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Review

Formulations with Boric Acid or Aryl-Organoboron Compounds for Treating Diabetic Foot Ulcers

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Abstract: Boron-containing compounds (BCCs) have been proposed for the treatment of diabetes and its complications. Recent studies have reported an improvement in the design and development of pharmaceutical formulations (often gels) containing boric acid applied to the foot ulcers of humans diagnosed with diabetes. The proposed mechanisms of action of boric acid include antimicrobial effects, the modulation of inflammation and metabolism, and the induction of cell differentiation. On the other hand, recent studies have suggested that boronic acids are potent antibacterial and antifungal compounds, effective modulators of inflammation, and inducers of vascular regeneration as well as inducers of healing, and they confer attractive properties such as adhesion, interaction, and the formation of complexes in formulations. Moreover, only a handful of studies conducted in animals have suggested the effective role of some BCCs as potent enhancers of wound healing, including their actions on induced and/or infected wounds in animals with disrupted metabolism. Also, it should be mentioned that no strong interactions between boric acid and the boronic acids present in formulations have been described. The developed combination could act as an additive and complementary therapy in the treatment of diabetic ulcers in humans. Further studies are required to support the hypothesis that this combination acts through diverse mechanisms to improve healing while avoiding or limiting a local or disseminated infection. Furthermore, the safety of BCCs used for foot ulcers should be established, as should the role of these formulations as a complementary therapy in current protocols for treating patients with diabetic foot ulcers.

Keywords: boric; boronic; ulcer; gel; wound healing; inflammation

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1. Introduction

Boron-containing compounds (BCCs) have emerged as bioactive agents and potential drugs [1]. The interest in their ability to modulate human metabolism and their applications for maladies is increasing [2]. In this sense, BCCs have shown direct effects on mammalian metabolism [3]. Some BCCs have affected glycemia and lipidemia in animals and humans; moreover, they have been applied for treating some complications of chronic conditions that are linked to metabolic disruptions, for example, the application of BCCs in the treatment

of foot ulcers in patients with diabetes [4]. The advances in this field have led to the use of BCCs in humans, and it has been observed that some BCCs actively improve the healing of wounds and mechanistically act on some signaling pathways.

In fact, in the 21st century, there have been some reports of boric acid improving wound healing in animal models of diabetic foot ulcers (see details in the following sections). Also, there are recent studies supporting the use of boric acid in some formulations for humans for avoiding local infections in wounds and accelerating the wound-healing process [5,6].

On the other hand, in recent years, multiple studies have demonstrated that some boronic acids can modulate the inflammatory process, with a few boronic acids exhibiting antimicrobial potential. Moreover, a few boronic acids that were found to be potent antimicrobial agents were also reported to be agents that modulate the production of antibodies, the action of cells, and the production of some biomolecules linked to the cicatrization processes [7–9]. However, to the best of our knowledge, no mixture of boric and boronic compounds has been proposed or tested for wound healing thus far. In this study, the current advances regarding the action of boric and boronic acids are presented, along with the analysis of some interactions and potential benefits of this mixture in new formulations. The combination of boric acid and specific boronic acids in formulations could act as an additive and complementary therapy in the treatment of diabetic ulcers in humans. In this sense, data were collected that reported results after boric or boronic acid administration and suggested the mechanisms of action by which they can act in an additive manner. Further studies are required to support the idea that the combination can be safely applied to open wounds in humans and that it can act through diverse mechanisms for improving cicatrization while avoiding or limiting a local or disseminated infection. Moreover, these formulations act as indicators for assessing the presence of some substances (reactive oxygen species, polyamines, etc.) or microorganisms (v.gr., necrotic, etc.), which require special attention in ulcer treatments.

2. Search Methodology

In this study, we reviewed the effects of boric acid or boronic acids in wound healing, particularly in diabetes induced in murine models or in humans. Information was collected and revised from the National Center of Biotechnology Information, PubMed, Global Health, Embase, Web of Science, Google Scholar, and clinical trial databases.

3. Experimental (Preclinical) Data of Boric Acid Pertaining to Wound Healing

Boric acid has established therapeutic effectiveness, and it has a positive effect on wound healing due to its anti-inflammatory and antioxidant properties [10]. Moreover, different studies demonstrated that a 3% boric acid solution promotes the healing of deep wounds through the regulation of tumor necrosis factor (TNF)-α and extracellular matrix [11,12].

Some relevant examples supporting the positive role of boric acid are provided in the following paragraphs. Thus, Tepedelen et al. (2016) [13] investigated the effect of boric acid on the wound-healing process, and they found that 100% wound closure occurs in 12 h at a concentration of 1 mM of boric acid, and after 24 h, they observed that the wound was almost completely closed in 1 and 2.5 mM boric acid-treated cells. They determined the positive effect of boric acid on wound healing in the presence of DNA-damaging agents. As a result, they observed that boric acid might reduce cytotoxic chemotherapy-induced oxidative DNA damage and inflammation in normal human epithelial cells, which is evidenced by the decreased $\gamma H2AX^{(Ser139)}$ foci formation and accelerated wound healing [13].

On the other hand, Demirci et al. [14] studied boric acid and sodium pentaborate pentahydrate as regulators of wound healing in streptozotocin-induced diabetic wound healing, and they measured factors exhibiting promotional effects on dermal cells in vitro; antimicrobial activity; and effects on proliferation, cell migration, and angiogenesis. Their study results revealed that boron-containing hydrogel formulations could be useful in managing diabetic foot ulcers [14].

Regarding the antimicrobial effects, Liu and collaborators published a study in which the application of 3% boric acid solution on cutaneous infections inhibited the growth of *Candida albicans*, and it reduced the diversity of skin microorganisms, for example, Proteobacteria, Enterobacteriaceae, and Escherichia-Shigella, and reduced the abundance of *Firmicutes*, *Staphylococcaceae*, and *Staphylococcus* [15].

Moreover, Konca and Korkmaz suggested that the co-administration of boric acid (10 mg/kg) orally with boric acid (3%) topically showed improved benefits [16]. In histopathological examination, re-epithelialization, granulation tissue formation, collagen formation, inflammatory cell formation, and neovascularization were found to be superior in local and oral and local groups compared to the control groups. In addition, blood and wound tissue malondialdehyde levels were lower in the groups receiving the oral administration of boric acid compared to the control and topical administration of boron groups, suggesting the improvement was related to the antioxidative activities of BCCs.

Additionally, it should be noted that multiple studies support the antimicrobial effect of boric acid in solutions with (weight/volume) concentrations higher than 2%. Among these is the report of Katsukawa et al. (1993) that shows the action of boric acid (with a minimum inhibitory concentration (MIC) of $\leq$1% for most tested species) on Gram-positive and Gram-negative bacteria and fungi related to dermatological infections [17], while other authors report that higher doses of boric acid are required to observe advantageous effects when compared to those of available compounds. An example of the latter is the report by Zan et al. that suggests that only concentrations higher than 4% of boric acid are effective in diminishing more than 50% of the common pathogenic agents in some biological media [18].

Also, gel formulations with sodium tetraborate and zinc borate have shown similar activities, but further research is required to disprove the notable differences observed among inorganic BCCs [19–21]. In fact, Dogan and collaborators [21] reported that sodium tetraborate and its pluronic could have applications in dermatological clinics, and they could represent a future solution for chronic wounds. Moreover, an in vitro study has demonstrated that erbium borate nanoparticles are effective agents that can be used for scarless wound healing [22].

4. Experimental (Preclinical) Data of Boronic Compounds Pertaining to Wound Healing and Diabetes

Wound healing is classified into two categories, i.e., primary and secondary healing, and non-complicated healing or non-infected wounds are classified as primary healing. Wound healing comprises different phases that include inflammation, proliferation, and remodeling. Therefore, the search for new therapies and strategies to treat wounds is still an urgent need [23]. In reality, wounds are still considered a significant problem, and countries such as the United Kingdom and Denmark report 3 to 4 people per 1000 people experiencing this problem, and unfortunately, in many cases, wounds become a chronic issue, leading to undesirable effects, for example, the amputation of limbs and even death [24]. Chronic ulcers represent a huge problem for the health system and particularly for the elderly or patients who suffer from systemic disorders such as diabetes. BCCs have

been described as efficacious agents for wound healing, as they promote cell migration and proliferation and reduce inflammation [5,25].

In this sense, boronic acids are interesting agents with diverse applications in medicine. In the field of wound-healing enhancers, boronophenylalanine exhibits promising effects [26]. These boronic compounds have been commonly included in gel formulations, and their interactions with other ingredients seem favorable for medical applications (see below).

Among boronic compounds with promising applications are phenylboronic acid (PBA) and 4-formyl phenylboronic acid (4FPBA); they inhibit pathogens causing diabetic foot ulcers (such as *Pseudomona aeruginosa*, *Staphylococcus aureus*, and *Salmonella typhi*, isolated from patients with confirmed diabetic foot ulcers) [27]. In fact, 4FPBA had an MIC of 3.125 μg/100 mL on the Gram-negative bacterial agents, while the complex with quercetin had an MIC of 1.5625 μg/100 mL. Interestingly, the wound-healing properties of the 4FPBA–quercetin complex were higher in infected diabetic rats when compared to non-infected diabetic rats. Histopathological evaluations showed significantly enhanced wound healing, re-epithelialization, fibroblasts, and angiogenesis in wounds of diabetic rats.

Several formulations (gels, creams, nanoparticles, etc.) have been tested, including boronic acids for enhancing wound healing. PBA and its derivatives are known to form covalent bonds with polyol compounds. Thus, PBA derivatives conjugated with chitosan or other polyols have several potential applications; their ability to function as glucose-sensitive polymers enables self-regulated insulin release in the treatment of diabetes, and they also function as diagnostic agents. Notably, these conjugates have been used for wound healing and tumor targeting [28].

Other formulations have also shown promising results. For example, graphene platforms with boronic acid (GPBA) were able to wrap bacteria and destroy them in a short time. They showed antibacterial and anti-parasitic activities as well as a wound-healing ability; thus, they were investigated for diabetic wound-healing potential. In vivo experiments showed that GPBA are more efficient than phenytoin, as they restore both infected and non-infected diabetic wounds in 10 days. Furthermore, GPBA are promising candidates for other biomedical applications [9].

Zhao et al. tested an injectable curcumin–PBA hydrogel (named GOHA-Cur), and it has self-healing and self-adaptive properties, being attractive for application in surgical procedures. GOHA-Cur exhibits reversible adhesive properties, facilitating it to be peeled off and, thus, to withdraw damaging substances, including an excess of carbohydrates, acids, bacteria, and reactive oxidative species present in wounds. Moreover, GOHA-Cur exhibits a pH- and glucose-responsive release of curcumin. It shows excellent antibacterial, antioxidant, and anti-inflammatory activities in vitro. Additionally, animal experiments have shown that GOHA-Cur can inhibit inflammation and promote wound regeneration [29]. Zhang et al. reported a novel glucose-responsive hydrogel containing fluvic acid, PBA, and hyaluronic acid (named HA-PBA-FA/EN106). This hydrogel demonstrates a glucose-responsive release of drugs. In fact, a key observation is that the release of FEM1b-FNIP1 axis inhibitor EN106 diminished oxidative stress and enhanced angiogenesis by regulating the FEM1b-FNIP1 axis. Both in vivo and in vitro results of Zhang et al. demonstrated accelerated diabetic wound repair [30].

For their part, Temel et al. reported a novel boronic ester compound derived from PBA and quercetin (PBQ). The new formulation with the boron-containing compound showed antioxidant, antibacterial, anti-enzyme, and anticancer activities and electrochemical oxidation abilities in in vitro experiments. Also, the histological evaluation of this agent was performed on rat organs using the hematoxylin–eosin staining method. PBQ was found to be effective against E. coli (ATCC 25922), and its MIC value was 6.50 mg/mL. Thus, due to

the high biological activity potential of PBQ, it has the potential to be used in food, feed, pharmaceutical, and cosmetic industries [31].

Moreover, Abid et al. recently tested PBA–quercetin nanoparticles (PBA-Qt NPs) as enhancers of wound healing. PBA-Qt NPs exhibited superior oxidant scavenging compared to PBA and quercetin. PBA-Qt NPs showed significant antimicrobial activities against Gram-negative and Gram-positive bacteria. Their minimal inhibitory concentration for *Pseudomonas aeruginosa* was around 1 μg/100 μL, and for *Staphylococcus aureus*, it was around 8 μg/100 μL. They accelerated wound healing by 60–99% in infected diabetic rats in a better way than phenytoin. PBA-Qt NPs stimulated angiogenesis, tissue repair, and regeneration, improving wound closure. Moreover, PBA-Qt NPs demonstrated superior wound contraction and granulation tissue formation in all groups where it was applied [32].

5. Data from Studies Using BCCs for Wound Healing in Humans

Treatments with formulations containing boric acid were conducted in humans in the beginning of the 21st century, and multiple studies have provided evidence supporting their use. For example, Corradino et al. found boric acid to have promising effects on open wounds related to necrotizing fasciitis caused by *Acinetobacter baumannii*. Wounds were dressed daily with a 3% boric acid solution and a silver sulfadiazine-impregnated dressing; an extensive surgical debridement was performed to control the infection, and wounds were finally covered with skin grafts. In this way, the infection was successfully treated 35 days after admission, while the graft taken was 100%; a follow-up conducted at 6 months showed benefits of the treatment in terms of both functional and esthetic results [33].

In another study, Krisp et al. developed a gel that enhanced healing and cicatrization. They tested a combination of bovine alpha-1-acid-glycoprotein (A1AG) and alpha-2-HS-glycoprotein (fetuin A) enriched using boric acid gel affinity chromatography (BAGAC). Specifically, the glycoproteins in the wound fluids of patients with diabetes mellitus having chronic foot ulcers were analyzed after BAGAC enrichments. These findings demonstrated the capability of the BAGAC material to enrich glycosylated proteins from complex human wound fluids; these findings can be used for the development of diagnostic and therapeutic agents for patients with diabetes [34]. Furthermore, Firat et al. found some benefits of using a simple 3% boric acid solution on wounds with repetitive debridement. Debridement was repaired with split-thickness skin grafts or fasciocutaneous flaps or healed with secondary intention. The boric acid solution was found to promote granulation tissue in all the wounds [35].

Some more advances from the last decade are provided below. Additional BCCs were tested. Thus, boric acid and sodium pentaborate pentahydrate (NaB) were evaluated on dermal cells in vitro and in rats in a similar way as in humans to consider their viable applications. Moreover, they displayed remarkable antimicrobial effects against bacteria, yeast, and fungi, and NaB displayed a high antimicrobial activity as well as gene and growth factor expression-inductive effects, thus furthering the exploration of BCCs for this medical application [14].

In the search of hydrophilic, biocompatible, and responsive hydrogels for accelerating the healing process, several other formulations were probed. An example is a gel with chitosan oligosaccharide, aldehyde hyaluronic acid, and boric acid that was tested. This preparation yielded a thermosensitive and pH-responsive injectable self-healing (FCAB) hydrogel, loaded with the drug deferoxamine (DFO) for the accurate release and promotion angiogenesis in diabetic foot ulcers. In vitro and in vivo experiments verified that the FCAB-DFO hydrogel promotes migration and angiogenesis. Thus, FCAB-DFO hydrogel exhibited unique physicochemical properties, excellent biocompatibility, and significantly enhanced therapeutic effects for diabetic foot ulcers [36].

Other gels have probed its functionality and advantages in humans; Sahin et al., in a randomized, double-blind placebo-controlled trial (registered in the clinical trial database, IRCT20190212042686N1) using topical NaB gel, demonstrated that it may help to treat and decrease the grade of diabetic foot ulcers and prevent the recurrence of diabetic foot ulcers. Most participants in the intervention group had a lower ulcer grade after 25 days of the treatment (modified from 2.37 to 1.37, n = 120) than the control group (modified from 2.41 to 2.33, n = 41), as they used the Wagner classification for evaluation (scale, grade 0: pre- or post-ulcerative lesion; grade 1: partial/full-thickness ulcer; grade 2: probing into tendon or capsule; grade 3: deep abscess formation or osteomyelitis; grade 4: partial foot gangrene; and grade 5: extensive gangrene), and there was no case of recurrence in the intervention group, while the recurrence rate was 40% in the control group [25]. In fact, there is a study registered with ClinicalTrials applying 3% NaB (compared to placebo gel containing polymer of 1% carbopol ultrex) in patients with ulcers classified by the International Working Group of the Diabetic Foot (IWGDF) as grades 1 and 2 (approximately corresponding to grades 0 and 1 of the Wagner scale) (https://clinicaltrials.gov/study/NCT02087215, accessed on 15 January 2025), but no results have been reported.

Moreover, as local wound therapies are used in appropriate cases to prevent situations that may result in the need for amputation, low-cost proposals have been tested in humans. Some of them could be considered inexpensive for use in patients who require it. Thus, boric acid powder (BAP) was used in the treatment of two patients with diabetic wounds. The application of BAP effectively cleared necrosis and accelerated wound healing, and Coskun suggested its use because of its low cost and beneficial effects on the wounds of patients, but it should be mentioned that this application must be carefully explored and used in addition to systemic therapy [6].

Finally, it should be mentioned that no evaluation for the repeated topical administration of boric acid, NaB, or boronic acids for a period longer than two months has been reported in patients with diabetes. However, there are some studies that support the absence of adverse effects of boric acid in healthy rats [37], while it seems to have similar pharmacokinetics in rats and humans [38]. However, the study in humans must be conducted more extensively to avoid the reported adverse effects of boric acid, especially in human infants with skin diseases [39].

6. Antibiotic Effects on Specific Microorganisms Related to Infections Associated with Diabetic Foot Ulcers

Chronic or acute diabetic wounds, particularly in diabetic foot ulcers, are vulnerable to bacterial infections because of a disruption in wound microbiota and the failure of neutrophils and macrophages to eliminate invading microorganisms. Moreover, impaired angiogenesis, the overexpression of pro-inflammatory cytokines, and chronic inflammation induced by bacterial infections may slow down the wound-healing process during the healing of diabetic foot ulcer wounds [40,41]. In addition, oxidative stress linked to local infection is generally thought to be one of the main reasons for poor wound healing in diabetic foot ulcers [42].

However, the current strategies cannot adequately meet the dynamic demands of the diabetic foot wound-healing process. Some microorganisms are particularly linked to the infection in diabetic foot ulcer cases, and Gram-positive bacteria such as *Staphylococcus aureus* and *Corynebacterium striatum* and Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Alcaligeneses faecalis*, commonly known for their flexible biofilm properties and stable profile against antibiotics, are the most common diabetic foot ulcer pathogens, while fungi or protozoal are not often involved [43,44]. Today, diverse strategies are used for the prevention of ulcer infections (among these are the cleaning of wounds, the control

of glycemia, and local assessment), while antibiotics are used in diabetic foot ulcers for the treatment of bacterial infections when diagnosed by a physician and modified after a biological test or wound evolution. The used antibiotics either kill the bacteria or inhibit their proliferation, and their mechanisms of action mainly include interfering with the cell wall structure of target bacteria or preventing their proliferation by disrupting their protein synthesis. It is important to reveal the antibiotic effects of BCCs (especially boric and boronic acids), promising alternatives to traditional treatments, on specific microorganisms that cause diabetic foot ulcers, as boron-based compounds are suggested to be resistant to some antibiotic resistance mechanisms, thus disrupting biofilm-forming pathogens and acting as antimicrobials; they are effective wound-healing agents that promote cell migration and proliferation and reduce inflammation in the wound area [44].

In this context, it has been determined that some BCCs regulate the turnover of the extracellular matrix (ECM) and augment the release of TNF-α, which plays an important role in the repair process of wounds such as diabetic foot ulcers by increasing the release of proteoglycans, collagen, and proteins [45,46]. Therefore, BCC formulations may have some positive effects on wound healing in patients with diabetic foot ulcers that become chronically infected and are a major clinical problem (Figure 1). On the other hand, BCC hydrogels or microgels show potent antibiotic activity on some specific microorganisms that cause diabetic foot ulcers. Among these hydrogels, boronate ester-based gels formed by esterification reactions between boric/boronic acids and cis-diols have antioxidant activity that inhibits harmful bacteria that cause diabetic foot ulcers, and they have emerged as a highly promising strategy for accelerated chronic wounds in recent years [47]. The simple preparations containing 2–3% boric acid or boronic acid solutions also greatly improve the healing of deep wounds, in part due to their bactericidal and fungicidal properties [10].

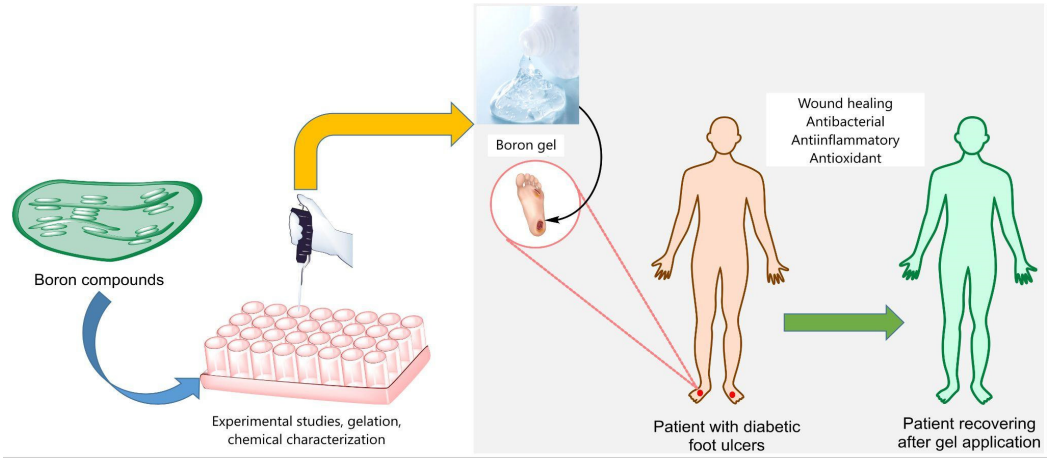

Figure 1. Effects of boron-based gels on microorganisms associated with diabetic foot ulcers.

Although the mechanisms of action of BCCs (especially boric and boronic acids) in diabetic foot ulcers are not known in detail, they are thought to involve the disruption of the cell structure formed by the coulombic or covalent interactions with lipopolysaccharides, which are found in the outer membranes of target Gram-negative bacteria. Furthermore, some BCCs have shown activity against proteasomes, lactamases, and other proteases [48,49].

The details of the mechanisms of action of BCCs are beyond the scope of this study; however, some of them are mentioned in the following paragraphs. Thus, the effects of some BCCs (NaB, sodium metaborate tetrahydrate (SMTB), calcium metaborate, zinc borate, sodium tetrafluoroborate, potassium tetrafluoroborate, ammonium pentaborate, and ammonium tetrafluoroborate) on bacteria obtained from blood culture were established using the MIC method. The biofilm formation potentials were examined on microplates, tubes,

and Congo red agar. The SMTB molecule was effective against all the tested pathogens (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, methicillin-resistant coagulase-negative *Staphylococcus*, *Staphylococcus hemolyticus*, *Enterobacter aerogenes*, and *Acinetobacter baumannii*), with *Staphylococcus aureus* showing the most substantial biofilm ability; these BCCs were not toxic to fibroblast cells up to a concentration of 1 μg/L. In cell culture experiments, these BCCs inhibit biofilm-forming pathogens in a short treatment period (e.g., in 2–4 h, they inhibited the biofilm formation of microorganisms associated with antibiotic resistance and immune evasion) [50].

Furthermore, some pyridine–boronic acids act on NorA, the most studied chromosomal efflux pump of *Staphylococcus aureus*, and NorA is responsible for the resistance of Methicillin-resistant S. aureus. Those BCCs are active on their own, but they can potentiate the activity of ciprofloxacin (as NorA expression drives tolerance to ciprofloxacin). In addition, it has been shown that 6-(3-Phenylpropoxy)pyridine-3-boronic acid and 6-(4-phenylbutoxy)pyridine-3-boronic acid compounds promote Ethidium Bromide (a DNA-fluorescing substrate of the NorA pump) accumulation in microorganisms, thus corroborating their potential mode of action as NorA inhibitors [51].

As mentioned above, several other mechanisms have been reported to explain the antimicrobial effects of BCCs. In E. coli, the boron center is thought to have an antibacterial mechanism of action, such as inhibiting the growth of ribosomal RNAs for the large ribosomal subunit and preventing the inhibition of fatty acid biosynthesis [52,53]. Also, BCCs can reverse the dysfunctional inflammatory environment, alleviating the hypoxic microenvironment and preventing scarring that favors microorganism growth, triggering effective diabetes foot ulcer healing [54]. Some drug candidate compounds such as boric or boronic acid have different chemical and physical binding abilities with the glycoprotein in the cell membrane, and they have been shown to result in the proliferation of lymphocytes and other cells in the target systems, leading to the faster healing of diabetic foot ulcers [9,55].

On the other hand, resistance mediated by β-lactamases is the major and leading cause of resistance to lactamates among Gram-negative bacteria. Among the compounds developed in this field, Bavorbactam, a BCC, has been tested as an efficient antibiotic. It forms an acyl-enzyme complex with Pseudomonas aeruginosa Penicillin-Binding Protein-3 (PBP3) and inhibits it; its binding to PBP3 increases the protein's thermal stability by about 2 °C. The crystallographic analyses of the PBP3/vaborbactam complex reveals that vaborbactam forms a covalent bond with the catalytic Ser294, and it also interacts with Asn351, Thr487, Ser485, Ser349, Val333, and Tyr503, thus making it a high-affinity ligand. These findings support the potential development of novel cyclic boronate-based PBP inhibitors to overcome β-lactamase-mediated resistance mechanisms [56].

Complex systems such as boric acid-functionalized carbon dots (B-CDs) with negative surface charge were tested for their ability to form bonds with the cis-diol groups of polysaccharides in bacterial cell walls. In the in vitro experiments assessing antibacterial activity, B-CDs showed bactericidal activity against *E. coli* with a minimum bactericidal concentration of 12.5 μg/mL. The mechanism suggested for antimicrobial action of B-CDs was that they entered the cell by diffusion and caused selective damage to the *E. coli* DNA, while B-CDs exhibited low toxicity in host cells. The results support the development of boron-based nanomaterials [57].

The testing of antimicrobial activities of BCCs is continuously being conducted, for example, the reports on the antimicrobial activities of molecules containing more than one boron atom. Thus, diborolane derivatives were synthesized and tested against clinically important Gram-positive and Gram-negative bacteria and Candida species, with at least five compounds being effective against the tested bacteria. Three of these compounds, named compounds 2, 6, and 8, are promising antibacterial candidates against

biofilm-forming and antibiotic-resistant strains; additional evaluations should be carried out for these candidates in the near future [58].

7. Chemical and Physiological Interactions of Boric and Boronic Acids in Formulations: Complementary Action in Treatment

7.1. Potential Chemical Interactions

The BCCs discussed in this study, which are cheap, easy to synthesize, and stable, are promising candidates for a wide range of future biomedical applications as they have the potential to be used in the treatment of many diseases, especially diabetic wound ulcers, due to their hydrophobic and electrostatic interactions with different biosystems under mild reaction conditions.

The potential of boric and boronic acids is evident when the hydroxyls in the *gem* position with respect to the boron atom are towards a donor site on a biologically active target molecule as a new agent, facilitating the strong hydrogen and covalent bonds that these compounds form with targets. In this context, to improve the antimicrobial activity of compounds such as boric/boronic acid, i.e., to increase their antibiotic effect on some specific microorganisms, they must be equipped with functional groups that can bind strongly to the membrane of pathogens. Thus, hydrophobic and electrostatic interactions occur between these functional groups in the structure of boron compounds and the target pathogen and are thought to help the treatment of diabetic foot ulcers.

In particular, bacterial outer membranes containing teichoic acid or lipopolysaccharide moieties are structures with the cis-diol functionality and are suitable targets for covalent interactions with adjacent hydroxyl groups present in the boric or boronic acid structure due to high glucose and/or ROS sensitivity (Figure 2). In the presence of a high level of glucose and/or ROS, predominantly due to electron donation and sequestration, the covalent bond breakage of target boric or boronic acids can occur, resulting in the release of glutathione, which has an antibiotic action [59,60]. The product of this covalent interaction can be used as a gel or biofilm on some specific microorganisms, potentially shortening the diabetic wound-healing process.

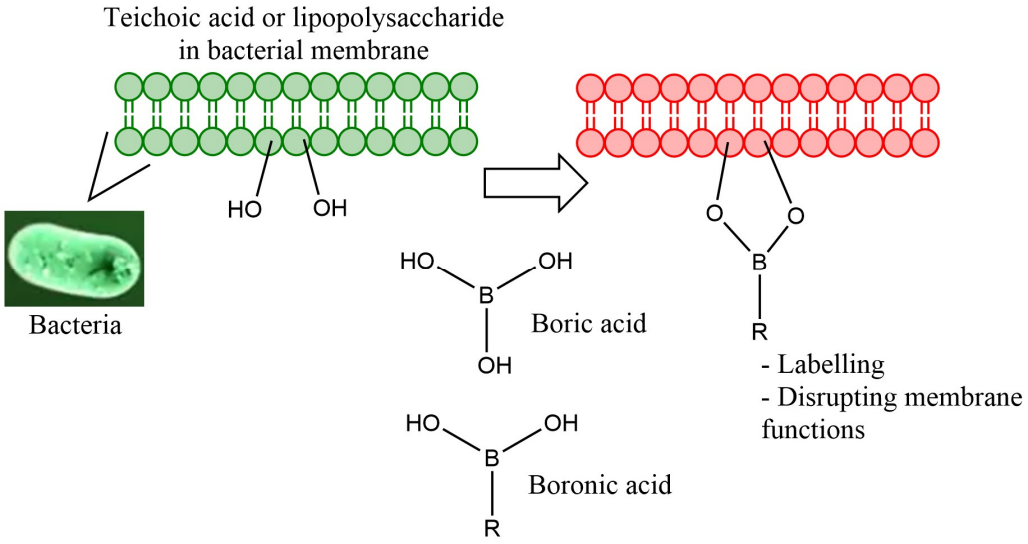

Figure 2. The covalent interactions of the hydroxyl groups of boric/boronic acid with teichoic acid or lipopolysaccharide, making them likely agents for diagnosis and treatment in diabetic foot ulcers.

Furthermore, boron compounds with sp3 hybridization and tetrahedral geometry are formed because of the covalent interaction between boronic and boronic acids with sp2 hybridization and trigonal planar geometry, which can interact with Lewis bases or

nucleophiles due to their empty *p*-orbitals and allow for the formation of bacterial outer membranes with the cis-diol functionality through strong dative covalent bonds [61]. Depending on the conditions, these tetrahedral boron compounds usually contain a positively charged center and hydrophobic residues attached to this center, which allows them to resolve electrostatic interactions between their cationic membranes and anionic bacterial membranes. As a result of these electrostatic interactions, the target boron compounds enter the membranes of pathogenic bacteria, where they have usually resulted in pore formation and cause bacterial cell death, acting as potential drugs, and thus become stable against metabolism and resistance [62,63]. However, as small molecules, a high number of covalent hydrogen bonds in boric/boronic acids have a short bond length and high binding energy, increasing their binding affinity to specific targets through different hydrophobic and electrostatic interactions, thus mimicking specific biological processes, which may allow boron-based drugs to target drug-resistant mutations in diabetic foot ulcers [64,65].

Little information is available regarding the putative interactions of boric and boronic acids in a formulation or in the environment. Boric and boronic acids can interact in gel formulations with the cys-diols of some components like sugars, mannitol, polyethylene glycol, and triethanolamine [66,67], forming reversible interactions; these esters/adducts are Lewis acids with low pKa values. Moreover, some observed interactions allow research groups to design enhanced self-restoring materials with advantageous biological applications [68]. Also, the interactions of boronic acids could improve formulation characteristics; for example, mannitol is used as a bulking agent in freeze-dried formulations of the alkyl boronic drug bortezomib, and this formulation can be administered through the subcutaneous route. Dosing in this way is possible because the solubility of bortezomib is enhanced by the formation of a readily reversible mannitol ester [69]. The nature of interactions observed in these materials supports our hypothesis that stronger interactions may occur between bortezomib and some hydroxyls present in biological targets [70]. Specifically, interactions with targets are easy and firmly established when 1,2-diols are found in the protein targets in both tricoordinated and tetracoordinated forms, and such interactions are observed in several complexes found in the protein data bank repository [71].

7.2. Potential Complementary Effects in Wound Healing and Beyond

A combination therapy to treat foot ulcers seems advantageous over a single therapy; the surgical approach, oral and topical drug treatment, and hyperbaric oxygen therapy and negative wound pressure therapy have reported benefits [72,73]. Regarding the involved mechanisms, undoubtedly, the central role in these mechanisms is played by inflammatory cytokines and the avoidance of pathogens to enhance wound healing; moreover, other underlying factors, including aging, nutrition, hypoxia, stress, infections, drugs, genetics, and chronic diseases, modulate wound evolution [73]. In fact, oxidative stress in the related processes plays a key role [74].

In this sense, the applications of formulations containing boric or boronic acids could improve wound healing through diverse and complementary mechanisms (Figure 3) [75]. In brief, boric acid decreased the elastase and alkaline phosphatase activity. Furthermore, in an in vivo model using fibroblasts, boric acid enhanced the trypsin-like, collagenase, and cathepsin D activities; also, it enhanced phosphorylation, supporting the fact that it may affect living cells via mediators, such as TNF-α [10,76].

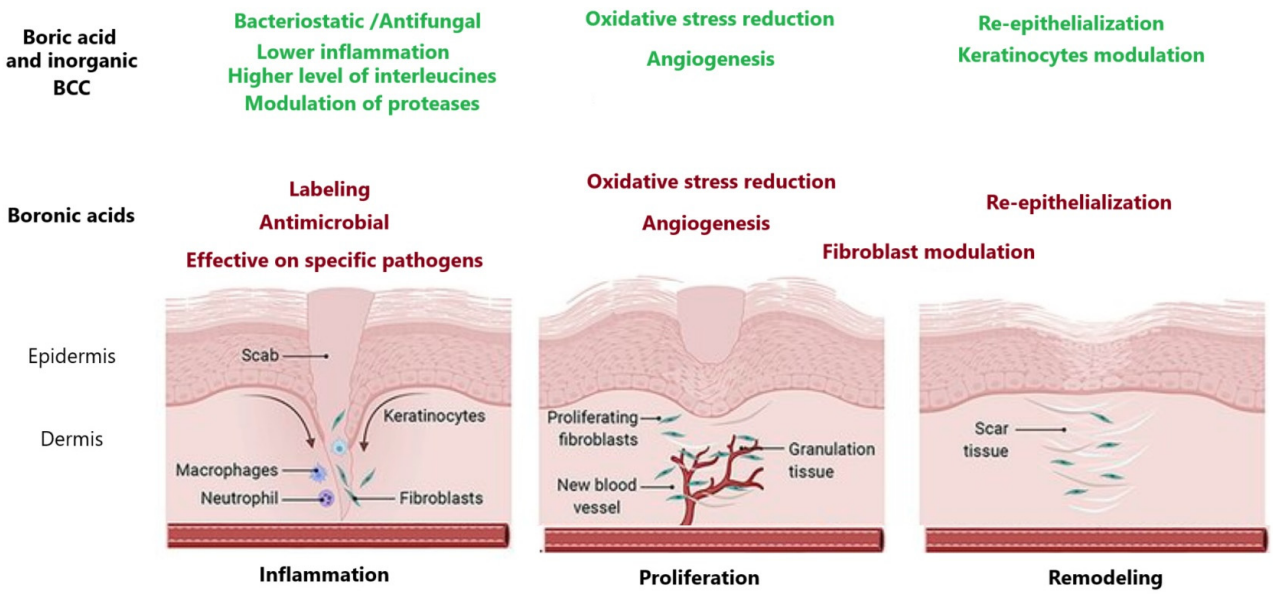

Figure 3. The predominantly reported effects of boric acids and boronic acids as well as their potential complementary effects in diabetic ulcer treatment. Some effects seem shared, but the supporting evidence is greater in one of the two compound groups.

Boric acid and other inorganic compounds (such as sodium tetraborate) also increased the proliferation, migration, vital growth factor, and gene expression levels of dermal cells, as recently reported by Sedighi-Pirsaraei et al. [75], along with displaying remarkable antimicrobial effects against bacteria, yeast, and fungi [14]. Additional mechanisms have been proposed to be key in boric acid's mechanisms of action, such as increasing EphrinB1, EphrinB2, and EphB4 [77] and producing epidermal growth factors [78].

In the case of boronic acids, specific effects are crucial in the evaluation of wounds, the identification of infective agents, and wound-healing benefits. Thus, the antioxidant properties of boronic acids help to protect cells from oxidative stress, which could be improved in BCCs containing boron and aromatic rings as common features that could exert benefits on wounds with impaired healing. Additionally, these BCCs stimulate cell proliferation and migration as well as essential tissue regeneration and wound closure processes. PBA has demonstrated the potential for targeted bacterial drug delivery, enhancing antibacterial efficacy and trapping free lipopolysaccharides and peptidoglycan from dead bacteria, to reduce undesirable inflammation. In a diabetic mouse model, a system mixing PBA, dextran, and curcumin exhibited antibacterial, anti-inflammatory, and antioxidant activities, ultimately promoting efficient and safe wound healing in diabetic mice [79]. For example, 4-formyl phenylboronic acid-induced enhanced wound healing in diabetic rats significantly enhanced wound healing, re-epithelialization, fibroblasts, and angiogenesis in wounds of the diabetic rats after 10 days [27]. Also, 3-fluorophenylboronic acid derivatives induced anti-inflammatory and antioxidative effects and accelerated wound healing in diabetic rats [80].

Finally, it should be mentioned that in the identification of some damaging bacterial pathogens of wounds, several boronic acids can be used; these potential tags or biosensors can be adapted to different formations (including colorimetric, fluorescent, surface-enhanced Raman spectroscopy, electrochemical, etc.). In many cases, boronic acids have acted as labels for identifying *Staphylococcus aureus* [81], *Klebsiella pneumonia* [82], and *Escherichia coli* [83]; these three species are often found in diabetic foot ulcers. This application is under development, as the industrial implementation of boronic-based biosensors

for pathogen detection proves that boronate affinity platforms require improvement in terms of sensitivity, specificity, pH adaptability, and signal discrimination [84].

8. Conclusions

After describing the biological actions of BCCs (particularly boric and aryl-boronic acids) and the advances in comprehending their various mechanisms of action involved in the benefits obtained from the modulation of skin maladies, these compounds have been proposed in several applications as drug candidates for diabetic foot ulcers.

Particularly, several reports support the topical application of formulations with BCCs improving wound healing in patients with diabetes. In this sense, boric acid seems to be an accelerator of wound healing with antimicrobial action, while boronic acids serve as metabolism modulators, microorganism labels, and antibiotics, and the interest in them has increased, as some boronic acids are active against specific microorganisms involved in the delay of wound evolutions or complications in diabetic foot ulcers. In contrast, there are some reports suggesting careful observations, as the repeated administration of BCCs in skin lesions can increase the risk of vascular and dermal damage, as observed in lethal cases involving human infants.

In this context, the search, development, and additional evaluation of new BCCs and their combinations in formulations to be evaluated in models of wound healing are necessary; if the toxicity, pharmacodynamic, and pharmacokinetic results of the in vivo evaluation are favorable, they can be proposed for use as a complementary therapy for patients with diabetic foot ulcers to improve the results of conventionally available therapy, with regular assessments by a specialist, potentially expanding their application to other skin diseases.

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