Journal of Drug Delivery Science and Technology xxx (xxxx) 104753

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

Advanced nanoparticles, the hallmark of targeted drug delivery for osteosarcoma-an updated review

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ARTICLE INFO

Keywords:
Osteosarcoma
Drug delivery
Nanoparticles (NPs)
Nanocarriers (NCs)
Advanced strategies

ABSTRACT

Osteosarcoma could be a sort of threatening tumor that starts in a bone and spreads to adjoining bone cells. Among the different sorts of bone malignancies, osteosarcoma is the foremost common essential Bone cancer (BC). The common medical analysis procedure for fundamental deleterious bone tumors consists of radiotherapy, cryotherapy, and surgery. Due to the need for viable medications, later inquiries about has centered on different elective helpful modalities. The advancement of novel designated ways to deal with treating bone malignant growth and bone recovery is one of the new restorative ideal models made conceivable by nanotechnology-based anticancer treatment. The survey looks at current osteosarcoma treatments, their deficiencies; arising restorative methodologies considering nanocarriers worked with combinatorial carriage frameworks, and their possibilities in osteosarcoma treatment. To conquer the limitations of existing treatments, methodologies, for example, simultaneous conveyance of different medication cargoes to work on the pharmacokinetic drug discharge profile have been additionally tended to. Concerning the extraordinary highlights of cutting-edge nanoparticles (NPs), the survey endeavors to investigate NPs as signs of designated drug conveyance for BC.

1. Introduction

Malignant bone tumors are the diverse collections of illnesses that can be further separated into orthotopic and metastatic tumors. The most frequent type of orthotopic bone cancer is osteosarcoma and considered as the third most common malignancy in children and adolescents. Osteosarcoma (OS), a predominant main malicious bone cancer, is estimated approximately 60% of all bone malignancies [1,2]. OS is a complex disorder affecting adults with a typical tumor associated with a few genetic abnormalities. The precise cause of OS is unknown, despite the correlation of several genetic variables with the condition. Chemotherapy is the conventional approach to treat OS, followed by surgery and adjuvant chemotherapy. Bone metastases frequently occur with a poor prognosis for cancer patients. Specifically in adults, bone metastasis occurs significantly more regularly than initial bone malignancies. When cancer cells penetrate the bone and too many bone cells form, osteoblastic metastases happen. The bone becomes sclerotic or extremely dense. When prostate cancer metastasizes to the bones, osteoblastic metastases commonly occur. Osteolytic metastases happen when metastatic cancer cells kill too much bone, creating it extremely fragile. As the bone breaks down, holes could develop in the bones. In comparison to osteoblastic metastases, osteolytic metastases appear

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https://doi.org/10.1016/j.jddst.2023.104753
Received 24 May 2023; Received in revised form 5 July 2023; Accepted 10 July 2023
1773-2247/

more frequently. And both can occur concurrently in the exact location of the bone, as in the case of metastatic breast cancer.

However, the practical application of different chemotherapeutic drugs is restricted due to low tumor cell selectivity and sensitivity, toxicity to normal cells, multidrug resistance (MDR), and low pharmacological medicine. Additionally, the blood-bone marrow obstruction decreases the bloodstream to the bone and anticipates the shipment of antitumor pills to the bone [3,4] eventually hindering the advent of creative, multi-faceted OS treatment plans. However, as a result of their multiple pathways, Nanoparticle (NP) combinations are more effective overall than single treatments or combinations of several anticancer drugs. Additionally, these combination strategies can lower the risk of Multidrug resistance (MDR). To treat OS effectively, drugs should be targeted specifically to the bone. To overcome the shortcomings of standard chemotherapy, different nanotechnology-based complete drug transport systems, including NPs, micelles, liposomes, dendrimers, and nanogels, have been created and validated [5]. These nanocarriers (NCs) can extend circulation time, potential to improve porosity along with retention (Enhanced permeability and retention-EPR) impact, and medication targeting malignant cells. Nano-scaffold may release medication in response to positive stimuli for example temperature, pH, magnetism, and ultrasound [6]. There have been numerous investigations using lipidic nanocarriers to stop cancer and metastasis so far. The primary concerns, however, are safety and high patient compliance. Before recommending any dosage type or medication, a doctor always has major worries about medications. The high toxicity profile of anticancer medications resulted in higher treatment costs, higher fatality rates, and more complex side effects. As a result, several problems with the effectiveness of treatment and drug-related toxicity were not resolved by standard dose forms [7]. Biogenic calcium carbonate is helpful to play a key role in improving biocompatibility, gradual biodegradability, pH sensitivity, and osteoconductivity when compared to other NPs [8,9]. The treatment could be directed at the bone through focused passive or active interventions. By conjugating carriers or ligands with drugs, it is possible to target carrier-drug conjugates specifically to different tumors. Several targeting ligands owing to their high affinity for hydroxyapatite (HA), like *N*-(2-hydroxypropyl)-methacryl amide (HPMA), bisphosphonates (BP), and tetracycline have exhibited their potential for bone targeting treatment of metastatic malignant tumors [10,11]. Gene therapy is currently being investigated as a possible way to improve the efficacy of existing medications. Complex disorders caused by genetic flaws, such as OS, can be effectively dealt with by gene therapy. Another cutting-edge method for the therapeutic option to treat OS is genetically engineered T-cell therapy. High morbidity and mortality rates can be caused by bone metastases, which typically occur as the illness progresses, notably in individuals with prostate and breast cancer. Most medications seldom reach the bone, making them therapeutically unproductive for treating bone metastases. For successful therapy of bone metastases, either drugs concentrated on technology or technology-focused drugs must be developed. Tetracyclines, bisphosphonates, aspartic acid, and aptamers are only a few of the numerous bone-concentrated ligands developed and utilized as a source of calcium supply for bones. In the sector of bone drugs concentrated on systems, drugs conjugated with bone-concentrated ligands were first developed, followed by macromolecular societies and NPs have additionally been created. The unique biological and physicochemical properties of nanostructures are gaining significant ground in treating cancer as drug delivery systems (DDS) for administering pharmaceutical combinations or combining diagnostic and specific therapies [12]. Recent boundaries within the creation of bone-targeting structures and their approaches are discussed in this review. Future drug formulation advances such as the use of innovative drug formulations, may aid in boosting the medication's targeting efficiency. The tumor microenvironment (TME), which consists of malignant cells, fibroblasts, blood vessel cells, and cells from the immune system, creates conditions that promote tumor growth. Evidence shows that TME-derived soluble modulators adversely influence the maturation, proliferation, and effector function of NK cells (Fig. 1).

2. Bone-targeting ligands

Technology-focused drug treatments must be compelled to be created for the viable conveyance and therapy of bone metastatic tumors. Aspartic acid, aptamers, bisphosphonates, and Tetracyclines, are only a few bone-concentrated ligands used for the transport of antitumor nucleic acid, peptide/protein medications, and diagnostic purposes of bones. Tetracycline, bisphosphonate, carboxylic acids, amino acids, and aptamers have all been used in several studies to create bone-Targeted drug delivery systems (TDDs) [12].

2.1. Tetracycline

Tetracycline has been used as an antibiotic for a long time [11]. Tetracycline affects both gram-negative and gram-positive bacteria, including Shigella and *Escherichia coli*, as well as diseases such as rickettsial and chlamydial infections. Tetracycline was shown to have a

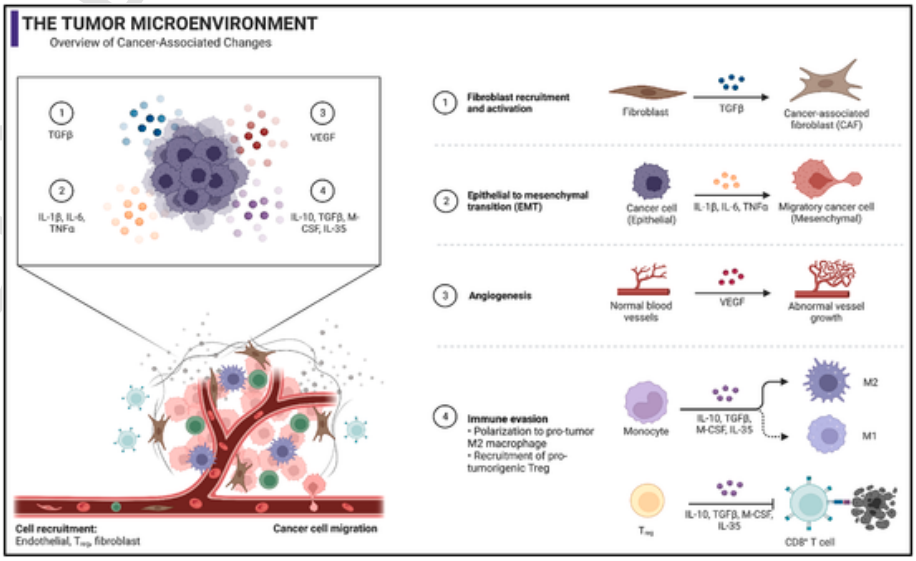

Fig. 1. Tumor microenvironment and alteration during the stage.

higher affinity for HAP and to be responsible for the yellowing of children's teeth in 1965, but it also enables bone targeting feasible. It was identified as the first bone-targeting ligand, through chelate interaction between calcium present in HAP and oxygen atoms in the tetracycline molecule [13].

2.2. Bisphosphonate (BP)

BP is a primary agent that functions as a phosphate-carbon-phosphate group and acts as a key role that helps as the physiological controller in loss due to osteoporosis and osteoclastic bone resorption [14]. Paget's disease, osteoporosis, and hypercalcemias are some bone-related disorders and calcium metabolism anomalies that can be treated and prevented using BPs [15,16,17]. According to reports, after being administered intravenously, BPs dispersed primarily to the bone have shown a strong affinity for HAP. A few BPs conjugates, protein medications, and NPs have been detailed to be successful in the treatment of OS [18,19,20]. Alendronate and Zoledronate have been employed as bone-targeting BPs through the conjugation with the drug and drug carrier via various chemical linkers, functioning as bone-targeting ligands. Several BP conjugates, protein drugs, and NPs are being identified as potential OS regulators [19,20].

2.3. Amino acids and carboxylic acids

Osteocalcin (OC), which has a high carboxylic acid protein-rich composition and is adsorbed onto the HAP surface, is thought to create hard bone tissue [21]. Carboxylic acids, such as carboxylate glutamic acids (Glu acid), aspartic acid (Asp), and glutamic acid, form a tight spherical shape in OC. Following intravenous injection, bone accumulates a variety of oligopeptides such as (Glu)n, (Asp)n, and (Asp-Ser-Ser)n [22,23]. Furthermore, hexa-Asp peptide-conjugated estradiol accumulates primarily in bone following IV administration [24].

3. Osteolytic cancer bone metastasis

When a metastatic tumor develops, neighboring normal cells engage in interaction with tumor cells, which alters their biological function and obliterates the initial microenvironment [25,26]. Metastatic cells seek unique microenvironments known as “niches” in the bone [27,28]. The sluggish blood flow in bones, their mechanical properties, and a variety of chemokines and growth hormones all help tumor cell proliferation [29,30]. The “vicious circle” connecting osteoblasts, osteoclasts, and cancer cells, in the osteolytic milieu, promotes osteoclast activation and inhibits osteoblast activity. Cancer cell proliferation is also continually stimulated [31,32]. In essence, PTHrP, TNF-a, IL-11, and other substances enhance the production of receptor activators of nuclear factor-κB (NF-κB) ligands and get excreted by metastatic cancer cells (RANKL) on osteoblasts. On the membrane of pre-osteoclasts, RANKL and RANK, receptor activators of NF–B, work together to speed up osteoclast development and maturation [33]. To stimulate the activation of osteoclast precursors, cancer cells additionally produce the Notch ligands Jagged 1 and VCAM-1 [34–36]. The bone matrix releases the various above-mentioned growth factors when mature osteoclasts resorb bone [37]. TGF-β affects cancer cells to promote their growth and increase PTHrP production. RANKL decay dissolvable receptor commonly known as Osteoprotegerin (OPG), which is also made by osteoblasts, can stop the production of osteoclastic bone resorption. However, during this “vicious circle,” Matrix Metallo Proteinases (MMPs) decreases the formation of OPG [38]. Additionally, osteoclasts' RON tyrosine kinase receptor is directly activated by the macrophage-stimulating protein (MSP) secreted by cancer cells [39]. Modern-day clinical treatments for osteolysis include radiotherapy, surgery, systemic pharmacological therapies (chemotherapy, hormone therapy), and targeted therapy.

4. Current therapy for bone tumors and bone metastases

Depending on the kind and severity of cancer, different primary bone tumor treatments are currently available [40,41,42,]. Due to their greater chemosensitivity, OS, and ES are typically treated with neoadjuvant chemotherapy before undergoing extensive surgical resection. In general, the OS is immune to chemotherapy and radiation, and the initial course of treatment is preferably a huge surgical excision [43]. Due to the constrained prevalence of remote metastases, Grade one CS within side the extremities is an exception to this norm and is most effectively dealt with intra-lesion curettage [44]. Surgical resection strategies such as removal, coalition extraction, and appendage rescue are utilized depending on the measure and area of the tumor. On account of the emergence of micro-metastases that might cause tumor recurrence, surgical excision alone, except for grade one CS, is frequently not curative [45,46]. As a result, surgical excision is frequently employed as a palliative care strategy to reduce tumor-associated pain [47]. Neoadjuvant chemotherapy helps to reduce tumor growth and BMs are working before surgical operation whereas adjuvant chemotherapy helps to reduce the hazard of tumor recurrence after surgical operation [48,49]. Although chemotherapy is the primary treatment of preference for those suffering from systemic disorders, and is also linked with main side effects such as fever, neutropenia, allergic reactions, and cardiotoxicity as a result of nonspecific drug biodistribution [50]. Furthermore, the affluent extracellular matrix of bone tissue and the bone marrow microenvironment, serving as a development medium for most cancer cells and initiator of medicate resistance, reduces the adequacy of chemotherapy [51]. For primary and metastatic bone cancers, the most often utilized chemotherapeutics consist of doxorubicin, cisplatin, methotrexate (MTX), cyclophosphamide, and ifosfamide [52]. The use of high-dose cycles of doxorubicin, cisplatin, and MTX are exclusively utilized in the treatment of individuals with both essential and metastatic OS [53–55]. Radiation treatment and radiopharmaceuticals can be used separately and in conjunction with chemotherapy or surgery [56]. Radiopharmaceuticals, and other radiation-enhancing materials on account of their capacity to regulate the dosage of delivered radiation, which lowers the infamous side effects have received a lot of interest in recent years when used jointly with conventional radiotherapy. Also, radiopharmaceuticals may be applied as theranostic contraptions to complete all tumor imaging and treatment in a single step [57]. The maximum broadly used remedy plan, called VDC/IE is based on a first-line regimen of vincristine, doxorubicin, and cyclophosphamide, followed by a second-line regimen of ifosfamide and etoposide for uncommon bone cancers of Ewing's sarcoma (ES) [58]. As a follow-up to this therapy, surgery or radiotherapy is usually done [59,60]. Likewise, vincristine, doxorubicin, cyclophosphamide, and etoposide are frequently used to treat Chondrosarcoma CS [61]. Vincristine, doxorubicin, and cyclophosphamide are favored treatments for metastatic CS. The use of bisphosphonates (BPs) in treating BMs and primary bone malignancies has increased recently, because of their capability to lift the binding affinity of calcium ions to Hydroxyapatite (HA), they have been employed to promote bone targeting and have received medical approval [62,63].

5. Targeted drug delivery (TDD) approach to treat bone cancer

Since conventional methods for delivering drugs have several shortcomings, it's critical to concentrate on target-specific drug delivery techniques that enable us to administer drugs without them degrading. A formulation scientist has several barriers, but one of many essential ones is obtaining the medication to the correct place at an appropriate time. Delivering drugs specifically to their intended sites of action is known as targeted delivery of medicines [64]. The cornerstone of anti-metastatic osteolysis is anticancer measures; however, they are ineffective without single conveyance inside the osteolytic quarter or pharma-

cological interaction with anti-bone desorption drugs. Improved focused transport strategies often depend upon NPs, which could efficiently supply anticancer or *anti*-osteolysis medicinal drugs by specializing in metastatic bone and spotlighting bone tumor-targeting ligands (Fig. 2). Through systemic management strategies such as IV injection, focused transport structures pay attention to bone and tumor drug distribution. Ligands such as BP, tetracycline, chelating agents, salivary proteins, and oligopeptides have a prominent target in bone [65]. Bone targeting exploits BPs to restrain cancer cells and reduce osteoclasts. NPs loaded pharmaceuticals may be physically encapsulated, chemically conjugated, or absorbed and released through diffusion [66]. The application of these tailored nanocarriers depends on the physicochemical characteristics of drugs [67]. To prevent being emptied by macrophages and the kidneys, nanocarriers must be lower than 200 nm in size and cannot be more than 400 nm [68]. The smaller ones (10–70 nm) can flow through the sinusoidal capillary pores in the bone. Larger NPs (320 nm) are seven times less efficient than tiny neutral NPs (150 nm) for bone marrow localization. By avoiding plasma proteins, NCs surfaces with hydrophilic, neutral, or moderately anionic features are more likely to be present in the bone marrow and to resist macrophage attack. They modulate the surface-associated emulsifier's composition, resulting in a neutral surface charge. Polymeric NPs owing to their extraordinary biocompatibility and biodegradability, are often used in drug launch structures. Nanocomposites have become a promising approach for drug delivery in the pharmaceutical field due to several benefits and current research development. Polymer nanocomposites (PNCs) are blends of nanomaterials and polymers with at least one-dimensional structure and one component in the sub-100 nm range. Nanocomposites are promising drug delivery systems due to several advantages, including surface and rheological characteristics [69]. Table 1 List of the nanomaterial-based TDDs for the therapy of bone cancer. Table 1 describes the nanomaterials-based TDDs for the management of bone cancer [70–89].

6. Nanocarriers-based management for bone cancer

For numerous cancers, anticancer drugs remain the preferred therapy choice. Oncologists continued searching for tumor-specific anticancer drugs, notwithstanding their efficacy in minimizing side effects in patients. However, their use is restricted due to side effects and the development of resistance in the widely used chemotherapy medications for the cure of osteosarcoma [90]. Various nanoplatforms have been developed in an attempt to deal with these issues and boost the efficacy of chemotherapeutic treatments for osteosarcoma. Both passive and active targeting methods have been tested with notable clinical outcomes utilizing delivery systems based on nanotechnology. High-precision cancer therapies could be made possible by nanoparticles (NPs) with programmable physicochemical properties. Biomimetic nanotechnology protects NPs from the immune system and is at the cutting edge of nanomedicine [91–93]. Nanotechnology has also been suggested as a possible treatment option for osteosarcoma. This review provides a retrospective summary of current developments in nanocarriers for osteosarcoma medication delivery (Fig. 3). We address many specific forms of drug-delivery NPs that are commonly used to give controlled medication release in response to a variety of stimuli provocation and different methods for modifying nanoparticles (NPs) for fo-

Table 1
Nanomaterials based TDDS for the treatment of bone cancer.

Types of NPs	Encapsulated bioactives	Ligand	Ref
MSNs	DOX, ZOL	ZOL	[70]
	ZOL, Au	ZOL	[71]
Calcium phosphate NPs	MTX, ALN	ALN	[72]
Liposome	DOX	Asp 8, folate	[73]
	ALN, DOX	ALN, hyaluronic acid	[74]
nMOFs	ZOL	Folate	[75]
Bioactive glass NPs	DOX	Not reported	[76]
Micelles	ALN, curcumin	ALN, Oligosaccharide of hyaluronan	[77]
	BTZ, ALN	ALN	[78]
	Docetaxel	Quinolone nonpeptide	[79]
	DTX, ALN	ALN	[80]
Quantum dots	ALN, DOX	ALN	[81]
Polymeric NP	DOX, ALN	ALN	[82]
	Cabazitaxel, ALN	ALN	[83]
	PTX, ALN	ALN, folate	[84]
	SN38, ALN	ALN	[85]
	GANT58, ALN	ALN	[86]
Dendrimer	Pt NPs	Carboxyl terminals	[87]
	BTZ	RGD	[88]
	DTX, ALN	ALN, hyaluronic acid	[89]

DOX; doxorubicin, PTX (Paclitaxel), HA; hydroxyapatite, RGD; Arginyl-glycyl-aspartic acid, MSNs; mesoporous silica nanoparticles, BTZ; bortezomib, ZOL; zoledronic acid,ALN; alendronate.

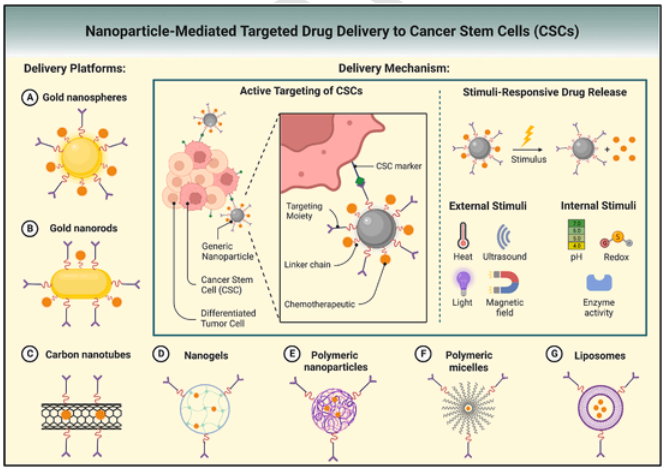

Fig. 2. Active targeting wherein NCs surface decorated with ligands interact with cancer cells and internalized via receptor-mediated endocytosis mechanism.

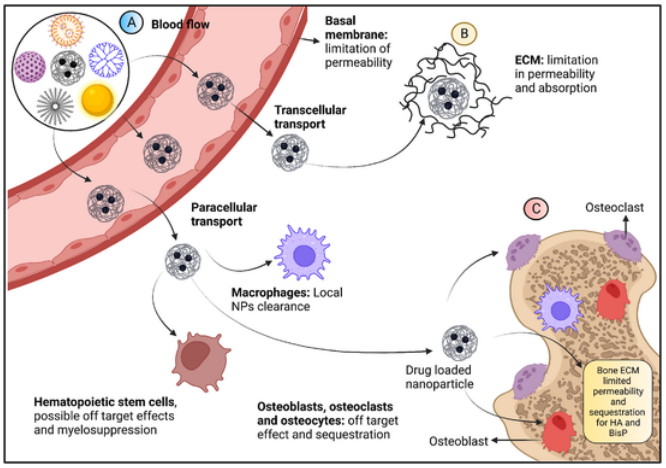

Fig. 3. Schematic representation of IV administered NPs path from the blood flow through the bone tissue: A) NPs extravasate from the bone capillaries either through transcellular pathways such as receptor-mediated transcytosis or through a paracellular pathway, using capillary fenestrae of varying size; B) the NPs reach the bone marrow and can interact with its ECM, or with the resident immune and hematopoietic cells populations; C) From the bone marrow, NPs can diffuse in the trabecular bone, encountering different bone-specific cells populations and its denser mineralized ECM.

cused delivery of medications. In addition, the use of NPs in the treatment of metastatic osteosarcoma is concisely reviewed. Organic and inorganic carriers can be found in nanosized drug delivery systems. The most frequent organic nanocarriers utilized to carry medications to treat osteosarcoma include liposomes, polymers, micelles, and dendrimers. Metallic NPs, mesoporous silica nanomaterials, carbon-based nanomaterials, and calcium phosphate carriers are the main types of inorganic nanocarriers. Nonetheless, it is disputing to develop advanced and versatile nanocarriers from a particular nanomaterial. Therefore, contemporary models of drug-delivery nanosystems are typically deliberate for drug-delivery purposes (Fig. 4). Numerous cancer treatments, including those against bone cancer, breast cancer, lung cancer, and cervical cancer, have made substantial use of nanocarrier-based medication delivery systems [94,95]. It is challenging to target the metastatic niche since primary solid tumors have vascularization and desmoplasia [96]. This setting makes it difficult for EPR to use passive targeting in the development and use of NPs. Apart; the diverse genetic profiles of BM cells due to their varied ancestry make it challenging to identify universal markers [97]. Potentially, this review not only offers viewers a complete review of the present situation in osteosarcoma research nanomedicine but also inspires further research into newfangled drug delivery NPs for osteosarcoma therapy.

7. Impact of nanomedicines on bone cancer

With the advent of nanomedicine, it is feasible to diagnose and treat different cancer, as well as bone metastasis [34, 35]. Nanocarriers can enhance the absorption houses of drugs, focused on efficacy, *in-vivo* stability, and dynamic performance, as well as pharmacokinetic; manipulate release, and aspect effects [98]. By employing smart NPs strategies, it is possible to successfully target the bone with small therapeutic molecules and macromolecules. Numerous nanocarriers have efficiently dealt with osteosarcoma, including liposomes, quantum dots, injectable hydrogels, SLNs, dendrimers, and micelles [99–101]. The RES, macrophages, mononuclear phagocytes, and inflammatory tissues are the main uptake websites for those nanocarriers. The tight endothelial connection of capillary blood vessels accounts for those NCs that now no longer extravagate into wholesome tissues. However, because of the leaking vascular and insufficient lymphatic drainage in many solid tumors, those NCs correctly spread extravasate and remain within the tumor interstitial (the EPR effect). NCs must be long circulating to accumulate medicines at tumor locations. Coating NCs' surfaces can accomplish this with PEGylation. NCs with a size of 50–100 nm can enter liver cells, whereas those with a diameter of less than 50 nm, it is possible to reach the spleen and bone. To prevent NCs from being absorbed by the liver and to increase their distribution in the bones, the size of NCs must be reduced. By protecting the medications against quick clearance, extending the time spent circulating, and increasing the concentration of drugs at tumor sites, functionalized smart nanocarriers could deliver chemotherapeutic agents, improving therapeutic efficacy and minimizing side effects. The shortcomings of conventional anticancer drug delivery systems, such as their burst release, non-specificity, and severe adverse effects and harm to healthy cells, have been overcome using nanocarriers. These carriers, which also promote preferential accumulation at the target location, enhance antitumor medication bioavailability and therapeutic effectiveness. Numerous nanocarriers have been created, but only a small number of them have received clinical approval to transport anticancer medications to their designated regions of action [102] (Fig. 5).

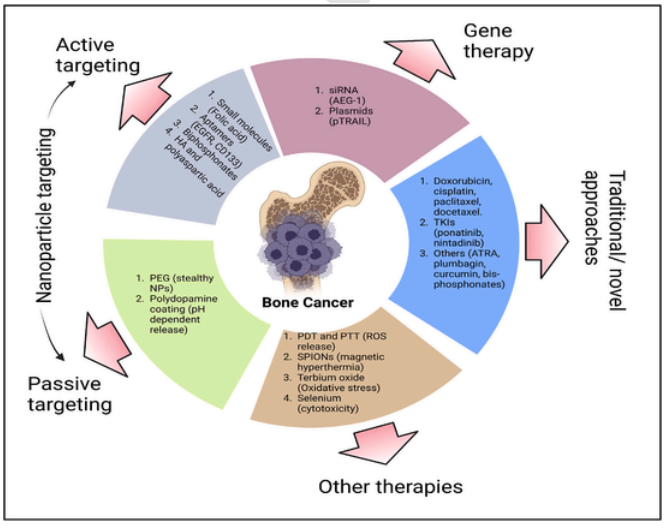

Fig. 4. Schematic representation of the different approaches for theranostic nanoparticles delivery to bone primary and metastatic tumors.

8. Types of nanocarriers for the treatment of bone cancer

8.1. Liposomes

Drugs with a variety of solubility can be enclosed in liposomes, in which water-soluble Drugs can be sealed in the center watery core, while hydrophobic medicine can be confined by the lipid bilayer [103]. The first nanocarriers that have been successfully modified for use in clinical settings are liposomal formulations. In addition, several liposomes used in cancer therapy have received approval from the Food and Drug Administration of the United States or have passed various clinical trials, comprising those for the management of osteosarcoma [104]. Surface-modified liposomes accompanying various modifications display better discrimination, less overall clearance more interminable, well-controlled medicate discharge, and circulation time [105]. Over the past few years, numerous nanoscale liposomes have been investigated for the delivery of anti-osteosarcoma agents. Liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE), involving clinical trials, has been revealed to increase the long-term survival of individuals with osteosarcoma, both fundamentally and clinically [106]. Normal liposomes can be regarded and removed with the

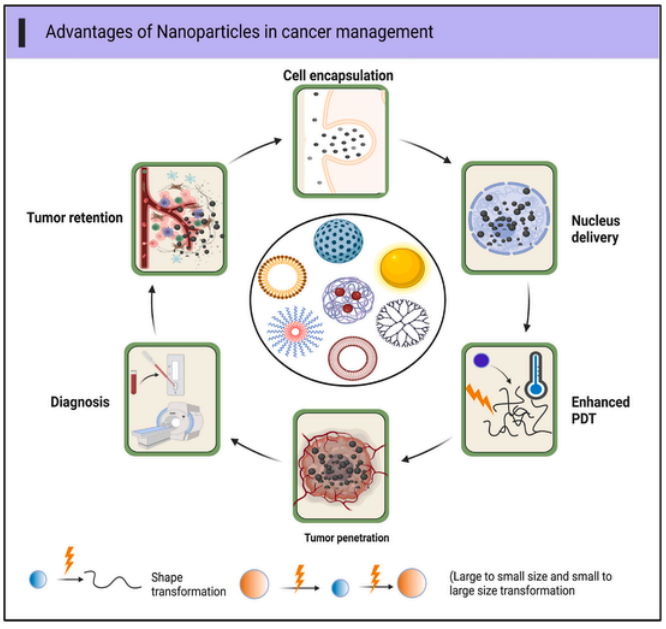

Fig. 5. Advantages of Nanoparticles: Smart transformable nanoparticles could undergo size or shape transition as the requirement of different conditions, showing great potential in future tumor theranostics.

aid of using RES. For instance, the biocompatible hydrophilic polymer polyethylene glycol (PEG) may be hired to regulate surfaces to useful resource liposomes in escaping from RES and extend circulate duration. PEGylated liposomal NCs co-loaded with hydrophobic Clofazimine and hydrophilic Gemcitabine have currently been discovered to have anti-osteosarcoma properties [107]. The hydrophobic clofazimine was confined in a lipid bilayer while the hydrophilic gemcitabine was enveloped in the aqueous core. Furthermore, despite staying stable, this co-loaded nanoscale formulation displayed synergistic cytotoxicity on osteosarcoma cells *in-vitro* [107]. H. Liu et al. [108], have designed a type of hydrophobic natural antitumor drug called betulinic acid-loaded PEGylated liposomes coated in gold Nanoshells. Other intelligent PEGylated liposomal formulations containing DOX for the treatment of osteosarcoma have also been reported [109].

8.2. Micelles

Micelles, often created by amphiphilic polymers, have garnered a lot of interest as potential NCs for drug delivery vehicles. Tumor-targeting moieties can be added to the micelle's outer shell, while the typically hydrophobic micelle core can capture poorly water-soluble agents [110,111]. Micelles, rather than liposomes, are regarded to be more suitable for less water-soluble compounds [112]. The use of different micelles for the treatment of osteosarcoma has been documented in numerous studies [113]. Fang et al. [114] have developed and produced DOX delivery using RGD-modified PEG-block-poly (trimethylene carbonate) block copolymers. A novel DOX conjugate micellar delivery technique is generated by Stewart A. Low et al. [115] for the treatment of osteosarcoma.

8.3. Dendrimers

Dendrimers are water-soluble macromolecules that are globular, radially symmetric, nanoscale, and have a high density of changeable functional groups [116]. The “proton sponge” consequence caused by the many tertiary amines in them makes it easier for medications or nucleic acids to be released from endosomes [117]. Drugs can either be covalently linked to their surface functions or noncovalent contained in their internal cores. Cationic dendrimers are excellent NCs for gene delivery due to the ample cationic groups, which not only provide a variety of nucleic acid binding sites but also boost the efficacy of gene transfection [118–120] thus qualifying them as desirable nanocarriers for transporting drugs and genes. Surface variation is a frequently utilized technique to lessen the charge and get around these issues. Dendrimers as chemo-drug or gene delivery systems in osteosarcoma have been studied. Generation 5 (G5) PAMAM dendrimers and DOX have recently been added to alginate (AG) nano gels to create a novel class of DOX-containing nano gels [121]. The nano gels' stability, DOX loading capacity, and *in-vitro* release profile have all been enhanced by the G5 dendrimers' presence. Meanwhile, the dendrimer's charge could be protected by coating with AG, making them more biocompatible. The researchers have also discovered that human osteosarcoma cells are capable of successfully internalizing the DOX-loaded nano gels, which then intracellular get delivered DOX to exert its cytotoxicity [121].

8.4. Inorganic nanocarriers

Metallic particles like gold, silver, and copper, as well as metallic compounds like oxides and Mxene, as well as hybrid polymers made of groups like metal-organic frameworks (MOFs), can all be used as metallic nanocarriers [122]. The most frequently researched pure metallic N·P.s for osteosarcoma treatments are gold and silver. Because of their exceptional properties, such as their high surface area to volume ratio, solid nature, multi-functionalization, ease of synthesis, high permeability, retention effect, and photothermal conversion capability, gold nanoparticles (AuNPs) have long been considered a potential device for cancer therapy [123,124]. The proliferation of osteosarcoma cells could be inhibited by spherical glycogenic Au NPs, according to a study by Rahim et al., [125]. Steckiewicz et al. [126], have examined how the geometry of Au NPs has affected their ability to kill osteosarcoma cells, and they have found that stars are more toxic than rods and spheres. There have also been reports of AuNPs in osteosarcoma as carriers for drugs or genes [127]. It has been noted that gold Nano shells exhibit strong near-infrared (NIR) absorption as well as high photothermal conductivity. A gold Nano shell-lined liposomal drug shipping gadget has been created by Liu Y et al. [128]. The nanocarriers may want to quickly convert NIR from mild to warmness upon NIR irradiation, increase mobile absorption, and reason the discharge of medicines. The cytotoxic results of silver NPs (AgNPs) in osteosarcoma have been studied in addition to AuNPs [129,130]. Most of the metal compounds primarily based on totally NPs used to combat osteosarcoma are metal oxides that can act as inherent healing mediators without the addition of chemotherapy drugs. For instance, osteosarcoma cells are used to assess and affirm the anti-most cancers result of titanium dioxide (TiO_2), terbium oxide (Tb_2O_3), zinc oxide (ZnO), and cerium oxide (CeO_2) NPs [131–133]. However, these studies have not gone any further in looking at the biocompatibility and anticancer efficacy *in-vivo*, Iron oxide, such as ferric oxide (Fe_3O_4), has been the maximum often researched metallic oxide nanomaterial in osteosarcoma. Fe_3O_4 NPs with a Gemcitabine conjugate have been successfully made by Popescu et al. [133]. Additionally, the cytotoxicity of these nanoconjugates against human osteosarcoma cells has shown promising results [134].

8.5. Mesoporous silica nanocarriers

Mesoporous silica NPs (MSNs) have been a cynosure for medicate or gene delivery since of their exceptional properties: a clear manufacture handle, uniform morphology, movable molecule estimate, variable surface, tunable pore estimate, and volume, and FDA-recognized biosafety [135]. MSNs can load a variety of agents with a high loading capacity because of their porous structure and vast surface area. MSNs can accomplish tumor targeting and regulated drug release due to surface modification with various functional groups [136]. It has also been extensively reported that MSNs are used in osteosarcoma as medication or gene delivery vehicles. Shahabi et al. investigated the effects of MSN surface changes on DOX encapsulation and release from cancer cells [137]. In contrast to non-functionalized MSNs, antibody-conjugated MSNs, or even free DOX, they discovered that sulfonate-functionalized MSNs exhibit increased doxorubicin entrapment and *in-vitro* release. Paris et al. have designed a smart hierarchical ultrasound-responsive MSN. Raising the temperature of the MSNs using ultrasound, the PEG shell will get separated from it, exposing the positively charged surface favoring particle internalization, which heightens the cytotoxic effect [138] Martnez-Carmona et al. established tumor-targeted, pH-responsive MSNs loaded with DOX for osteosarcoma therapy [139]. The anticancer efficacy of this nanoscale drug carrier may be increased while its toxicity to healthy cells may be decreased. Lu et al. [140], have shown that smart MSNs have significant photothermal chemotherapeutic synergy and high specificity for osteosarcoma. When compared to other inorganic nanocarriers, MSNs are thought to be superior which makes them more efficient in cancer therapy.

8.6. Carbon-based nanocarriers

An excellent photo-thermal conversion ability, excessive adsorption capacity, and the easy-to-adjust surface of nanomaterials derived from carbon such as carbon nanotubes (CNTs), graphene oxide (GO), mesoporous carbon (MC), and carbon dots (CD) have attracted the massive interest of worldwide researchers to explore them as drug delivery vehicles in cancers therapy [141,142].

The most regularly cited carbon nanomaterials in osteosarcoma have been GO and CNTs. Tang et al. [143] assessed the harmfulness and fundamental action of GO on osteosarcoma cells and established numerous customs like ROS production, apoptosis, and autophagy working out means to mitigate the impact of the GO-caused anti-osteosarcoma effect. Recently, graphene oxide-chitosan NPs with pH sensitivity has been created to hold siRNA, and the nanocarrier has proven green siRNA launch in acidic circumstances [144]. Trastuzumab (TRA), an anti-HER2 antibody, has been noncovalently attached to GO to generate stable TRA/GO nano-complexes, which have shown dramatically improved HER2-binding efficacy as well as potent anti-osteosarcoma properties [145]. In addition to this, CNTs have garnered a lot of interest in cancer therapy. Single-walled carbon nanotubes and graphene have been combined to produce a hybrid material called G/SWCNT, which Yan et al. [146] have tested for cytotoxicity against osteosarcoma cells. When graphene and SWCNTs were compared to the G/SWCNT hybrids, cytotoxicity was found to be lower. Cheng et al. [147], engineered PLGA-modified CNTs to deliver the pro-apoptotic protein caspase-3. The conjugate demonstrated a high rate of transfection and a sizable *in-vitro* anti-osteosarcoma effect. Another study found that SWCNTs could precisely kill the dedifferentiation process that TGF-α-induced osteosarcoma cells undergo, as well as the development of stem cell phenotypes [148].

8.7. Calcium phosphates nanocarriers

Calcium phosphates (CaP) NPs, in particular, hydroxyapatite NPs (HANPs) are regarded to be attractive nanocarriers for bone tissues because they are environmentally friendly, non-immunogenic, pH-sensitive, and easily modifying [149,150]. Studies revealed that these particles preferentially accumulate in bone tissues. CaP-based NPs are frequently employed to deliver anticancer drugs in osteosarcoma [151–153]. CaP-alginate nanocomposite loaded with anticancer medicines engineered by Son et al. reported in the literature [154]. Using electrostatic contact and hydrogen bonding, the CaP-polymer-drug complexes were manufactured. Drug-loaded nanocomposite displayed anticancer activity on osteosarcoma cells and demonstrated an extended drug release at pH 7.4 and an instant release at pH 4.5 required for the therapy. Wang et al. reported a new class of biodegradable and pH-sensitive hydroxyapatite NPs as Se-HANs [152], and tested them for *in-vitro* and *in-vivo* evaluation of osteosarcoma growth. Through a caspase-dependent apoptosis pathway that is built into tumor cells and is coordinated synergistically with ROS production, the selenium unconfined from Se-HANs may cause tumor cell apoptosis. Table 2 describes several osteosarcoma-targeted medication delivery techniques and their pharmacological efficiency [153–166].

9. Advanced nanocarrier-based treatment

9.1. pH-responsive nanocarriers

Blood has a pH of about 7.4, whereas tumors have extracellular pH between 6.0 and 7.2. Both Endosomes and lysosomes have a pH of 5.0–6.0, while endosomes adhere to the lower range of pH 4.0–5.0 [167]. These pH-sensitive nanocarriers can stock and maintain anticancer drugs at physiological pH even during the hasty release of medicines in an acidic environment [168]. Recently, the use of pluronic block copolymer F127 has been exploited and utilized in the fabrication of mesoporous zinc hydroxyapatite (ZnHAP) as a promising drug delivery vehicle [169]. Methotrexate (MTX), a commonly used chemotherapeutic drug, was used for the surface modification of NPs using an amide bond. In the occurrence of basic pancreatic protease from cows, NPs were evaluated for MTX release at various pH values from 4 to 7.4 [169]. A considerable quantity of MTX was released at pH 4.0 to simulate lysosomal environments. A multifunctional Nano device operating

Table 2
Several osteosarcoma-targeted medication delivery techniques and their pharmacological efficiency.

NPs Types	Targets	Cargos	Effects	Ref
HANPs	Medronate	JQ1	Selectivity and greater toxicity to OS cells in comparison to primary fibroblasts	[153]
LbL liposomes	alendronate	DOX	Speedy and efficient cell uptake; *in-vitro* Superior accumulation in xenografts	[155]
BP NPs	BP	DOX	Increased cell uptake and therapeutic effect *in-vitro* compared to free DOX Tumor targeting capability, prolonged tumor site retention	[156]
Lipopolymer NPs	LC09 aptamers	CRISPR/Cas9 plasmids encoding VEGFA gRNA and Cas9	Improved cellular uptake, successful gene silencing, and improved antitumor effects *in-vitro*. CRISPR/Cas9 has a superior tumor suppression effect when expressed and distributed specifically in tumor cells in vivo.	[157]
Polymeric NPs	CD133 aptamers	salinomycin	*In-vitro:* enhanced cytotoxicity to CD133 + OS cells due to specific internalization by CD133 + OS cells. Better antitumor activity in vivo, lower proportion of CD133 + OS cells	[158]
lipid-polymer NPs	CD133 aptamers	ATRA	*E*nhanced cytotoxic effect on CD133 + OS cells with specific targeting to CD133 + OS cells *In-vivo:* improved antitumor activity, lower proportion of CD133 + OS cells	[159]
polymer-lipid hybrid NPs	EGFR aptamers	salinomycin	Increased cellular absorption and cytotoxicity in comparison to non-targeted NPs and free salinomycin, and a decrease in the number of CD133 + OS cells *in-vitro* None *in-vivo*	[160]
liposomes	HA	DOX	*In-vitro:* more cytotoxic to MG63 cells than LO2 cells, preferentially internalized to MG63 cells over LO2 cells Strong and long-lasting selective tumor accumulation and heightened antitumor effects *in-vivo*.	[161]
liposomes	HA and alendronate	DOX	Dual targeting, fast internalization of liposomes were more toxic than other liposomes *in-vitro;* Improved tumor targeting competence and antitumor effects *in-vivo*	[162]

(*continued on next page*)

Table 2 (*continued*)

NPs Types	Targets	Cargos	Effects	Ref
polysaccharide derivative NPs	folate	AEG-1 siRNA	Improved cellular uptake and transfection effectiveness *in-vitro*, as well as improved anti-proliferation and anti-invasion properties Greater tumor-suppressive effects *in-vivo* than with non-targeted nanocomplex	[163]
polymeric micelle	RGD	DOX	Improved cell targeting capabilities and a more potent antitumor effect *in-vitro* None *in-vivo*	[164]
MSNs	RGD	DOX	Enhanced tumor cell uptake *in-vitro* Outstanding tumor targeting ability *in-vivo*	[165]
liposomes	YSA	DOX	*In-vitro*: higher and more nuclear uptake than non-targeted liposomes *In-vivo*: none	[166]

NPs, nanoparticles; HANPs, hydroxyapatite nanoparticles; JQ1, a small-molecule bromodomain inhibitor; OS, osteosarcoma; LbL, layer-by-layer; DOX, doxorubicin; BP, bisphosphonate; ATRA, all-trans retinoic acid; EGFR, epidermal growth factor receptor; HA, hyaluronic acid; AEG-1, astrocyte elevated gene-1; RGD, arginine-glycine-aspartic acid peptide; MSNs, mesoporous silica nanoparticles; YSA, a 12- amino acid peptide which is an Ephrin A1 mimic and a ligand for EphA2.

as a drug delivery platform with pH sensitivity has been created by a different research team [170]. An acid-cleavable acetyl linker remained to bind a polyacrylic acid (PAA) shell to the surface of the MSNs, inhibiting the early release of the drug and giving the nanocarrier pH-responsive capabilities. In both the protein-containing cell culture medium and the protein-free PBS, the release rate was much higher at pH 5.3 as compared to pH 7.4.

9.2. Redox-responsive nanocarriers

The disulfide bonds in nanocarriers can be weakened by glutathione (GSH), a potent antioxidant. GSH values vary from 2 to 10 mM in interior habitats and from 2 to 10 mM in environments outdoors. It has been found that the attention of GSH in most cancer cells improves much more than in healthy cells. Once the nanocarrier is internalized, the distinction in redox ability between intracellular and outside quantities of GSH may be exploited for intracellular regulated drug release [171]. Redox-touchy and tumor-centered nanocarriers have been created with the aid of Chi et al. [172], to beautify osteosarcoma treatment. A particular removable PEG coupled with LDL cholesterol through a reducible disulfide linker is utilized to stabilize the liposomes. *In-vitro, the* issue of DOX was tightly regulated at physiological conditions, while the more than 60% burst release in the presence of 10 mM GSH was seen in comparison to non-redox sensitive nanocarriers.

9.3. Light-responsive nanocarriers

There has been extensive use of light with a certain wavelength has been widely utilized as an outward stimulus for starting on-demand medication administration because of its noninvasiveness and spatiotemporal accuracy [173]. A recently developed visible light-responsive MSN was tested in osteosarcoma cells for drug release and anticancer efficacy [174]. Through ROS-cleavable connections, porphyrin Nano caps inhibit the pore outputs of drug-loaded MSN. Porphyrin Nano caps may yield ROS when exposed to visible light that can break sensitive bonds, leading to pore uncapping and drug release. Some nanomaterials with high NIR light absorption rates have the potential to convert photon energy into heat, raising the localized temperature and causing the release of drugs from nanoplatforms [175].

9.4. Magnetic field-responsive nanocarriers

With the use of a magnetic field, magnetic NPs can transform magnetic energy into heat. The drug-loaded nanocarriers may undergo structural changes because of the heat produced by these particles, leading to “on-demand” drug release [176]. Rare reports of osteosarcoma involve the use of magnetic field-responsive NPs for medication delivery. To deliver DOX locally and as needed, Jalili et al. [177], combined thermo-responsive polymers and magnetic NPs to create an injectable Nano engineered hydrogel. This nanocomposite drug release was temperature responsive, and drug release was even further improved by altering the magnetic field.

9.5. Stimuli-responsive nanocarriers

Nanocarriers that respond to stimuli are used to delay the release of drugs. There are two ways to design drug delivery systems that react to stimuli: endogenous and exogenous. Endogenous stimuli, additionally called organic or inner stimuli, are described as unique inner factors, gifts inside the tumor microenvironment or interior of most cancer cells that could act as particular activities for managing drug launch, prodrugs activation, endosome/lysosome escape, and tumor-unique imaging [178]. It takes precise substances to reply to predetermine endogenous stimuli, which purpose the rapid launch of the enclosed drug with the aid of using the shape of nanocarriers, to create a kind of shipping system. The structural rupture of the nanocarriers caused by exogenous stimuli such as heat, magnetic fields, electronic fields, etc., might lead to drug release at the besieged tissue [179,180]. The ability to control the location and intensity of the stimuli, the addition or removal of external stimuli based on the situation, the ability to use multiple external stimuli to achieve multi-functional performance in cancer theranostic, and the ability to administer stimuli for hours to days are the main advantages of these stimuli. However, external stimuli would not be practical for certain metastatic lesions whose location is uncertain. To attain effective targeting of different cancers, researchers have recently been concentrating on the different stimulus-responsive systems [181,182]. Table 3 [183–187] lists the various stimulus-responsive nanocarriers reported against O·S., and the same are detailed here. To target osteosarcoma, Ting and colleagues created hyaluronidase-responsive multilayer liposomes (HRML) bearing cisplatin and Nrf2 siRNA (siNrf2). HRML considerably could slow down the growth of Tumors in

Table 3
The reported stimuli-responsive nanocarriers for the treatment of OS.

Type of nanocarrier	Therapeutic	Type of stimuli	Outcomes	Ref
NPs	DOX and PTX	reduction/pH	Greater cytotoxicity against K7 cells in vitro compared to free DOX and PTX, plain DOX NPs	[183]
Hydrogel	MTX and ALD	Thermosensitive	ALD and MTX release that is sustained *in-vitro*. Significant tumor-inhibiting effect in mice when performed *in-vivo*.	[184]
CeO2NPs	DOX	pH sensitive	pH-dependent controlled release of DOX.	[185]
Liposomes	DOX	Reduction and (GSH) sensitive	*R*emarkable cytotoxicity to MG63 OS cells than LO2 liver cells.	[186]
Hydrogel	PLK1-shRNA and DOX	Thermosensitive	Hydrogels loaded with a single drug exhibit exceptional cytotoxicity.	[187]

xenograft osteosarcoma mice, along with the fewest systemic side effects [188].

10. Nanoparticulate therapeutics and their active targeting

Active targeting can be accomplished with the use of targeting molecules such as particular ligands coupled to medication molecules. NPs' surfaces can be embellished with specific ligands to enable active payload targeting. To target bone, the chemicals that attach specifically to the H.A. are employed as therapeutic carriers (ligands). Compounds such as bisphosphonates (BPs), phosphonic acid, MAbs, and oligopeptides can be employed as carriers (ligands) in NPs targeting the bone because of their strong affinity for HA [189,190]. Table 4 [191–197] represents the various actively targeted nanocarriers for OS.

11. Shape effect of NPs in cancer targeting

Recent developments in NPs technology have made it possible to fabricate NPs classes in a variety of sizes, shapes, and materials, which has significantly advanced the area of nanomedicine. Nanomedicine offers several advantages and cutting-edge methods for addressing the complexity of cancer because of the special material features that emerge at the nanoscale. To get to the target location, NPs must pass through several bio carriers created by the tumor's aberrant physiology, which includes physically impaired vasculature, erratic blood flow, high interstitial fluid pressure, and irregular extracellular matrix [198].

Table 4
Active targeted NPs reported for osteosarcoma treatment.

Type of nanocarrier	Targeting moiety	Bio-active	Outcomes	Ref
Lipid-polymer NPs	CD133 apt	ATRA	Ligand decorated NPs significantly reduced tumor volume in BALB/c nude mice bearing osteosarcoma xenografts	[191]
Liposomes	HA	DOX	Potent tumor suppression as NRS and NHA liposomes in MG63 xenograft mouse model.	[192]
PMs	RGD	DOX	Remarkable cytotoxicity against MG-63 and MNNG/HOS OS cells than non-targeted DOX PMs.	[193]
LC09-PPC-CRISPR/Cas9 NPs	LC09 aptamers	CRISPR/Cas9 plasmids encoding VEGFAgRNA and Cas9	Increased cellular uptake over PPC-CRISPR/Cas9. Enhanced LC09-PPC-CRISPR/Cas9 NP accumulation in mouse lung	[194]
BP nanoparticles	BP	DOX	*In-vivo*: Mice bearing Saos-2 human OS xenografts have enhanced antitumor efficacy compared to free DOX.	[195]
Polymeric NPs	CD133 apt	SAL	Surface modified NPs shown increased cytotoxicity to Saos-2 CD133+ and U-2 OSCD133+ cells than SAL-NP.	[196]
LbL liposomes	Alendronate	DOX	Ligand appended LpL liposome showed an improved anti-tumor efficacy in nude mice bearing 143 B xenografts.	[197]

The first design guidelines on the consequence of NPs magnitude on tumor dosage and anticancer effectiveness have been developed to circumvent the aberrant bio barriers present in tumors [199]. According to a study, blood circulation that affects tumor accumulation, tumor retention, and drug release, is significantly impacted by NPs size [200]. Recent research has demonstrated that the link between particle size and hemodynamics of the Tumor location greatly influences the transport of NPs in that region [201]. The extravasation of NPs is dependent on capillary filtration, which finally depends on the hydrostatic pressure gradient [202,203]. Due to increased vascular leakiness and decreased lymphatic drainage, the usual IFP of solid tumors is typically substantially higher than that of normal tissues. Thus, the degree of resistance to NPs extravasation in tumors is determined by the normal decreased blood flows and elevated interstitial flow pressures (IFP) in tumors. In this condition, faster blood flow patterns are required to offset increasing IFP in tumors as particle size increases. Several manufacturing methods have enabled the production of highly precise non-spherical NPs in a variety of sizes and shapes. These NPs are made of various materials and have varying degrees of flexibility. Particles with two-dimensional polygonal, three-dimensional polyhedral, rod shapes, branching structures, and other complicated forms like snowflakes are created using diverse techniques [204,205]. NPs must first be able to move through the blood circulation without being absorbed by macrophages, especially in the RES system, to reach and bind to their biological target [206–209]. A spherical NP's propensity to marginate depends on its size [210]. Large spherical NPs are transported mostly by convection, which makes it more difficult for them to migrate away from the flow and toward the vessel wall. The transference of smaller NPs has a suggestively higher diffusion component that makes it easier for them to travel laterally in the blood artery [211]. It is anticipated that an NP's form may impact the pace of tumor deposition and therapeutic effectiveness since it influences the binding affinity, NPs blood circulation, and ability to marginate. The EPR effect and subsequent therapeutic efficacy have both been thoroughly demonstrated to be influenced by NPs size [212]. Based on vascular pharmacokinetics, pore size, and capacity to overwhelm high interstitial pressures via flow-induced convection, these investigations have determined that 100 nm is the ideal length for the deposition of spherical NPs into tumors. Different types of tumors have exclusive vascular wall pore shapes along with diverse tumor microvascular systems. The consequence of NPs size and shape on drug delivery is illustrated in Fig. 6.

12. Challenges for nanoparticulate drug delivery in OS

Under good manufacturing practices (GMP) guidelines, the production of NPs must be scalable, controllable, and reproducible [213]. There can be significant changes in the physicochemical characteristics and properties of NPs by modifying raw materials and manufacturing methods. The biological effects of the nanomedicines are ultimately influenced by these physicochemical changes. Finding the best techniques to explain the biological or physicochemical characteristics of NPs is also difficult from a technical and regulatory perspective. Despite the remarkable progress made in NCs for OS therapy, a few challenges still need to be overcome. In addition to the ineffective diffusion of drugs into tumor cells, the arbitrary targeting, and the absence of the EPR effect in a few cancers, NCs that passively target tumors using the EPR effect also have some disadvantages. B.P., for instance, aggressively targets the bone more successfully than OS at the same time. Furthermore, prolonged BP exposure in bone tissue may suppress osteoclast activity and bone homeostasis [214]. Due to NPs' interaction with cells and biomolecules, their safety profile is subsequently changed. Regulating bodies have devised strict protocols for clinical studies of NPs because of poor understating of long-term effects on human health. In addition, the clinical trials of NPs are cost-consuming and require a rigorous approval process before they can be used on humans. Before

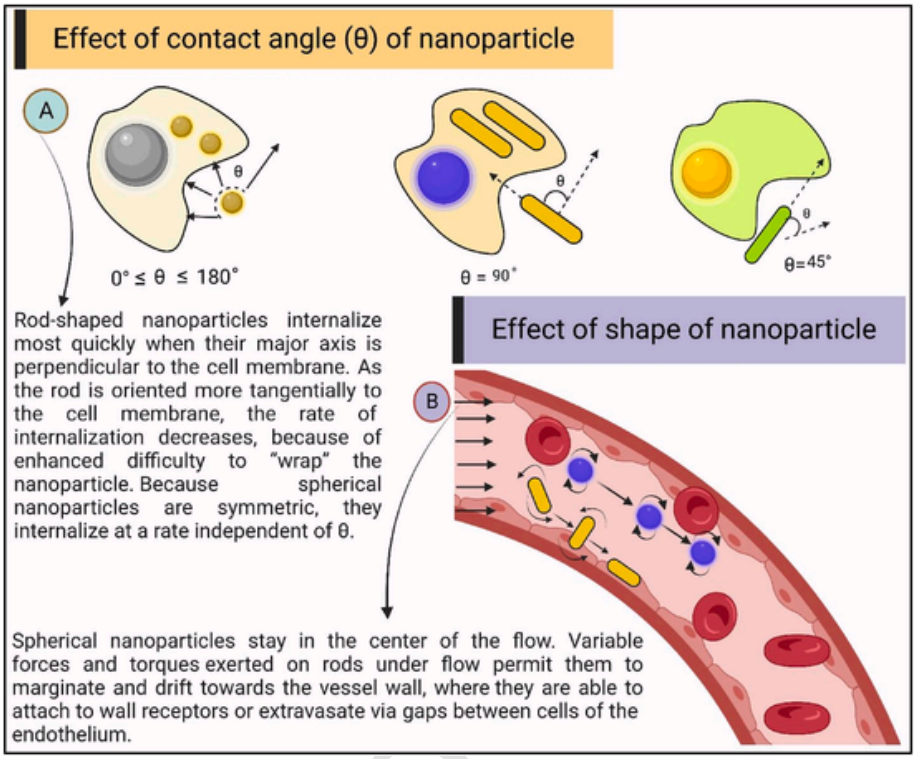

Fig. 6. (A) Impact of contact angle in the internalization of nanoparticles. (B) Effect of shape of nanoparticles on the retention and flowing into the blood vessels.

using nanomedicines in clinical settings, significant research is required to discover any potential toxicities. Although there are numerous nanomedicines on the market, their production, biophysical characterization, and clinical application have been hindered by the absence of specific regulatory guidelines.

13. Regulatory issues of nanomedicines

Despite the excitement around the newly emerging subject of nanotechnology, there's still a dearth of guidance in this area. Many nanomedicines work by interacting directly with genetic materials or with biomolecules necessary for normal genome functioning and cell division [215], all of which can result in genotoxicity and mutagenicity [216]. The inflammatory response of neutrophils and macrophages causes the creation of reactive oxygen and nitrogen species, which generate oxidative and nitrosative stress [217]. The accumulation of these kinds of free radicals in the human body could result in serious harm [218]. This damage may take place in several ways, including generating oxidative DNA damage, which leads to sequence damage, protein denaturation, and lipid deposition causing cancer, causing damage to mitochondrial membranes leading to cell death and necrosis, and transcription of genes responsible for carcinogenesis and fibrosis [219]. A lot of data demonstrates the accumulation of these particles inside the liver and transfer to sites such as the central nervous, cardiovascular, and renal systems when delivered intravenously [220]. There are simply too many unresolved issues in the case of particles that cannot be tracked after delivery. Many nanomedicines' specific interactions with biological systems are yet unknown, making comprehending, recognizing, and drawing conclusions concerning their physicochemical and toxicological includes challenging.

However, in the absence of unified regulatory guidance in this field, much has changed. It should also be noted that 'one-size' does not fit all in this process, as the distinctive characteristics observed at the nanoscale are highly dependent on nanoparticle type, surface properties, administration route, and, particularly, nanoparticle morphology, which can be diverse, something that is certainly slowing down the regulatory procedure. In the past, regulatory bodies were correct to be cautious; market permission had been granted for nanoparticles utilized in medical imaging, only to be withdrawn after the development of unexpected patient events after administration [221]. The European Medicines Agency (EMA) declined a recommendation for marketing authorization. It withdrew Sinerem®, an ultra-small superparamagnetic iron oxide (USPIO) contrast agent for magnetic resonance imaging (MRI), from the market in 2008 due to issues expressed in clinical trials. These concerns included significant adverse reactions involving muscle pains, notably in the lower back, and also allergic reactions that resulted in one death. As a result, it was determined that the hazards linked with this specific Nano molecule significantly outweighed any potential advantages, and it was refused marketing authorization [222]. The US Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the European Commission's Health and Consumer Protection Directorate have all taken steps to address the possible concerns posed by nanoparticles [223]. Local (or semi-local) communities have put together and sponsored initiatives such as the REFINE project, which seeks to clarify the criteria for regulatory demands for the clinical application of nanomedicines and nanomaterials [224]. The FDA released a first draft of guidelines in June 2011 despite criticism for their lack of nanoparticle regulation; nevertheless, a definitive guidance document for nanoparticles in medicine has not yet been established [225]. Despite the urgent requirement for a formal regulatory document, the FDA keeps disregarding previously collected data on toxicity profiles; rather, they are taking a precautionary approach to the regulation of Nanomedicine, possibly in the hope of preventing future negative public opinion, treating them as an equal counterpart to their bulk equivalent. This may lead to a delay in the commercialization of nanoproducts [226].

Arguably, the biggest issue for the regulation of nanomedicines is the fact that regulatory bodies such as the FDA use safety data based on bulk materials, which do not display the same pharmacodynamics and pharmacokinetics. The fact that regulatory authorities such as the FDA

employ safety information based on bulk materials, which cannot demonstrate the same pharmacologic and pharmacokinetic activities as nanomedicines, is arguably the biggest hurdle to the regulation of nanomedicines [227]. This means that data generated on safety and efficacy will not be typical of what might happen when the nanomedicine is utilized in clinical settings once it has received marketing authorization. This causes problems when developing regulations for the safety and efficacy criteria of nanomedicines because a non-nano version may meet regulatory standards, but a nanomedicine may not. Defining the pharmacokinetics of nanomedicines is a significant regulatory obstacle [228,229]. The use of safety data based on bulk materials by regulatory agencies such as the FDA, that can't demonstrate the same pharmacologic and pharmacokinetic actions as nanomedicines could be to be the biggest obstacle to nanomedicine regulation [227]. This implies that data obtained on both safety and effectiveness will not be representative of what could occur when a nanomedicine is used in clinical settings after it has been approved for commercialization. This creates issues when designing regulations for nanotechnology safety and efficacy criteria since a non-nano version may meet regulatory standards, but a nanomedicine may not. The definition of nanomedicine pharmacokinetics is a serious regulatory issue [228,229]. This is due to the diverge from the typical path of tiny medication molecules. As a result, they are bioavailable for a longer amount of time, posing a serious threat to the general people if nanotechnology products were to be used over the counter. The regulatory bodies must decide if a specific nanomedicine should reach the market under careful supervision or be accessible over the counter. However, due to the lack of toxicity information and statistics currently accessible, it is very difficult to provide a definite answer on this subject. Another difficulty with regulating nanomedicines is the question of who should be in charge of developing nanomedicine guidelines. This decision involves a consultative process that involves many stakeholders made up of academics and clinicians. Thus, there is a further instant need to establish regulatory, high-caliber laboratories at a federal level along with risk assessment of personnel, guidelines, and technical standards needs to be developed.

Notwithstanding the absence of explicit regulatory guidance, more than fifty nanomedicines have entered the market, and the number is constantly rising. These are mainly used for cancer therapy due to the difficult toxic chemicals required and the challenging tumor landscape, which hinders effective treatment. The lack of institutional regulation of nanomedicines and nanomaterial synthesis for health-related purposes is a global issue. Due to inconsistencies across government bodies, certain nanomedicines are classified as medical devices while others are classified as medicines. What is deemed fit for purpose in one jurisdiction does not transfer to others. Because tiny substances tend not to be licensed globally for this reason, the nanomedicine community demands urgent coordination throughout the government sector for development to continue according to expectations.

14. Clinical trials

Cancer clinical trial recruitment has been recognized as a sign of quality care and is regarded as being the best practice. Clinical trials allow for rigorous testing of novel medicines with the potential to enhance survival for future generations of cancer patients. Because of the discomfort, higher fracture risk, poorer quality of life, and decreased overall survival outcomes, bone metastasis is a difficult-to-treat medical condition. Multiple cancers can colonize the microenvironment of bones and develop metastatic lesions. Understanding recent advances in bone metastasis research is critical for developing new bone-targeted medicines. The numerous current clinical trials are expected to end in better treatment options for people with bone metastatic malignancies [230]. There are numerous fascinating alternative therapies in preclinical development and clinical trials at present, providing hope for improved therapies and results in people with bone cancer. Table 5 describes the nanomedicines under clinical trial investigation for Osteosarcoma treatment [231].

Table 5
List of 3 clinical trials of nanomedicine for Osteosarcoma [231].

Study Title	Condition	Therapeutic approach	Status
A Phase I Clinical Trial of Neoadjuvant Chemotherapy With/Without SPIONs/SMF for Patients With Osteosarcoma	Osteosarcoma	Neoadjuvant chemotherapy + SPIONs/SMF	Not yet recruiting, Phase 1
Construction of Microfluidic Exosome Chip for Diagnosis of Lung Metastasis of Osteosarcoma	Osteosarcoma	Not mentioned	Completed
NanaBis™ an Oro-buccal Administered delta9-Tetrahydrocannabinol (d9-THC) & Cannabidiol (CBD) Medicine for the Management of Bone Pain From Metastatic Cancers	Bone Cancer Related Pain	NanaBis™, Oxycodone CR	Not yet recruiting, Phase 3

15. Design of bone-targeted nanomedicine

There are relatively few alternatives to treatment for bone cancer, as evidenced by the unavoidable and destructive progression of metastatic breast, prostate, and blood malignancies. Because it is difficult to eradicate bone cancer, novel, alternative treatments that control tumor cells and their microenvironment with minimal off-target consequences are required [232]. Due to their versatility in conjugating secondary functional groups, capacity to traverse to the sick site in bone, and customizable drug release kinetics, nanomaterial drug delivery systems have proven enormous potential to treat bone disorders. These potential delivery systems can be constructed from various organic and inorganic materials using a variety of surface modification and bioconjugation processes. As a result, various delivery vehicles and management systems are emerging to treat bone diseases, providing many possibilities for future personalized medication. Concurrently, a greater therapeutic index could be predicted as functionalized nanomaterials can correctly target and distribute medications into subcellular areas [233]. Due to their excellent targeting efficiency, nanomaterial-based drug delivery technologies are transforming traditional medication delivery in orthopedic disorders in terms of efficacy and safety. Despite the tremendous progress made by nanotechnology in treating bone disease, the majority of the findings discussed here continue to be in the early stages of the study. Critical obstacles such as a lack of understanding of Nano toxicity, limited drug-loading capacity, low delivery efficiency, and rigidity of drug release kinetics continue to make nanomaterial-based drug delivery systems difficult to translate into the clinic. Multifunctional nanoparticles may incorporate several therapeutic molecules to operate on the biological target simultaneously, increasing the therapeutic index. Co-delivery of an anticancer medication and a DNA intercalating agent, for example, might exploit the synergistic therapeutic effects of drug and gene loading [234]. Despite numerous obstacles on the path to clinical trials, nanomaterial-based drug delivery systems remain a viable method for treating bone disease due to their excellent targeting and delivery efficiency. The primary benefit of using nanomaterials is that they could be developed and engineered with the same functional moieties to deliver to the particular bone microenvironment and subcellular compartment.

15.1. Encapsulation of anticancer drugs by targeted nanoparticles

Nanomedicines are increasingly being used in tumor therapy as nanotechnology develops. However, biological hurdles in nanoparticle transport remain to limit their use in tumor therapy. Particle size, one of the most fundamental features of nanoparticles, is critical in nanoparticle delivery [235]. PLGA, which has good biocompatibility and degradability, is a popular material for bone-targeted nanomedicine. Drug-loaded PLGA nanoparticles can be made by emulsion or Nano precipitation, in which pharmaceuticals are encased within PLGA during the manufacturing process. PLGA can frequently be functionalized with PEG to escape capture by the reticuloendothelial system and consequently prolong its blood circulation. PLGA nanoparticles can be changed with bone-targeting ligands using one of three methods: post-modification, pre-modification of PLGA monomers, or both [236]. Similarly, amidation between the amine groups on ALN and the carboxyl groups on PLGA has been employed to conjugate ALN onto PLGA nanoparticles [237]. Another often-described strategy for producing bone-targeted PLGA is to pre-modify PLGA monomers. Other targeting ligands, including aptamers, were coupled on PLGA nanoparticles for targeted chemotherapy, in addition to BPs. For targeted drug delivery to osteosarcoma CD133+ stem cells, CD133 aptamer-adorned PLGA was loaded with salinomycin or all-trans retinoic acid. Non-targeted formulation significantly reduced the therapeutic effect on osteosarcoma Saos-2 and U2OS xenograft mice than the produced nanomedicine [238]. The platinum buildup was four times greater in bone metastatic lesions than in healthy bones whenever targeted liposomes were loaded with platinum drugs [239]. ALN-targeted liposomes loaded with doxorubicin exhibited a 70% reduction in tumor size in a bone metastatic breast cancer model [240]. ALN and hyaluronic acid dual-targeted liposomes loaded with doxorubicin also showed a prolonged survival period in an osteosarcoma model [241]. Yan Y et al. (2022) described a bone-targeted protein nanomedicine for the treatment of bone cancer. Saporin, a toxin protein, was co-assembled into a boronated polymer for intracellular protein delivery, and the resultant nanoparticles were coated with an anionic polymer poly (aspartic acid) to shield the nanoparticles' positive charges while maintaining the bone-targeting function. Both *in-vitro* and *in-vivo*, the produced ternary complex nanoparticle exhibited substantial bone accumulation. As a result, the bone-targeted and saporin-loaded nanomedicine could efficiently minimize the progression of osteosarcoma xenograft tumors and bone metastatic breast cancer *in-vivo* [242]. Zhou et al. (2019) discovered a naturally occurring phytic acid (PA) with bone-targeting properties in addition to anticancer potential. *In-vitro* and *in-vivo*, the PA-capped platinum nanoparticles exhibited a high affinity towards hydroxyapatite and maintained both the natural anticancer ability of PA and the photothermal effect of platinum nanoparticles. PA-capped nanoparticles collected four times more in osteolytic lesions than sodium citrate-templated nanoparticles. They effectively prevented bone tumor growth and tumor-associated osteolysis when exposed to near-infrared light [243]. Wang Y et al. (2021) developed polyethylene glycol-conjugated alendronate-functionalized and chloroquine (CQ)-loaded polydopamine nanoparticles (PPA/CQ) to break the vicious cycle of bone tumor treatment. The nanoparticles were efficiently accumulated in the bone tissues; especially the osteolytic lesions around tumors and the *in-vivo* experiment revealed that PPA/CQ-associated treatment efficiently inhibited both tumor growth and osteolysis [244].

15.2. Covalent conjugation of anticancer drugs by targeted nanoparticles

Targeted nanomedicines comprising physically encapsulated medicines are unstable and may trigger burst drug release during blood circulation. This challenge may be solved by covalently conjugating therapeutic medicines to targeted carriers via cleavable links [245]. Nano precipitation of pamidronate-modified PLA-PEG and PLA-doxorubicin conjugates was used to create the nanomedicine. The material design benefits from excellent drug loading efficiency, complete degradability, and regulated drug release. In orthotopic osteosarcoma mouse models, the targeted nanomedicine significantly slowed the growth of the tumor. Furthermore, it demonstrated improved tumor accumulation and therapeutic effects in dogs with spontaneously occurring osteosarcoma. The developed nanomedicine demonstrated remarkable clinical translation potential in treating malignant bone cancers [246]. Bortezomib is a highly efficacious anticancer medicine for multiple myeloma, but it is less effective for solid tumors due to low penetration and considerable side effects [247]. Through the catechol-boronate linkage, it is readily coupled to catechol-grafting polymers [248]. pH-responsive nanomedicines containing natural polyphenols and bortezomib have been developed using this simple chemistry to treat bone metastatic tumors. PROTACs (proteolysis-targeting chimeras) are synthetic protein degradation strategies. The target protein and E3 ubiquitin ligase are recruited by a bifunctional PROTAC molecule with two covalently coupled ligands to initiate proteasomal degradation of the target proteins by the ubiquitin-proteasome system. This illustrates the PROTAC technique's remarkable capability, as it is not just a potential treatment tool but also a prospective diagnostic method [249].

15.3. Targeted nanoparticles for photothermal therapy of bone tumors

Photothermal therapy offers various advantages over chemotherapy, including excellent therapeutic efficacy, low side effects, time-spatial controllability, a short therapeutic period, and minor drug resistance. In general, the therapy is based on photothermal reagents' high photothermal conversion effectiveness. At the immediate irradiated area, the reagents absorb NIR light and convert it to heat. As a result, it offers a highly localized therapeutic technique for cancer treatment. Based on a recent clinical trial, gold-silica nanoparticle-mediated photothermal therapy successfully ablated tumors in 94% (15 of 16) of patients, and the treatment was shown to be safe and viable in males with low- or intermediate-risk localized prostate malignancies. Photothermal therapy has been recommended as an alternative therapeutic approach for bone cancers [250]. Platinum nanoparticles were used in a groundbreaking investigation [251]. To encourage bone formation, the photothermal nanoparticles were additionally coated with bone-targeting ligands. Photothermal nanoparticles were coupled with Asp-rich peptides in another investigation for bone targeting [252]. A metal-thiol bond was attached to a thiol-terminated D8 peptide to a dendritic platinum-copper alloy nanoparticle (DPCN) [253]. D8-modified DPCN accumulated tibias more than 5-fold more *in-vitro* and *in-vivo*. The bone-targeted nanomaterials significantly suppressed tumor development during photothermal treatment. For bone-targeted photothermal therapy, mesoporous silica-coated gold nanorods adorned with ZOL therapy [254] and melanin-like PDA nanoparticles conjugated with ALN [255] were produced in addition to platinum nanoparticles. These findings demonstrated that focused photothermal therapy could effectively slow the growth of bone cancers. Wang Y et al. (2017) developed a bone-targeted nanoparticle, aspartate octapeptide-modified dendritic platinum-copper alloy nanoparticle (Asp-DPCN), for photothermal therapy (PTT) of bone tumors. Asp-DPCN showed a much higher affinity toward hydroxyapatite and bone fragments than the non-targeted DPCN *in-vitro*. Furthermore, Asp-DPCN accumulated more efficiently around bone tumors *in-vivo* and resulted in a higher temperature in bone tumors during PTT [256].

15.4. Targeted nanoparticles for gene therapy of bone tumors

Gene therapy is a potential treatment option for cancer. Advances in nanotechnology have rendered it possible to deliver nucleic acid-based treatments such as plasmid DNA, mRNA, small interfering RNA (siRNA), and microRNA (miRNA) into tumor cells [257]. Since nucleic

acids are negatively charged and have undesirable physicochemical properties for passing through cell membranes, nanoparticles, and polymers have been used as carriers to deliver nucleic acids inside cells [258]. These compounds may bind nucleic acids, increasing their serum and nuclease stability and encouraging cellular internalization and endosomal escape. Liposomes, dendrimers, proteins, and inorganic nanoparticles have previously been utilized as carriers for genetic therapies [259,260]. Cancer patients may benefit through gene therapy. Nanotechnology advancements have enabled the delivery of nucleic acid-based therapies such as plasmid DNA, mRNA, small interfering RNA (siRNA), and microRNA (miRNA) into tumor cells [257]. Since nucleic acids are negatively charged and have poor physicochemical properties for passing through cell membranes, carriers, that include nanoparticles and polymers, have been used to deliver nucleic acids into cells [258,261,262]. These chemicals can potentially bind nucleic acids, improving their serum and nuclease stability and promoting cellular internalization and endosomal escape. Liposomes, dendrimers, proteins, and inorganic nanoparticles have all already served as genetic therapy carriers [259,263,264].

16. Conclusions

At the outset, Osteosarcoma remedy is difficult due to its unsure etiology, excessive genetic instability, big histological heterogeneity, loss of unique biomarkers, excessive stage of nearby aggressiveness, and the ability for fast metastasis [264]. Although chemotherapy capsules are a success in treating osteosarcoma, nonetheless, are a few detrimental side effects, including damage to wholesome tissues, the improvement of medication resistance, and fast blood clearance. Numerous nanoplatforms are accomplished in precisely distributing the therapeutic material and handing over the healing substance to the tumor site to enhance curative effects and reduce aspect effects. Despite positive trends in tumor biology research and the introduction of several multifunctional drug transport systems that can also additionally preserve the remarkable potential for the dealing of osteosarcoma in the future, those nanomaterials are not suitable for practice in osteosarcoma patients. Despite the significant progress in medication delivery to OS, it is necessary to test the effectiveness of newly created innovative drug delivery systems *in-vitro* and *in-vivo* utilizing a range of animal models. For a better understanding of OS's genetic foundation, animal models are crucial. The majority of the advanced OS formulations and approaches are assessed utilizing *in-vitro* tissue cultures. The lack of a precise depiction of the human state is the main drawback of the renovated OS cell line. Also, during the *in-vitro* culture studies, the OS cell lines show slanted gene expression. The cost and period needed for tumor initiation, growth, and response to the treatment are the two additional drawbacks of OS tissue culture.

Abbreviations

OS	Osteosarcoma
Bone cancer	BC
NPs	Nanoparticles
NCs	Nanocarriers
MDR	Multi drug resistance
EPR	Enhanced permeability and retention
BPs	Bisphosphonates
HA	hydroxyapatite
HPMA	*N*-(2-Hydroxypropyl) methacrylamide
TME	Tumor micro-environment
NK	Natural killer
TDDs	Targeted drug delivery systems
OC	Osteocalcin
NF-κB	Nuclear factor-Kappa beta
IL-11	Interleukin 11
OPG	Osteoprotegerin

Funding

Not applicable.

Availability of data and materials

Data sharing does not apply to this article as no new data were created or analyzed in this study.

Ethical statement

Not applicable.

Author contributions

Conceptualization & writing; Sumel Ashique, Md. Faiyazuddin, Investigation; Obaid Afzal, original draft preparation; S. Gowri, Review and editing; Afzal Hussain, Formal analysis; Neeraj Mishra, Software; Ashish Garg, Shayan Maqsood, Mohammad Shabib Akhtar, Visualization & supervision; Abdulmalik S.A. Altamimi.

Uncited References

[2]; [3]; [17]; [18]; [45]; [260]; [261]; [262]; [263], [42].

Declaration of competing interest

No conflict of interest after all.

Data availability

No data was used for the research described in the article.

Acknowledgment

The authors are thankful to Pandaveswar School of Pharmacy, West Bengal, India, Al- Karim University, India, and Najran University KSA for supporting the preparation of the draft of the paper.

MMPs	Matrix Metallo Proteinases
MSP	macrophage-stimulating protein
MTX	methotrexate
ES	Ewing's sarcoma
HA	Hydroxyapatite
PNCs	Polymer nanocomposites
SLNs	Solid lipid nanoparticles
PEG	polyethylene glycol
PAMAM	Poly(amidoamine)
AG	alginate
MOFs	metal-organic frameworks
AuNPs	gold nanoparticles
ZnO	zinc oxide
Tb_2O_3	terbium oxide
Fe_3O_4	ferric oxide
CD	carbon dots
MC	mesoporous carbon
GO	graphene oxide
SWCNT	Single walled carbon nanotubes
siRNA	Small interfering RNA
TGF-α	Transforming growth factor alpha
CaP	Calcium phosphates
DOX	Doxorubicin
ZnHAP	zinc hydroxyapatite
PAA	polyacrylic acid
GSH	glutathione
ROS	Reactive oxygen species
IFP	interstitial flow pressures
EMA	European Medicines Agency
MRI	magnetic resonance imaging
FDA	Food and Drug Administration
PLGA	Poly (lactic-co-glycolic acid)
PA	phytic acid
CQ	chloroquine
PROTACs	proteolysis-targeting chimeras
DPCN	dendritic platinum-copper alloy nanoparticle
PTT	photothermal therapy
miRNA	microRNA

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