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Boron and beyond: Where do we stand in cancer diagnosis and treatment?

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ABSTRACT

The element boron (B) is in the IIIA group of the periodic table, with atom number 5 and molecular weight of 10.81 mol/g. B is a rare element involving many biological processes such as embryonic development, bone structure, and function, oxidative stress, etc. Over the last decades, studies have shown that B-containing compounds regulate reactive oxygen species (ROS) levels, involve DNA damage mechanisms, and inhibit different enzymes. Improvements in medicine led researchers to think about B's potential usage in cancer diagnosis, treatment, and prevention. Nowadays, different research groups have studied B-based compounds on several types of cancer including prostate, lung, breast, colon, skin, brain, melanoma, etc. Studies revealed that B compounds can affect different types of cancers with different pathways/mechanisms. Based on the potential therapeutic effects of B, the first B-containing anti-cancer drug and a first-in-class proteasome inhibitor Bortezomib (Velcade®), was approved by the Food and Drug Administration (FDA) in 2003. On the other hand, boron neutron capture therapy (BNCT) is a very important clinical cancer treatment based on B and B-containing delivery agents. During the past 20 years, researchers developed several new B delivery agents both for BNCT and B itself. In summary, this review article offers an overview of B compounds used for cancer diagnosis and treatment, delivery agents for BNCT, new therapeutic approaches containing B carriers, and novel B-based cancer detection approaches.

1. Introduction

Boron (B) is a rare element on Earth, and it generates just 0.001% of all the elements in the world [1]. 73.4% of all known B reserves are in Türkiye [2]. Two major producers, approximately 62% of Türkiye and 23% of America supply most of the world's B consumption [3]. B belongs to the periodic table's IIIA group, which is a metalloid (half-metal) with an atom number 5 with molecular weight of 10.81 mol/g. There are 230 known B derivatives, however, there is no B in its free form in nature. The most important B types are borax or tincal ($Na_2B_4O_7.10H_2O$), boric acid (H_3BO_3, BA), colemanite ($CaB_3O_4(OH)_3.H_2O$), kernite or rasorite ($Na_2B_4O_7.4H_2O$), and ulexite ($NaCaB_5O_9.8H_2O$). B is found in sedimentary rocks, water, soil, and air in nature. Organisms absorb a trace quantity of the B into their bodies through the water and food they consume. Almost all the B entering living systems is absorbed by the gastrointestinal system. Green vegetables and fruits, nuts, fish, milk, and meat have a high content of B [4]. A wide range of application areas may benefit from B's advantages, and it can be used in more than 400 different industries, including the nuclear, pharmaceutical, fertilizer, automotive, glass and ceramics, chemistry, cleaning, aerospace, cosmetics, weapon, agri-food industries, energy and construction industries, metallurgy, superconductors, electronics, and medicine [5]. Studies on the biological and toxicological effects of B on a variety of organisms have led to an increase in the usage of B in medicine. Studies have shown that it participates in calcium metabolism and hormone activity. However, the role of B in biological processes is not fully known yet. Though it is not classified as an "absolutely essential element" for humans, the World Health Organization (WHO) defined B as a "possibly essential element" in 1996 [6]. Daily consumption of B shows different rates in every country and human. However, the average amount of B taken was determined as 1.5-3.0 mg B/ day. WHO defined the maximum daily consumption amount of B as 1-13 mg B/ day for adults [4]. B has effects on many mechanisms, including carbohydrate metabolism, mineral uptake, enzyme function, and the regulation of hematological processes along with the undefined effects. In addition, studies have shown that B and its derivatives may have important roles in the treatment and prevention of some cancer types [7,8].

1.1. Effects of Boron on Human Health

Human intestinal epithelia are capable of absorbing B, and most of the B that has been ingested into the body is excreted in the urine, whereas 2% is excreted

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in feces and a negligible amount by sweat, breath, and bile. Over the decades, studies have shown that B has a good influence and important roles in embryonic development, energy metabolism, hormone metabolism, bone structure and function, inflammatory response, wound healing, oxidative stress, etc. (Figure 1).

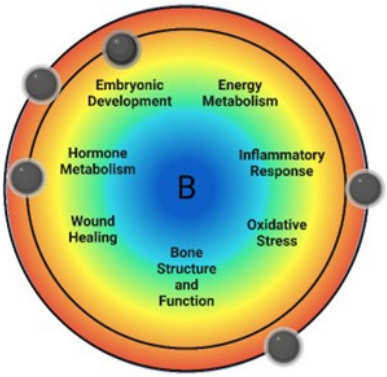

Figure 1. Important processes and pathways that B is involved and has regulatory role (Created with BioRender.com).

B can interact with riboflavin, adenosine monophosphate, pyridoxine, pyrimidine nucleotides, ribose, and polysaccharides [9]. Furthermore, B functions as an inhibitor for proteasome, arginase, nitric oxide synthase, and transpeptidase. Therefore, B-containing drugs could be beneficial for the treatment of various diseases like; arthritis, metabolic abnormalities, neurological issues, and numerous chronic and infectious diseases. For decades, several B compounds have been investigated as antibacterial and antifungal agents such as natural biomolecules, diazaborine, oxazaborolidines, diphenyl borinic esters, and benzoxaborole [10-12]. Studies showed that B-containing compounds regulate reactive oxygen species (ROS) levels and are involved in DNA damage response mechanisms. Based on these properties, researchers defined B and B-containing compounds as important chemopreventive agents [13-16].

1.2. Boron-containing Drugs in Use

To develop new pharmaceutical drugs, the utilization of substances that aren't typically found in organisms has a high chance of yielding unexpected biological action. If a B atom is logically placed into a biologically active molecule (at a site that is close to a donor area in the target protein), interactions with the target protein may be anticipated that involve both covalent and hydrogen bonds, and these interactions would result in a powerful biological activity [17]. Based on this knowledge, various B-containing small molecules have been reported to inhibit different enzymes (Figure 2).

The proteasome inhibitor and anti-cancer drug Bortezomib (Velcade®) was approved by the Food and Drug Administration (FDA) in 2003. In solid tumors and hematological malignancies, it facilitates

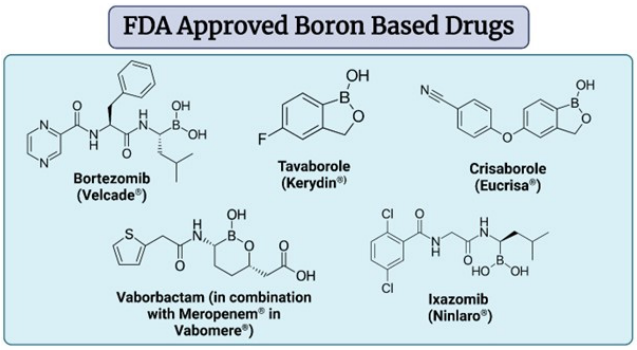

Figure 2. B-containing drugs approved by FDA (Created with BioRender.com).

apoptosis and disrupts the cell cycle [18]. It was the first B-containing drug on the market and a first-in-class proteasome inhibitor. A significant association has been observed with the bortezomib doses and positive regulation of prostate-specific antigen (PSA). When combined with other treatments like radiation or other chemotherapeutics, bortezomib is effective to treat androgen-independent prostate cancer [19]. In addition, the anti-cancer activity of bortezomib has been demonstrated alone and with other cytotoxic agents such as 5-fluorouracil (5-FU), paclitaxel (PTX), gemcitabine (GMT), or doxorubicin (DOX) in other tumor types [18]. Late, two more B compounds, Tavaborole (Kerydin®) and Crisaborole (Eucrisa®), were approved by the FDA in 2014 for treating onychomycosis and atopic dermatitis, respectively [20]. The second-generation B-containing proteasome inhibitor Ixazomib (Ninlaro®) was approved by the FDA in 2015, for multiple myeloma patients who have already undergone at least one prior therapy [21]. Vaborbactam® was the first boronic acid β-lactamase inhibitor to receive FDA approval in 2017 [22]. The FDA also approved the use of Vaborbactam® in combination with Meropenem® (namely Vabomere®) to treat urinary tract infections.

2. Boron as a Chemopreventive and Chemotherapeutic Agent

As the number of people suffering from the disease is increasing around the world, development of novel treatment strategies is gaining more importance. Investigations aim to identify new compounds with novel and effective anti-cancer characteristics. Amongst, B-containing compounds have been demonstrated to have promising effects so far for prostate, breast, cervical, lung, and melanomas [23-25]. Several studies have shown that low B intake is associated with the progression of different types of cancer. An epidemiological study by Cui and coworkers (2014) suggested an inverse relationship between daily B uptake and prostate cancer [23]. Furthermore, some studies revealed that B intake was adversely related to the ratio of cervical cancer [24] and lung cancer [25]. Based on these studies, natural and synthetic B compounds such as borates, sugar-borate esters (SBEs), B polyketides, boranes, boronic acids/esters, borinic acids/esters, and dipyrromethene

boron difluoride (BODIPY) for cancer therapy have been further investigated (Figure 3).

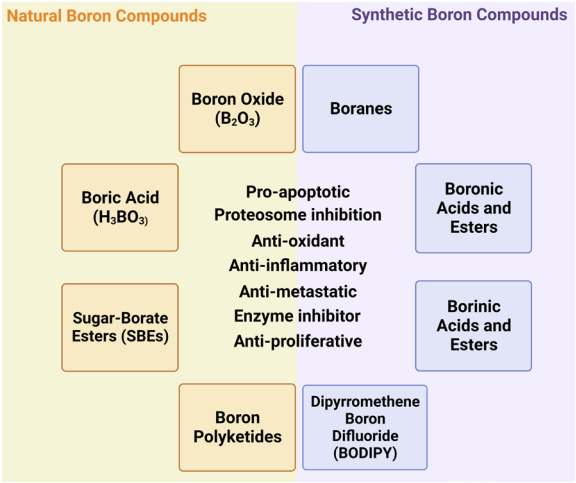

Figure 3. B-containing natural and synthetic compounds and their potential therapeutic effects on cancer (Created with BioRender.com).

Natural B compounds contain BA, boron oxide (BO), sodium pentaborate pentahydrate (NaB), disodium pentaborate decahydrate (DPD), sodium perborate tetrahydrate (SPT), sodium pentaborate decahydrate (SPD), borax pentaborate decahydrate (BP) and numerous different molecules. These natural chemicals contain B-oxygen bonds, and they belong to the borate family. Since they are natural compounds and showed effective therapeutic effects on different diseases, various studies have been investigating their effects on cancer. SBEs are one of the most important members of B-containing natural compounds, and may be found in many different structures like trigonal or tetragonal and mono- or di-esters [26] (Figure 4).

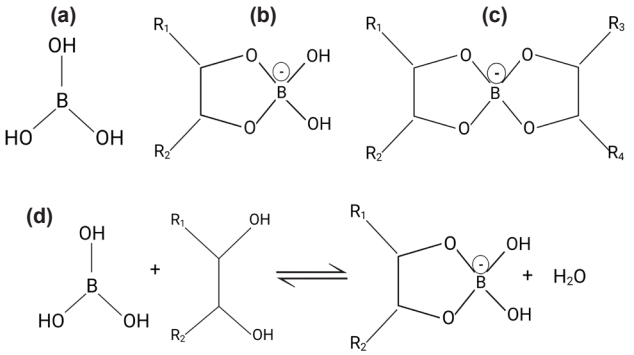

Figure 4. BA a). anionic monoesters b). and anionic diesters with sugars containing cis-hydroxy groups c). d). Esterification reaction of BA with sugars containing cis-hydroxy groups (R=H, alkyl, aryl, acyl, created with BioRender.com).

Amongst, calcium fructoborate (CaFB) is naturally absorbed by animals, and it is less toxic than almost all B compounds. CaFB has shown to be effective in preventing and treating several diseases, including osteoporosis and osteoarthritis. Besides, it also exerted anti-cancer effects through different mechanisms [27]. Another important group is B-containing antibiotics, which include boromycin, tartolons, borophycin, etc. which have been studied for their antibacterial, antifungal, and anti-cancer properties [28].

Boromycin may also cause selective cell cycle arrest of different cancer cell types during the G2 phase and increase the susceptibility of cells to a variety of anti-cancer drugs [29]. In addition, boranes showed important therapeutic effects on many diseases. The most important borane compounds are amine-carboxyboranes, amine-cyanoboranes, carboranes, trimethyl cyanoborane (TACB), and amine-boranes. Studies revealed that amine-carboxyboranes were cytotoxic and exhibited antineoplastic properties against leukemias, lymphomas, sarcomas, and carcinomas [30]. Amine-boranes also showed cytotoxic activities on a variety of cancer cells, and they are potential boron neutron capture therapy (BNCT) agents. TACB was also suggested as a therapeutic agent for its inhibitory function on DNA and protein synthesis [31]. Due to their distinctive characteristics and anti-cancer effects, boronic acids and esters have been researched for decades as potential cancer treatments. Boronic acids are more selective for cancer cells and more stable than BA, which make them attractive compounds for clinical use. Recent developments in BNCT and targeted drug delivery strategies based on boronic acids showed important results for the treatment of cancer. Phenylboronic acid (PBA) and diphenylboronic esters (DPBE), which function as serine protease inhibitors, are the most effective boronic acids and derivatives [30,31]. Another synthetic group, borinic acids contain borinates and oxoboranes which function as enzyme inhibitors and regulators of membrane ion channels. Amongst, BODIPYs are one of the most promising agents for development of therapeutic and diagnostic strategies. BODIPYs are B-based fluorophores probes that can be used to identify specific molecules. BODIPY derivatives can also be used as diagnostic or prognostic tools to identify biomarkers of infections, diabetes, chronic nervous diseases, cancer, and metabolic disorders [31]. Over the decades, important developments in cancer treatment based on B-containing compounds showed very promising results for future clinical applications. Recent studies showed that B-containing compounds can be used for chemotherapy, radiation therapy, targeted drug delivery, bio-imaging tools, and other therapeutic and diagnostic strategies. In this review article, we are mainly interested in the anti-cancer effects of BA, BO, CaFB, PBA, boron nitride (BN), and BODIPYs which are the most investigated and promising B compounds. Furthermore, we will also discuss their potential use in novel drug delivery systems as well as combinational cancer treatment and diagnostic strategies.

2.1. Borates and Their Anti-cancer Effects

As discussed in the previous section, borates are very important B-containing therapeutics. Among these compounds, BO, and BA (Figure 5) tests for cancer treatment are a very common strategy.

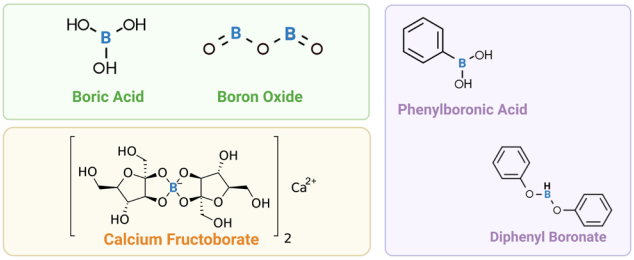

Figure 5. Structures of the most studied B compounds for their chemopreventive and chemotherapeutic potencies (Created with BioRender.com).

Due to its structural characteristics, like carbon, BA can serve as a competitive inhibitor for a variety of carbon-containing molecules. Due to this quality, BA is an excellent candidate to work as a pharmaceutical agent [16,29]. Therefore, chemopreventive and chemotherapeutic effects of BA have been investigated on different types of cancer cells. The proliferation of prostate cancer cells was inhibited in a concentration-dependent manner [32,33], as well as the non-tumorigenic prostate cell lines, though the required concentrations to kill DU-145 and LNCaP prostate cancer cells were lower respectively [32]. BA induced apoptosis, upregulated the pro-apoptotic genes, and downregulated the anti-apoptotic ones in ovarian cancer cells [34]. Cell cycle arrest-related genes were unaffected by BA application. Additionally, the expression of miR-21, miR-200a, miR-130a, and miR-224 was downregulated in the BA-treated groups. Findings suggested that the anti-tumor activity of BA may be related to altered miRNA levels as these miRNAs are indicators of poor prognosis of ovarian cancer. Interestingly, the oxidative stress index was higher in the BA-treated groups, which also claims partition of oxidative stress in cell death [34]. Hepatocellular carcinoma cells had also showed decreased cell viability, survival, colony formation capacity, migration, and spheroid growth due to BA treatment. Furthermore, reduction of the AKT phosphorylation was observed suggesting BA-induced downregulation of the AKT survival pathway [35]. Cebeci and colleagues (2022) demonstrated the anti-cancer properties of borates against a small-cell lung cancer model, DMS-114, for the first time. The findings demonstrated that BA, NaB, and SPT caused apoptosis by upregulating pro-apoptotic genes and downregulating anti-apoptotic ones. Additionally, cell cycle arrest in the G2/M and sub-G1 stages was brought on by BA and NaB. Conclusively, three B-containing compounds studied showed promising results for their effects on small-cell lung cancer cells in comparison to their effects on healthy cells [36]. In another study, 24 mM BA caused a senescence-like profile and DNA breaks on hepatocellular carcinoma HepG2 cells [37]. BA also inhibited growth, caused cell cycle arrest, and promoted apoptosis in medullary thyroid carcinoma cells, and therefore, may be employed as a potential treatment agent for medullary thyroid carcinoma [38].

Tütüncü and associates (2022) examined the impact of BA and DPD on cell survival and apoptosis induction using metastatic prostate cancer cells; DU-145 and PC-3. In both cell lines, DPD and BA therapy lowered cell invasion and decreased cell proliferation. Additionally, BA and DPD-induced the caspase-3-dependent apoptosis. Results indicated that the anti-cancer effects of DPD on the prostate cancer cells were superior over BA [39]. To test the possible effects of BA as a PSA inhibitor and chemopreventive supplement, Gallardo-Williams and coworkers (2004) used androgen-dependent human LNCaP cells to obtain mice xenografts that produce PSA after transplantation [40,41]. Although LNCaP cells developed tumors in nude mice supplemented with BA supplementation, treatment with low and intermediate doses of BA had impacts on growth rate and size of the tumors [42]. Korkmaz and colleagues (2014) showed that DPD therapy caused DU-145 prostate cancer cells to undergo apoptosis by decreasing the activity of the human telomerase reverse transcriptase (hTERT) enzyme at a rate of 38%. In DPD-exposed cells, the regular arrangement of actin filaments was also disturbed, causing change in cell shapes. Overall, findings suggested that DPD may cause cytotoxicity by reducing telomerase and interfering with the dynamic characteristics of actin polymerization [43]. Another compound from the borate family is BO. Albuz and coworkers (2019) studied the effects of BO on colorectal cancer cells for the first time [44]. BO showed strong cytotoxicity on both healthy mouse L929 and DLD-1 colorectal adenocarcinoma cell lines, with no genotoxicity. Kirlangic and coworkers (2022) investigated the cytotoxicity and apoptotic effects of borax on the DLD-1 colorectal adenocarcinoma cell line in combination with 5-FU. The viability of DLD-1 cells significantly decreased by the combined therapy, and the anti-proliferative effects of BA or 5-FU alone or in combination were by induction of apoptosis [45]. Simsek and coworkers (2019) tested the anti-carcinogenic, anti-angiogenic, and anti-oxidant effects of BA, BP, and SPD on the breast adenocarcinoma MDA-MB-231 cells. Results showed that BP and SPD inhibit the angiogenic potential of cells via the vascular endothelial growth factor (VEGF) pathway. This study was also the first one to report the relationship of BP and SPD application with VEGF and inducible nitric oxide synthase (iNOS) expression in a breast cancer cell line [46].

Overall, borates are amongst the most investigated B-containing compounds for their cancer treatment potencies. Single borates and borates in combination with chemotherapeutics have been mostly studied on colon, breast, lung, prostate, and hepatocellular carcinomas. Different types of borates have anti-cancer effects on various cancer types through complex cellular pathways and mechanisms which involve VEGF release, PI3K/Akt pathway, hTERT activity, DNA damage, induction of apoptosis, etc.

2.2. SBEs and Their Anti-cancer Effects

CaFB (Figure 5) is one of the most intriguing SBE compounds due to its properties (Section 2). Tepedelen and coworkers (2017) first investigated the link between CaFB and VEGF expression on MDA-MB-231 cells. According to cytotoxicity tests, CaFB reduced cell viability. Additionally, there was a rise in the levels of phosphorylated ATM and p53 levels, and, but there is no noticeable alteration in ATM or p53 expression. Results also indicated a decrease in VEGF and an increase in caspase-3 and 9 levels [47]. Another study described the time-course biodistribution of liposome-encapsulated CaFB in the BALB/c mice breast cancer model for the first time [48]. Accordingly, a concentration of 35 mg 10B/g enhanced the accumulation of the drug within a 24-hour incubation period following the drug introduction. The findings can be used as a reference point for biologic distribution, and accumulation of the designed drug-containing B for the better understanding of B targeting linked to the drugs. Kisacam and associates (2020) sought to shed light on the preventive effects of CaFB by studying effect of CaFB on the PI3K/Akt pathway in a DMBA (7,12-Dimethylbenz(a)anthracene)-TPA (12-O-tetradecanoylphorbol13-acetate) induced *in vivo* skin cancer model. 92 female ALB/c mice were separated into 6 experimental groups. HRAS, HIF1, Akt, and PTEN protein and mRNA levels increased significantly after topical DMBA and TPA treatments with more TUNEL-positive cells in the DMBA-TPA group. CaFB decreased the mRNA and protein levels of HRAS and HIF1[49]. In addition, the anti-inflammatory and anti-oxidant effects of CaFB were also studied in this model. In contrast to control groups, the DMBA-TPA group had higher levels of GAPDH activity, PGD, GSH, IL-6, IL-1, and TNF-α, but malondialdehyde levels were lower. Depending on the distribution time, the CaFB application reduced the DMBA-TPA-induced effects. Conclusively, CaFB was suggested as a potential chemopreventive against skin cancer [50]. In another study, they have also shown that CaFB affects Akt and PTEN levels and apoptosis in the same skin cancer model [51]. IC_{50} of CaFB for colon cancer cells was reported to be 10 mM, at which apoptosis and autophagy were induced. CaFB modulated the P13K/Akt/p70S6k pathway, elevated Bax, and decreased Bcl-2 levels at 10 and 20 mM. CaFB has the potential to inhibit carcinogenesis, particularly for the skin.

2.3. Boronic Acids/Esters and Their Anti-cancer Effects

As we previously discussed in section 2 PBA and DPBE (Figure 5) are the most effective derivatives of boronic acids, which show selective inhibitory effects on the migration and viability of various types of cancer cells. Therefore, they are considered one of the most important B compounds for the treatment of various cancer types. The inhibitory effects of PBA and BA on the migration of breast and prostate cancer cells were investigated [13]. One mM BA and PBA was administered to DU-145 prostate cancer cells for 8 days. Cell migration decreased after 24-hour treatment with BA or PBA. PBA, on the other hand, had a long-term effect that reduced cell viability whereas exerted short-term anti-migratory effect. In a different experiment, the use of BA or PBA altered the actin distribution of DU-145 cells that were grown on fibronectin, reduced the activity of spreading proteins including the Rho family GTPases and their targets, and caused growth arrest [14]. Another study examined the anti-cancer effects of PBA against mouse dermal fibroblasts L929, hamster lung fibroblast V79, mouse mammary adenocarcinoma 4T1, and mouse squamous cell carcinoma SCC VII cell lines [52]. All cancer and non-cancer cell lines were affected in a concentration-dependent manner. After tumor transplantation into mice, PBA was found to suppress the proliferation of tumor cell lines in comparison to the control. In conclusion, PBA is a better candidate as a novel anti-cancer agent since it is a more effective and specific inhibitor than BA. The use of PBA in diagnostic biosensors and as a drug carrier will be covered in section 3.3.

3. Boron Carriers and Their Applications for Cancer Treatment

Non-specificity, quick clearance, development of drug resistance, toxicity, and damage to healthy cells, side effects, and immune system failures are the major drawbacks of conventional chemotherapy [53]. Innovative targeted drug delivery systems can increase therapeutic and diagnostic efficacy and minimize negative side effects for cancer treatment. Targeted and controlled drug delivery methods are one of the most significant and appealing subjects of nanotechnology to fight against cancer. Main goal in a controlled delivery system is to maintain the medicine at optimum therapeutic levels that are below toxic thresholds while increasing the effectiveness through continuous drug release. The goal of controlled drug delivery systems is to give the drug or chemotherapy at a specific location at a set pace for a longer period of time [54]. For the delivery of chemotherapeutics, many polymeric delivery systems have been developed, such as hydrogels, liposomes (LP), dendrimers, micelles, and nanoparticles (NPs) (both inorganic and polymeric) (Figure 6) [55].

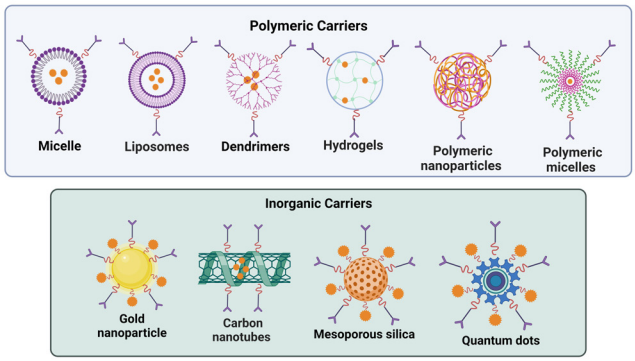

Figure 6. Nano-sized drug delivery systems for cancer treatment (Created with BioRender.com).

Furthermore, these nanocarriers have also been used in different therapeutic strategies, including both photodynamic and photothermal therapies (PDT and PTT), chemotherapy, radiation, hormone, gene, and immunotherapy therapy (Figure 7). When treating cancer, combined chemotherapy is clearly superior to single-agent therapy due to its increased efficacy and fewer restrictions brought on by the emergence of multidrug resistance (MDR) [54]. Combining diverse therapeutic mechanisms in one carrier improves anti-cancer benefits, and using two or more anti-cancer drugs at once maximizes their therapeutic effects [56]. BNCT and advanced B-compounds for drug delivery strategies have taken attention and B-containing compounds and treatment strategies were combined with traditional cancer therapy and chemotherapeutic drugs [57].

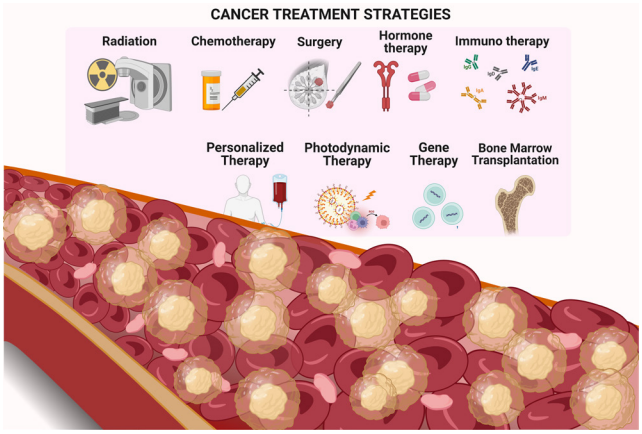

Figure 7. Different strategies for cancer treatment (Created with BioRender.com).

The cutting-edge advancements in pharmaceutical nanotechnology, particularly in BNCT, have found crucial uses for B-based nanomaterials. Both boron nitride nanotubes (BNNT) and hexagonal boron nitrides (h-BN) are desirable nanostructures because they have an enormous surface area, outstanding mechanical properties, and necessary biocompatibility [58]. In addition, PBA has been frequently introduced to drug nanocarriers [59]. So, in this part of the review, the focus is BNCT with emphasis on the different B-containing compounds as drug carriers, and PBA, h-BN, and BODIPY application areas in terms of treatment and diagnosis of cancer.

3.1. BNCT for Cancer Treatment

Since the last decades, BNCT has been used to treat cancer when chemotherapy and radiation therapy have been ineffective. A two-part radiotherapeutic method BNCT employs B neutrons to cure cancer. When the stable isotope B-10 (^{10}B) is exposed to low-energy thermal neutrons (0.025 eV), which turn out thermalized as they diffuse the tissue, nuclear capture, and fission processes happen. This results in the production of recoiling lithium-7 (^{7}Li) nuclei and high-linear energy transfer (LET) alpha (α) particles (^{4}He) [60] (Figure 8).

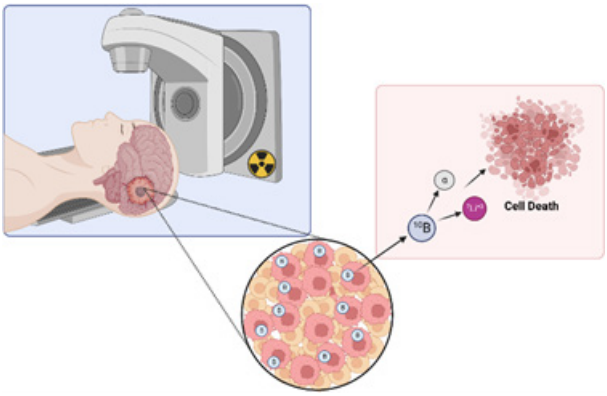

Figure 8. Illustration of the BNCT principle in graphical form (Created with BioRender.com).

A deadly ^{10}B (n, α) ^{7}Li capture reaction must be able to occur for the tumor cells to receive approximately ~20 μg/g of ^{10}B per weight of the tumor and be able to absorb enough neutrons. Particles can only injure cells that contain B because of their incredibly short travel distances (5-9 m), while they save nearby healthy cells. The majority of clinical attention in BNCT has been interested in patients with high-grade gliomas, individuals with repetitive head and neck malignancies who have not responded to traditional therapies, and a far smaller population of individuals suffering from cutaneous or extracutaneous melanomas. The most crucial criteria for BNCT delivery agents are low intrinsic toxicity, high tumor absorption (~20-50 μm ^{10}B), swift removal from the bloodstream and healthy tissue, and constant in tumor for at least a few hours during neutron radiation exposure. For this, new formulations with significant B contents are generated.

3.1.1. Boron delivery agents for BNCT

The proper number of ^{10}B atoms needs to be added to neoplastic cells that can survive an enough amount of neutron radiation to successfully complete the BNCT reaction. More than 1000 individuals have received BNCT treatment using two different types of B-containing compounds i.e. boronophenylalanine (BPA) and sodium borocaptate (BSH) [61]. New B delivery agents have emerged over the past 20 years, along with new methods of chemical synthesis and enhanced biological and biochemical understanding of B delivery. These agents are divided into three generations [62-65] (Figure 9). In this part of the review, we will be focusing on the 3-generation B delivery agents for BNCT with *in vitro* and *in vivo* applications.

3.1.1.1. First and second-generation BNCT compounds

The first-generation B-containing compounds used for BNCT were not developed for this use but were chosen since they were readily available, had well-known pharmacology, and had non-toxic properties. BA and its derivatives were the earliest B agents used in BNCT in the 1950s and early 1960s. However, they lacked tumor retention and had a low tumor/tissue

therapeutic index since they were non-selective drugs [62]. Second-generation agents BSH and BPA were used in the 1960s, and they are less toxic, stay inside the tumor longer, and show supra-unitary therapeutic indices for the brain, blood, and tumor. BSH is the most promising one among the B clusters due to its superior and stable B amounts in tumors with low systemic toxicity. There is a lot of interest in the use of BPA for the treatment of malignant melanoma. BPA can preferentially be absorbed by malignant melanoma cells due to its chemical structural similarity with tyrosine, which is necessary for melanogenesis. However, neither BSH nor BPA meets the requirements of effective B delivery agents [64-67]. The difficulty in accurately determining the optimum B concentration in a patient's tumor due to patient-to-patient variability is one of the most important drawbacks of BNCT. This issue might be solved by double-modality agents used in positron emission tomography (PET) guiding BNCT, which provide real-time tracking of B accumulation in patients' tumors. The radiolabeled derivative of BPA called 4-borono-2-^{18}F-flurophenylalanine (^{18}F-BPA) is a dual-modality BNCT agent. Numerous other tumor forms, including malignant melanomas, malignant gliomas, and various head and neck cancers, have also been treated with ^{18}F-BPA [66].

3.1.1.2. Third-generation BNCT compounds

To eliminate the drawbacks of first and second-generation BNCT compounds, a wide spectrum of low- to high-molecular-weight B delivery agents targeting tumor cells have been developed in recent years. Third-generation compounds that contain one or multiple polyhedral anions of borane or carboranes have been investigated. This group includes stable B delivery molecules with low and high molecular weights covalently bound to tumor-targeting moieties [68]. The three subgroups of low and high-molecular-weight substances include B-containing molecules with small sizes, B-compound conjugates, and B-delivery NPs.

3.1.1.2.1. Low molecular weight agents

This section will concentrate on low molecular weight substances that comprise boronated amino acids, peptides, nucleosides, derivatives of boronated porphyrins, and DNA-binding compounds.

3.1.1.2.1.1. Boronated natural and unnatural amino acids for BNCT

During the past 60 years, different amino acid-based B carriers have been synthesized. However, only a few of them have been investigated based on their biological properties. Among these boronated amino acids, the most-studied compound is BPA [69,70]. There are boronated amino acids both non-natural and natural. Naturally amino acids that have been examined include cysteine, tyrosine, aspartic acid, alanine, methionine, and glycine (Figure 10) [71]. The advantage is that, based on their weight, they contain more B than BPA, which enables them to deliver more intratumoral B without increased toxicity. The boronated derivatives of 1-aminocyclobutane-1-carboxylic acid (ABCHC) (Figure 10 a,b) and 1-amino-3-boron cyclopentane carboxylic acid (ABCPC) (Figure 10 c,d) are two examples of these substances [72]. Most amino acids used in BNCT have been documented for the precise treatment of malignant brain tumors [73]. As a theragnostic agent for both B administration and cancer diagnostics, Li and coworkers (2019) [74] reported the metabolically sustainable B-derived tyrosine (fluoroboronotyrosine, FBY) (Figure 10 e),

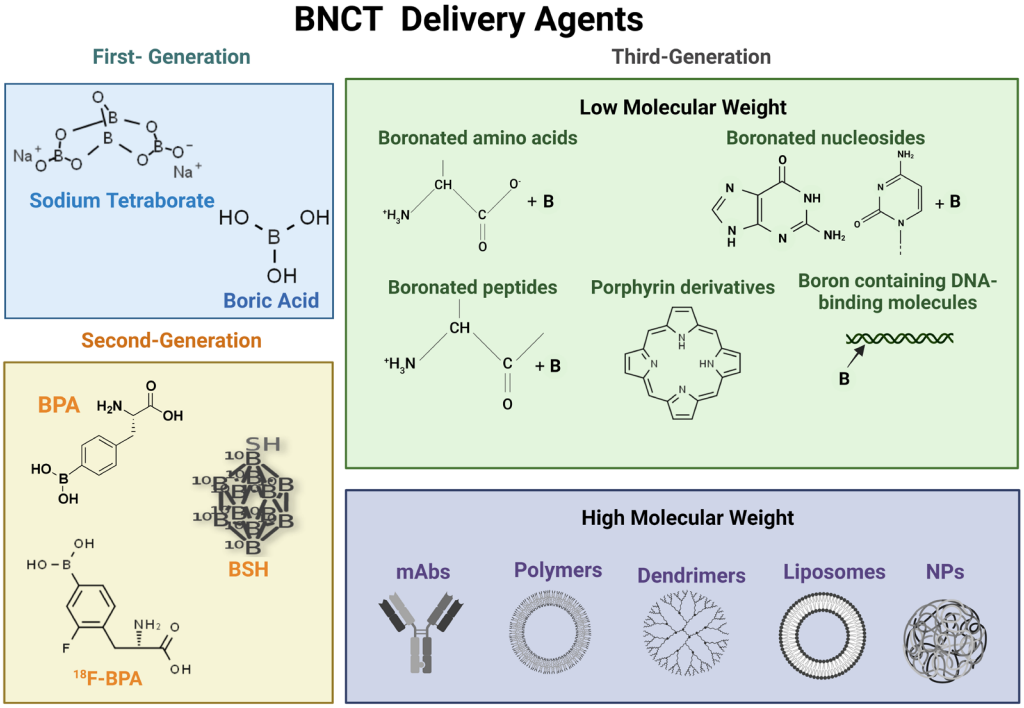

Figure 9. 3 generations of BNCT delivery agents (Created with BioRender.com).

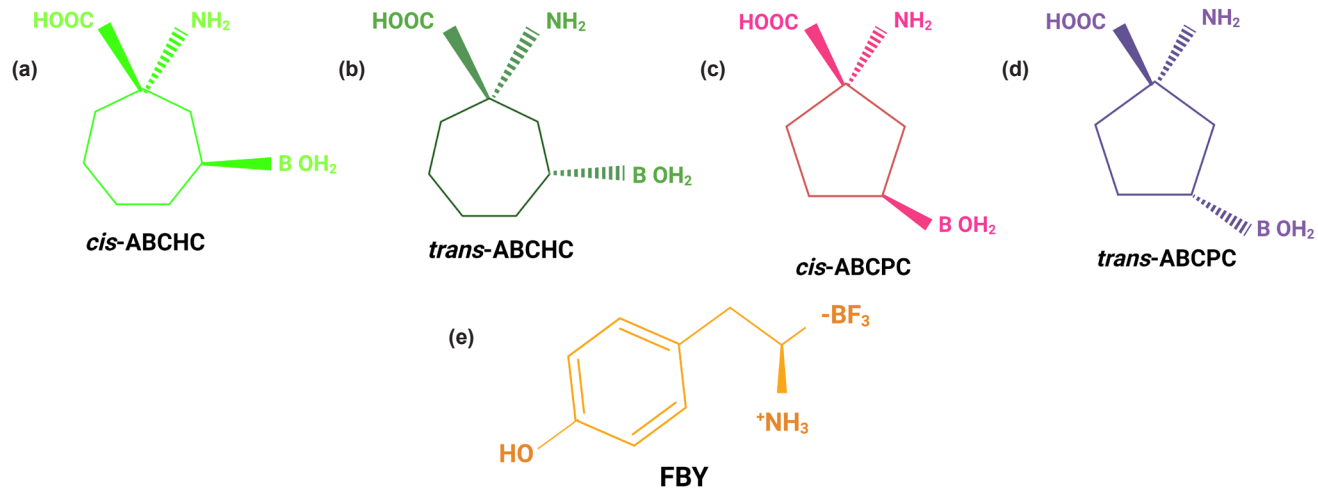

Figure 10. Examples of boronated amino acids. a). *cis*-ABCHC, b). *trans*-ABCHC, c). *cis*-ABCPC, d). *trans*-ABCPC, and e). FBY (Created with BioRender.com).

which paved the way for PET imaging-guided BNCT. The produced FBY was shown to have a high degree of resemblance to natural tyrosine. Additionally, the administration of an effective dose of FBY combined with an (^{18}F) FBY tracer revealed significant accumulation in the tumor of B16-F10 melanoma cells derived mouse model and minimal uptake in healthy tissue. The prospect of detecting B concentration by a noninvasive technology is suggested by the link between the PET images and B biodistribution. Thermal neutron irradiation was performed on B16-F10 tumor-bearing mice that received FBY injections, and the mice had longer median lives without experiencing any systemic damage. The use of FBY in clinical trials and as an effective diagnostic agent for imaging-guided BNCT offers a practical means of determining the local B concentration using PET imaging. 4-Borono-L-phenylalanine (4-BPA) was launched as Borofalan (Steboronine®) in Japan in May 2020 for people suffering from severe or localized chronic unreported head and neck cancer [75] following the publication of encouraging findings from two clinical trials. Even though 4-BPA is the only BNCT agent that is commercially available, there are several problems with it because of how poorly it dissolves in water. This research produced 3-borono-L-phenylalanine (3-BPA), an isomer of 4-BPA that is considerably more soluble in water. In an experiment, Kondo and coworkers (2022) administered 3-BPA without the solubilizer fructose, which is contained in 4-BPA formulations and has adverse consequences due to its great water solubility. Studies utilizing 3-BPA-Fru and 4-BPA-Fru demonstrated identical levels of B accumulation both *in vitro* and *in vivo*. Additionally, 3-BPA had a similar distribution within cells to 3-BPA-Fru, which made it possible to get rid of the solubilizer. 3-BPA becomes a promising agent for BCNT because it targets tumor tissue as effectively as 4-BPA and has a higher level of water solubility [76].

3.1.1.2.1.2. Boronated peptides for BNCT

Due to their significant capacity to bind receptors or transporters that are overproduced in tumor cells with excellent sensitivity and selectivity, peptides have garnered a lot of interest as targeted B delivery agents [61]. Peptides both linear and cyclic containing B administered to BSH have been investigated since they exhibit low toxicity, simple to synthesize, non-immunogenic, and strong tissue penetration properties [86]. Peptide ligands targeting overexpressed receptors on tumor cells, such as the somatostatin receptors, the VEGRF [78], and the endothelial growth factor (EGFR) [79-81] are of special interest. Isocyanato-closo-dodecaborate was used to functionalize poly ($_{DL}$-lysine) and bind it to monoclonal antibodies (mAbs) [80]. Polymeric linker minimized the reduction of immunoreactivity of mAb when the B clusters were present. Because they maintain 40 to 90% of immunogenicity and contain over 1000 B atoms per macromolecule, the bioconjugates are able to distribute BNCT. To attack the excessively expressed human Y1 (hY1) receptor seen in cancerous cells, a peptide molecule was created. The deoxygalactopyranosylated carborane building blocks used to create this peptide were functionalized by two lysines. The saccharide moieties made the peptides appropriately soluble in water and permitted the inclusion of up to 80 B atoms. Low *in vitro* toxicity on MCF-7 cells and high receptor responsiveness with hY receptor subgroups, in (d) rticular with hY1, were two characteristics of the bioconjugate systems [82]. A prospective diagnostic and therapeutic target, peptide transporter 1 (PepT1) is an oligopeptide transporter that is overexpressed in a variety of malignancies [83,84]. Miyabe and coworkers (2019) discovered that a PepT1-mediated mechanism was responsible for the uptake of dipeptides of BPA and tyrosine to AsPC-1 human pancreatic cancer cells [85] which paved the way to administer B to tumor cells via PepT1.

3.1.1.2.1.3. Boronated nucleosides for BNCT

Other substances that have been proposed as BNCT compounds include pyrimidine compounds thymidines, purines, nucleosides, and nucleotides.

As an illustration, the thymidine kinase-1 (TK1)-expressing cancer cells are preferentially targeted by 3-carboranyl thymidine analogs (3CTAs) (Figure 11 a,b) [86-88]. These substances may increase the caption and intratumoral retention of B through nucleotide synthesis. Since the incorporation of these agents into DNA takes place in the S phase and the mechanism of action is cell cycle-dependent, the effects may be enhanced by combining with a cell cycle-independent agent [86]. For instance, *in vivo*, biodistribution, and BNCT tests were performed on rats with brain tumors after *in vitro* experiments of the thymidine analog N5-2OH showed specific tumor absorption, a good rate of phosphorylation, and minimal toxicity (Figure 11 c) [89]. Convection-enhanced delivery (CED) with N5-2OH showed success in delivering efficacious dosages of B to tumors with incredibly high tumor: blood and tumor: brain percentages in rats bearing intracerebral RG2 gliomas without producing any concomitant toxicity. The median survival time (MST) in the tumor-bearing rats significantly increased following BNCT. Studies utilizing the nearly same F98 rat glioma, which also showed elevated TK1, suggest that N5-2OH may not be as a successful B delivery agent as originally believed. In these tests, there was just a very slight rise in MS [87].

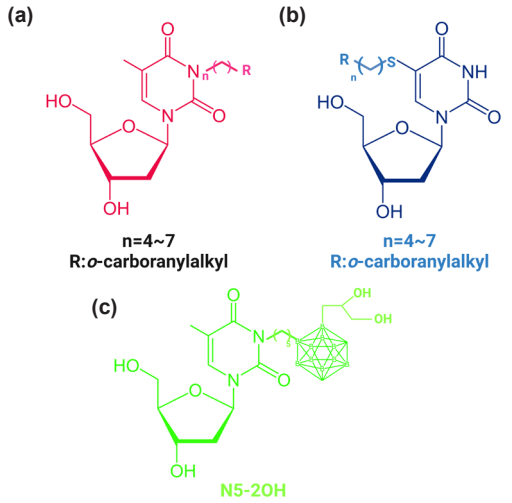

Figure 11. BExamples of boronated nucleosides as BNCT agents. a) and b). 3-carboranyl thymidine analogs, c). N5-2OH (Created with BioRender.com)

3.1.1.2.1.4. Boron-containing porphyrin derivatives for BNCT

B-containing porphyrin derivatives have been extensively studied because of their minimal toxicity and natural affinity for tumors. Several B clusters might be joined to a single porphyrin skeleton to give a lot of B. Due to the development of porphyrin-DNA conjugates that cause significant tumor uptake and protracted retention of the chemical substrates, porphyrin derivatives as B carriers have come under increased scrutiny. Research on selective B delivery of porphyrin derivatives *in vitro* and *in vivo* will be covered in this section. Since 1992, Miura and colleagues have concentrated on lipophilic porphyrins that include the B atom and created a small number of metal-complexed porphyrins (Figure 12a) [90-93].

The most extensively *in vitro* and *in vivo* studied porphyrin derivatives have been Cu (II) and Zn (II) complexed porphyrins, which are CuTCPH and ZnTCPH. After receiving injections of ZnTCPH or CuTCPH, the macro distributions of B in various organs were comparable with EMT-6-bearing animals, with the liver absorbing a greater quantity of B than the cancerous tissue. The ZnTCPH-injected tumor-bearing animals also displayed fluorescence in the spleen, liver, and tumors. Additionally, CuTCPH or ZnTCPBr probes are applied to ^{67}Cu-based single-photon emission

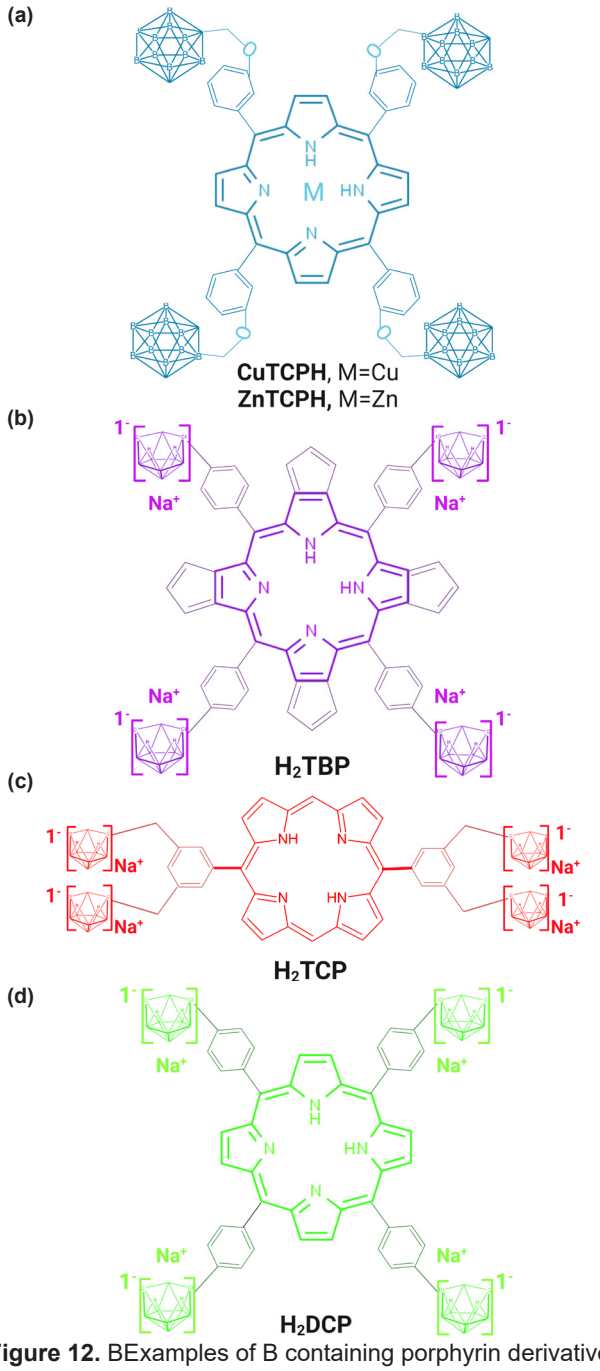

Figure 12. BExamples of B containing porphyrin derivatives as BNCT agent. a). metal-complexed porphyrins, b). H2TBP, c). H2TCP, d). H2DCP (Created with BioRender.com)

computed tomography (SPECT) or ^{64}Cu-based PET for imaging tumors [94]. Vicente and coworkers (2018) focused on the evaluation, characterization, synthesis, and biological assessment of porphyrin analogs for BNCT, such as anionic carbonylated porphyrins, porphyrin-labeled carbonyl phosphate diesters, cobaltacarborane-porphyrin-HIV1-Tat 48-60 conjugate, etc. [95]. The derivatives and conjugates were successful in penetrating T98G cells and were visible under fluorescence microscopy, but they had limited blood-brain barrier (BBB) solubility *in vitro*, which may be related to their elevated hydrophilic properties, high molecular weight, and propensity to aggregate [96]. Carborane was included in BODIPY to further increase permeability. The BBB permeability was increased throughout human hCMEC/D3 brain endothelial cell monolayers, with higher cellular uptake and B content, less cytotoxicity, and minimum cell damage [97,98].

The effectiveness of carboranyl porphyrins as B delivery agents for BNCT was first demonstrated by Kawabata and coworkers (2011) [99] in brain tumor-bearing rats. After assessing the photosensitizing potential and positioning of water-soluble H2TBP (Figure 12b), H2TCP (Figure 12c), and H2DCP (Figure 12d), the researchers determined the biodistribution and effectiveness of H2TBP and H2TCP as B delivery systems for BNCT in F98 glioma-bearing rats. Rats given an intracerebral injection with either CED or ALZET osmotic pump infusion experienced increased tumor B concentrations that persisted for 24 hours. Low B amounts were found in the healthy brain. Histopathologic analysis of the brains of BNCT-treated rats revealed enormous amounts of extracellular aggregation and porphyrin-containing macrophages, suggesting limited tumor cellular absorption and intracellular localization.

Viaggi and colleagues (2004) have investigated the effects of the B-containing tetrakis-carborane carboxylate ester of 2,4-bis-(a b-hydroxyethyl)-deutero-porphyrin IX (BOPP) (Figure 13a) on animal models of different malignancies [100,101]. In the Phase I clinical trial of PDT for high-grade early-stage gliomas, they assessed the appropriate dosage, toxic effects, and pharmacokinetics of BOPP and discovered moderate effects [102]. These are used as a point of reference for the BOPP application in BNCT. When BOPP and BPA were administered together, thyroid tumors exhibited higher B uptake. In their study of BOPP's toxicity, biodistribution, and CED. Ozawa and coworkers (2005) found that switching from intravenous injection to CED, BOPP delivery dramatically increased the B content in 9L tumor-bearing rats [103]. Additionally, Ozawa and the research group (2004) synthesized a series of tetraphenyl porphyrins (TABP, TEBP, and TOBP) (Figure 13b) with polyhedral borane anions, and they assessed the biological characteristics of the compounds *in vivo* [104]. Studies on the production of porphyrin analogs containing B and their application in BNCT have been carried out over the years. Patients with various malignancies may benefit from using porphyrin derivatives as BNCT agents.

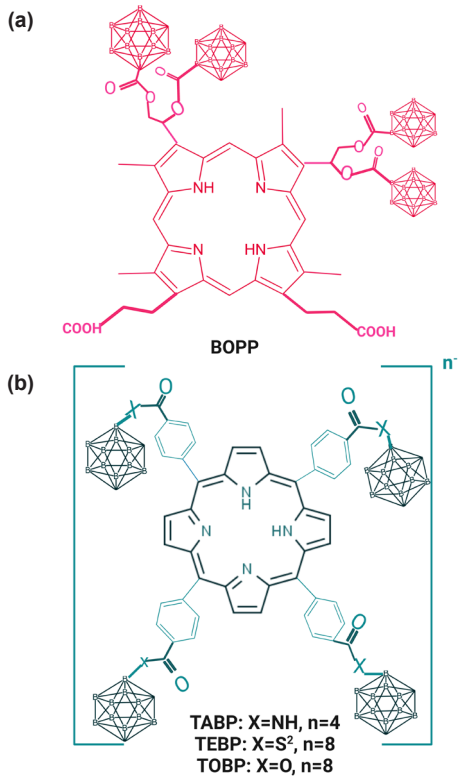

Figure 13. BExamples of B containing porphyrin derivatives as BNCT agent. a). BOPP, b). Tetraphenyl porphyrin derivatives (Created with BioRender.com)

3.1.1.2.1.5. Boron-containing DNA binding compounds for BNCT

Alkylating compounds, minor groove binding agents, platinum complexes, DNA intercalators, polyamines, and derivatives of aziridines, acridines, phenanthridines, and carbonyl polyamines are examples of B-containing-DNA binding substances. Because of their affinity for binding to the DNA of healthy cells and/or numerous cationic charges, some of these chemicals exhibit minimal tumor selectivity and substantial toxicity. Peptides, polyamines, and antisense oligonucleotides have also been studied as alternative agents to B delivery. Nicotinamides, which also have radio-sensitizing properties, have been studied either in combination with a B delivery agent or administered prior to the agent. B-complexed sugars, including analogs of glucose, maltose, ribose, mannose, and galactose have been studied, and the results showed increased water solubility. This group of compounds often has low tumor uptake but low tumor toxic effects, in part because of their hydrophilic properties and quick tissue elimination. They can be connected to other compounds, such as steroid hormone antagonists, that have an affinity for certain [105,106].

3.1.1.2.2. High molecular weight agents

Due to their exceptional characteristics, advanced

nanomaterials have drawn a lot of interest as potential new B delivery systems. The most studied high molecular weight boronated agents include mAbs, polymeric systems, NPs, dendrimers, and LPs. This class of agents has the most significant outcomes due to their targeting and selective binding properties. High molecular weight agents are studied *in vivo* and *in vitro* for various cancer types.

3.1.1.2.2.1. mAbs for BNCT

High molecular weight B delivery methods based on mAbs have been intensively studied based on mAb's ability to detect tumor-associated epitopes. Barth and coworkers have used EGFR mAbs for BNCT [79-81,107]. As B delivery agents, tEGF bioconjugates that exhibit sensitivity for tumors overexpressing EGFR can be employed. Highly boronated dendrimers with five dendritic generations to bind EGFR targeting mAbs cetuximab (Erbitux™) [81], EGFRv targeting mAbs L8A4 [80] or EGF [107] itself have been employed as heterobifunctional reagents. These bioconjugates led to a two- to three-fold enhancement of MST in comparison to controls when combined with intravenous BPA injection. Rats carrying receptor-positive F98 glioma-bearing animals [99] received these bioconjugates intracerebrally through CED. Additionally, according to Sun and colleagues (2016), a highly boronated poly (amido amine) (PAMAM) dendrimer might be delivered to specifically target stem cells both *in vitro* and *in vivo* using a mAb against the widely expressed stem cell marker CD133 on glioma cells. BSH was used to fill the gaps in the PAMAM dendrimer structure (Figure 14).

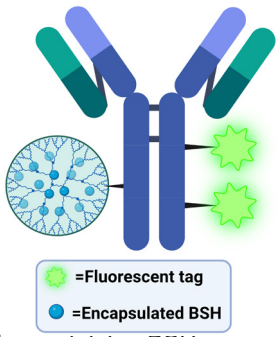

Figure 14. BmAbs containing BSH encapsulated within the PAMAM dendrimer (Created with BioRender.com)

Glioma stem cells are resilient cells that avoid cell death induced by traditional radiation and chemotherapy and promote tumor development. Studies showed that the CD133 negative SU2 cells received more than 10^9 B atoms which are above the B concentration threshold defined for BNCT. Survival was significantly prolonged when BNCT was given to BALB/c mice with intracerebral CD133(+) SU2 cells as opposed to CD133(-) SU2 cells. When the B-containing bioconjugate and free BSH were given before neutron irradiation, the MST was prolonged. Compared to animals with intracerebral CD133(-) SU2 glioma cells, BALB/c mice with these cells had a considerably longer lifespan [108]. These results suggest that more investigation on bioconjugates is required to evaluate their potential. Overall, mAbs have been used extensively for BNCT treatment. Researchers used combination therapy strategies with chemotherapeutic agents and radiation and combined the agents that are already used for BNCT such as BSH. When B-containing drugs were combined with mAbs, they showed effective results for cancer treatment as they are targeting the factors that are overexpressed in tumors.

3.1.1.2.2.2. Polymeric systems for BNCT

Due to their high B content, most polymeric systems use carborane derivatives as B compounds. Polymers are an alternative delivery system for B compounds, and they may improve their solubility and pharmaceutical kinetics by increasing their half-lives in the bloodstream and tumor accumulation. Over the past 20 years, different strategies to generate B-based polymeric systems such as B-conjugation, B-encapsulation, or conjugation with specific targeting or labeling moieties (Figure 15) have been studied.

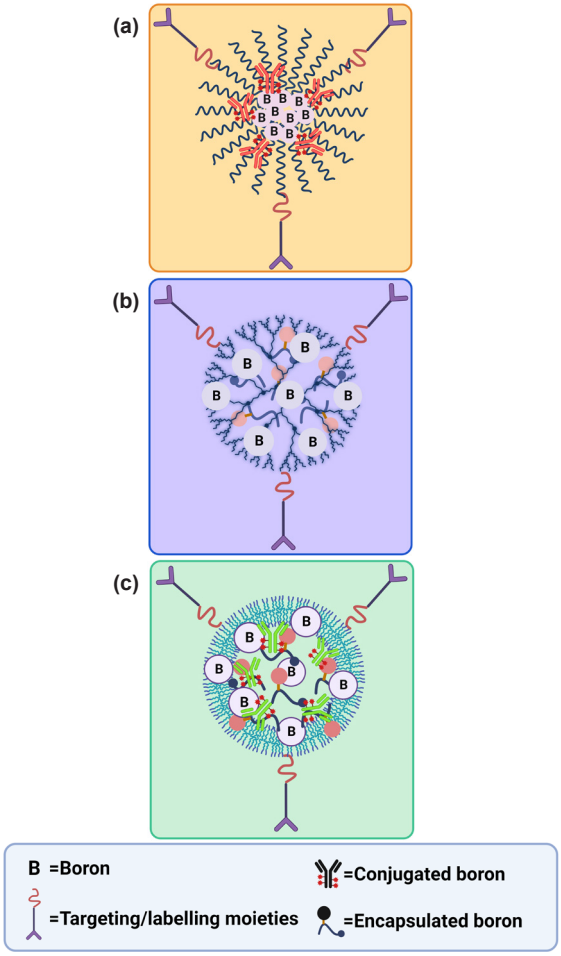

Figure 15. BA list of the various B-based polymeric systems, including those that are conjugated or encapsulated, along with any potential conjugations to targeting or marking moieties. a). Micelles derived from polymers or polymers that have been dendronized; b). Dendrimers; and c). LPs (Created with BioRender.com)

Amphiphilic carborane-conjugated polycarbonate micelles were synthesized using a carborane cyclic carbonate monomer and a poly (ethylene glycol) (PEG) macroinitiator. Polymeric micelles with varied sizes were produced. Even though the larger ones showed more liver uptake, tumor cells were more probable to be absorbed by the smaller ones. The NPs were not cytotoxic to L929 and HeLa cells, but the monomer containing carborane had a higher 50% inhibitory concentration on L929 cells (1.8 mM) compared to other small molecules [109]. In order to produce polymeric NPs via the thiol-ene reaction in a slightly different manner, researchers emulated the organization of a tiny surfactant with the carborane unit as the hydrophobic head and the PEG2000 unit as the hydrophilic tail [110]. The hydrophilic rhodamine B dye was applied to the second accessible site of the carborane unit to further mark the polymeric chains. When compared to BSH, either alone or in combination with other carborane-containing PEG compounds, the molecules did not cause toxicity in HepG2 cells and had a greater *in vivo* circulation time. *In vitro* fluorescence analyses of U87 cells revealed that the fluorescent substance had accumulated in the cytoplasm. The fluorescent molecules were administered intravenously to mice, and it was found that they concentrated in the spleen but not in other organs, indicating their potential as drug delivery systems. As boronic acid delivery methods, different acrylamide and N-acryloyl-diaminoethane pipes were produced to form boronated cationic copolymers [111]. After boronic polymers were administered intravenously, the resulting tri-block polymer produced 14 to 21 g/g of B/g of tumor and had a higher cationic monomer ratio in the cancerous tissue compared to healthy peri-colonic tissue. PEGylated-polyglutamic acid is one such polymer that was created by coupling BSH with sulfur via a disulfide bond. After 24 hours, there was a 5-fold increase in tumor B content when BSH was combined with PEGylated-Polyglutamic Acid (PEG-b-P(Glu-BSH), which boosted tumor cell absorption within an hour [112,113]. BALB/c mice that had received dermal implantation of the C26 malignant colon cancer cell line was given the PEG-b-P(Glu-BSH) intravenous injection.

24 hours after providing mice with tumors through intravenous injection of PEG-b-P(Glu-BSH), *in vivo* BNCT was carried out to show that enough ^{10}B had been given to eradicate the tumor. Accordingly, larger tumor: normal tissue ratios and better tumor: blood ratios suggested that Glu-BSH was more effective than BSH [114]. For the active and targeted administration of B and DOX in BNCT, Chen and colleagues (2019) suggested iRGD-modified polymeric NPs. They synthesized ^{10}B-polymers by covalently grafting the 10B-enriched BSH onto PEG-PCCL, altering their surface with iRGD, and then physically incorporating DOX into the polymers. After 24 hours of injection, the resultant polymers exhibit improved ^{10}B accumulation in tumors and longer blood circulation when compared to BSH as well as optimal B concentration ratios for human normal tissue in A549 tumor-bearing mice. However, additional research is required to use these polymers in clinical trials [125]. Another important type of polymeric materials for drug delivery systems and cancer therapy strategies is NPs. Polymeric NPs have been investigated as promising delivery systems for gadolinium neutron capture therapy (Gd-NCT) and delivery of drugs to metastatic malignancies [116].

It has been demonstrated that micelles containing B have better blood circulation, tumor accumulation, and stability [117]. Redox NPs made of B clusters have recently been obtained, and they exhibited great therapeutic efficacy, little side effect, and scavenged ROS [118]. They were created by combining positively charged polymers with BSH conjugates and positively loaded polymers with redox-responsive sections in a static process. After 48 hours, these NPs increased C26 tumor absorption by more than 5% of the injected amount per gram tumor and demonstrated an extended blood circulation length.

3.1.1.2.2.3. Nanoparticles for BNCT

Directing the drug to the tumor with minimal harm to healthy tissue is one of the key challenges of cancer chemotherapy. Since all chemotherapeutic agents are naturally cytotoxic, targeting or localizing these drugs close to the tumor enables the administration of decreased drug concentrations. This can be achieved by coupling the therapeutic agent to a biomolecule that is highly expressed in cancer cells or a receptor molecule. Using some external means to physically drive a cancer drug to the tumor also increases its effectiveness. Fundamentals of magnetically targeted therapy are based on this strategy [119]. The benefit of this approach is that fewer cytotoxic medications would be needed, lowering the risk of unfavorable side effects. This method can be considered a suitable vector for BNCT treatment. Pure B NPs are effective B carriers because of their substantial B content. The production of magnetic dopamine-functionalized B NPs with a size range of 100-700 nm was reported [120]. The production of magnetic compositions including PEG, Fe_3O_4, and mono- or bis-(ascorbatoborate) was also studied by this group [121]. The final nanocomposites were typically 10-15 nm in size and exhibit good paramagnetic properties. Since the composites are effective anti-cancer agents and radical scavengers when paired with ascorbic acid, these materials are considered possible magnetic biomedicine components. One study showed that it is possible to create encapsulated magnetic materials with an efficient amount of loaded carborane cages and analyze their biodistribution properties in cancer cell lines [122].

There have also been reports of other B-containing NPs made from B carbides, block copolymers, B powder, borosilicates, and gold NPs (AuNPs) with mercaptocarborane caps [123-131]. B carbide

functionalized with the transacting transcriptional activator peptide and the synthetic dye lissamine; the final nanomaterials can be relocated into B16-F10 malignant melanoma cells. Following neutron irradiation, the particles considerably suppressed the proliferation of both loaded and unloaded neighboring cells [123]. By using neutron capture, the functionalized B carbide NPs exhibited promising results for suppression of the growth of aggressive solid tumor B16-OVA melanoma *in vivo* [124]. By radical copolymerization of acetal-PEG-block-poly(lactide)-methacrylate with 4-vinyl benzyl substituted closocarboranes, polymer-based B-containing NPs were synthesized. The particles from the copolymerization of 1,2bis(4vinylbenzyl) closocarboranes demonstrated prolonged circulation time and increased tumor cell accumulation [118]. The same group has reported similar outcomes for particles made from mono-4-vinyl benzyl substituted closocarborane self-assembly and copolymerization [125]. By milling a $2SiO_2$-BO xerogel, borosilicate NPs with a size range of 100 to 200 nm were obtained [126]. The resultant particles showed enhanced incorporation to the tumor cells and hemocompatibility after being functionalized with FA [127]. Two nm AuNPs with mercaptocarborane ligands on the surface were obtained, and these monolayer-protected clusters (MPCs) displayed substantial toxicity, the ability to access the majority of cell sections, and an increased tendency to accumulate inside membranes [128]. The material should be appealing as a B-rich BNCT agent. Ciani and associates (2013) obtained unique B carriers utilizing ortho-carborane functionalized AuNPs (GNPs). The hydrophilic nature of GNPs was further increased to facilitate cell absorption by covering them with a properly suited diblock copolymer (PEObPCL). To anchor the pre-functionalized GNPs, this polymer additionally included pendant carboranes. Testing on osteosarcoma cells revealed outstanding biocompatibility in addition to the ability to concentrate B atoms in the target, which is encouraging for further *in vivo* applications. *In vitro* tests on rats with osteosarcoma cells revealed that these modified AuNPs had no discernible toxicity and were capable of accumulating B atoms which is extremely encouraging for their use in BNCT [129]. Using the water-in-oil emulsion approach, the production of pure B NPs made of an LP of azolectin-based phospholipid has been recently suggested [130]. This unique substance is composed of poly (maleic anhydride-alt-1-octadecene) and PEG on the surface, along with B NPs and Cy5 near-infrared (NIR) dye that is fluorescent in its center (3PCB). A folate-functionalized LP was made by combining folic acid (FA), a tumor-specific targeting ligand, with PEG. This increased B accumulation and allowed for more precise delivery to cancer cells. The aggregation of FA-conjugated LP in C6-brain cancer cells was discovered to be significantly greater than that of non-FA-conjugated LPs under the same conditions. Under physiological circumstances, these LPs exhibit exceptional stability, BBB crossing capability, and low cytotoxicity. Therefore, these LPs are thought to be novel B carriers for BNCT. Wu and colleagues (2019) [131] have employed theranostic AuNPs with B cage assembly (B-AuNPs) to assess its practicality for BNCT use. The commercially available citrate-coated AuNPs experienced PEGylation, azide addition, and surface carborane change. They also created 61-BAuNPs by coupling anti-HER2 antibodies with B-containing AuNPs with increased absorption. Based on the findings of this study, noninvasive imaging may prove to be a practical technique for monitoring the concentration of B in the tumor and assessing the mechanism of action of AuNPs.

3.1.1.2.2.4. Dendrimers for BNCT

Dendrimers are interesting materials for drug delivery and imaging applications because of their negligible toxicity, accessibility to reactive terminating groups, and potential inclusion into active targeting moieties [132]. Numerous researchers have investigated the selectivity of dendrimers and tumor-targeting agents in BNCT. The targeting of dendrimers with EGF, FA, and VEGF may enhance the targeted transport of B [78,107,133]. mAbs and other biomolecules attached to boronated PAMAM dendrimers have been thoroughly explored by Barth and colleagues (2003). Wu and colleagues (2004) linked Cetuximab, an anti-EGFR mAbs, to B-rich PAMAM dendrimers to function as a B delivery agent for BNCT. In rats with F_{98}EGFR gliomas, the combination was effective in specific targeting of EGFR by intratumoral injection [134]. The thiol-maleimide "click" chemical reaction is one among the several techniques developed to obtain boronated EGF. Starburst dendrimers of repeated PAMAM groups have their terminal amine groups functionalized by an isocyanate polyhedral borane to engage with the maleimide groups of EGF derivatives. It was found that 960 B atoms were included in each stable bioconjugate with a fourth-generation dendrimer. Each antibody molecule needs to travel 1000 B atoms to achieve a critical local B concentration [107] (Figure 16).

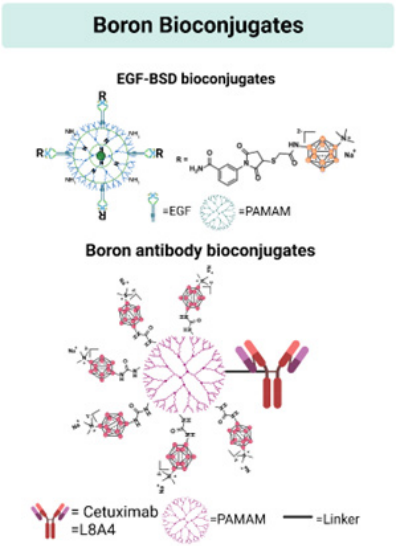

Figure 16. B bioconjugates used for BNCT (Created with BioRender.com).

The initial focus of BNCT was glioblastomas, which could not be treated using current therapeutic methods. To improve tumor absorption, CED (Figure 17) was studied by Yang and colleagues (2002) utilizing a highly boronated dendrimer EGF bioconjugate. CED is a method that can transport drugs directly into the extravascular area of the central nervous system skipping the BBB [135].

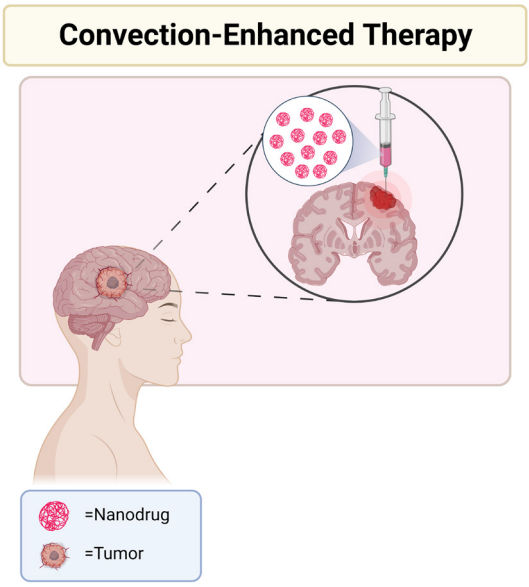

Figure 17. Schematic representation of convection-enhanced delivery (CED) (Created with BioRender.com).

Additionally, the IB16-6 antibody was linked to PAMAM dendrimers that were functionalized using a decaborane cluster. The presence of the antibody on the outer shell of the dendrimer enabled localization in *in vitro* studies. However, *in vivo* studies on rats with B16 melanomas showed that there was no tumor-specificity, and the tumors tended to be concentrated in the liver and spleen [136]. Parrott and colleagues (2005) developed polyester dendrimers rich in B with interiors filled with as many as 16 p-carboranes to improve the efficacy of boronated dendrimer delivery to tumor sites. They demonstrated the possibility of using these structures as BNCT agents in the future [137]. In additional trials, carborane cages were also incorporated into the dendritic structure to improve the distribution of boronated dendrimers to tumor cells [138]. These findings suggest that dendrimers are good platforms for B delivery in BNCT because they naturally have low cytotoxicity and may be generated with a range of reactive terminal functionalities [139]. According to Shukla and coworkers (2003), boronated PEG containing PAMAM dendrimers modified with FA that lowers their absorption by using reticuloendothelial system (RES) via mononuclear phagocyte system (MPS) might attain the B concentrations required for BNCT [133]. Hosmane and colleagues (2012), obtained tiny dendrimers with phenylene cores and three, six, or nine o-carborane clusters on the periphery [138]. The dendrimer containing nine carborane units was evaluated *in vitro*, and the results revealed that after 20 hours of incubation, it either accumulated in or was bound to the surface of human hepatocellular carcinoma cells. However, no additional research has been done on these systems. Additionally, the use of an exclusive core composed of AuNPs that is customized by dendrons with thiol moieties on the top and carborane and PEG units at the outside was investigated [140], though the BNCT properties of these water-soluble AuNPs have not been investigated.

3.1.1.2.2.5. Liposomes for BNCT

LPs have drawn attention for therapeutic and diagnostic applications due to the entrapment capacity of hydrophilic agents and the prevention of their release in circulation. LPs were the first nanomedicines in clinical trials after Doxil®, a PEGylated LP formulation encapsulating DOX, was approved by the FDA in 1995 [141]. B LPs stand as another possible agent for B delivery. Similar to the dendrimers, LPs may be coupled with mAbs, peptides, or polymeric materials. The first LP-encapsulated ^{10}BSH which coupled with mAbs was reported in 1989. It has been demonstrated that the immunoliposomes specifically target tumor cells *in vitro* and inhibit their proliferation after thermal neutron irradiation [142]. Though numerous B-encapsulated LPs have been obtained over the past few decades, most of these formulations lacked the necessary amount of B in their core, preventing them from achieving the therapeutic range required for BNCT [143]. The production of encapsulated BSH with 10% distearoyl B lipid (DSBL) LPs with a high B concentration to be used as a BNCT carrier has been reported demonstrating high performance for B delivery to the tumor [144]. The functionalized LPs combined with thermal neutron irradiation had better anti-cancer activity. Three weeks after receiving thermal neutron irradiation at a dose of 15 mg B/kg through injection, the tumors in mice carrying C26 had entirely vanished. The conjugation of LP with a v3 ligand and a cyclic arginine-glycine-aspartic acid-tyrosine-cysteine peptide (c(RGDyC)-LP) was demonstrated by thiol maleimide coupling. These functionalized LPs demonstrated promising results for delivering precise amounts of B to glioblastoma multiforme (GBM) when connected to a B cage. As a result, 70-80% cell death was attained in 3 hours [145].

3.2. PBA-based Diagnostic and Therapeutic Strategies for Cancer

As previously discussed in section 2.3. boronic acid derivative PBA has significant roles in cancer treatment and has been investigated extensively. PBA has advantages like being inexpensive, highly stable, compact, immune-suppressive, and simplicity of chemical modification. Based on these properties' materials functionalized with PBA have a wide range of application areas. PBA can quickly and irreversibly bind with 1,2 or 1,3-diols to obtain cyclic boronated esters [13,14,146]. The use of PBA compounds as an affinity chromatography ligand for the separation of

RNA has received substantial attention. The following developments involved applications for optical and electrical chemosensing, some of which focused on glucose detection. PBA can also interact with a range of biological membranes.

PBA-based functional compounds have been used in drug administration, cellular imaging, and glycoprotein detection (Figure 18). Since PBA-based chemicals can detect glycoproteins, whether these materials might bind to sialic acid (SA) on the surface of cancer cells was investigated.

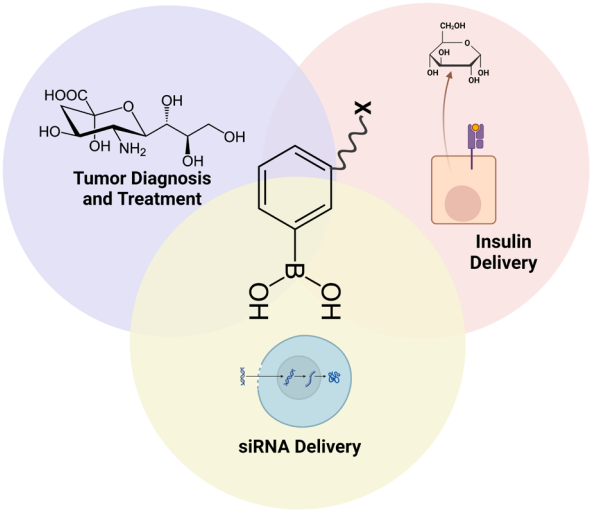

Figure 18. PBA-based therapeutic strategies (Created with BioRender.com).

The diol structure of PBA and SA can combine to produce reversible borate (Figure 19), which aids malignant cells to accept PBA-based functional chemical compounds. In concordance, it is possible to visualize cancer cells that overexpress SA using PBA and fluorophores. PBA and nanocarriers make it possible for therapeutic medications to be transported effectively, improving their accumulation at tumor locations, and boosting their anti-cancer potential. PBA contains a chemical functional group that can be used to target therapeutic medicines and nano drugs to tumors and malignant cells. This section of the article will provide a summary of the most current uses of PBA-based effective nanomaterials in cancer therapy, imaging, and diagnosis.

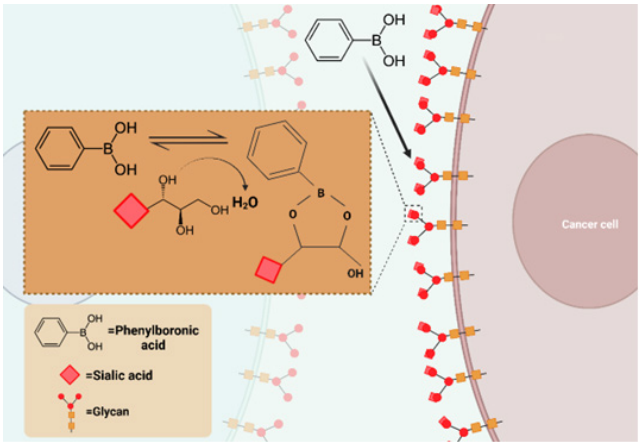

Figure 19. Phenyl boronic acid and sialic acid interaction and cyclic boronated esters formation via binding to 1,2-diols or 1,3-diols (Created with BioRender.com).

3.2.1. SA targeting strategies

PBA and its derivatives are most frequently employed in insulin delivery for diabetes mellitus treatment using glucose-responsive polymers that can detect blood glucose [147]. The capacity of PBA-based polymeric NPs to bind SA in acidic environments, such as the tumor microenvironment, makes them useful in anti-cancer drug delivery systems. The strong specificity and selectivity of PBA to SA can improve carriers' capacity to target cancer cells, increase duration in tumors, and slow down the quick clearance from tumors, which places PBA in an important place in nanomedicine. SA overexpression on cell membrane is related to the malignant and metastatic phenotypes of numerous cancer types, including lung, breast, prostate, colon, bladder, and stomach [148]. Therefore, methods for tracking SA expression would have particular importance for both diagnosis and treatment of cancer [149]. Based on this, PBA and SA detection methods such as biosensors have been investigated for both synthetic and natural polymeric materials.

Chen and colleagues (2013) generated a density-tunable dendrimeric array for in situ monitoring of glycan density based on overexpressed SA on the BGC-823 cell surface. They first modified the slide with PAMAM before electrostatically coating it with functionalized gold nanoclusters (AuNCs) made of 3-aminophenyl boronic acid (APBA). The plot of change compared to dendrimer density was used to determine the SA density on the cell surface [150]. Based on the PBA's capacity for the selective recognition of SA from other saccharides, Matsumoto and coworkers (2009) developed a technique to directly assess the expression of SA on the surface of cancerous cells by a PBA-modified electrode. Potentiometric detection can measure SA on cell surfaces under physiological circumstances without the use of enzymes or labeling techniques. The experiments with the electrode showed that the amount of SA presented on metastatic murine melanoma cells B16-F10 was about four times as high as the number of healthy pneumocytes. It was discovered that the amount of SA on the outside of the H22 murine hepatic cancer cell was roughly 1.9-fold greater than that on the surface of normal murine hepatocytes, showing that the enhanced expression of SA on the cell surface is related to malignancy and cancer spread. Thus, it has been demonstrated that SA is overexpressed on the surfaces of numerous different types of cancer cells utilizing borate ester chemistry [151].

Using surface-enhanced Raman scattering spectroscopy (SERS), Deng and colleagues (2018) designed a glucose-bridged and 4-mercapto

phenylboronic acid-decorated silver NPs (Glucose-MPBA@AgNPs) as a nanoprobe for hypersensitive identification of SA expression profiles on the surface of both normal and cancer cells. This unique complex demonstrated extraordinarily strong SERS enhancement activity, which is comparable to the SERS hot spot effect. Accumulation was significantly different from HepG2 cells and BNL CL.2 cells expressing differing quantities of SA on their surfaces. Nanoprobe may be advantageous in delivering highly efficient recognition of the edges of tumor tissues in clinical settings [152]. In recent years, numerous studies have used polymeric NPs with diverse designs and combinations as drug delivery agents based on PBA-SA recognition for cancer therapy. For instance, Zhang and colleagues (2016) used AuNP-labeled biotinylated PBA (biotin-APBA) to design an SA-recognition system. The average amounts of SA expressed on MCF-7 and HepG2 cell surfaces were reported to be $7.0x10^9$ and $5.4x10^9$, respectively [153]. This approach may be applied to diverse biological research and clinical diagnostics. Because SA overexpression is correlated with tumor aggressiveness and a bad prognosis, PBA-mediated targeting presents a highly translational approach to the clinical diagnosis and therapy of solid malignancies. It also offers safety and non-immunogenicity. Deshayes and coworkers (2013) developed PBA-functionalized polymeric micelles by incorporating PBA moieties into block copolymers to target SA overproduced on cancer cells. Additionally, they synthesized a PBA-PEG-b-poly (L-glutamic acid) copolymer (PBA-PEG-b-PLGA) [154]. To show the selectivity of the PBA-modified copolymer for SA, they investigated the steady-state fluorescence quenching affinities of PBA-PEG-b-PLGA and a number of sugars, including glucose, mannose, galactose, and N-acetylneuraminic acid (Neu5Ac). It was discovered that PBA had a higher SA binding affinity in the intratumoral environment, suggesting that SA would be the main target of the PBA-containing micelles in the highly acidic environment of tumors. Based on these tests, dichloro (1,2-diamino-cyclohexane) platinum (II) (DACHPt), an anti-cancer drug, was added to the PBA-PEG-b-PLGA micelles. DACHPt-loaded PBA-installed micelles exhibit better anti-cancer efficacy than DACHPt-loaded micelles without PBA providing another practical strategy for the treatment of solid malignancies. Another drug delivery system was generated by Zhao and colleagues (2016) which is the PBA-terminated PEG monostearate (PBA-PEG-C_{18}) and pluronic P_{123} (PEG_{20}-PPG_{70}-PEG_{20}) targeted system. They created fructose-coated PBA-targeted mixed micelles that could precisely attach and be absorbed by tumor cells via pH-triggered competitive binding to overcome the nonspecific interaction of PBA with normal cells or other components in the circulation. In a physiological environment, the shielding of fructose on the outside of the combined micelles successfully lowered the targeting affinity of PBA for normal cells; however, in a highly acidic tumor environment, it would reactivate due to the competitive binding of fructose and SA overexpressed on tumor cells. Therefore, this simple decorating method may make it simpler to create PBA-targeted NPs for the delivery of chemotherapeutics to tumors [155].

In addition to synthetic polymers, natural polymers could also be coated with PBA to target SA specifically. In order to enhance targeting and delivery to tumors, NPs containing 3-aminomethyl phenylboronic acid (AMPB)-functionalized chondroitin sulfate A (CSA)-deoxycholic acid (DOCA) have been synthesized. CSA-DOCA-AMPB NPs could target and penetrate tumors through reactions of boronic acid with SA and CSA with CD44 receptor, which could be tracked by NIR fluorescence imaging. In xenograft animal models, multiple intravenous injections of CSA-DOCA-AMPB NPs packed with DOX successfully inhibited the growth of A549 tumors. These NPs with high boronic acid content demonstrated promise as imaging and cancer therapy tools [156,157].

3.2.2. Drug delivery strategies

Chemotherapeutic medications have severe adverse effects and systemic toxicities. For chemotherapy to be effective, patients must give and utilize the drugs often over an extended period of time. Multidrug resistance (MDR) may also develop against chemotherapeutic drugs. PBA, combined with various materials, is frequently used to transport and administer anti-cancer drugs. Exosomes have recently received attention as potential anti-cancer drug delivery systems as they are nanosized particles made by cells. To achieve anti-cancer effects, significant concentrations of drugs must be loaded into exosomes. The surface is decorated with APBA and 4-carboxyphenylboronic acid (CPBA) to load DOX into exosomes. The DOX-loaded PBA-conjugated exosomes showed enhanced cytotoxicity in comparison to free DOX and DOX-loaded non-conjugated exosomes on the MDA-MB-231 cells. Results indicated that PBA might increase the uptake of DOX by exosomes, leading to increased cytotoxicity of PBA-conjugated exosomes in tumor cells [158]. Consequently, PBA conjugation to exosomes for the delivery of anti-cancer agents is a potential method to enhance the efficacy of chemotherapy. In another study, DOX-loaded low molecular weight gels (LMWGs) based on oligopeptides modified with PBA were administered by intratumoral injection to reduce systemic toxicity and increase treatment effectiveness. According to *ex vivo* imaging, DOX was continuously released from gels while maintaining an efficient chemotherapeutic concentration. The addition of gel caused a decrement in the systemic toxicity of DOX, and its adverse effects were significantly diminished, which makes the gel a promising local chemotherapeutic drug delivery mechanism [159].

In order to obtain a water-soluble nano construct, Kim and colleagues (2017) first synthesized a boronic ester of the cis-1,3-diol of andrographolide (AND) and hydrophilically polymerized PBA (pPBA). This construct

displayed improved tumor targeting both *in vitro* and *in vivo* [160]. DOX-loaded fluorescent NPs based on PLA-PEI copolymer with boronic acid modifications were developed by Li and colleagues (2014) for cellular imaging and pH-responsive drug administration. DOX-loaded NPs showed pH-responsive drug release and effectively slowed the growth of MCF-7 breast cancer cells. The fluorescent NPs also allowed for real-time imaging to track the endosomal escape procedure [161]. Zhang and coworkers (2017) [162] presented enzyme and redox dual-reaction polymeric micelles with active targeting capacity. Polymerized micelle prodrugs were also created by conjugating camptothecin (CPT) to monomethyl PEG by a redox-responsive linker. Through receptor-mediated endocytosis, micelles were able to specifically infiltrate tumor cells, and by simultaneously energizing redox and enzyme processes in the cytoplasm, therapeutic medicines could be released quickly. With only minor negative effects on healthy tissues, this had strong inhibitory effects on tumor cells. CPT and GMT were successfully self-delivered in a synergistic manner via a rod-shaped nanomicelle coated with CPBA [163]. Assembled nanomicelles modified with 4 CPBA also improved cellular internalization. Based on the PBA's active targeting capability, assembled nanomicelles appeared to congregate preferentially near the site of the tumor, decreased adverse effects, and enhanced the therapeutic potential.

3.2.3. siRNA delivery systems

Another application area of PBA is siRNA delivery. Amphiphilic PBA-decorated PEI (PEI-PBA) NPs were obtained as a quick and adaptable siRNA delivery strategy to study anti-cancer RNA interference efficiency. Findings demonstrated that PEI-PBA NPs encapsulated siRNA to generate a stable form of PEI-PBA/siRNA nano complexes. These nano complexes not only significantly increased the cellular uptake of siRNA via the chemical interactions between PBA and SA on cancerous cell surfaces, but also influenced siRNA to escape from the lysosome effectively inhibiting the target gene expression. Gene silencing and anti-tumor effects of PEI-PBA/siRNA were also tested in nude mice which revealed considerably increased effectiveness. PEI-PBA was identified as a straightforward and highly effective nanocarrier that could bind with increased SA residues on cancer cell membranes to transport siRNA specifically to cancer cells [164].

In order to obtain composites based on polyion complex (PIC) micelles, electrostatic relations among anionic siRNA and cationic polymers are used. Using simple PBA functionality, Naito and colleagues (2012) published a method that includes all the siRNA stabilizing techniques mentioned previously [165]. A platform cationic polymer known as 3-fluoro-4-carboxyphenylboronic acid (FPBA)-modified PEG-block-poly(L-lysine) (PEG-b-PLys) has been assembled. The ratio of siRNA to polymer and the level of PBA modification were both tuned. The stability of the complex under quasi-extracellular circumstances was demonstrated to be maintained by the hydrophobic interactions of PBA and the binding of the PBA moieties to the 3'-ends of ribose at both ends of the double-stranded siRNA. They also found that ATP interfered with the ideal complex at a range near its intracellular concentration. A well-known proto-oncogene called polo-like kinase 1 (PLK-1) was dose-dependently silenced by the PIC micelle. PIC micelles with PBA may be able to deliver siRNA to intracellular settings.

3.2.4. Imaging-guided phototherapy

Phototherapy (PT) is a noninvasive method that targets the treatment spot and minimizes the adverse effects of therapy. It holds great promise for cancer treatment. Examples of PT include photothermal therapy (PTT) and photodynamic therapy (PDT). With the development of cellular imaging technologies, a novel cancer treatment approach called image-guided tumor therapy has also evolved. The PTT generates heat while damaging the cells at the light-irradiated site. The most frequently used photothermal agents are magnetic NPs, polydopamine (PDA), and AuNPs [166]. LAPONITE (LAP)-Fe_3O_4 NPs were coated with PBA as a novel photothermal agent for the improvement of surface modification capacity and the PTT effect [167]. PBA photothermal NPs presented multimode imaging and selective targeting properties. Magnetic resonance image of the tumor deteriorated after intravenous delivery, although the photoacoustic (PA) signal increased. The NPs were collected in the tumor through the bloodstream. The tumor responded positively to the PBA targeting in terms of suppression within two weeks. Indocyanine green (ICG) and the anti-cancer agent SN38 loaded PBA-functionalized multivalent peptide nanotubes (I/S-PPNT) for the controlled release were assembled [168]. Confocal imaging was carried out utilizing PNNTs with different PBA graft densities in order to demonstrate the roles of PBA and SA in targeting. The intracellular fluorescence intensity grew gradually as graft density increased, but it reduced abruptly in cells treated with PBA, suggesting that PBA can target cells with high SA expression selectively. To demonstrate the effectiveness of tumor therapy, intravenous injections of PBS, PPNT, I-PPNT, and I/S-PPNT solutions were administered at the same ICG and SN38 dosages. Combining PDT and chemotherapy resulted in an approximate 90% I/S PPNT-mediated tumor inhibition. In addition to significant inhibition of pulmonary metastasis and tumor growth, the combination of precisely targeted and locally activated therapy also led to significant PPNT material accumulation in tumors. Another study is interested in an optical substance known as an up-conversion nanomaterial (UCNP), which is triggered by NIR light to produce ROS. When activated by NIR light, UCNPs-lanthanide-doped optical nanomaterials-can emit UV and visible light. Hyaluronated fullerene (HAC60) and amino APBA-functionalized UCNPs

(APBAUCNPs) were employed to build the nano platform by a specific binary borate condensation. It resulted in a dual-target nano platform with dual-color fluorescence imaging [169]. Fluorescence resonance energy transfer (FRET) between APBA-UCNPs and HAC60 helped to produce $^1O_2$. The nanomaterial might concurrently target polysialic acid (polSA) and CD44 for precise targeting of cancer cells. Experiments on cells have demonstrated that PBA can target overexpressed SA on PC12 cells. Dual targeting improved tumor cell uptake as evidenced by the simultaneous presentation of higher fluorescence intensities in tumor cells by UCNPs with dual targeting. Functional compounds based on PBA that are used as photosensitizers and photothermal agents are currently being investigated as potential pharmaceuticals to carry out proper PT.

3.2.5. Fluorescence imaging

The technique of biological imaging is crucial for understanding the composition and biological processes. Fluorescence imaging (FLI) has a variety of uses for biological imaging due to its high sensitivity, selectivity, variation, and noninvasive nature. When FLI is utilized for *in vivo* cell imaging, fluorescent probes are typically stimulated with light in order to generate fluorescence signals for imaging. By effectively differentiating normal cells from cancer cells and normal tissues and tumor tissues, the functionalized fluorescent probes enable early cancer diagnosis and imaging-based tumor therapy. A glycoprotein that is overexpressed on cancer cells can be recognized by fluorescent probes with PBA groups, enabling fluorescence imaging of tumors. A modular and affordable fluorescence-based imaging system was generated in 1999 by Atlamazoglu and colleagues by using Rhodamine derivatives [170]. Rhodamine B-leucine amide and rhodamine B-phenyl boronic acid discriminate healthy tissue from malignant colon tissue sections. Both products are primarily accumulated in neoplastic crypts. Both fluorescence-based optical biopsy approach and fluorescence microscopy can be used to diagnose colon cancer using this strategy. As SA imaging agents, cyclic metal iridium (III) polypyridine complexes functionalized with APBA and transition metal complexes as fluorophores [171] were developed. While the probe without PBA (complexes2) only showed sporadic fluorescence in cells, the PBA-containing probe (complexes1) was successful in imaging HepG2 cells. Since the binding affinity of PBA to SA on the cell surface reduces in the presence of free Neu5Ac and neuraminidase, the probe was unable to image cells. Because HEK293T cells have less SA on their surface, they did not emit any light when incubated with complexes1 under identical conditions, demonstrating that complexes1 are able to recognize SA residues on the cell surface and exhibit cellular selectivity. These results suggested a novel approach to the cancer diagnostic probes. The surface glycosylation of polymers, "clicking" polymer brushes, and cell surface modification are only a few biological alterations that could be made via the thiol-ene click reaction. In this study, well-dispersed FSNPs were first produced via reverse microemulsion, and these FSNPs were afterward surface-modified with PBA tags using a 'thiol-ene' click reaction [172]. Effective silica fluorescent probes with PBA tags were created for visualizing SA on living HeLa cells. As a result, the PBA-FSNPs can be utilized to develop a rapid, precise, and non-invasive method for tagging SA on living cells. This method may one day be useful for the clinical diagnosis of cancer and its therapy. Fluorescent 3-(dansylamino) phenylboronic acid (DAPB) was used to functionalize AuNPs embedded with polSA for in situ imaging and detection of SA. The assembly of DAPB was released from the surface of polSA-embedded AuNPs in the presence of more SA or SA-abundant cells due to the competitive binding of DAPB with SA and polSA, which caused DAPB to fluoresce on the surface of SA-abundant cells. The proposed approach employed a dual functional molecule to generate FRET from DAPB to AuNPs and the precise recognition of SA by the boronic group. They hypothesized that the suggested methodology would be advantageous for investigating biological processes, cancer diagnosis, and developing SA-targeted anti-cancer therapies [173].

4. Boron Nitride Nanomaterials for Cancer Treatment

Designing efficient, soluble, biocompatible, and physiologically stable nanocarriers for anti-cancer medications remains difficult. Due to their biocompatibility, significant surface area, and superior mechanical strength, h-BN and BNNT are attractive nanomaterials that have the potential as anti-cancer drug nanocarriers. Due to their distinct physicochemical characteristics, hBN NPs have attracted a lot of attention [159]. On BNNTs or h-BN nanosheets, peptides, proteins, single-stranded DNA, and polysaccharides have been conjugated. The bio-conjugation improved biocompatibility and biorecognition while facilitating water solubility. Combining bN materials with conventional cancer treatment strategies such as radiation therapy, phototherapy, and delivery vehicles for anti-cancer drugs such as DOX is a promising strategy for cancer therapy (Figure 20) [174].

Investigations on the therapeutic effectiveness of hBN against prostate cancer were made in comparison to BA, a potential degradation product. The outcomes show that hBNs significantly restrict DU145 cell growth in a concentration-dependent manner. A detailed cell cycle analysis revealed that both hBN- and BA-exposed DU145 cells were arrested in the mitotic phase during extended incubation periods. Long-term incubation of the highest concentration of hBN enhanced ROS production in DU145 cells which resulted in a higher apoptosis rate. The gradual long-term breakdown of hBN NPs, which results in a therapeutic effect on prostate cancer cells, explains the inconsistencies between the effects of hBN and BA

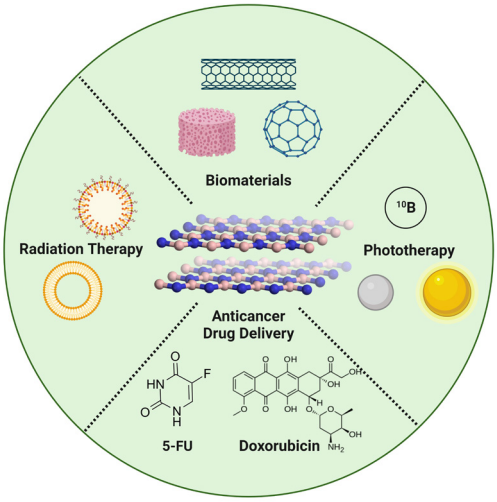

Figure 20. Different areas of boron nitride nanomaterials have been used (Created with BioRender.com).

[175]. A comparative study to explore the potential of BNNTs and hBNs as novel drug carrier was conducted by Emanet and coworkers (2017). They demonstrated that BNNTs could be loaded with a higher concentration of DOX than hBNs. The medium pH at the time of loading and release was significant. The enhanced drug release from BNNTs was sparked by the drop in pH. Since intracellular compartments like lysosomes are acidic, this can be a crucial time for optimal release following uptake into the cells. Additionally, the coupling of folate with DOX-BNNTs aids in the efficient targeting of cancer cells. The findings show that even when the DOX molecules were coupled to the carrier BNNT structures, they still accumulated in the cell nuclei. In order to increase therapeutic efficacy and lessen adverse effects [176], study reveals that BNNTs are a possible contender as an efficient carrier of chemotherapeutic medicines that include aromatic rings. AuNP-containing h-BN is regarded as a promising material for PDT and cancer medication delivery. The exfoliated h-BN was functionalized with AuNPs to produce nano-hybrid (h-BN with Au) particles. The h-BN-Au particles significantly suppressed MCF-7 cell proliferation compared to L929 cells after 72 hours of incubation. The results offer new information regarding the potential of hybrid materials for cancer treatment [177]. Li and colleagues (2017) examined the effects of hollow BN spheres on the apoptosis, necrosis, and proliferation of prostate cancer cells *in vitro*, and found that they increased caspase 3/7 activity and LDH release. Male BALB/c-nu/nu mice models implanted with LNCap cells exhibit a markedly reduced incidence and formation of tumors when hollow BN spheres are used. Hollow BN spheres and PTX work together synergistically to produce the most potent antitumor effectiveness of any combination. Rather than preventing prostate cancer in healthy people, the data suggest that hollow BN nanospheres may be used therapeutically to reduce tumor recurrence in prostate cancer patients [178]. Feng and coworkers (2018) developed a novel pH-responsive DOX delivery technique for cancer chemotherapy. pH-responsive poly (allylamine hydrochloride)-citraconic anhydride (PAH-cit) functionalized boron nitride nanospheres (BNNS) (DOX@PAH-cit-BNNS) were created for the transport and regulated release of DOX into cancer cells. Up to a high concentration of 100 g/mL, PAH-cit-BNNS complexes had no effect on MCF-7 and HeLa cells. However, DOX@PAH-cit-BNNS complexes demonstrated improved drug-release characteristics in an acidic environment. Due to their controlled drug release and pH responsiveness, PAH-cit functionalized BNNS is another promising delivery agent for cancer therapy [179].

DOX-loaded BN NPs (DOX-BNNPs) were assessed on drug-resistant cells by Zhitnyak and coworkers (2017). The DOX-BNNP nanoconjugates were internalized by both sensitive and multidrug-resistant neoplastic cells and localized in the cytoplasm between actin bundles. Results demonstrated that sensitization of the leukemia cells to doxorubicin carried by the DOX-BNNPs was the highest. DOX internalization of DOX-BNNP nanoconjugates by the endocytic mechanism was different from that of free DOX, and allowed maintenance of high and stable DOX levels in nuclei of MDR cells [180]. Sukhorukova and coworkers (2015) obtained a novel and straightforward technique for chemical vapor deposition manufacturing of BNNPs. These structures were discovered to have high cellular absorption and negligible cytotoxicity. These BNNPs, which have porous architectures, can be used as nanocontainers to transport various chemotherapeutic drugs to MDR cells. At equal concentrations, the cytotoxicity of BNNPs-DOX was comparable to that of free DOX. Endocytic pathways allowed BNNPs-DOX nanocarriers to enter IAR-6-1 cancer cells. Following the release of DOX from the nanosized drug delivery carriers, it accumulated in the cytoplasm and nucleus and caused cell death [181]. FA-conjugated BNNS complexes were created to transport DOX intracellularly. When compared to free DOX, complexes had stronger anti-cancer effects *in vitro*. These encouraging *in vitro* results and the possible application of BNNS in BNCT suggest that BNNS-FA/DOX may be further developed to improve the efficacy of cancer therapy *in vivo* [182]. The production and characterization of chitosan/OH-BNNS nanocomposites were studied by Dhanavel and coworkers (2021). Different methods were described to prepare a nanocomposite that was loaded with 5-FU and CUR in single and conjugated forms. Chitosan/OH-5-FU BNNS and CUR release profile has been studied. 5-FU-loaded, CUR-loaded, and 5-FU+CUR-loaded CS/OH–BNNS nanocomposites were prepared using the simple chemical synthesis method, and their cytotoxicity has been assessed on the HT-29 human colon cancer cell line. At dual-drug-loaded composite, the loading and encapsulation efficiencies of 5-FU were calculated to be 85.4% and 91.2%, respectively [183].

5. BODIPY Theranostics for Cancer Diagnosis and Therapy

Since John Funkhouser first presented theranostics

as a cancer treatment in 1998 [184], it has been proven to be the most successful treatment strategy. NPs or molecules with therapeutic and imaging characteristics are theranostic agents. Theranostic agents with imaging capabilities can all be used to visualize *in vivo* release and delivery of drugs, and other pharmacokinetic characteristics variables, such as FLI, photoacoustic imaging (PAI), PET, computed tomography (CT), and photothermal imaging (PTI) [185-187]. Combining theranostics with conventional cancer treatment methods provides some advantages in dose administration, therapy frequency, and recovery projections.

Theranostic medications with tumor-targeting and stimulus-responsiveness characteristics have shown tremendous promise for the treatment of cancer during the past 20 years. The 'one-for-all' theranostic system BODIPY, which typically uses multimodal imaging and treatment, is very intriguing to researchers in the medical, chemical, and life science fields. Theranostics has been applied in monotherapy via a variety of techniques. Haeberle and colleagues developed the BODIPY, a non-tetrapyrrolic photosensitizer, for the first time in 1970 [188]. BODIPYs have shown outstanding photophysical properties due to their varied electronic properties and effective transition energy. BODIPY dyes are used in a wide range of areas such as organic lasers (Figure 21a), bioimaging (Figure 21b), PDT (Figure 21c), light harvesters (Figure 21d), and photovoltaic devices (Figure 21e) [189].

BODIPY chemical dyes are simple to make and work great as a basis for various imaging modalities. High NIR absorption (kabs>650 nm), NIR-I/II emissions (650-1700 nm), and adjustable fluorescence quantum outputs are typical properties of BODIPY dyes. Modifications in the molecular structure can be used to control the PDT and PTT efficacy of BODIPY [190-192]. BODIPY agents can be modified with other chemically functionalized molecules, such as drugs, tumor-targeting ligands, etc. for novel therapies and imaging techniques. Additionally, BODIPY dyes have essentially minimal influence on biological processes with excellent photostability, minimal toxicity, strong molar extinction value, and strong phototoxicity. Therefore, a lot of BODIPY-based theranostics with applications in multimodal therapies (PDT/PTT/chemotherapy) and multimodal imaging (FLI/PAI/PTI) have been created (Figure 22) [193].

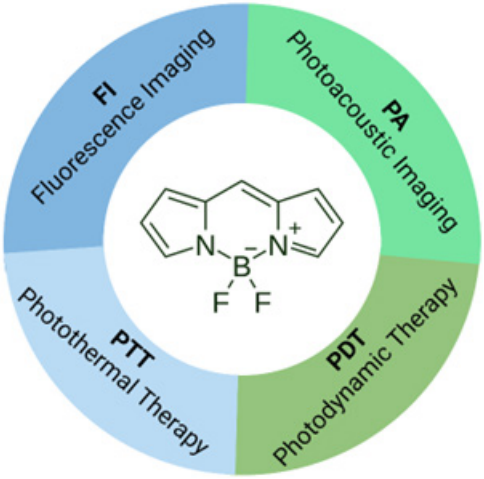

Figure 22. Different cancer diagnostic and therapeutic strategies that BODIPY can use alone or in combination with conventional strategies (Created with BioRender.com).

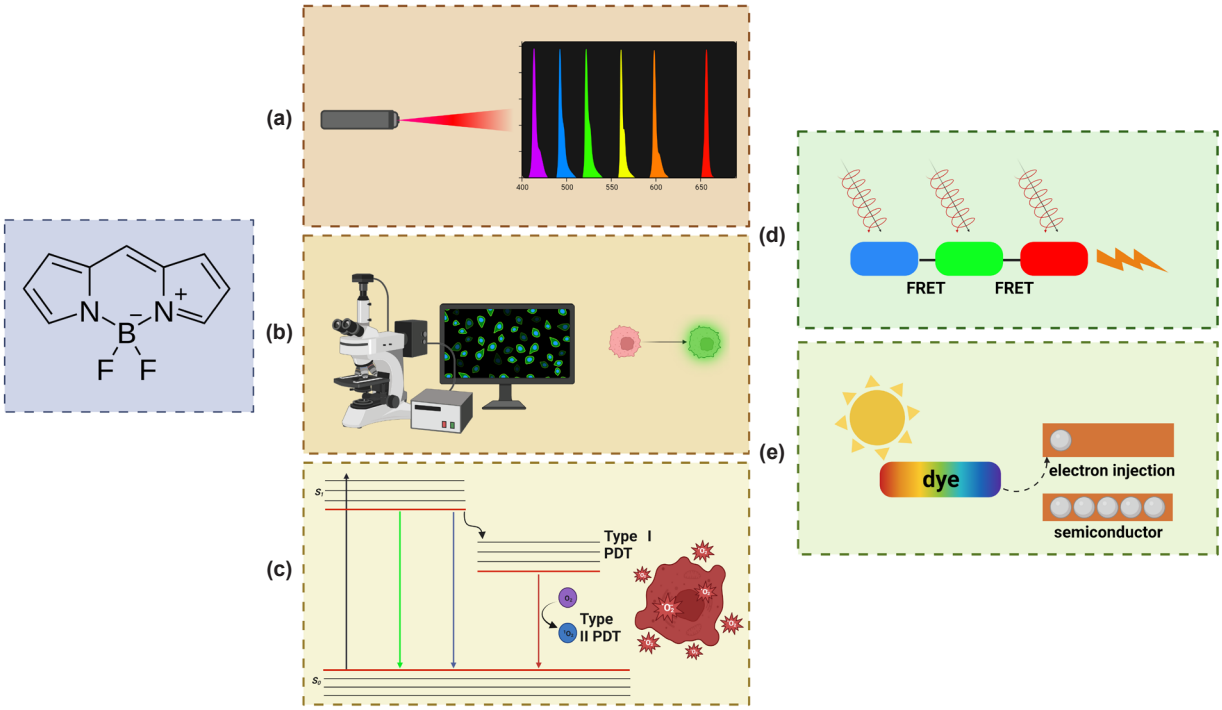

Figure 21. BODIPYs main usage areas; a). tunable organic dye lasers, b). fluorescent probes and sensors for bioimaging, c). photosensitizers for photodynamic therapy, d). light-harvesting artificial antenna, and e). dye-sensitized solar cells (Created with BioRender.com).

The chromophoric core of BODIPY, which is easily accessible for a broad variety of organic synthetic routes, is primarily responsible for the success and adaptability of the compound. The BODIPY core has been thoroughly and arbitrarily functionalized using reactions such as electrophilic and nucleophilic replacements, Pd-mediated C-C coupling, Knoevenagel, Suzuki, Sonogashira, and Liebeskind-Snögl [194].

BODIPYs cover the full visible spectrum in terms of emission and absorption. Molecular cassettes made solely of BODIPY building blocks can be modified by grafting blue-emitting and/or green-emitting derivatives to a red-emitting dye (Figure 23).

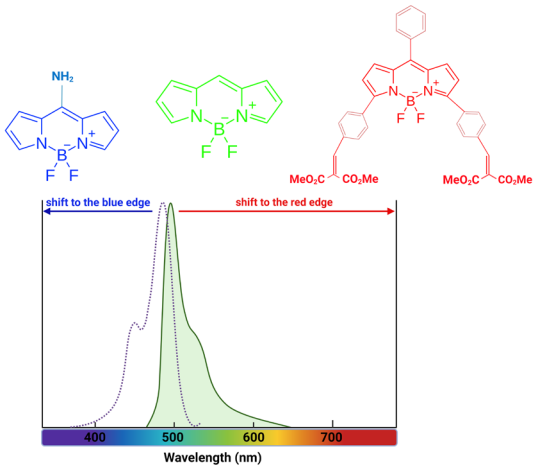

Figure 23. BODIPYs that have adjustable emission and absorption across the entire visible spectrum (Created with BioRender.com).

Other dyes, such as coumarin or rhodamine, which have complementary spectral bands at the visible orange-red and UV blue edges of the spectrum, can also be used. There are two types of BODIPY dyes: Aza-BODIPY and conventional BODIPY dyes (Figure 24 a). Aza-BODIPYs have extended NIR absorption as well as emission durations and easier chemical group modification due to the substitution of nitrogen for the meso-carbon in typical BODIPY dyes [195]. Due to the numerous modification sites, BODIPY dyes can be developed into theranostic platforms such as PAI, PDT, and PTT, in addition to NIR fluorescent fluorophores. In theory, visible to near-infrared photon absorption causes individual states of excitement (S_n, n=1,2, and 3) in BODIPY dyes. There are two probable ways for the "S_n" state BODIPY dye to reach its ground stage (S_0): fluorescence and non-radiation channels (heat or PAI signals). Intersystem transfer (ISC) crossover is used to move the "S_1" state BODIPY into the triplet state (T_1) (Figure 24 b). Through two different pathways, BODIPY dye in the "T_1" phase returns to the S_0 to create ROS. The one involved converting local oxygen into $^1O_2$, commonly referred to as "type-II PDT," via transporting energy. In contrast, "Type-I PDT" involves moving electrons to oxygen, water, or different substrates to create radicals such as the superoxide anion and hydroxyl radicals. The one entails producing $^1O_2$, also known as "type-II PDT," by transferring energy to nearby oxygen. The adjustable photochemistry characteristics of BODIPY dyes, shown in the Jablonski diagram in Figure 24 b, make them reliable theranostic platforms [196,197]. Mao and coworkers (2023) published a review article and they divided BODIPY-based theranostics into six groups fluorescence imaging-guided chemotherapy, fluorescence imaging-guided PDT and PTT, fluorescence imaging-guided multi-modal-therapies, PAI-guided phototherapy, and multi-modal imaging-guided multi-modal therapies. There have been numerous well-generated BODIPY-based theranostic platforms developed in recent years, many of which combine chemotherapy and fluorescence [190].

Overall, BODIPYs showed important improvements in cancer diagnosis and treatment. Furthermore, BODIPYs hold great promise for future clinical applications not only for cancer treatment but also for the treatment of other diseases. Since all BODIPY-based theranostics and therapy or combined therapy strategies have their unique features and important results in this article we will not discuss their specific cancer applications further.

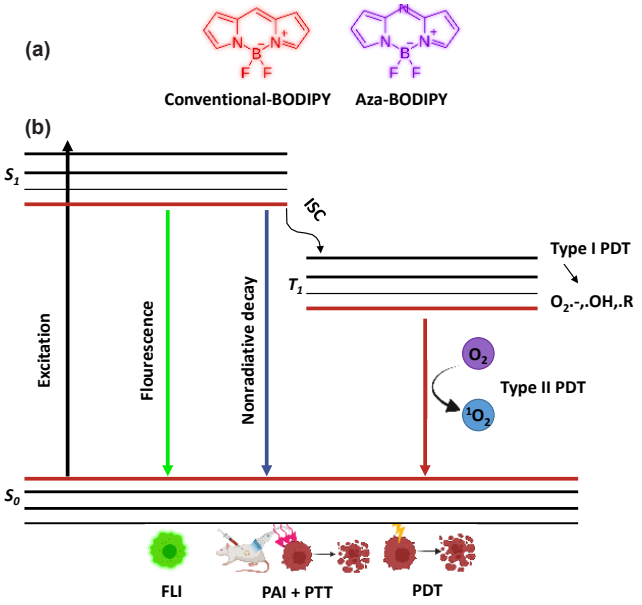

Figure 24. a). Conventional-BODIPYs and Aza-BODIPYs structures and b). therapeutic strategies for BODIPYs developed based on Jablonski Diagram (Created with BioRender.com).

6. Conclusion

Over the decades, studies showed important bioactivities of B such as regulation of cellular pathways, involvement in energy and hormone metabolisms, involvement in inflammatory and wound healing processes, and impacts on embryonic development, bone structure, and function. However, the main reason for clinical use of B is based on its enzyme inhibition properties. Studies have shown

that B-containing drugs may be beneficial for the treatment of various diseases like arthritis, metabolic abnormalities, neurological issues, and numerous chronic and infectious diseases. Over the decades, several B-based antibiotics, antimycotics, and enzyme inhibitors have been developed so far. In addition, there is growing evidence of the potential usage of B as a chemopreventive, chemotherapeutic, diagnostic agent for cancer as discussed in this review.

Some B-based drugs for clinic usage are approved by the FDA and are currently in clinical use for treatment of different diseases including cancer. Although various B derivatives have been used for cancer treatment, the underlying molecular mechanisms of B in cancer cells are still under investigation. Carbon-like features of B enable use in different drug designs, and provide the advantage of chemical modification of other bioactive agents. Cancer cells generally have very active energy metabolism due to their unlimited cell division and growth. Since B and its derivatives can interact with energy metabolism, reducing the levels of the essential molecules involved energy metabolism by B is important. In addition, cancer cells have high levels of ROS. B and B-containing molecules can be involved in ROS mechanisms and deregulate ROS levels. Interaction of B and B-containing molecules with the pyrimidine nucleotides, ribose, and other molecules seems to be another mechanism in which excess DNA damage may cause cancer cell death in transformed cells in particular with reduced DNA repair capacity. Inhibition of several crucial enzymes such as nitric oxide synthase or kinases by B compounds may disturb critical signaling pathways including cell cycle regulation, PI3K/Akt, VEGF, ATM, p53 etc.

On the other hand, the most important and most used clinical treatment approach where B is used is BNCT. A lot of strategies have been developed for the combination of B-based compounds, treatment strategies, and conventional cancer treatment methods such as chemotherapy, PDT, PTT, radiation, etc. Approaches consider B derivatives such as PBA, hBN, BODIPY, and others rather than B itself. Recently, B-based compounds gained more attention in biomedical research and applications, particularly in drug delivery systems and BNCT. Due to the unique features of the boronic acids, especially PBA is frequently introduced to drug nanocarriers. Additionally, h-BN and BNNT are promising nanomaterials due to their excellent properties. On the other hand, BODIPYs have excellent properties to be considered as diagnostic and therapeutic agents for cancer in future clinical applications. Although there are review articles based on the above-mentioned topics in the literature, almost all application areas of B and its derivatives from borates to BODIPYs with numerous studies and novel approaches in terms of cancer are covered and revisited, currently. Finally, B and B-containing compounds are of great interest for the development of new-generation bioactive diagnostic and therapeutic agents for cancer.

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