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Review Article

Recent Breakthrough of Bismuth-Based Nanostructured Materials for Multimodal Theranostic Applications

Dhanraj Ganapathy,[1] Chitra Shivalingam,[1] Rajeshkumar Shanmugam,[2] Ashok K. Sundramoorthy,[1] Karthikeyan Murthykumar,[3] Sivaperumal Pitchiah,[1] Saravanan Sekaran,[1] and Sathish Kumar Ramachandran[1]

[1]*Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India*
[2]*Nanobiomedicine Lab, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India*
[3]*Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, India*

Correspondence should be addressed to Rajeshkumar Shanmugam; rajeshkumars.sdc@saveetha.com and Ashok K. Sundramoorthy; ashok.sundramoorthy@gmail.com

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Cancer is a lethal disease ravaging mankind claiming millions of lives. Most frequent methods of management include surgery, radiotherapy, chemotherapy, or a combination of all the above-mentioned methods. However, there is no specific medication available to cure this condition completely and several compounds and drugs are constantly explored for their therapeutic effects. Recently, photothermal therapy, photodynamic therapy, radiotherapy, targeted drug delivery, and hyperthermia have shown to be of great interest in cancer treatment. In this direction, bismuth oxide (Bi_2O_3) nanoparticles can be a promising option in cancer treatment and diagnosis as well. Bi is a well-known radioactive isotope; this emits high-energy gamma (γ) rays to the affected cells. This technology can pair with existing chemotherapy to enhance the therapeutic efficacy.

1. Introduction

Bismuth (Bi) is one of the significant nanoparticles (NPs) with specific spatial, physical, chemical, and compositional characteristics to integrate diverse attributes, including an affirmatively elevated X-ray attenuation coefficient [1]. This material exhibits outstanding photothermal transition effectiveness and a protracted promulgation half-life, as a nontoxic as well as cost-effective diamagnetic heavy metal [2]. Bismuth-doped nanoparticles (BiNPs) have been found to offer promising properties in the areas of combinational tumor therapy, photothermic and radiation therapeutics, augmentative imaging, theranostics, drug transport, biosensors, and tissue engineering (Figure 1) [3].

Day by day, cancer is becoming more severe as well as a common disease all over the world; 2 million women were affected by breast cancer in the year 2018; similarly, prostate, colorectal, stomach, and lung cancer cases are also drastically increasing. Breast cancer causes leading counts of death among females in over 103 countries [4]. Generally, constipation, dizziness, dermatitis, dry mouth, nausea, headache, insomnia diarrhea, and drowsiness are the common problems by the time of cancer treatment. Hence, upcoming technologies are encouraged to solve this problem with a better cure and lower side effects. Detailed toxicological aspects and the exact mechanism of action in therapeutics and nanoparticle interaction with other cellular/intracellular components and their reaction mechanism are bottlenecks

[5]; to explore the technology, a lot more research is essential to prove the concepts and bring them into practical applications.

2. Current Therapeutics

Currently, nanotechnology is proving a plethora of possibilities for theranostics in terms of a contrast agent for magnetic resonance imaging (MRI), hyperthermia, and targeted drug delivery; in this direction, radioactive isotope of higher atomic number elements is also possessing research breakthroughs towards the cure of tumor because of their improved photoelectric effect. Z element's interaction with X-rays is higher than light elements such as O, N, H, and C; therefore, those elements could enhance the energy deposition as well as radiolytic hydrolysis in and around the materials. Iron oxide, germanium nanoparticulates, iodine, lanthanide compounds, Cs_xWO_3 [6], and nuclear targeting gadolinium nanoparticles can act as an adjuvant to stimulate cellular radiation [7]. Generally, the combination of various functional materials hooked on one complex form of nanomaterials for multitasking functions balances several factors to perform relevant applications. However, those materials have severe drawbacks owing to their complex composition, mutual intrusion, and drug leakage. In contrast, one material with several element-like composites in the perfect crystal lattices satisfies all the above-mentioned strategies to employ one material to achieve all the intrinsic properties for multifunctional purposes (multimodal imaging modalities and photothermal therapy). Generally, surgery and chemotherapy followed by radiation therapy are the ongoing common treatment for the cure of cancer. Similarly, immunotherapy, targeted therapy, hormone therapy, bone marrow, and stem cell transplant are also sequentially developing in the field of cancer treatment [8]. In the recent era of cancer treatment, CAR T cell therapy, monoclonal antibodies, immune checkpoint inhibitors, and immune system modulators are emerging to establish better treatments [9].

3. Properties of Bismuth Nanoparticulates

Bismuth nanoparticles are the best among the nanostructured materials due to their incredible properties such as high surface area, excellent stability, high electrical, strong diamagnetic, and magnetoresistance properties in the presence of a magnetic field; it has chemical inertness, catalytic activity, cost effectiveness, low toxicity, adoptable functionalization, radiosensitization, radiostability, and high X-ray attenuation. Bismuth (Bi) is a high Z ($Z = 83$) element, and the X-ray attenuation coefficient of this component is larger than that of gold (Au), platinum (Pt), and Iodide (I). Hence, Bi-based nanocomponents such as Bi_2S_3 nanorods, Bi_2S_3 nanodots, and Bi_2Se_3 nanostructures with various morphologies have been recemented as contrast agents (CT) photothermal/radiotherapy sensitizing agents [7]. Remarkably, Bi_2Se_3 nanostructures possibly release vivacious selenium ions for reducing the fatality and occurrence of the prostate, liver, and lung cancers compared with Bi_2S_3 [10] and also stated that two-dimensional materials have remarkable attention in X-ray irradiation and related metabolization to inhibit the growth of tumor [11]. Bi is one of the less-reactive heavy metals in the biological environment with minimal toxicity, and this is more appropriate for *in vivo* applications than other metals like silver [12].

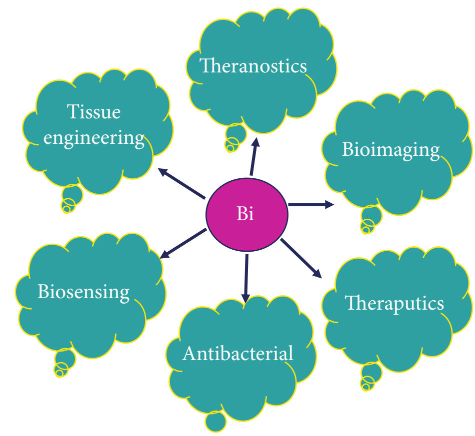

Figure 1: Bismuth nanoparticle's potential impact in biomedical applications.

Nanovaccines may show enhanced efficacy in immunotherapy, and they play an impactful role in all the aspects of therapeutics for cancer. Nanoparticles explicate superior inhibition and denaturation of cancer cells with relevant current technologies. However, the major limitations of nanoparticulates are toxicological aspects of reactive nanoparticles and researchers need more attention to detailed demonstration to explore these nanoparticles at the next level [13]. Bismuth (Bi) is a diamagnetic semimetal with nominal bandgap, and also, this material exhibits attractive properties like thermal conductivity, magnetoresistance, and dominant anisotropic electronic features; these potential characteristics of bismuth nanoparticles trigger and tune the electronic properties, which may influence the sensitization enhancement ratio (SER) towards the development of cancer treatment [14].

4. Radioactive Properties of Bi_2O_3

Bismuth oxide revealed tremendous radiotherapy effects owing to its optimal physiobiochemical effect. Bi is heavy metal, so it explicates side effects like brain toxicity, renal toxicity, and neurological problems. The toxicological effect of bismuth can be ascribed in terms of the following: Bi binds to enzymes belonging to sulfhydryl groups in the human body; as a result of this, enzymes may denature and the functionality of that is also inhibited. As of now, Bi compound's metabolic as well as toxicological aspects are not clear and thus need to be explored. Hence, investigating biodegradability and interreaction with drug components as well as the human biological system may generate a significant platform for medical society [15]. It was declared that genotoxicity aspects of bismuth with genomic DNA of tumor cells were rapidly higher than the nonexposed tumor cells' DNA; these results suggested that bismuth nanoparticles inhibit the growth of tumor cells in a

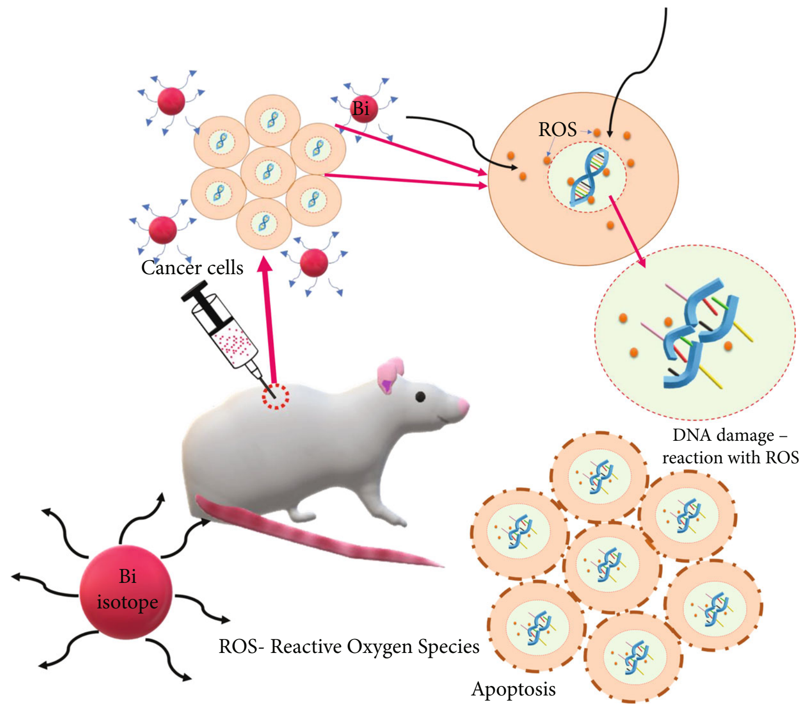

Figure 2: Conceptual diagram of Bi radioactive isotope reaction strategies for cancer treatment.

dose-dependent manner [16]. In another recent report, [17] investigated the radiosensitization effect of bismuth oxide nanostructured rods by megavoltage radiotherapy treatment technology; and the authors also quantified the generation of sensitization enhancement ratio (SER) via photon and electron beams with respect to cancer cell death and further summarised that ultrasmall Bi_2O_3 nanoparticulates regulate the efficient radiotherapy [16].

Radiation therapy comprises brachytherapy, and this is suggested as an acceptable palliative curing therapy for cancer patients. Radioactive isotopes percolate internally near the surrounding specific region of cancer and emit high-dose energy of gamma (γ) to the affected cells [18]. This radiotherapy is generally paired with chemotherapy to improvise therapeutic efficiency to cure cancer. Mostly, drugs like doxorubicin, gemcitabine, and cisplatin are collectively enhancing the lethal efficacy of radiation as a radiosensitizer [19, 20]. These are the common treatment currently followed to cure malignant tumors. Recently, research is moving towards the significant radiosensitization effect with high atomic number metallic nanoparticles. High radiation energy damages cancer cells as well as adjacent healthy cells/tissues and also causes several complications. Hence, nanoparticles may possess potential radiosensitization properties; this possibly targets the DNA of cancer cells, so that healthy cells will not rupture. Bismuth nanoparticles were considered promising materials for cancer treatment such as chemoradiotherapy [21], thermochemotherapy [22], radioimmunotherapy [23, 24], and thermoradiotherapy [25, 26], with enhanced inhibition of cancer cells than the existing monotherapies.

Bismuth oxide (BiO) nanoparticles and cisregulatory element combination produce the reactive oxygen species, and these materials possess a radiosensitization effect under the irradiation of photons and electrons in terms of radiotherapy and high-dose-rate (HDR) brachytherapy. It was reported that BiO nanoparticles with cisregulatory combination with photon/electron effect (brachytherapy) on MCF-7 breast cancer cells exhibited the maximum sensitization enhancement ratio (SER) values [27] (Figure 2).

Brachytherapy is a kind of internal treatment mechanism that uses radionuclides as a source to emit high gamma (γ) ray; this induces radiation surrounding the target sites [18]; this energy contains mainly radium along with cesium-137, iridium-192, gold-198, palladium-103, and iodine-125 [28]. Currently, brachytherapy (radionuclides) is gaining more attention due to the source half-life, flexibility, and gamma- (γ-) energy properties than other external therapies related to photons and electrons. Radiosensitization effect was predicted with various kinds of cancer cells such as human squamous-cell carcinoma (A431) [29], lung cancer cells (A549), cervical cancer cells (HeLa), and prostate cancer cells (DU145) to analyze the morbidity tolerable properties [30].

5. Nanoparticle-Dependent Cancer Therapeutics

In another dimension, photothermal therapy (PTT) is one of the promising therapeutic techniques for tumor ablation due to its low invasion, high efficiency, and remote controllability. Carbon-based quantum dots, magnetic nanoparticulates, gold nanoparticulates, tungsten bronzes, bismuth and copper-based compounds, nano-shell-like structures, and organic polymers are the extensively focussing PTT agents [31]. Bismuth selenium (Bi_2Se_3) has gained enormous attention in imaging because of its optical, thermoelectric, photoelectric, and chemical properties. Bi is an effective element for contrast agents (X-ray) owing to its high atomic number [31].

Bi has been conventionally following material in the generation of pharmaceutical products for the therapeutic purposes of hypertension, gastrointestinal disorders, and syphilis. On the contrary, the nanoform of bismuth was analyzed in various domains to estimate the active features in X-ray radiotherapy, heavy-metal ion detectors, biosensors, bioimaging, tissue engineering, microbial inhibition assessments, and cancer therapy [32–35]. The single compound of Bi can be used to fabricate intermediate materials like bismuth-chalcogenides (Bi_2S_3, Bi_2O_3, and Bi_2Se_3), bismuth-oxyhalides-BiOX (X-Br/I/Cl), and bismuth selenide (Bi_2Se_3), which may influence and enhance the properties of the material. Nanostructured bismuth-based compounds may possess various crystal growth owing to the nucleation, growth, and saturation, and those properties resemble morphological features such as nanorods, nanowires, nanotubes, nanoneedles, nanoflakes, nanosheets, nanoflowers, nanoplates, and nanooctahedra. In another mode, multicomponent bismuth nanostructures ($BiFeO_3$, Bi_2MoO_6, Bi_2WO_6, and $(Bi_2O)_2CO_3$), $BiPO_4$, $BiVO_4$, and Bi dimercaptopropanol (BisBAL) are possessing great importance in biomedical applications. Generally, in the case of nanoparticles, morphology-dependent application aspects such as photocatalytic degradation, sensing ability, compatibility properties, and imaging efficiency were analyzed. Besides, there are not many strenuous reports on the morphological importance of cancer treatment that have to be explored by the research community. Various kinds of morphologies and crystal structures are possible to develop via feasible wet chemical approaches, which include solvothermal, hydrothermal, evaporation methods, precipitation methods, sol-gel approaches, chemical reduction, microemulsion techniques, sonochemical synthesis approaches, microwave irradiations, laser-mediated fabrication techniques, and all the possible chemical synthesis routes. Material-dependent properties are essential to analyze the interreactive functions to exactly execute the applications [12, 36].

6. Important Findings of Bi_2O_3 towards Theranostics

Song et al. investigated the bismuth selenide nanosheets for imaging purposes as a targeted theranostic agent and found that Bi_2Se_3 has outstanding tumor targeting ability and also showed the potential radiosensitization efficacy for imaging and radiotherapy and also mentioned the *in vivo* biocompatibility of the material [7]. Similarly, according to Cheng et al., bismuth sulfide-based nanoagents for photothermal therapy damage the DNA of cancer cells due to the enhanced radiation dose and also, as a CT contrast agent, have an influential parameter in multimodal imaging; and they summarised distant metastasis inhibition mechanism they have explained in the tumor model [37]. Yang et al. proposed that 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC) membrane-coated Bi NPs revealed significant photothermal conversion efficiency, CT/PA contrast imaging, biocompatibility, photostability, efficient cellular uptake, and tumor accumulation through EPR effect; this material has a multifunctional theranostic platform to cure cancer [38]. Sisin et al. illustrated that Bi nanoparticles induce ROS in and around the cells and enhance the SER value during brachytherapy and high radiosensitization [4]. Stewart et al. demonstrated that dose enhancement factor (DEF) simulation studies exhibit a lower Sensitisation Enhancement Ratio (SER) found via cell survival experiments; the authors found cell population in simulated DEF compared to experimental SER measurements [32].

7. Management Strategies in Cancer

Despite decades of dedicated research on cancer monotherapy, effective tumor eradication at an incipient stage persists as a significant hurdle. The majority of tumors are not identified until they have grown to a substantial size, increasing the chances of poor treatment response and spread. To address the drawbacks of individual therapies, an alternate option is to combine more than one therapy technique with diagnostic tools [39, 40]. The utilization of imaging modalities and multitherapy at the same time necessitates the development of versatile nanotheranostic agents [41]. BiNPs was advocated in this regard due to their wide range of uses, including CT imaging, phototherapy, and radiotherapy. Bi_2Se_3 nanodots possess steep photothermal translation effectiveness in phototherapy while also functioning as CT imaging-piloted synergistic sensitizers in radiotherapeutics [42].

8. Application of Bismuth Oxide Nanoparticles in Cancer Theranostics

BiNPs' inherent properties have been coupled with different imaging aspects or treatment techniques, in particular, MRI, chemo, and immunotherapeutics, to create unique theranostics. These monodisperse multicomponent nanoagents are very promising as cancer theranostic agents due to their fast cellular uptake, substantial tumor accumulation, good in vivo dispensation, minor acute toxicity, and excellent photothermal tumor ablation without recurrence.

Another innovative strategy recently emphasized targeting multitherapeutic cancer ablation is combination phototherapy with immunotherapy employing BiNPs [43]. Song et al. developed immune-adjuvant encased Bi_2Se_3 nanocages in metastatic treatment with enhanced photothermal properties [43]. Through enhanced production of inflammatory cytokines such as TNFa and interferon g, along with IL-12p40, employing this immunogenic NP effectively ablated the photoexposed cancerous tissues but also elicited significant antineoplastic immunity to prevent the formation of a remote subsidiary tumor. These nanomedicines' potential can be leveraged in future research and development as multifunctional theranostics.

Alyani Nezhad et al. used the intraoperative radiotherapy technique to explore and measure the average dose enhancement component in the proximity of nanoparticles.

A unique hydrothermal approach was used to make bismuth oxide nanoparticles (Bi_2O_3 NPs) as sheets and spherical shapes. As a result, IORT in combination with Bi_2O_3 NPs may be able to minimize treatment duration and normal tissue dosage, as well as deliver localized dose augmentation [44]. Bi_2O_3NPs may have harmful consequences at the intracellular level, according to Alamer et al., who recommend additional research before using them for medicinal purposes [45].

Researchers attempted to propose multifunctional bismuth gadolinium nanoparticles ($BiGdO_3$) as a novel theranostic vehicle in irradiation treatment, computed tomography, and magnetic resonance imaging. The biocompatibility of $BiGdO_3$ nanoparticles was assessed using the CCK-8 test after they were synthesized and surface modified with PEG. They used gel dosimetry, in vitro, and in vivo experiments to study the nanoparticles' dosage amplification characteristics. The findings of their experiments showed that $BiGdO_3$-PEG coupled nanoparticles had multimode imaging along with radiosensitizing characteristics. The findings suggest that nanoparticles should be investigated furthermore as a potential novel theranostic agent [46].

Abudayyak et al. intended to evaluate the harmful effects of Bi oxide (Bi_2O_3) nanoparticles in cell cultures of the HepG2 hepatocarcinoma cells, NRK-52E kidney epithelial cells, Caco-2 colorectal adenocarcinoma cells, and A549 lung carcinoma cells. All cells readily absorbed Bi_2O_3 nanoparticles (149.1 nm) and demonstrated cytotoxic and genotoxic impacts. The predominant cell death mechanisms in HepG2 and NRK-52E cells included apoptosis with necrosis in A549 as well as Caco-2 cells treated with Bi_2O_3 nanomaterials, respectively. In these cancer cell lines, the levels of glutathione, malondialdehyde, and 8-hydroxy deoxyguanosine too were dramatically altered, with the exception of the A549 cell [47].

In hominin breast tumor (MCF-7) cells, Ahamed et al. investigated the dosage-dependent cytotoxic effects and apoptotic responses of Bi_2O_3 NPs, as well as probable pathways of the lethality of Bi_2O_3 NPs via oxidative stress. Bi_2O_3 NPs possess a crystalline architecture and spherical form with an average dimension of 97 nm, according to a physicochemical investigation. Bi_2O_3 NPs diminish cell viability but also produce dose-dependent membrane injury within a concentration spectrum of 50-300 g/ml, according to toxicological tests. The cell cycle in MCF-7 cells was likewise disrupted by Bi_2O_3 NPs. They discovered that exposing MCF-7 cell types to Bi_2O_3 NPs caused apoptosis, as seen by poor modulation of the Bcl-2 and Bax, as well as caspase-3-specific genes. Bi_2O_3 NPs promoted lethality in MCF-7 cells via modifying redox balance via Bax/Bcl-2 cascade, according to the researchers [48].

The conjunction of BiONPs and cisplatin has been shown as a potential radiosensitization enhancer that would improve tumor control effectiveness while protecting healthy tissues at a lower dose. Cisplatin and BiONPs are possible radiosensitizers that might increase the efficacy of radiation in eradicating cancer cells. When used in radiotherapy, this combination of such powerful radiosensitizers may have numerous implications [4]. It was demonstrated that BiONPs, cisplatin, and combined brachytherapy had a synergetic effect that will benefit future chemoradiotherapy approaches in cancer medicine [49].

Bismuth nanorods with ultra-small-size nanoparticles generate an enhanced sensitization enhancement ratio, which supports potential reduction in cancer cells and also explicates effective radiotherapy. Bismuth oxide showed optimal compatibility and effective radiation therapy, and also, it was reported that it has a tendency to bind bimolecular such as proteins and enzymes that may drive the targeted therapies [50]. In this review, we collectively drew the properties of Bi_2O_3 nanoparticle's impact in cancer treatment, existing nanoparticles' potential contribution to cure cancer, and a brief overview discussing the aspects of relevant properties to achieve reaction mechanism towards theranostics. Currently, there are existing therapeutic technologies for cancer as well as challenges faced to attain appropriate applications in terms of imaging, radiotherapy, drug delivery, etc. Overall, the view of Bi as a radioactive isotope and the importance of γ rays have been discussed along with the toxicological aspects of the material. Hence, the pros and cons of Bi_2O_3 and other nanoparticles' impactful role in cancer treatment, as well as expected technologies to fulfill current problems, were briefly discussed.

9. Future Perspectives and Conclusion

Bi_2O_3 is one of the influential isotopes that possess radioactive properties, which is encouraged in radiotherapy to cure cancer. Similarly, optimal biocompatibility was reported by earlier research articles. The simple alteration of these BiNPs' interfaces with biopolymers and proteins potentially optimizes their pharmacokinetics, culminating in greater colloidal stabilization and longer blood circulation but also lower toxicity. The theranostic role of BiNPs can be experimented in cell line studies and animal and human trials for various neoplastic transformations. The key biomedical scientific topics employing BiNPs have created a novel paradigm regarding their promising therapeutic application including potential cancer progression suppression. BiNPs hold great promise to function as both definitive and adjunct.

Data Availability

The review data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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