]. According to the study by Uzun-Yaylacı et al (2021), 3.09 and 1.54 mg/mL concentrations of BA have been shown to be effective against aquatic pathogens such as *Aeromonas veronii* [189]. Also, the blend of ascorbic acid and curcumin-BA has been proved to be useful in treating *Salmonella enteritidis* infections [190]. In the study by Brittingham and Wilson (2014) demonstrating the antimicrobial effect of BA on *Trichomonas vaginalis*, BA concentrations above 0.1% had a important effect on the growth and viability of *T. vaginalis*. Concentrations of 0.4% or greater completely inhibited the growth of parasites. Additionally, BA was shown to exhibit strong antimicrobial activity against *T. vaginalis* across a broad physiological pH range [191]. Moreover, boron-based compounds such as boronic acids have demonstrated strong antibacterial activity as β-lactamase inhibitors against Gram-negative bacteria. Boronic acids and borinic esters have shown versatile potential in antibacterial strategies by targeting penicillin-binding proteins, quorum sensing mechanisms, and methyltransferases. Optimization of these compounds could enable the development of new and effective treatments against resistant bacteria [192]. However, further molecular studies are needed to better understand the effects and mechanisms of these compounds.

Antifungal activity of boric acid and boron-containing compounds

The natural human microbiota of the skin, oral, GI, and genitourinary tracts includes *Candida* species. Only a small number of the 200 or so species in the genus Candida are opportunistic infections in humans. Candida-caused invasive infections are particularly significant in severely ill patients admitted to intensive care units [193]. The most prevalent species linked to invasive fungal infections is *Candida albicans* [194]. Currently, boron components are known to have antifungal effects [195]. BA has been used as a topical antifungal drug for vaginal infections for many years [196]. In the study conducted by De Seta et al (2009), *C. albicans* strains were inhibited at intravaginally achievable concentrations. They reported that BA exhibited fungistatic properties, as indicated by a decrease in CO_2 production. BA works by decreasing oxidative metabolism, which lowers cellular ergosterol production and interferes with hyphae transformation by preventing apical development through cytoskeletal disruption [197]. Likewise, BA breaks down cytoskeletal processes, such as actin rearrangement, in Candida hyphal production, leading to aberrant hyphal development, according to Pointer and colleagues [198]. Larsen et al (2018) aimed to investigate whether organoboron compounds provide antifungal activity similar to BA and whether they possess other beneficial properties in addition to their antifungal effects. To this end, they examined the sensitivity of Candida species to BA and organoboron compounds. The study found that *C. glabrata* was inhibited by both BA and organoboron compounds, and that organoboron compounds have potential as topical therapeutics [199]. Furthermore, the *in vitro* antifungal effects of pure boron were investigated against yeasts and molds isolated from patients with superficial mycosis caused by Candida, Trichophyton, and *Aspergillus fumigatus*. The study's findings demonstrated that boron prevented the growth of molds and yeasts. At very low quantities, boron showed antifungal action when diluted in distilled water with an alkaline pH. As a result, it is proposed that boron might be a substitute for conventional antifungals in the treatment of superficial mycosis [200].

Antiviral activity of boric acid and boron-containing compounds

In late December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared, causing a pandemic of acute respiratory disease known as "coronavirus disease 2019" (COVID-19), which poses a hazard to human health [201, 202]. The COVID-19 pandemic poses an obstacle in determining efficacious drug therapy approaches for both prevention and treatment [201, 202]. According to recent data, COVID-19 infection may be effectively managed by therapeutic drugs with antiviral, anti-inflammatory, and immunomodulatory qualities [202, 203]. Thus, boron citrate and oleoylethanolamide (OEA)

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have been investigated in COVID-19 patients by Akbari et al (2022). The study's results showed that O_2 saturation and respiratory rate were markedly enhanced by boron citrate supplementation, either by itself or in conjunction with OEA. Furthermore, the boron citrate and combination groups showed notable increases in the number of white blood cells and lymphocytes [204]. Moreover, curcumin has a unique chemical structure that makes it a potential chelating agent [205]. Its esters interact with BA to generate rosocyanine, a complex that is frequently used to measure the quantity of boron in different organic and inorganic matrices [206]. Curcumin decreased the inhibition activity of human immunodeficiency virus (HIV)-1 and HIV-2 proteases, whereas rosocyanine boosted the inhibition activity of HIV-1 and HIV-2 proteases by more than ten times [207]. These substances are thought to have potential applications as medications in the future to enhance blood circulation throughout the body and prevent pandemic viral attacks like SARS-CoV-2. In conclusion, a number of boron-based chemicals could be made to prevent COVID-19 viral illness and curcumin's capacity to create boron complexes [208]. Additionally, *in silico* studies have demonstrated that BCCs may exhibit antiviral effects against viral conditions through docking analysis [209, 210].

Antiprotozoal and antiparasitic activities of boric acid and boron-containing compounds

Parasitic diseases are among the world's most severe and widespread infections, affecting millions of morbidities and deaths each year. Presently, however, climate and vector ecological changes, a major increase in international travel, armed conflicts, human and animal migration have impacted the transmission of various parasitic diseases in developed countries [211]. Using a variety of dosage schedules, four case reports demonstrated *Trichomonas vaginalis* clearance with BA. According to *in vitro* research, BA has pH-independent anti-*T. vaginalis* action. Intravaginal BA may offer a well-tolerated alternative anti-infective treatment that reduces the population's need of systemic antibiotics if it is shown to be safe and effective [212]. BA was used to amidate benzenesulfonamides in Ugwu et al (2018) investigation on the synthesis of novel carboxamide derivatives comprising substituted benzenesulfonamides against human African trypanosomiasis parasite infection. The work showed that novel carboxamides with exceptional yields were generated by amidation of benzenesulfonamides and p-aminobenzoic acid mediated by BA [213]. Particularly in the underdeveloped countries, infectious disorders brought on by protozoan parasites constitute a substantial unmet medical need [214–216]. *Trypanosoma brucei*, *Plasmodium falciparum*, and *T. cruzi* are among the significant protozoan diseases that have been found to be susceptible to the intriguing activity of a class of boron-containing chemicals known as benzoxaboroles in recent years [217]. Lindenthal et al (2005) demonstrated that the boronate analog MLN-273 inhibits *P. falciparum*'s intraerythrocytic development and *P. berghei*'s exoerythrocytic development [218]. ZL3B and bortezomib, two boronates, were shown by Reynold et al (2007) to be strong inhibitors of the intraerythrocytic cycle in *P. falciparum* strains that are both drug-sensitive and resistant [219].

Antiobesity activity of boric acid and boron-containing compounds

The WHO considers the rapid rises in obesity prevalence across all age categories, particularly since the 1970s, to constitute a global obesity epidemic. Today, obesity affects roughly 650 million adults, and 340 million children and adolescents aged 5 to 19 years [220, 221]. Given the absence of a definitive treatment for obesity, these studies explored the potential of this substance as a novel therapeutic option aimed at alleviating symptoms and modifying disease progression. It was reported in literature that BA inhibited adipogenesis in common cellular models. In the model by Doğan et al (2017), BA and sodium pentaborate pentahydrate ($Na_2B_4O_7 \cdot 10H_2O$) therapy suppressed the expression of adipogenesis-related proteins and genes, as well as decreased mitotic clonal expansion through cell cycle gene regulation [222]. Aysan et al (2011) have investigated the influence of oral BA administration on body weight and have discovered that a very low dose (0.2 mg/kg) oral BA administration results in substantial body weight reduction in mice [223]. Also, Farrin et al (2022)

have conducted a meta-analysis to analyze the effect of BA on body weight. According to findings, BA administration orally resulted in a considerable decrease in body weight [224].

Antidiabetic activity of boric acid and boron-containing compounds

Diabetes mellitus is a severe global public health issue. It affects 463 million people globally, and by 2045 this figure may rise to 700 million [225]. Diabetes mellitus is a metabolic disorder defined by high or low levels of fasting blood glucose, caused by the partial or complete lack of insulin hormone and the equivalent damage to carbohydrate, lipid, and protein metabolism [226]. Based on the lack of definitive treatment for diabetic diseases, the studies have investigated the potential of this substance as a novel therapeutic option for alleviating symptoms and slowing disease progression. Previous study by Cakir et al (2018) found that increased serum lipid peroxidation levels with diabetes significantly decreased, and although not statistically significant, serum TAC levels came towards those of the control group; additionally, insignificant increases in high-density lipoprotein cholesterol (HDL-C) levels were observed in experimental diabetic administration BA on rats with two groups [227]. In addition, lipase activities, low-density lipoprotein (LDL) and blood glucose serum cholesterol have reduced significantly in the diabetes BA with one group [227]. According to the findings of this recent study by Cakir (2024), the increase in total cholesterol triglyceride, glucose, LDL-cholesterol levels and ALT, AST activities in streptozotocin-induced groups were decreased with BA administration [228]. While HDL-C levels dramatically reduced in the streptozotocin group, they approached control group levels following BA treatment. Although peptide levels increased statistically significantly following BA administration, they did not approach the control group values. Cakir's research suggests that BA might be an appealing therapeutic element [228].

Effects of boric acid and boron-containing compounds on the immune system

Immunity is essential for preserving health because it shields the body from infection by both endogenous and foreign pathogens [229]. There have been some documented effects of boron compounds on the immune system [230–233]. Recent studies on the impact of BA on the differentiation of lymphocyte clusters in mice and rats are among these [229, 234]. Routray and Ali (2016) demonstrated that T and B-cell populations in mice significantly increased following oral borax delivery, as seen by an increase in CD4 and CD19 [234]. Also, the lipopolysaccharide (LPS)-primed macrophages' production of TNF-α, interleukin 6 (IL-6), IL-1β, nitric oxide (NO), and inducible nitric oxide synthase (iNOS) was induced by borax [234]. Jin et al (2017) showed that adding rats' drinking water with 20 and 40 mg/L of boron raised their serum immunoglobulin G levels, hemoglobin concentrations, leukocyte, erythrocyte, lymphocyte, and monocyte counts, induced an increase in splenic $CD3^+$ T cells [229]. This improved both general and specific immune responses. Furthermore, it raised the amount of $CD4^+$ T cells in the spleen and the number of $CD4^+/CD8^+$ T cells. This led to the spleen producing and secreting more IL-2, interferon-gamma (IFN-γ), and IL-4, which improved cellular immune activities [229].

Antiatherosclerotic activity of boric acid and boron-containing compounds

Plaque buildup inside arteries causes atherosclerosis, a cardiovascular condition that can result in fatalities, heart attacks, and strokes [235]. Development and progression of atherosclerotic coronary arteries result in coronary heart disease. Depending on degree of artery damage, angina or heart attack occurs [236, 237]. Among the main treatments for atherosclerosis are statins, which lower serum levels of LDL and cholesterol and stop the production of foam cells [238]. Also, antioxidant-based treatments have been explored because inflammation and lipoprotein oxidation play important roles in the development of atherosclerosis [238]. Boron may be a viable alternative for maintaining a healthy cardiovascular system because it plays a role in the control of signaling pathways related to inflammation, oxidative stress, or lipid metabolism [239]. Some studies have shown that BCCs may provide protection against atherosclerosis through their antioxidant effect by reducing ROS and SOD activities [240–242]. Moreover, a study by Asadi et al (2023), in which animal models with atherosclerosis were given 4 mg/kg BA, showed that BA could prevent atherosclerosis over time by

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DOI: 10.19163/2307-9266-2025-13-3-202-238

preventing lipid buildup and cholesterol absorption from tissues [235].

Effects of boric acid and boron-containing compounds on wound healing

One of the biggest and fastest-growing issues in the world today is wounds. The incidence of chronic wounds has increased, particularly as a result of the fast aging of the population and the rise in the prevalence of chronic illnesses [243]. Chronic wounds are those that exhibit abnormalities during the healing process [244]. Chronic wounds are particularly vulnerable to bacterial colonization and biofilm formation because of the lack of the epithelial barrier and the high pH of the surrounding environment. This can lead to severe oxidative stress, an inflammatory storm, and impaired angiogenesis. Wound healing is further hampered by these pathological alterations [245]. The process of wound healing is dynamic and involves the cooperative action of several cells, growth factors, proteins, and cytokines [246]. It is well known that BA, a dynamic and advantageous trace element, contributes to the healing of wounds [1, 247]. Because of their effects on the extracellular matrix, BA shows a notable improvement in the wound healing process [248]. According to a study by Roy et al (2010), which used hydrogel wound dressing containing BA, hydrogels were very flexible and had potent antibacterial qualities. So, the use of boron as a wound dressing care material was advised [249]. Demirci et al (2016) showed exceptional antibacterial properties of BA and NaB against bacteria, yeast, and fungi in addition to considerably increasing the proliferation, migration, essential growth factors, and gene expression levels of dermal cells. Furthermore, they demonstrated that the gel formulation containing NaB improved wound healing rates and histopathological scores in diabetic animal models created in rats [250]. Moreover, the most recent findings show that mixing NaB with pluronic block polymers increases cell migration, SOD activity, gene expression linked to essential wound contraction and healing of human primary fibroblast cells, and collagen deposition [251]. *In vitro* study's findings showed that erbium borate nanoparticles are a suitable substance for scarless wound healing [252]. Kurtoğlu and Karataş (2009) demonstrated that wounds that occurred in the lower limbs as a result of diabetes caused weak blood circulation, and that wound dressings having boron content were useful in wound healing when systemic antibiotic treatment was ineffective [253]. Chupakhin et al (2017) also found that hydrogels containing silicone and boron enhanced wound healing, regeneration, and antibacterial activity in an *in vitro* investigation [254]. In conclusion, despite the fact that the precise mechanism of boron in wound healing remains unclear, some boron compounds like BA show a variety of therapeutic actions during the healing process. These include encouraging angiogenesis, inducing TNF-α secretion by macrophages, increasing neutrophil migration and activation, boosting fibroblast proliferation and activation, encouraging keratinocyte migration and proliferation, and exhibiting antibacterial properties [255, 256].

Protective roles of boric acid and boron-containing compounds

Cardioprotective effect

About 30% of deaths worldwide are caused by cardiovascular diseases (CD), which include a variety of conditions affecting the heart and blood vessels as well as the negative consequences they are linked to [257]. It has long been recognized that a lack of boron in soils causes a decrease in BCCs in food, which has been linked to an increased risk of arthritis, an inflammatory condition that is also linked to cardiovascular health [258, 259]. Potential advantages for the cardiovascular system are suggested by the beneficial impact of natural organic BCCs on lipid levels. The two main risk factors for CD are oxidative stress and chronic low-grade inflammation. Through nicotinamide adenine dinucleotide (NAD+) and/or cyclic adenosine diphosphate ribose binding, BCCs have been demonstrated in numerous studies to regulate oxidative stress and inflammatory responses [90, 260]. Additionally, a study by Karimkhani et al (2021) concluded that in their study's statistical analysis that BA had preventive effects on cellular damage in MI; electrocardiography and light microscope results backing up the findings [261]. Furthermore, almost all types of cardiac disorders, especially heart failure (HF), are related to myocardial fibrosis (MF). Trans-differentiation of fibroblasts, the appearance of myofibroblasts, and the early activation of pro-fibrotic signaling pathways

prior to unfavorable ventricular remodeling are the earliest characteristics of MF. In a rat model of MI-induced HF, the study examining the effects of borax, a sodium salt of boron, supplementation on cardiac function, MF, apoptosis, and regeneration revealed that borax treatment significantly improved systolic and diastolic functions when compared to the control [262]. Borax treatment showed a significant decrease in MF and apoptosis in injured hearts, underscoring borax's preventive role in ischemic hearts [262]. Additionally, compared to the saline group, the MI borax-treated rats showed ten times as many nuclei positively stained for the cell cycle marker Ki67 in thin myocardial slices. Crucially, it may promote the entry of cardiomyocytes into the cell cycle and maybe promote the regeneration of damaged cardiac muscle [262].

Hepatoprotective effect

The liver is essential for the body's metabolism and toxin removal. Liver ailments are among the most urgent global health concerns [263, 264]. Herbal and natural chemicals play a major role in the curing of liver disorders [265]. By regulating insulin release and aiding in the metabolism of energy substrates, boron salts may play a crucial role in regulating lipid and energy metabolism [266]. It has been stated by Abdik et al (2021) that giving mice NaB might lower the weight of their liver and white adipose tissue while also suppressing adipogenic genes [267]. The study by Şahin et al (2023) also revealed that NaB and BA supplementation boosted peroxisome proliferator-activated receptor gamma (PPARγ) expression while decreased sterol regulatory element-binding protein 1c (SREBP-1c), liver X receptor alpha (LxR-α), and FAS expression in the liver of rats, which is in line with earlier research showing the effects of BA and NaB on genes associated to lipid metabolism [267–269]. Furthermore, it was shown that by blocking LxR-α and the LxR-α/SREBP-1c/FAS cascade, BA and NaB could control lipogenesis in the rat liver [268]. Moreover, liver damage occurs with an overdose of acetaminophen (APAP) [270]. Accordingly, Çelik and Aydın (2022) investigated the efficacy of 4-hydroxyphenylboronic acid (4-OHFBA), a boronic acid derivative, in APAP-induced liver damage [271]. It was demonstrated that increased AST and ALT levels, markers of cell death and liver cell damage, decreased with 4-OHFBA treatment, while cell viability in the HepG2 cell line increased. These findings suggest that 4-OHFBA may be effective in APAP-induced cell death and liver damage and boron compounds' antioxidant and anti-inflammatory properties have considerable promise in liver injury treatment [271].

Neuroprotective effect

Pharmacological study indicates that boron compounds have neuroprotective properties [35]. Several studies in recent years have shown that BA has a strong neuroprotective effect in a range of *in vitro* and *in vivo* models of neuronal injury. According to Turkez et al (2022), boron compounds, particularly BA, borax, and ulexite, can be given to people at specific dosages to help avoid hematological and neurological diseases [178]. Many neurological illnesses are characterized by oxidative stress [272]. Anti-inflammatory and antioxidant abilities of boron compounds can lessen neuroinflammation and protect nerves [273].

Effects of boric acid and boron-containing compounds on diseases

Antiparkinson's disease activity

Parkinson's disease (PD) affects an estimated 8.5 million individuals worldwide, as reported by the WHO [274]. PD is a neurodegenerative condition defined by dopaminergic cell death in the substantia nigra compacta nigra pars, and the disease produces uncontrollable movements known as motor symptoms such as bradykinesia, tremors, dystonia and rigidity [275, 276]. Given the absence of a definitive treatment for PD, the studies explored the potential of this substance as a novel therapeutic option aimed at alleviating symptoms and modifying disease progression.

BA's pharmacological, behavioral, and biochemical effects on rats with experimental PD produced by rotenone were examined in a study by Ozdemir et al (2022), BA showed dose-related improvement, notably in the brain tissue and there was noticed significant rise in tyrosine hydroxylase immunoreactivity [276]. In a study investigating the ameliorative effects of hexagonal boron nitride nanoparticles (hBNs) against 1-methyl-4-phenylpyridinium (MPP+) toxicity in an experimental PD model, the results showed that hBNs increased

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cell viability and that TAS and TOS analyses revealed an increase in antioxidant capacity and a reduction in oxidant levels after hBN application [277]. Furthermore, the administration of hBNs considerably inhibited MPP+-induced apoptosis. Therefore, the results suggest that hBNs have great potential against MPP^+ toxicity and may serve as a novel neuroprotective agent in PD treatment [277]. In the study by Yavuz et al (2023), the effects of BA and quercetin (QCT) on oxidative stress markers and behavioral tests were investigated. These results of the study indicate that the combined application of BA and QCT positively affects the oxidant-antioxidant balance by preventing the pathogenesis of PD [278].

Antialzheimer's disease activity

AD, which accounts for 60-70% of dementia cases, is a neurological ailment that normally begins slowly and worsens with time [279]. Approximately 60% of the world's 55 million dementia patients live in low- and middle-income countries [280]. Aggregation of amyloid beta (Aβ) peptides is a key component in the etiopathogenesis of AD [281]. Pharmacological therapies are currently being researched that will block or decrease the nerve deterioration that causes AD, and the FDA approved drugs only temporarily ease symptoms by boosting neurotransmitter levels in the brain [282]. In AD, the most common kind of dementia, oxidative stress plays a significant pathophysiological role [283]. BA has an important function in protecting the brain by lowering lipid peroxidation and increasing antioxidant defense [280]. Özdemir et al (2023) showed that in rats with streptozotocin-induced dementia, BA administration improved learning and memory abilities by lowering oxidative stress [283]. The stereological and histopathological findings of Çolak et al (2011) demonstrated that BA, as a proteasome inhibitor, can lessen the negative impacts of aluminum chloride on the cerebral cortex [284]. Moreover, in both *in vitro* and *in vivo* models of AD, some studies have discovered that certain BCC treatments, such as 2-aminoethylborinic acid or borolatonin, significantly reduced inflammation in a pathogenic association with Aβ buildup [35]. Also, Lu et al (2018) produced a number of new BCCs that act as multi-target-directed ligands against AD. According to the study, these substances have a strong capacity to prevent self-induced Aβ aggregation and may have antioxidant properties [285].

Effects on osteoporosis

Osteoporosis affects an estimated 200 million people worldwide, with one in every three women over the age of 50 and one in every five males over the age of 50 suffering from osteoporosis-related fractures. Osteoporosis is a metabolic bone disorder characterized by microarchitectural deterioration and low bone mass of the bone tissue, resulting in lesser bone strength and an increased risk of low-energy fractures or fragility [286–290]. Boron contributes favorably to calcium metabolism, which is a highly significant factor in preventing osteoporosis and bone loss [88]. Xu et al (2023) in their *in vitro* studies demonstrated that BA therapy for 5 days suppressed osteoclastic bone resorption and osteoclast formation in a dose-dependent manner [291]. BA reduced the expression of osteoclast markers such as cathepsin K, nuclear factor of activated T cells 1, c-Fos and tartrate-resistant acid phosphatase. BA also inhibited receptor activator of NF-κB ligand-induced activation of the protein kinase R-like endoplasmic reticulum kinase-eukaryotic initiation factor 2α pathway, as shown by immunoblotting studies. According to their in-vivo findings, BA significantly decreased LPS-induced bone loss [291]. Moreover, Toker et al (2016) also shown in their study that BA may reduce alveolar bone loss in a rat model with periodontitis and osteoporosis [292].

Effects on ischemia/reperfusion

A pathological state known as ischemia and reperfusion (I/R) is defined by an initial restriction of an organ's blood supply, followed by a subsequent restoration of perfusion and simultaneous reoxygenation [293]. Organ ischemia can have serious repercussions such as cerebral infarction and MI, leading to irreparable tissue damage [294, 295]. Tissue reperfusion helps to prevent further ischemia; but, in some instances, it may worsen the injury via a process known as I/R injury, which may take place in many organs and result in incapacity, severe diseases and even death [293, 296, 297]. A protective agent against I/R injury is BA. BA has promising results according to Güler et al (2021) in the treatment of experimental I/R injury of the cholestatic liver because of its antioxidant

properties [298]. Also, Çolak et al (2022) explored the role of BA in ovarian tissue damage induced by I/R, demonstrated that BA has a protective effect on ovarian tissue against I/R damage in the rat model [299].

Effects on epilepsy

About 50 million individuals worldwide suffer from epilepsy, a chronic, recurring, and progressive neurological condition [297]. The presence of paroxysmal, self-limited convulsive or non-convulsive seizures characterizes epilepsies, which are persistent neurological diseases [300–302]. All forms of epilepsies include recurrent and spontaneous seizures, which are defined by synchronized high-frequency firings of brain neuronal populations [303, 304]. Being a complex condition with a wide variety of clinical characteristics, epilepsy cannot be sufficiently explained by a single pathogenic process. It is known that *in vivo* studies have been conducted on epilepsy, and in these studies, the effects of BA and BCCs have also been investigated [35]. To ascertain the impact of BA on epileptiform activity, Karademir and Arslan (2019) administered four distinct dosages of BA half an hour after injecting penicillin. Proconvulsant action was demonstrated by BA treatment without altering the spike amplitude. The antiepileptic medication gabapentin decreased the frequency of spike activities and when combined, BA prevented gabapentin's anticonvulsant effects [305].

The effects of boric acid and boron-containing compounds on cell viability

BA has been shown to significantly affect the viability and osteogenic differentiation of adipose-derived mesenchymal stem cells, with no observed toxic effects on these cells [306]. A study by Lu et al (2020) investigated the effects of BA at seven different concentrations on cultured rat Sertoli cells [307]. The results showed that concentrations of 0.5 mmol/L and below increased cell viability and resulted in the lowest rates of necrosis and apoptosis. However, as the concentration increased, toxic effects on the cells were observed, leading to decreased cell viability and increased necrosis and apoptosis [307]. In a study where different concentrations of borax pentahydrate (BPH) were applied to human umbilical vein endothelial cells (HUVEC), BPH was reported to have a selective effect on HUVEC viability [308]. Ozansoy et al (2020) investigated the effects of two BCCs, sodium borate decahydrate and BA, against Aβ toxicity. The results showed that both compounds enhanced the survival of SH-SY5Y cells in an *in vitro* Aβ model. These boron compounds increased the expression of SIRT1, a protein with a protective function against cellular stress [34]. Additionally, in a study by Turkez et al (2022), various boron compounds (colemanite, ulexite, BA, and borax) were tested and found not to cause any cytotoxic damage in human blood cells or rat primary cortical neurons [178].

Safety and toxicity

It is of great importance to understand the safety profiles of BCCs, which have a wide range of uses from industrial applications to agriculture, from pharmaceuticals to materials science. Studies on the effects on human health reveal that the toxicological properties of boron and its derivatives vary depending on the level and duration of exposure [90]. The mechanisms primarily responsible for the toxicity of the boron compounds involve interference in cell membrane permeability and enzyme systems. BA and its derivatives have been found to react in a cis-diols of biomolecules. A typical interaction might interfere with essential biomolecule function, for instance, ribose containing molecules NAD+ and RNA [309]. Most acute inorganic boron toxicities have relatively low to moderate. For the first one, LD50 oral was set for 2660 mg/kg body weight for BA. It can also show GI irritation symptoms on acute contact-mostly characterized by vomiting and diarrhea [310]. In long-term exposure, the effects of boron compounds on the reproductive system come to the fore. The studies conducted in cases of occupational and environmental exposure showed that effects such as a decrease in the quality and number of sperms in the male reproductive system and ovulation disorders in females can be observed [311]. The studies performed regarding the metabolic effects of boron compounds revealed very important findings in postmenopausal women. Studies on the daily intake of boron through diet and its effects on health also reveal positive effects, primarily relating to bone metabolism. In a controlled study, Hunt et al (1994) showed that low intake of boron at 0.25 mg per day increased urinary

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DOI: 10.19163/2307-9266-2025-13-3-202-238

calcium excretion and impaired magnesium metabolism in subjects compared to high boron intake of 3.25 mg per day [312]. Results from experiments underscore the need for adequate boron intake for mineral metabolism [310–312]. Randomized controlled trials demonstrated that boron supplementation is likely to positively impact bone mineral density [258]. Mechanistic studies show that the involvement of boron relates to steroid hormone metabolism and vitamin D homeostasis [312]. In conclusion, toxic manifestations of boron and its compounds are related to the level and duration of exposure. Available scientific data on the industrial and agricultural use of boron compounds indicate that such applications have an acceptable safety profile, provided that proper precautions are taken, and the limits of exposure are not exceeded.

CONCLUSION

The prevalence of boron in natural goods and its overall safety as a mineral have garnered considerable interest from health science researchers. The findings of the extensive review indicate that BA and some BCCs exhibit significant effects, including neuroprotection, cardioprotection, hepatoprotection, gastroprotection, antidiabetic properties, and antimicrobial, antibacterial, antifungal, antiviral, antiprotozoal, antiparasitic, anti-obesity, antioxidant, anti-inflammatory, anti-atherosclerotic, anticancer, anti-apoptotic, ferroptosis-related, and immune-related effects.

As a result, synthetic BCCs have been created in recent years, accompanied by a significant rise in both preclinical and clinical research. At now, 5 BCCs drugs (tavaborole, vaborbactam, bortezomib, crisaborole and ixazomib) have been approved by the FDA for diverse clinical applications. It is also understood that more than 10 boron-based compounds (alabostat, TOL-463, sodium borocaptate, voromycin and others) are being investigated in different clinical trial phases. In addition, it is seen that clinical studies are continuing for combinations of various drugs with BCCs for use in new indications.

In addition, it is observed that boron and boron-containing compounds are widely used as supplements. It is known that boron and boron-containing compounds are used in various pharmaceutical forms; capsules, tablets, chewing gums, liquid and powder (or antifungal and antibacterial applications) forms, fortified foods and beverages, boron-enriched mineral waters and functional foods containing boron compounds.

The consensus is that most toxic research involving boron focus on BA. BA is readily absorbed by the gastrointestinal tract. Boron is primarily believed to be excreted via urine; however, it has been noted that it is also eliminated through the gastrointestinal tract following the application of hazardous quantities of boron transdermally. BA has demonstrated deadly effects in numerous instances following cutaneous and oral administration in preclinical trials. Preclinical study results indicated an absence of genotoxicity and carcinogenicity. Chronic investigations have demonstrated that BA is non-carcinogenic.

The chemical characteristics of boron augment its medicinal potential. Boron is extensively employed in research as a reversible covalent moiety in peptides for protease inhibition, owing to its reversible electrophilicity. Moreover, boronic acids and boron esters, which demonstrate stability and binding at physiological pH, work as bioisosteres for ionized functional groups like carboxylates, esters, and phosphates, thus enhancing pharmacokinetic qualities, biological activity, or structural attributes.

Current research indicates that boronic acids may enhance the delivery of drugs and macromolecules by incorporating into lipid bilayers for liposomal transport or by reversibly binding to proteins. These findings underscore boron's potential for innovative therapeutic applications and the enhancement of its clinical value. BA and several BCCs demonstrate considerable potential for the development of novel therapeutic strategies for human diseases.

FUNDING

This study did not have financial support from third-party organizations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

AUTHORS' CONTRIBUTION

Oruc Yunusoglu — concept development, conducting the study, preparation and editing the text, approval of the final version; Oruc Yunusoglu, Irem Kalfa, Mustafa Enes Demirel, Muhammed Ali Binzet, Uygar Zarif Sevinc, Idris Turel and Akif Hakan Kurt — concept development, conducting the study, preparation and editing the text, approval of the final version Oruc Yunusoglu, Irem Kalfa — conducting the study; Oruc Yunusoglu, Irem Kalfa, Idris Turel and Akif Hakan Kurt — conducting the study, resource support of the study; Oruc Yunusoglu, İrem Kalfa — conducting the study; Oruc Yunusoglu, Irem Kalfa and Muhammed Ali Binzet — conducting the study. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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