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Review

Prospect of (Nd^{3+}) Complexes and Its Nanoparticles as Promising Novel Anticancer Agents in Particular Targeting Breast Cancer Cell Lines

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Abstract: Breast cancer is the leading cause of tumor-related death in women around much of the world and a major health burden for modern medicine. This review highlights the prospect of (Nd^{3+}) complexes and nanoparticles as promising novel anticancer agents in particular targeting breast cancer cell lines. This study emphasizes the therapeutic and diagnostic potentials of Nd^{3+}-based metal complexes, especially in reversing drug resistance or enhancing targeted therapy. A comprehensive overview of diagnostic modalities underscores the imperative for the prompt identification and intervention of breast cancer. Nd^{3+} complexes demonstrate potential as anticancer therapeutics due to their significant cytotoxicity evidenced by their IC_{50} values. The research outcomes indicated that it could theoretically inhibit the growth and metastasis of cancer cell lines. Future research should focus on synthesizing novel Nd^{3+} complexes with enhanced bioavailability, solubility, and reduced toxicity to further advance their application.

Keywords: Nd^{3+}-based metal complexes; Nd-based nanoparticles; breast cancer; cytotoxic activity; metallodrug

Academic Editor: Fabrizio Schifano

Received: 20 November 2024
Revised: 15 December 2024
Accepted: 3 January 2025
Published: 14 January 2025

Citation: Abuilaiwi, F.A. Prospect of (Nd^{3+}) Complexes and Its Nanoparticles as Promising Novel Anticancer Agents in Particular Targeting Breast Cancer Cell Lines. *Future Pharmacol.* **2025**, *5*, 4. https://doi.org/10.3390/futurepharmacol5010004

1. Introduction

Cancer has a long historical presence. Evidence of this condition dates back around 4200 years, noted in the remains of an Egyptian woman [1]. Cancer is now the leading global cause of death, with its incidence increasing yearly [2]. Breast, endometrial, prostate, colorectal, and lung cancers are prevalent malignancies [3]. The most common disease among women globally and the primary cause of cancer-related death for women is breast cancer [4]. In 2018, an estimated 2.09 million new instances of breast cancer were detected, and 630,000 women died from the disease [5]. China has the highest number of breast cancer cases (17.6%) and deaths (15.6%), which is due to its large population and the increasing incidence over the past few years [6,7]. Numerous risk factors, including genetic predispositions such as gene mutations, hormonal impacts, lifestyle variables, and reproductive patterns, have been found [8]. The complex etiology of breast cancer is further influenced by environmental variables, age, and family history [9]. Cisplatin, a metallodrug, has been widely used in cancer chemotherapy since the 1960s [10,11]. However, side effects like nausea, poor hydrolytic stability, and the development of resistance in particular cancer cell populations limit its therapeutic usefulness [12]. These challenges have prompted scientists to examine metal complexes that show improved effectiveness as potential anticancer drugs. Researchers are now focusing on novel multi-target compounds since they are more efficient and less dangerous, which makes it more difficult for cancer cells to become

resistant [13,14]. Among other things, metal complexes are a possible source of compounds with biological activity, particularly those that destroy malignant cells [15].

Metal-based compounds have been in greater demand for cancer treatment [16]. Innovative medical and diagnostic in the rapidly developing field of inorganic chemistry applied to medicine, metals, and metal complexes are currently having an impact on medical practice [17,18]. Coordination chemistry advancements are required to better develop compounds to minimize adverse effects and comprehend their processes of action [19]. Numerous medications with metal-based compounds are frequently used to treat cancer. Significant adverse effects and innate or acquired resistance restrict the therapeutic effectiveness of lanthanide complexes [20,21]. Empirical studies have illustrated that lanthanide (4f) element complexes assume a pivotal role in chemotherapy. Lanthanide (La^{3+}) compounds have been evidenced to inhibit tumor proliferation, modify signal transduction pathways, and obstruct the synthesis of reactive oxygen species through their interaction with hydroperoxide. Table 1 shows the mode of action of various lanthanide series metals [22]. The potential of metal-based anticancer medicines has only been studied since the famous discovery of the biological activity of neodymium (Nd^{3+}), employed for therapeutic reasons in a more or less empirical way [23]. Nd^{3+}, a chemical element belonging to the lanthanide group, boasts several intriguing features for biological and photoluminescent applications, making it one of the most used elements in crystalline complex development [24]. Because of its capacity to interact with organic molecules and create stable complexes, it is a viable option for creating biological study probes and medicines [25,26]. Disease diagnosis, cancer treatment, and bacterial infection have all been accomplished with Nd^{3+} ions [27]. The creation of fluorescent markers to monitor cells and proteins in cell biology research is also made possible by its optical characteristics [28]. The adaptability and compatibility of Nd^{3+} with biological systems also make it a promising candidate for biomedical advancements [29]. Numerous Nd^{3+} complexes with potential anticancer characteristics have been created; some are now being tested in clinical settings, while others are being used for diagnosis and therapy [30]. Designing novel coordination compounds with enhanced pharmacological characteristics and a wider spectrum of anticancer action has received considerable interest [31]. Using carrier groups that have a high degree of selectivity in targeting tumor cells is one method for creating novel anticancer drugs [32]. These complexes are most useful in photodynamic therapy, where they produce ROS in the presence of light to destroy cancer cells. Due to their near-infrared absorption and emission properties, deeper tissue penetration is possible with Nd^{3+} complexes for tumor treatment in inaccessible locations [33]. Biologically, Nd^{3+} complexes have been shown to interact with cellular components like DNA and proteins, which alters their structure and function. These interactions can induce apoptosis (programmed cell death), disrupt cancer cell metabolic processes, and inhibit proliferation, highlighting their intrinsic cytotoxic effects. Their luminescence properties also make them of great value in imaging and diagnostics, allowing for the early detection and monitoring of cancer with high resolution and minimum interference from autofluorescence [34]. Metal-based nanoparticles come in a variety of sizes and forms, and their potential use in medication administration and detection has been studied. Neodymium, nickel, gold, silver, iron oxide, gadolinium, and titanium dioxide are the most widely accessible metal-based NPs [35]. The huge surface area of Nd nanoparticles made it possible to include a high medication dosage. Numerous susceptible and specific NP-based optical imaging platforms are being researched to increase the specificity of cancer detection. When compared to other agents, NP-based diagnostic systems provide a significant advantage [36]. Nanoparticles can be engineered for specific targeting of tumor cells, facilitating the accurate delivery of therapeutics and imaging agents. They serve multiple functions and exhibit unique optical, magnetic, and

structural characteristics absent in singular molecules [37]. Tumor-specific targeting necessitates the conjugation of nanoparticles (NPs) with molecules or biomarkers that bind to tumor cell receptors, making an understanding of these receptors, biomarkers, homing proteins, and enzymes critical for selective cellular uptake of therapeutic and diagnostic agents [38]. Nanoparticles have several benefits, but their disadvantages are also important to be considered for an appropriate perspective. One of the major disadvantages is that nanoparticles are toxic [39]. Moreover, their emission into the environment creates a threat of bioaccumulation and impacts ecosystems, including microbial communities in aquatic ecosystems [40]. Challenges further include their tendency to agglomerate under certain conditions; this reduces their stability and functionality, and the scalability becomes a problem in maintaining uniformity during large-scale synthesis. Therefore, these challenges need to be addressed toward responsible development and application [41]. The choice of Nd^{3+} metal ions for this review is based on their promising potential to advance diagnostics and therapeutics in breast cancer. The photophysical properties of Nd^{3+} ions are unique, including near-infrared (NIR) luminescence, high quantum yield, and deep tissue penetration in the biological transparency window. These properties make them very suitable for bioimaging applications, thus allowing for the non-invasive and real-time visualization of tumors at high spatial and temporal resolution. This review focuses on recent developments in Nd^{3+} compounds and their cytotoxic effects on cancer cell lines, highlighting innovative approaches to Nd^{3}-based drug design for cancer therapy. Additionally, it provides a comprehensive summary of earlier studies on the cytotoxicity of Nd^{3+} complexes. The review also emphasizes the crucial role that diagnostic technologies play in the early detection and treatment of breast cancer. By offering a thorough examination of the complex landscape of breast cancer, this article explores a broad range of risk factors contributing to its development and the latest advancements in diagnostic techniques.

Table 1. Mode of action of various lanthanide metals and their toxicity.

Lanthanide Metals	Cell Line	Mode of Action	References
La^{3+}, Nd^{3+}	MCF7	Apoptotic cell death	[42]
La^{3+}	MCF7 and MDA-MB-231	DNA-laddering phenomenon	[43]
La^{3+}	MDA-MB435	DNA intercalation	[44]
Ce^{3+}	MDA-MB-231 breast cancer cells, MCF-7	Mechanism of action remains unclarified DNA cleavage	[45,46]
Pr^{3+}, Er^{3+} and Yb^{3+}	Human breast cancer (MCF7), and cervical (HeLa)	Programmed cell death	[47,48]
La^{3+}	HeLa and MCF-7 cells	Complex accumulates within the mitochondria of HeLa cells and induces apoptosis, cleaves plasmid DNA	[49,50]
Eu^{3+}, Gd^{3+}, Nd^{3+}, Sm^{3+} and Tb^{3+}	HeLa and MCF-7 cells	Complex accumulates within the mitochondria of HeLa cells and induces apoptosis, cleaves plasmid DNA	[51]
Eu^{3+} and Tb^{3+}	MDA-MB-231 (mammary cancer) and PC-3 (prostate carcinoma) cell lines, HBL-100 human breast carcinoma cells, and MCF7 cell lines	Complex and ct-DNA binding, Liposomes, anti-	[52]

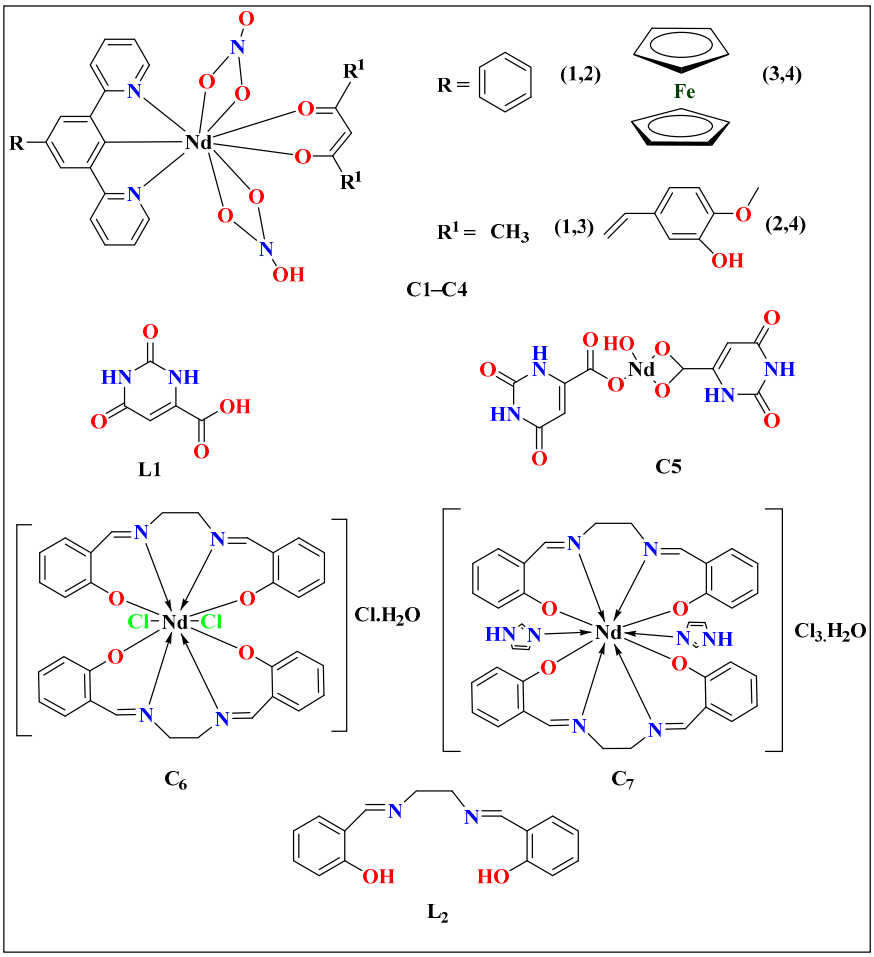
Table 1. *Cont.*

Lanthanide Metals	Cell Line	Mode of Action	References
Gd^{3+}	Human breast cancer MCF-7	angiogenic activity	[53]
Pr^{3+}, Er^{3+} and Yb^{3+}	human breast cancer (MCF7)	DNA fragmentation	[54]
La^{3+}, Er^{3+} and Yb^{3+}	MCF-7	Elevated the cellular levels of caspase-3 and caspase-9	[55]
La^{3+}, Sm^{3+} and Yb^{3+}	human breast cancer (MCF-7) cell lines	Intercalate into the double-stranded DNA (or) bind to the phosphate group of the DNA backbone	[56]
La^{3+} and Nd^{3+}	Ovarian (A2780), breast (MCF7)	Caspase activation, DNA fragmentation,	[57]
Ce^{3+}, Nd^{3+}, Gd^{3+} and Er^{3+}	MCF-7		[56]

Neodymium Complexes as anticancer agents

Lanthanide group elements exhibit anticancer activity, and literature data show that coumarins also possess similar properties. Their unique electronic configurations enable them [9] to interact with biological systems in diverse ways, potentially enhancing their therapeutic effects [58]. Coumarin compounds, known for regulating immune responses, cell proliferation, and differentiation, have shown increased pharmacological effects when binding to metal ions [59]. Derivatives of coumarins, both synthetic and natural, have important therapeutic uses. Researchers have looked at how harmful lanthanide complexes made from coumarins are to cancerous cells [58,60]. Nd^{3+}, Ce^{3+}, and La^{3+} complexes were synthesized with coumarin-3-carboxylic acid (HCCA). Of them, the Nd^{3+} compound showed more cytotoxicity than the others, suggesting that it could be a useful anticancer drug [61]. Sarkar et al. described Nd^{3+} coordination complexes as $[Nd(R\text{-}tpy)(O\text{-}O)(NO_3)_2]$, utilizing Nd^{3+} with R-tpy being either Ph-tpy or Fc-tpy, and (O-O) derived from Hacac or Hcurc. The synthesized structures (**C1**–**C4**) are illustrated in Scheme 1, which were determined using the X-ray crystallographic technique. In visible light, Complex **C1** and curcumin showed photocytotoxicity against MCF-7 cells with an IC_{50} value of 34 μM, but in the absence of light, they showed much less toxicity to normal MCF-10A cells (IC_{50} > 50 μM). Compared to **C4**, which does not include ferrocenyl moiety, **C2** was less harmful to MCF-7 cells. **C1** and **C3**, which do not contain photoactive curcumin, showed minimal toxicity in both light and dark conditions. The ferrocenyl moiety in **C4** likely enhances cell internalization and photocytotoxicity, positioning it as a potential candidate for photochemotherapy targeting mitochondria [46,62].

From bioinorganic chemistry to pharmaceutical and materials science, the coordination chemistry of orotic acid (**L1**) has been a topic of significant scholarly interest. The use of **L1** in the synthesis of new La^{3+} coordination complexes with this ligand is justified by the fact that it has demonstrated diverse coordination modes during the synthesis of coordination frameworks, especially in light of their possible use as anticancer treatments [63–65]. Kostova and colleagues synthesized a Nd^{3+} complex (**C5**) with (**L1**) and studied its cytotoxic effects using the MTT assay. The complex, featuring nitrogen and oxygen donor atoms, showed significant anti-proliferative activity, particularly against breast cancer cell lines such as MCF-7 (IC_{50} = 25 μM) and MDA-MB-231 (IC_{50} = 30 μM). Compared to the free ligand (**L1**), **C5** exhibited superior efficacy in reducing cell viability. These findings highlight the therapeutic potential of lanthanide complexes like **C5**, supporting further pharmacological and toxicological studies for cancer treatment applications (Scheme 1) [66].

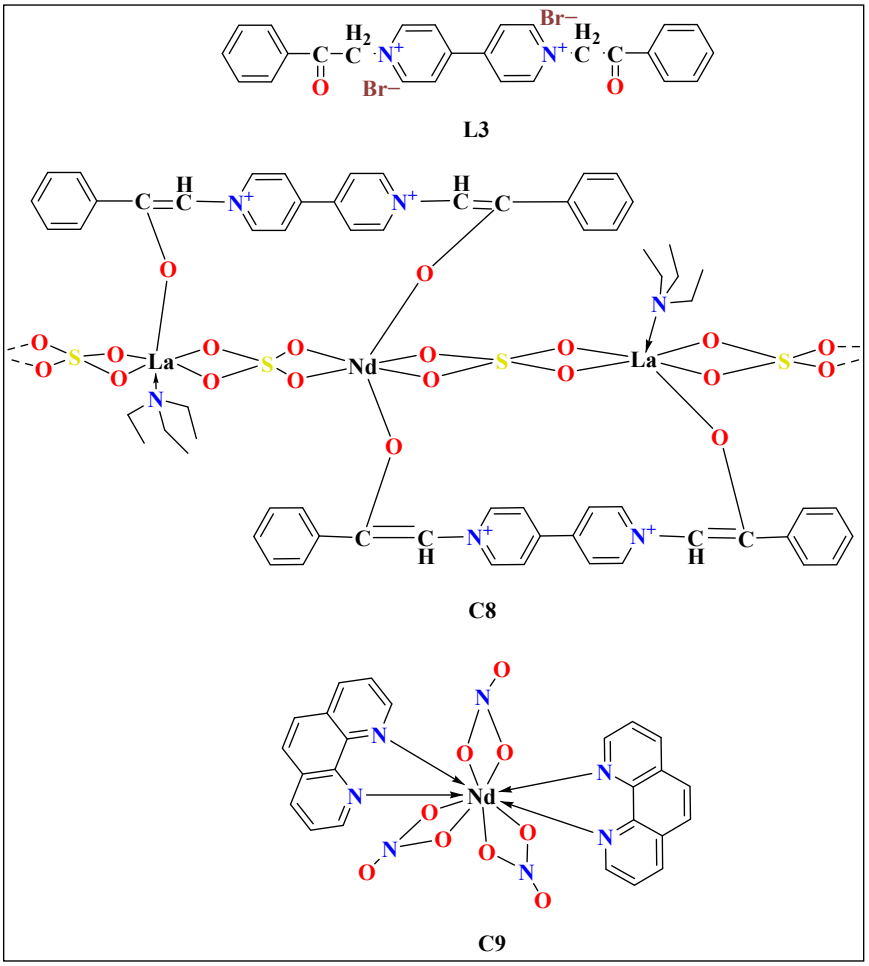


Scheme 1. Structural representation of the neodymium complexes and ligands (**C1–C7**, **L1–L2**).

Many investigations in recent years have concentrated on mixed ligand complexes that include Schiff base ligands and nitrogen-containing heterocyclic amines [67,68]. Nitrogen donor compounds, such as imidazole, feature heteroaromatic moieties that provide these ligands with additional properties, enhancing their pharmacological and therapeutic functionalities [69]. The influence of imidazole on the formation of ternary complexes warrants investigation, alongside the bioactivity of both binary and ternary complexes against various microbial strains. Additionally, assessing their anticancer efficacy against Hep-G2 liver carcinoma and MDA-MB-231 breast cancer cell lines would provide valuable insights into their potential therapeutic applications for cancer treatment and microbial inhibition [70]. Binary (**C6**) and ternary Nd^{3+} complexes (**C7**) were synthesized by Ehab M. Abdalla and his colleagues (Scheme 1), and they were thoroughly characterized using a variety of spectroscopic and structural techniques. The MTT assay, which gauges mitochondrial dehydrogenase activity as a sign of cell viability, was used to compare their biological activities to the MDA-MB231 breast cancer cell line. According to the findings, **C7** had more cytotoxic action than **C6**. After comparing the complexes with cisplatin, the IC_{50} values were as follows: **C7** > **C6** > **L2** > cisplatin [71].

As illustrated in Scheme 2, a novel mixed La^{3+} complex (**C8**) was synthesized by reacting a combination of La^{3+} and Nd^{3+} sulfate in a 2:1 M ratio with N,N′-diphenacyl-4,4′-dipyridinium dibromide (DPB) (**L3**) in the presence of triethylamine (Et_3N). The proposed linear polymeric structure suggests that both La^{3+} and Nd^{3+} ions are six-coordinated, which was confirmed using the X-ray powder diffraction technique. The cytotoxicity of **C8** was evaluated against the breast cancer cell line MCF-7. At 24 h, the IC_{50} value for **C8** was

1.6 ± 0.4 μM, indicating moderate activity. After 48 h, the IC_{50} significantly improved to 0.3 ± 0.2 μM, suggesting enhanced potency with prolonged exposure. In comparison, cisplatin exhibited higher IC_{50} values at both time points, with 45 ± 18 μM at 24 h and 20 ± 6 μM at 48 h. These findings highlight the greater effectiveness of **C8** against MCF-7 cells, especially with prolonged exposure, underscoring its potential as a more potent anticancer agent than cisplatin in this specific cell line [72]. Researchers synthesized the coordination compound $[Nd(Phen)_2(NO_3)_3]$ (**C9**) by coordinating a neodymium atom with four nitrogen atoms and six oxygen atoms from two phenanthroline molecules and three nitrate groups, forming a distorted decahedral geometry confirmed by X-ray crystallography techniques. In DMEM containing 10% fetal bovine serum, antibiotics, and antimycotics, MCF-7 (mammary adenocarcinoma) cells were cultivated at 37 °C with 5% CO_2. Cells were plated in 96-well plates at 1×10^4 cells per well and treated with **C9** at concentrations of 1–100 μM for 24 and 48 h. The complex exhibited significant cytotoxicity with IC_{50} values of 2.59 μM at 24 h and 2.21 μM at 48 h. In contrast, cisplatin demonstrated IC_{50} values indicating >80% inhibition against MCF-7 cells. The selectivity index for the Nd-complex was 4.75 and 5.06, suggesting reduced toxicity. Proliferation decreased significantly with increasing concentration and exposure time, with a 100 μM concentration leading to a 78.7% reduction in cell viability at 48 h. This finding parallels the cytotoxic activity of cisplatin, a widely recognized antineoplastic agent. These results underscore the potential of **C9** as an effective anticancer agent (Scheme 2) [73].



Scheme 2. Structural illustration of neodymium complexes and respective ligands (**L3**, **C8**–**C9**).

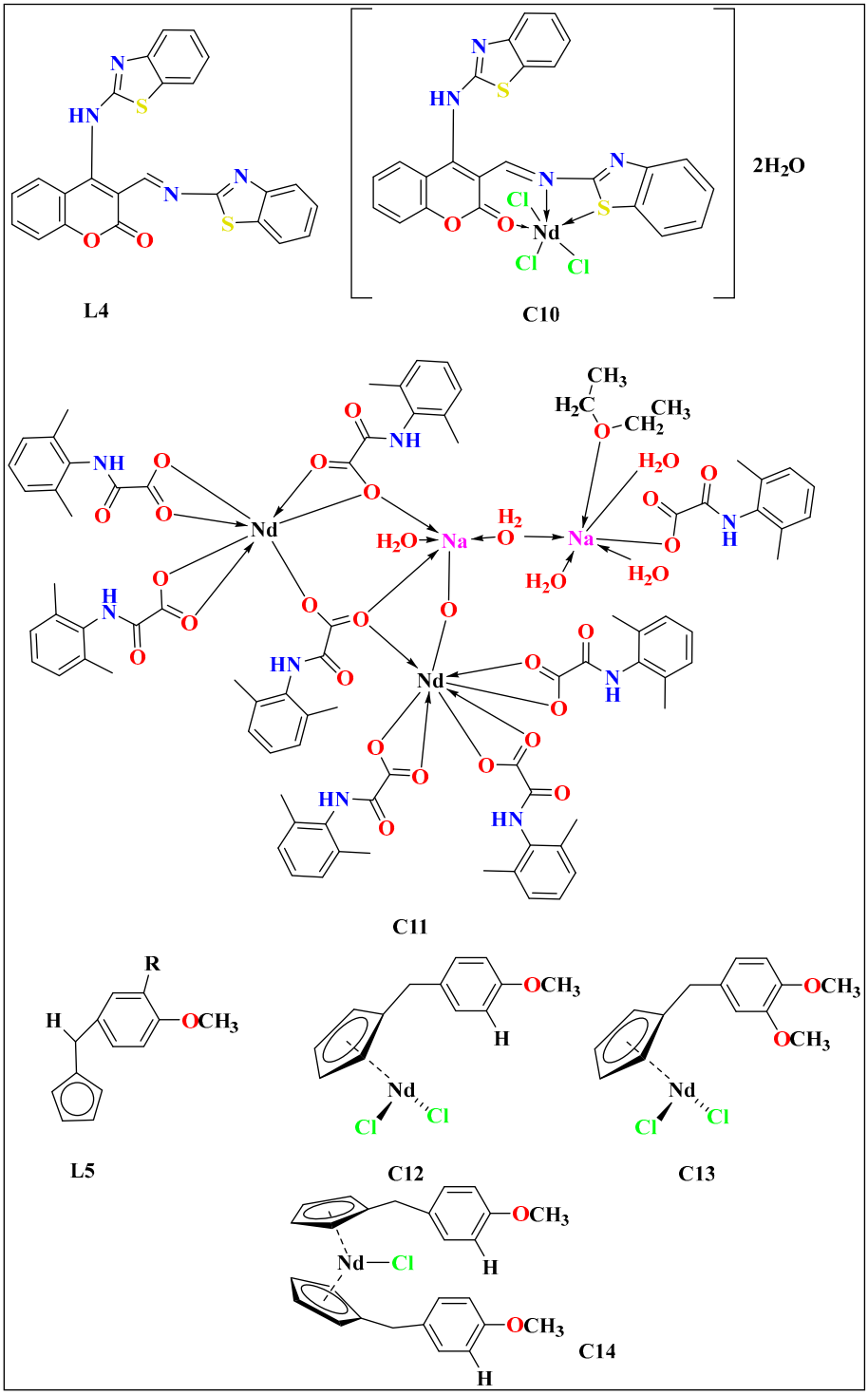
The predominant focus of research has been on synthesizing phenanthroline (Phen) complexes with rare-earth elements such as Ce, Pr, Nd, Sm, Eu, Tb, and Dy, while limited investigations have addressed their biological activity and physicochemical properties [56,74].

However, rare-earth compounds have garnered increasing interest recently for their potential in cancer treatment because of their unique physiological and biochemical properties [75]. Among these, trivalent neodymium (Nd^{3+}) stands out for its use in cancer research due to its ability to form stable complexes with organic molecules, making it a promising candidate for the development of therapeutic agents [76].

Because Nd^{3+} complexes can target tumor cells through a variety of ways, such as altering cancer cell metabolism, causing oxidative stress, and initiating apoptosis, they have been investigated for their possible anticancer action [77]. Moreover, the unique optical properties of Nd^{3+} enable it to act as a fluorescent marker, facilitating the real-time tracking of cancer cells during treatment, which enhances precision in targeting and monitoring tumor progression [78]. Nd^{3+} ions have shown promise not only in diagnosing and tracking cancer but also in direct therapeutic applications, such as photodynamic therapy (PDT) and as drug delivery agents. Nd^{3+} and rare-earth elements exhibit significant potential in cancer treatment, facilitating advancements in diagnosis and therapy [30]. In collaboration with others, Rehab S. Abo-Rehab synthesized a novel lanthanide chemical (**C10**) using the ligand (Z)-4-(benzo[d]thiazol-2-ylamino)-3-(benzo[d]thiazol-2-ylimino) methyl. In Scheme 3, 2Hchromen-2-one (**L4**) is shown. The MTT assay was used to assess the thiazole ligand and Nd^{3+} complex's in vitro cytotoxicity against MCF-7 breast cancer cell lines at doses of 7.812, 15.625, 31.25, 62.5, 125, 250, 500, and 1000 μg/mL. With an IC_{50} of 713.64 μg/mL (1.570 μM/mL) for the ligand and 304.23 μg/mL (0.410 μM/mL) for the La^{3+} complex, they demonstrated their potential as powerful inhibitors of cancer treatment [79].

Many studies have been conducted on the possibility of metal complexes with carboxylic acids, particularly those from the d- and f-block elements, as anticancer medications. One of the most fundamental carboxylic acid ligands being studied for its potential to inhibit tumor growth is oxamic acid [61]. Complexation investigations have revealed the intriguing chelating behavior of oxamic acid and its derivatives with d and f-block metals. These ligands usually coordinate in a bidentate form, either through one nitrogen and one oxygen atom or through both oxygen atoms, to increase their ability to bind to metal ions [62]. According to Scheme 3, recent results showed that coordination compounds, namely lanthanide(III)–sodium(I) complexes with Ln_2Na_2 (Ln = Nd and Gd) cores that generate $[Nd(NO_3)_3 \cdot 6H_2O]$ (**C11**), have been synthesized, and their structure was determined using the powder XRD technique, FTIR, and mass spectrometry. Oxamate ligands bridge these cores via a variety of bonding mechanisms, such as $\mu_2-\eta^1{:}\eta^1{:}\eta^1$, $\mu_3-\eta^1{:}\eta^2{:}\eta^1$, $\mu_2-\eta^1{:}\eta^2$ coordination, and μ_2-H_2O oxygen atoms. Two nine-coordinate Ln^{3+} ions with a capped square antiprism (CSAPR-9) geometry are present in the asymmetric unit of these complexes. The complexes also show their respective inversion symmetries and voids with enough electron density to contain one ethanol and one water molecule. The capacity of oxamate ligands (**L5**) to form stable complexes with lanthanides, and these structural characteristics point to potential uses in cancer treatment, including the development of novel metal-based tumor inhibition strategies. Following a 24 h exposure to 100 μM of the proligand Hdmp, Nd^{3+} nitrate salts, Nd^{3+} oxamate complexes, and curcumin, the viability of MCF-7 breast cancer cells was assessed. The findings demonstrated that Nd^{3+} complexes may have anticancer properties, as (**C11**) demonstrated considerable cytotoxicity against MCF-7 cells ($p < 0.05$). In contrast, curcumin had the strongest cytotoxic effect, lowering MCF-7 cell viability to 46.8 ± 6.46%. Curcumin's capacity to control several cell signaling pathways, such as those involved in cell division, senescence, apoptosis, and the protein kinase pathway, is thought to be the cause of this cytotoxicity. Although more research is

necessary to maximize their effectiveness, the encouraging cytotoxicity of (**C11**) in MCF-7 cells suggests the possible utility of Nd^{3+} complexes in cancer treatment [63].



Scheme 3. Structural illustration of neodymium complexes and respective ligands (**L4**–**L5**, **C10**–**C14**).

An important focus of cancer research is the development of new molecules that offer lower toxicity and greater selectivity for cancer cells compared to drugs currently used in clinical treatment. When compared to their corresponding inorganic salts, Group 3 metal and lanthanide complexes linked to coumarin have demonstrated increased activity in a variety of tumor models [64]. This heightened activity may result from distinctive interactions between metal ions and organic ligands, facilitating enhanced cellular uptake and

the selective targeting of neoplastic cells [65]. Angelamaria and colleagues synthesized Nd complexes (**C12–C14**) with significant anticancer activity. These complexes exhibited superior cytotoxicity relative to other metal salts, indicating potential for La-based compounds in oncology. Their findings underscore the potential of Nd complexes as therapeutic agents, paving the way for the advancement of metal–organic frameworks with specific biological properties for cancer treatment [66]. To evaluate the cytotoxicity of newly synthesized compounds on cancer cell growth, MDA.MB231 breast cancer cells were administered to each compound at concentrations from 5 μM to 100 μM. The IC_{50} values, which represent the concentration required to inhibit 50% of cell growth compared to untreated controls, were statistically analyzed using a nonlinear model. A polynomial fitting curve based on local regression (least square method) was applied to determine the dose–response relationship, with R^2 values ranging from 0.789 to 0.987 across the models, indicating not good but a medium fit [67,68]. Among the tested compounds, compounds **C12**, **C13**, and **C14** exhibited distinct cytotoxicity profiles. **C12** demonstrated strong inhibitory effects on MDA.MB231 cells, with an IC_{50} value of 12 μM. This activity is likely related to the structural properties of the ligand and the metal core, where the lower electronegativity of Nd^{3+}, compared to scandium and yttrium, may prevent the intramolecular coordination of the methoxy groups, thus impacting the complex's stability and activity. **C13** was less effective, showing an IC_{50} value of 50 μM, indicating moderate cytotoxicity. This could be attributed to the specific ligand coordination mode or the steric hindrance, which affects the overall stability and bioactivity of the compound. On the other hand, **C14**, despite being tested at higher concentrations, exhibited a low efficiency in inhibiting cell growth, particularly at the highest concentrations used. This suggests that its coordination structure and interaction with cellular targets may not be as effective in disrupting cell proliferation. These results suggest that while neodymium-based compounds have potential in cancer treatment, their cytotoxicity is highly dependent on both the ligand structure and the metal ion's coordination environment. **C13** stands out as a promising candidate for further investigation due to its notable inhibitory effect on MDA.MB231 cells [69]. Table 2 demonstrates the function of some Nd-based metal complexes as anticancer agents for breast cancer.

Table 2. Nd-based metal complexes used in breast cancer therapy.

Complex	Ligand	Geometry	Pathway	Doses Assay (IC_{50} = μm)		Time	Cell Line	Ref.
				Light	Dark			
C1, **C2**	-	Distorted square anti-prismatic	MTT assay	53.1 ± 2.5 (62.6 ± 2.8)	80.3 ± 2.1 (94.5 ± 3.1)	-	MCF-7	[46]
	-	-	MTT assay	4.2 ± 0.8 (9.6 ± 1.2)	>50 (>50)	-	MCF-7	
C3, **C4**	-	Tricapped trigonal prismatic	MTT assay	13.2 ± 1.6 (19.9 ± 1.8)	>50 (>50	-	MCF-7	
	-	-	MTT assay	0.7 ± 0.2 (2.1 ± 0.6)	>50 (>50)	-	MCF-7	
C5	**L1**	Distorted pentagonal bipyramidal	MTT assay	MCF-7 (IC_{50} = 25) MDA-MB-231 (IC_{50} = 30)		72 h	MCF-7, MDA-MB-231	[23]
C6	**L2**	Distorted octahedral	MTT assay	-		-	MDA-MB231	[71]
C7		Distorted octahedral	MTT assay	-		-	MDA-MB231	

Table 2. *Cont.*

Complex	Ligand	Geometry	Pathway	Doses Assay (IC_{50} = μm)	Time	Cell Line	Ref.
C8	**L3**	Distorted dodecahedral	Hoechst nuclei staining assay	1.6 ± 0.4 for **L3** 45 ± 18 for Cisplatin	24 h	MCF-7	[54]
				0.3 ± 0.2 for **L3** 20 ± 6 for Cisplatin	48 h		
C9	**-**	Distorted bicapped square antiprismatic	MTT assay	0.3 ± 0.2 for MCF-7	48 h	MCF-7 cells	[80]
C10	L4	Dodecahedral	MTT assay	0.861 ± 0.544	24 h	MCF-7	[79]
C11	**-**	Icosahedral	MTT assay	46.8 ± 6.46	24 h	MCF-7	[81]
C12	**L5**	**-**	MTT assay	6 ± 50	48 h	MDA. MB231	[82]
C13	**L5**	**-**	MTT assay	-	**-**	MDA. MB231	
C14	**L5**	**-**	MTT assay	**-**	**-**	MDA. MB231	

Neodymium-Based Nanoparticles as anticancer agents

Neodymium oxide (Nd_2O_3) and ionic liquid-assisted neodymium oxide (Nd_2O_3-IL) NPs were synthesized by Sundrarajan and his colleague. The MTT assay evaluated the efficacy of (Nd_2O_3) and (Nd_2O_3-IL) nanoparticles against MCF-7 breast cancer cells. Nd_2O_3-IL NPs exhibited superior inhibitory effects on cancer cells compared to Nd_2O_3 NPs. This enhanced activity was attributed to the release of metal cations and reactive oxygen species (ROS), which compromised the cell membrane integrity and facilitated cytoplasmic leakage in MCF-7 cells. Additionally, (Nd_2O_3) nanoparticles displayed a higher inhibition rate against MCF-7 cells than the standard, likely due to their reduced size. The cell viability percentages for Nd_2O_3 and Nd_2O_3-IL NPs at different concentrations (0–100 μg/mL, with 25 μg/mL intervals) were as follows: 100, 84.05, 62.57, 42.36, and 26.92% for Nd_2O_3 NPs, and 100, 83.61, 60.21, 40.44, and 25.82% for Nd_2O_3-IL NPs. The IC_{50} values for Nd_2O_3 and Nd_2O_3-IL NPs were 65 and 63 μg/mL, respectively. The MTT experiment revealed a dose-dependent suppression of mitochondrial dehydrogenase activity on MCF-7 cells for both NdO_3 and NP-embedded ILs [83].

Using a single-step sol–gel process, SiO_2@$Nd(OH)_3$ micro-cocoon structures were synthesized. Using MTT assays, the chemicals' potential for harm was assessed on MCF-7 breast cancer cells. The results showed that the more micro-cocoon structures there were (2–200 μg/mL), the lower the cell viability. Nevertheless, at the maximum dose (200 μg/mL), cell viability was maintained at about 80%, suggesting great biocompatibility for drug administration and bioimaging applications. At concentrations up to 25 μg/mL, viability surpassed 90%, and after 24 h, there was no discernible cell death. The low toxicity of SiO_2@$Nd(OH)_3$ structures was demonstrated by the gradual fall in cell viability beyond 25 μg/mL while remaining above 75%. Surface hydroxyl groups are probably responsible for this decreased toxicity, which could encourage bio-modification and improve possible uses in optical bio-probes, bioimaging, and pharmacology [74].

Numerous clinical trials are currently underway to investigate the remedial potential of Nd NPs against breast cancer, indicating a substantial improvement in cancer treatments. In these trials, the effectiveness of Nd NPs for tumor excision was evaluated in transgenic mice. Nd_2O_3 NPs were injected into the tail vein, and 12 h later, five pairs of mammary glands were effectively brightened in transgenic mice using 808 nm laser illumination. Nonetheless, near-infrared (NIR-II) signals were only detected in the reticuloendothelial (RES) organs and intestinal tracts of wild-type mice. Subsequently, all glands in the

transgenic group underwent sequential sections guided by NIR-II fluorescent pictures. Compared to normal tissues from the surgical bed, the ex vivo NIR-II fluorescence signal of all-resected glands was substantially higher. The excised glands from the wild-type group showed little NIR-II fluorescence signal. A semi-quantitative study of MFI from ex vivo excised mammary gland tissues indicated a twofold greater fluorescence signal in breast tumor tissue compared to healthy breast tissue. All of these findings demonstrate the successful differentiation of breast cancers using Nd-based nanoprobes. These results demonstrate that the Nd_2O_3 NPs probe appears acceptable for future translation into clinical practice [84].

To detect SLN (Sentinel lymph node) metastases, a new nanoprobe for in vivo fluorescence imaging in the NIR-II band was created. A common method for assessing axillary involvement in breast cancer is SLN biopsy. This nanoprobe helps identify metastatic SLNs by using rare-earth nanoparticles (RENPs) in conjunction with tumor-targeted hyaluronic acid (HA) to produce a bright fluorescence at 1525 nm. Both non-tumorigenic and malignant breast cell lines were used in MTT assays to evaluate the cytotoxic effects of RENPs@HA. Additionally, RENPs@HA effectively localized to SLNs and infiltrated metastatic breast cancer cells within 24 h through CD44-mediated endocytosis. In vivo studies indicated that RENPs@HA nanoprobes rapidly concentrated in metastatic inguinal lymph nodes, showing significant fluorescence. According to cell viability data, RENPs@HA did not appear to have any harmful effects in the presence of 0.2 mg mL^{-1} reference, showing (a survival rate > 95%) for RENPs@HA. It was noted less than 1.4% of MCF10A cells incorporated RENPs@HA was corroborated by flow cytometry [75].

Moreover, Nd-doped C-dots were prepared by hydrothermal method which further formed nanocomposite (NC) of β-cyclodextrin (CD). These nanocomposites contain the anticancer medication camptothecin (CPT) which is insoluble in water. The in vitro anticancer properties of NC were tested on MCF-7 breast cancer cell lines. Loading NC onto the CPT increases its antitumor efficacy on MCF-7 cells. The NC can be identified as a nanomaterial and utilized as a delivery system for anticancer medications using luminescence/MRI imaging. The apoptosis rates were 56.61% for CPT and 52.16% for the CPT-loaded nanocarrier at their respective IC_{50} concentrations. The NC drug loading content of 3.1 ± 0.4 demonstrated 86.3% effectiveness in trapping [76].

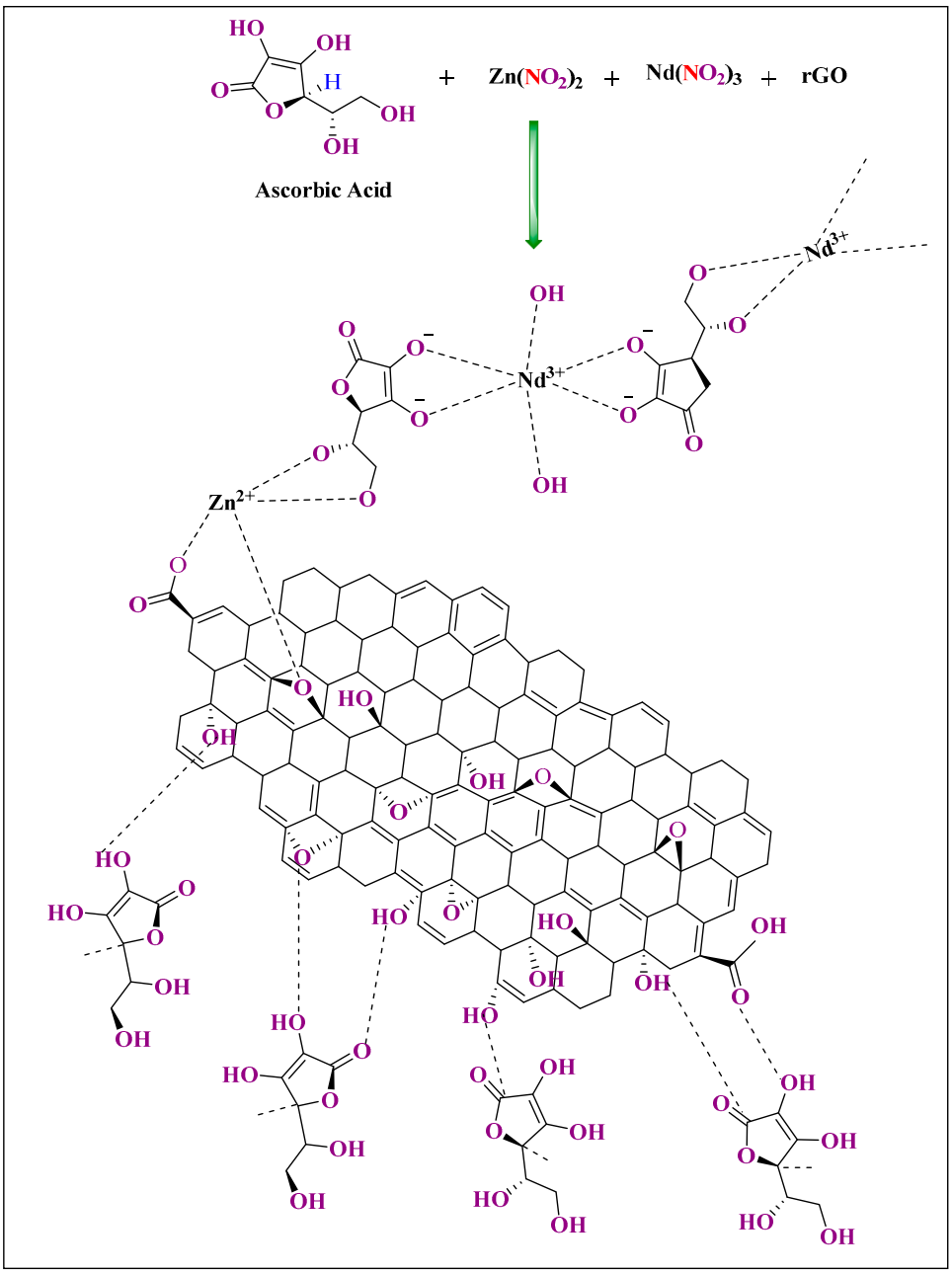
Further, Nd^{3+}-doped $GdPO_4$ core nanoparticles with spheres ranging in size from 3 to 6 nm were created using the solution combustion method. SiO_2 was applied to nano-phosphor to improve its biocompatibility. $GdPO_4$:Nd^{3+}@SiO_2 nano-phosphors are used to detect cytotoxicity against PC-3 and MCF-7 cancer cells. $GdPO_4$:Nd^{3+}@SiO_2 exhibits red luminescence at 681 nm and NIR luminescence at 797 nm upon photoexcitation at 532 nm. As the Nd^{3+} level increased from 1% to 5%, the fluorescence intensity of nano-phosphor increased twofold. Furthermore, it was found that increasing the gamma irradiation from 150 kGy to 300 kGy resulted in a gradual rise in the emission intensity from (2–3 folds) to (8–10 folds) by increasing radiation. $GdPO_4$:Nd^{3+}@SiO_2 nano-phosphor shows strong cytotoxicity against the MCF-7 (breast cancer cell line). Normal cells (mononuclear cells, or MNCs) are used to compare these cytotoxicity data. It was discovered that compared to mononuclear cells, the cell death rate was much greater in the cell lines of metastatic breast and prostate cancer. It is crucial to remember that a drop in cytotoxicity does not always mean that cells have died. The ideal concentration of $GdPO_4$:Nd^{3+}@SiO_2 to achieve the most cytotoxicity in cancer cells was 25 μg/mL. Furthermore, cancer cells can be effectively treated with increased NIR luminescence [77].

Likewise, doxorubicin-loaded poly(β-cyclodextrin) (PCD) and siRNA were electrostatically self-assembled to form PCD/siRNA nanocomplexes. An exterior layer of neodymium-integrated poly(β-cyclodextrin) (Nd-PC) was then added to create the PCD/siRNA/Nd-PC

nanoassembly. In conclusion, Nd-integrated supramolecular polymeric assemblies are a novel class of organic–inorganic nanotherapeutics with a wide range of potential uses in combating chemotherapy-induced multidrug resistance in cancer. In addition to introducing essential cationic features for efficient siRNA transport and anticancer medicines, it used the special qualities of lanthanide elements to improve cellular uptake and inhibit drug efflux. Using polyethylenimine-crosslinked γ-cyclodextrin (PC) as an intrasomal architecture, the nanocomposite was successfully employed to deliver siRNA and doxorubicin simultaneously into human breast cancer cells, specifically MCF-7/ADR (MCF-7), both in vitro and in vivo. This tactic reduces angiogenesis and increases necrosis at the tumor site. Based on the 50% inhibitory concentration (IC_{50}) obtained from MTT experiments, PC and Nd-PC showed minimal cytotoxicity in MCF-7/ADR cells at doses of 40 μg/mL or less, suggesting compatibility with MCF-7/ADR cells. Additionally, with an IC_{50} value of 34.0 μg/mL, PCD exhibited much greater cytotoxicity in MCF-7/ADR cells in comparison to doxorubicin (Dox). Doxorubicin is efficiently released from PCD into the cancer cells, enhancing cell-killing efficacy [78].

Ascorbic acid effectively chelates hydroxyl groups at furan **C3**, **C4**, **C6**, and **C7**. No established methodology exists for the accurate photosynthesis of nanomaterials in solution via plant extracts. However, it has been suggested that polar groups facilitate the formation of nanomaterials [79]. Scheme 4 depicts the proposed methodology for the extract's capping and attenuation effects. Concurrently, low-level laser treatment (LLLT) alongside reduced graphene oxide (rGO) hybrid nanocomposites (NCs) has demonstrated efficacy as a non-drug approach for targeting MCF-7 breast cancer cells. To enhance oncological treatment, the potential of rGO-based NCs in LLLT could be synergistically integrated with additional therapeutic modalities. Following NC concentration optimization, the laser treatment of MCF-7 cells was used to evaluate the antitumoral activity using MTT assays and DAPI staining. Notably, cell mortality was greatly increased by raising the irradiation dose from 8 to 32 J/cm^2, but the effectiveness was diminished by additional increases in laser dosage. Notably, 50% of the cells died at an irradiation dosage of 32 J/cm^2 with 20% ZnO/rGO present. Additionally, 630 nm lasers exhibited enhanced efficacy in LLLT for MCF-7. The MTT assay evaluated the cytotoxicity of various formulations, including GO, rGO, ZnO, ZnO/rGO (8%), and ZnO/rGO (20%) NCs, against MCF-7 tumor cells across different dosages. The results indicated that rGO-based NCs induced effective cell death in vitro at concentrations as low as 12.5 μg/mL with laser intensities between 8 and 32 J/cm^2. NIR irradiation and LLLT may augment the efficacy of rGO, ZnO/rGO, Ag-ZnO/rGO, and Nd-ZnO/rGO NCs in inhibiting MCF-7 breast cancer cell proliferation [80].

Table 3 demonstrates the function of some neodymium-based nanoparticles, nanodots, and nanoassemblies used as anticancer medicines for breast tumors. Moreover, multifunctional nanoplatforms must be cleverly designed for cancer treatment, and the $NaGdF_4$:Nd@Cu(II) boron-imidazolate framework should be developed. The nanoassemblies exhibited an exceptional photothermal conversion capacity (η = 41.7%) upon a single 808 nm laser irradiation. Crucially, the nanoassemblies concurrently deliver exceptional anticancer effectiveness by combination treatment using photothermal, photodynamic, and chemo-dynamic techniques in both in vitro and in vivo settings. In vitro, nanoassemblies demonstrated 88% cell death against MCF-7 cells and extremely effective solid tumor ablation in vivo when exposed to a single beam 808 nm laser irradiation. The impact on MCF-7 cell survival was minimal in the absence of laser irradiation at concentrations ranging from 0 to 400 μg mL^{-1}. The creation of CSNPs@Cu-BIF nanoassemblies, taken together, offers incalculable benefits for precise cancer treatment [81].



Scheme 4. The proposed process for the extraction-based capping stage and the creation of the as-prepared rGO NCs.

Table 3. Nd-based nanoparticles, nanodots, and nanoassemblies used in breast cancer therapy.

Nd-Nanoparticles	Synthesis Method	Dose Assay (IC_{50})	Cell Line	Pathway	Modal	Cell Viability	Ref.
Nd_2O_3-IL	Green Synthesis Method	63 µg/mL	MCF-7	MTT assay	-	25.82%	[83]
Sio_2@$Nd(OH)_3$	Sol–gel process	25 µg/mL	MCF-7 A-549	MTT assay	-	75%	[85]
Renps@HA	Thermal decomposition method	50 µg mL^{-1}	MCF-7 MCF-10A MDA-MB-231	MTT assay	In vivo	95%	[86]

Table 3. *Cont.*

Nd-Nanoparticles	Synthesis Method	Dose Assay (IC_{50})	Cell Line	Pathway	Modal	Cell Viability	Ref.
Nd-doped C-dots	Hydrothermal method	10 μg/mL 3.1 ± 0.4	MCF-7	MTT assay	In vitro	86.3%	[87]
$Gdpo_4:Nd^{3+}@sio_2$	Solution combustion method	25 μg/mL	PC-3 MCF-7	MTT assay	-	-	[88]
PCD/siRNA/Nd-PC	-	34.0 μg/mL	MCF-7 ADR cells	MTT assay	In vitro and in vivo	-	[89]
Nd-zno/rgo ncs	Hydrothermal process	25 μg/mL	MCF-7	MTT assay	In vitro	80%	[90]
Nagdf4:Nd@Cu(II)	Thermal decomposition method	400 μg/mL	Hela MCF-7	MTT assay	In vitro and in vivo	12%	[91]

2. Conclusions

The fight against cancer has a long history, and the persistent rise in cancer cases worldwide highlights the urgent need for innovative therapeutic approaches. Breast cancer, the most prevalent and deadly cancer among women, demands breakthroughs in both diagnosis and treatment. While traditional chemotherapy agents like cisplatin have played a pivotal role, their significant limitations, including toxicity and drug resistance, have driven the exploration of alternative metal-based therapies. Among these, neodymium (Nd^{3+}) complexes have emerged as promising candidates due to their unique electronic configurations and ability to form stable, biologically active structures. This study demonstrated the anticancer potential of Nd^{3+} complexes, such as the Nd^{3+}–orotic acid (**C5**) combination, with an IC_{50} value of 25 μM against MCF-7 cells. Moreover, the mixed La^{3+} complex (**C8**) exhibited exceptional potency, surpassing cisplatin, with an IC_{50} value of 0.3 ± 0.2 μM after 48 h. These findings indicate that Nd^{3+} complexes not only exhibit diverse anticancer activities but also offer reduced toxicity, positioning them as promising candidates for safer and more effective treatments. To fully harness their therapeutic potential, future studies should focus on key areas such as combination therapies, advanced drug delivery systems, comprehensive pharmacokinetic profiling, and long-term toxicity assessments. Investigating their effectiveness across a broader range of cancer types and integrating innovative delivery mechanisms could pave the way for clinical applications. By addressing these research gaps, Nd^{3+} complexes could represent a significant step forward in developing next-generation anticancer agents, offering hope for improved patient outcomes and reduced side effects.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflicts of interest.

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