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Cytotoxic Activity of Metal Nanoparticle Complexes †

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Abstract: Metal complexes are widely used in pharmaceutics, cosmetics, electronics, casting printing, and power generation. One of the major challenges due to their long-term use as medicines is their accumulation in the body. This issue needs to be resolved to avail better results of metal complexes as medicines. The use of metal-nanoparticles (MNPs) can be expected to reduce the toxicity of metal and their accumulation in the body. The aim of this paper is to give an insight about the variation induced in the cytotoxic activity of MNP-ligand complexes by replacing respecting heavy metals with their nanoparticles (NPs).

Keywords: nanoparticles; metal-NPs complexes; coordination; cytotoxicity; therapeutics; targeting strategies; toxicity

1. Introduction

Application of metal complexes in multidisciplinary areas of cosmetics, drugs and electricals have been known since time immemorial [1]. The discovery of cisplatin in 1965 [2] proved to be a boon for cancer patients. But though the drug had a curative effect, yet it was associated with long term side effects on the brain and kidney [3]. To solve the problem of side effects associated with cisplatin, scientists worked on other alternatives as a result carboplatin and oxaliplatin were synthesized, which showed similar drug response with additional advantage of limited side effects [4]. Since the exploration of Platinum in drugs, scientists have tried to explore other metal atoms like iron, cobalt, gold, titanium, ruthenium etc. as anticancer drugs, which proved to be effective as well [5,6]. But these drugs were also associated with long-term side effects [5]. The major reason for heavy metal toxicity was probably related to either Fenton's reaction pathway (Figure 1) [7] followed by heavy metal metabolism or their selective binding.

Thus, to solve the problem of toxicity of heavy metals in drugs, MNPs came up as a better alternative. Recent advances in nanomedicines indicate that smaller drug dosage is required, thereby helping in reduction of metal load or metal toxicity in the body. MNP complexes are reported to have quite less impact as compared to metal atom complexes, when used in gene and medication delivery in biosystems [8].

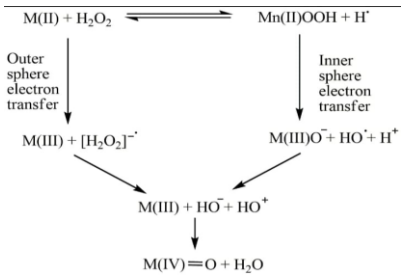

Figure 1. Fenton's reaction pathway.

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2. Metal-Nanoparticle Complexes

Increased ligand density on the surface of MNPs over single ligand coordinated with metal enhance binding and cellular absorption through multivalent interactions. MNPs can be functionalized with organic ligands generally in two methods. The two processes are the introduction of ligands to NPs prior to the fabrication of NPs and adsorption of ligand on the surface of NPs after the fabrication NPs [9].

Literature survey reveals that bonding of MNPs and synergistic effects improve the activity and reduce the side effects of MNP complexes. Around two decades ago, scientists initiated the work on MNP complexes. They suggested that MNPs provide a route for sustained release of encapsulated drugs thereby decreasing the accumulation of drugs in tissues and hence resulting in reduced toxicity. Various MNP complexes have proved to favor targeted drug delivery as well [10,11]. Cancer cells can be targeted by active targeting moieties like glucuronic acid, folic acid, hyaluronic acid and biotin, as well as macromolecules such as monoclonal antibodies, that specifically bind to receptors on cancerous cells. Ligands with active targeting molecules can significantly enhance the concentration of drugs in the target area, improve cellular uptake of drug-modified NPs, significantly decrease the adverse effects of the drug, thus effectively improve the therapeutic effects [12]. Size distribution and coherent functionalization of NPs affect the activity of the complex. Ligand coordination with NPs displayed enhanced activities as compared to ligand coordination with metal.

Several studies on metal complexes have been accomplished using transition metals, which have shown good promise against different cell lines. However, long-term use leads to accumulation of these drugs in the body which seems to be controlled by the use of NPs. In search of safer drugs much is to be explored with p-block metal complexes as these metals are less toxic in terms of their accumulation in the body. For example Bismuth(Bi) known as a semimetal or metalloid, due to its varied applications, can be considered as a good representative of p-block elements. Its multidimensional activity has generated interest for research in exploration of Bismuth-NP complexes [13]. Compounds of Bi-NP with chalcogens and oxyhalides have been reported to show good therapeutic and diagnostic properties [14]. Bi-selenide NPs (Bi_2Se_3 NPs) have been explored and are established to have theragnostic potentials [15]. Studies have reported the multiple roles of Bi-sulfide NPs and have established this as an efficient theragnostic for malignancy [16].

3. Anticancer Activity of MNP Complexes

Various groups of scientists have worked for synthesis of MNP complexes of cobalt, nickel, copper, cadmium, chromium, manganese, gold, ruthenium and lanthanum and demonstrated activity of these complexes against various cancer cell lines [17–19]. Some of these are described in Table 1.

Table 1. Anticancer activity of some MNP complexes for various cancer cell lines.

MNPs	Functionalized Ligand	Cancer Cell Lines	Reference
CoONPs	phosphonomethyl iminodiacetic acid	Jurkat (T-cell lymphoma) and KB (oral carcinoma) cell lines	20
NiNPs	2-(4,6-dimethoxypyrimidin-2-ylimino)methyl)-6-methoxyphenol (DMPMM)	human breast cancer (MCF-7), human lung cancer (A549) and human liver cancer(HepG2) cell lines	21
CuNPs	DMPMM	human breast cancer cell line (MCF-7)	22
CdSNPs	Chitosan	Human Jurkat cell and erythrocytes cell lines	23
AuNPs	quercetin	human breast cancer cell line (MCF-7)	24
RuNPs	epigallocatechin gallate	human liver cancer(HepG2) cell line	25
BiSNPs	Curcumin	Mouse breast cancer cell line(4T1)	26

M. Jarestan et al. (2020) synthesized cobalt oxide (Co_3O_4) NPs functionalized with glutamic acid and conjugated by thiosemicarbazide and investigated the cytotoxicity properties on gastric cancer (AGS) cell line [27]. N.M. Binu et. al. (2021) developed quercetin drug-loaded Nickel oxide NPs, surface modified with polydopamine and folic acid to target breast cancer cells [28]. O. Aktruk (2022) synthesized AuNPs complexes conjugated with doxorubicin and capped with levan polysaccharide and determined its cytotoxic activity against MCF-7 cancer cell line. The physicochemical experiments showed that increasing the levan quantity greatly improved colloidal stability and drug encapsulation efficacy [29].

4. Targeting Strategies of Drug-Loaded NPs

Because of their large surface area, small size and functionalization capacity with targeting ligands and therapeutic molecules, NPs are able to penetrate in many body parts without interfering with their regular processes. Generally, drug molecules are released at the target site after being adsorbed by the surface of NPs. The two main methods through which NPs target cancer cells are Passive targeting and active targeting [30].

4.1. Passive Targeting

In contrast to the normal cells, many solid tumors exhibit distinct physical traits such as reduced lymphatic drainage and hyperpermeable vasculature. Nanocarriers enter the circulatory system after being ingested or injected into the body. Then they extravasate the vasculature to reach the target and release their payload. Nanocarriers have the advantage of being incapable to pass across the tightly closed connection between normal vascular linings, however the defective vasculature of the cancerous area allows for an increase the amount of nanocarrier within the target cell. The accumulation of nanocarriers inside the tumor cell is significantly increased by the impaired lymphatic drainage. This phenomenon is the fundamental impetus for passive targeting and known as EPR (Enhanced Permeability and Retention) effect [30].

Through the EPR effect, drug-loaded NPs could target tumor cells in a passive manner. The pore size of angiogenic tumor vessels between adjacent vascular endothelial cells has generally found to be larger as compared to the blood vessels found in normal cells, therefore a higher concentration of the loaded drug are released specifically within the extracellular tumor cells by angiogenic tumor vessels. This enabling effective anticancer therapy with less harmful effects [31]. Figure 2A [32] shows the passive targeting strategy of drug-loaded NPs.

For example, the passive targeting approach has been effectively employed with polylactic-co-glycolic acid-based NPs functionalized with several anticancer agents like paclitaxel, cisplatin, and doxorubicin to improve time of circulation of blood, drug stability, and cytotoxic activity [33].

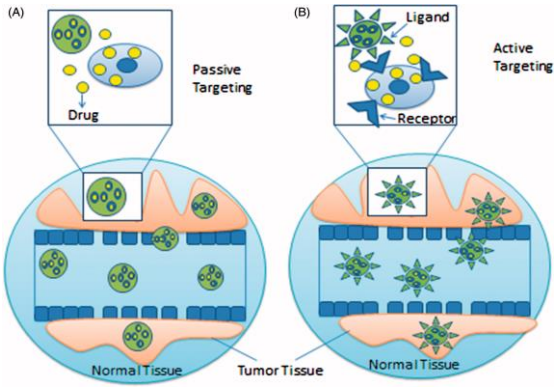

Figure 2. (**A**) Passive Targeting and (**B**) Active Targeting Strategy of drug-loaded NPs. (open access).

4.2. Active targeting

Although passive targeting may make it easier for NPs to be effectively localized in the tumor tissue, however it cannot further encourage cellular uptake by cancerous cells. NPs functionalized with ligands including nucleic acid aptamers, peptides, antibodies, and small molecules can be dynamically targeted on cancer cells to induce cellular uptake. This phenomenon distinguish the cancerous cells and normal cells. Active targeting strategy can be generally classified into two sub-categories. First is receptor-mediated endocytosis, in which drug-loaded nanocarriers are surface modified with specific ligands to identify the specific receptor in the tumor sites for its binding and subsequent cellular uptake. Second is the stimuli-responsive intracellular drug delivery, in which release of the drug depends on the small alteration in the microenvironment of the affected region [30]. Figure 2B [32] shows the active targeting strategy of drug-loaded NPs.

For example, to specifically target colorectal cancer cells, folic acid(FA)-modified polyethylene glycol (PGE) polymer-based drug delivery systems (PLGA-PEG-FA) containing oxaliplatin, was developed. This system when functionalized with NPs showed greater cellular uptake in comparison to untargeted molecules and free drug, and increased cell death by receptor-mediated endocytosis [12]. To deliver oxaliplatin to HCT-116 colon cancer cells, Tabasi et al. synthesized CD44(Cluster of differentiation)-conjugated Fe_3O_4 NPs. By MTT assay they observed that increased intracellular absorption of CD44-conjugated oxaliplatin-loaded NPs produces a considerable decrease in the IC50 measurement of oxaliplatin against HCT-116 cells [34].

5. Conclusions

Review of literature showed that there are several metal complexes have been successfully developed as anticancer agents. But these complexes also showed heavy metal toxicity and long term side effects. To resolve the side effects of metal complexes for the treatment of cancer scientists have explored the new ideas day-by-day. Recent advances of nano drug delivery systems as selective targeting to cancerous cells helping for the reduction of metal load and accumulation of drug in the body. Use of NPs improves cell uptake, efficiency as well as drug delivery and are safe. MNPs functionalized with ligands are reported to have less harmful effects as compared to the metal complexes, when used for the treatment of cancer. Generally, drug molecules with active targeting moieties are released at the target site after being adsorbed by the surface of NPs, hence increases the concentration of drug in the target area which improves the cellular uptake of drug-loaded NPs. There are the two main targeting strategies; passive targeting and active targeting, through which NPs are highly absorbed by cancerous cells. The review summarizes ligand functionalized MNP complex inhibitors to resolve the challenges of drug resistance and of metal toxicity due to the overloading of metal in the drug.

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