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DRUG DESIGN AND METAL COMPLEXES: AN ANALYSIS

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Abstract

Metals are vital, naturally selected cellular components that are required in several crucial biochemical processes for living organisms.

Transition metal complexes are important in materials synthesis, catalysis, photochemistry, and biological systems. Medicinal chemistry can utilize the unique properties of metal ions in the search of new drugs. The utilization of metals and their salts for medicinal purposes has been present throughout history. With the advancement within the field of chemistry the role of transition metal complexes as therapeutic compounds is becoming increasingly important. Recent advances in chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which may be used as therapeutic agent. This review illustrates the role of metals and therefore the recent progress within the field of medicinal bioinorganic chemistry with new approaches to the look of innovative metal-based drugs and their application.

***Keywords**: Metal Complexes, Metal-based Drugs, Medicinal Chemistry, Applications.*

Introduction

Metal ions play many critical functions in humans. Deficiency of some metal ions can result in disease like malignant anemia resulting from iron deficiency, growth retardation arising from insufficient dietary zinc, and heart condition in infants attributable to copper deficiency. The power to know at the molecular level and to treat diseases caused by inadequate metal-ion function constitutes a very important feature of medicinal bioinorganic chemistry. Metal ions are required in biology for his or her role as pharmaceuticals still as diagnostic agents. Metals are capable of with unique characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates. They are tightly regulated under normal conditions and abnormal metal ion concentrations are related to various pathological disorders, including cancer. For these reasons, coordination complexes, either as drugs or pro-drugs, become very attractive probes in medicinal chemistry. In nature, many biological systems make extensive use of metal ions, like zinc and copper, which play critical roles within the normal functioning of organisms [1]. Transition metals like copper, iron, and manganese, among others, are involved in multiple biological processes, from electron transfer to catalysis to structural roles, and are frequently related to active sites of proteins and enzymes [1]. However, deregulations of a number of these essential metals during normal biochemical processing are mixed up within the development of varied pathological disorders, like cancer [2]. These cellular functions only require the “trace metals” in miniscule but tightly regulated amounts. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metals demonstrate different oxidation states and might interact with some charged molecules. These properties of transition metals led to the event of metal-based drugs with promising pharmacological application and unique therapeutic opportunities. The advances in chemical science provide better opportunities to use metal complexes as therapeutic agents. The use of transition metal complexes as therapeutic compounds has become more and more evident. These complexes offer a good diversity in their action such as; anti-inflammatory, anti-infective and anti-diabetic compounds. Considerable efforts are made for the event of transition metal complexes as drugs. Beside several limitations and side effects, transition metal complexes are still the leading chemotherapeutic agents and make an outsized contribution to medicinal therapeutics [3].

Properties of Metal Complexes and Metal-Based Compounds

Metal complexes and metal-based compounds hold the flexibility to coordinate with ligands in a three-dimensional configuration, thereby allowing functionalization of groups that may be shaped to defined molecular targets [4].

i. Charge Variation: In solution, metal ions exist as charged species. Estimate on the prevailing coordination environment, the charge will be modified to get species that may be cationic, anionic or neutral. Most significantly, they form charged ions in solution that may bind to charged biological molecules [4].

ii. Structure and Bonding: Metal complexes can combine to **a good** range of coordination geometries that give them unique shapes. The bond length, bond angle and coordination site vary **looking on** the metal and its **oxidation number**. **Additionally to the present**, metal-based complexes **may be** structurally modified to **a range** of distinct molecular species that confer **a large** spectrum of coordination numbers and geometries [4-6].

iii. Metal-Ligand Interaction: Different **kinds of** metal–ligand interaction exist; however, these interactions usually **cause** the formation of complexes that are unique from those of individual ligands or metals. The thermodynamic and kinetic properties of metal–ligand interactions influence ligand exchange reactions. **The flexibility** of metals to undergo these reactions offers **a large** range **of benefits** to the metals to interact and coordinate with biological molecules [4].

iv. Lewis Acid Properties: Characterized by high electron affinity, most metal ions can easily polarize groups that are coordinated to them, thus facilitating their hydrolysis [4,7].

v. Redox Activity: Many transition metals tend to undergo oxidation and reduction reactions [7]. The **number of those** metals is **a crucial** consideration **within the** design of the

compound. In biochemical redox catalysis, metal ions often serve to activate coordinated substrates and to participate in redox-active sites for charge accumulation.

vi. Partially Filled D Shell: For transition metals, the variable number of electrons **within the** d shell or f shell (for lanthanides) influences the electronic and magnetic properties of transition metal complexes [7].

Metals in Medicine

Metal containing drugs are important for **some** medical applications including diagnosis and treatment.

Metals Application

A. Platinum: Platinum based compounds **are** shown to specifically affect Head and Neck tumors. These coordination complexes are thought to act cross-link DNA in tumor cells

B. Gold: Gold salt complexes are wont to treat autoimmune disorder. The gold salts are believed to interact with albumin and eventually be obsessed by immune cells, triggering anti-mitochondrial effects and eventually cell apoptosis.

C. Lithium: Li2CO3 are often wont to treat prophylaxis of Manic-Depression behaviour.

D. Zinc: Zinc will be used topically to heal wounds. Zn2+ may be accustomed treat the animal virus.

E. Silver: Silver has been **wont to** prevent infection at the burn site for burn wound patients.

F. Gold, Silver, Copper: Phosphine ligand compounds containing gold, silver, and copper have Anti-Cancer properties

G. Lanthanum: Lanthanum Carbonate often used under the **name** Fosrenol **is employed** as a phosphate binder in patients **laid low with** Chronic **nephrosis**.

H. Bismuth: Bismuth subsalicylate **is employed** as an antacid.

I. Platinum, Titanium, Vanadium, Iron: cis DDP (cis-diaminedichoroplatinum), titanium, vanadium, and iron **are** shown to react with DNA specifically in tumour cells to treat patients with Cancer.

J. Barium: X-ray diagnosis

K. Gadolinium, Manganese: **resonance** imaging

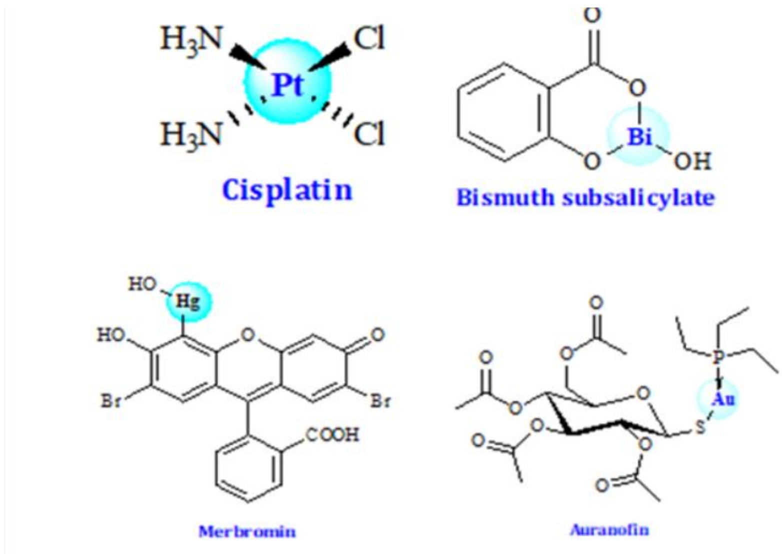
L. Mercury: Antiseptic and diuretic

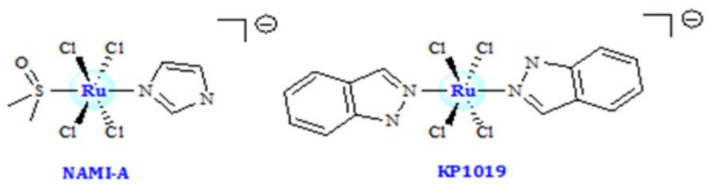
Some Important Metal-Based Drugs

NAMI-A and KP1019 are two potential ruthenium drugs possessing antitumor behaviours

Recent Advancements within the Field of Medicinal Chemistry Involving Metal-Based Drugs

Soon after the entry of cisplatin into the clinic a large range of related compounds were prepared and evaluated. Neutral Pt (II) complexes with a square-planar geometry, including two cis-coordinated leaving groups, were defined as critical structural features for anticancer activity [8]. Gold (III) complexes have long been probe for anti-cancer treatments. Many gold (III) complexes have displayed interesting anticancer potencies, but their medicinal applications have always been hindered by their poor stability in solution [9]. Che et al. [10] prepared a series of physiologically stable gold (III) complexes which possess significant in vitro and in vivo anti-cancer activities. Research showed that the [Au (TPP)] Cl (H2TPP = tetraphenylporphyrin) complex exhibited potent in vitro anticancer activities toward a panel of neoplastic cell lines (Figure 1).





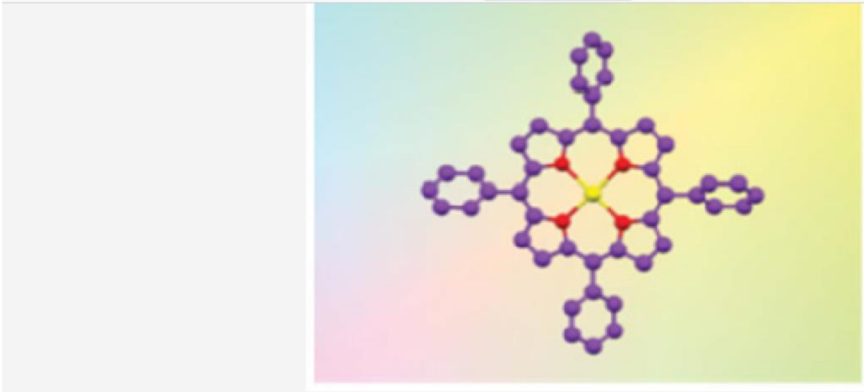


Figure 1: X-Ray crystal structure of [Au III(TPP)]+.

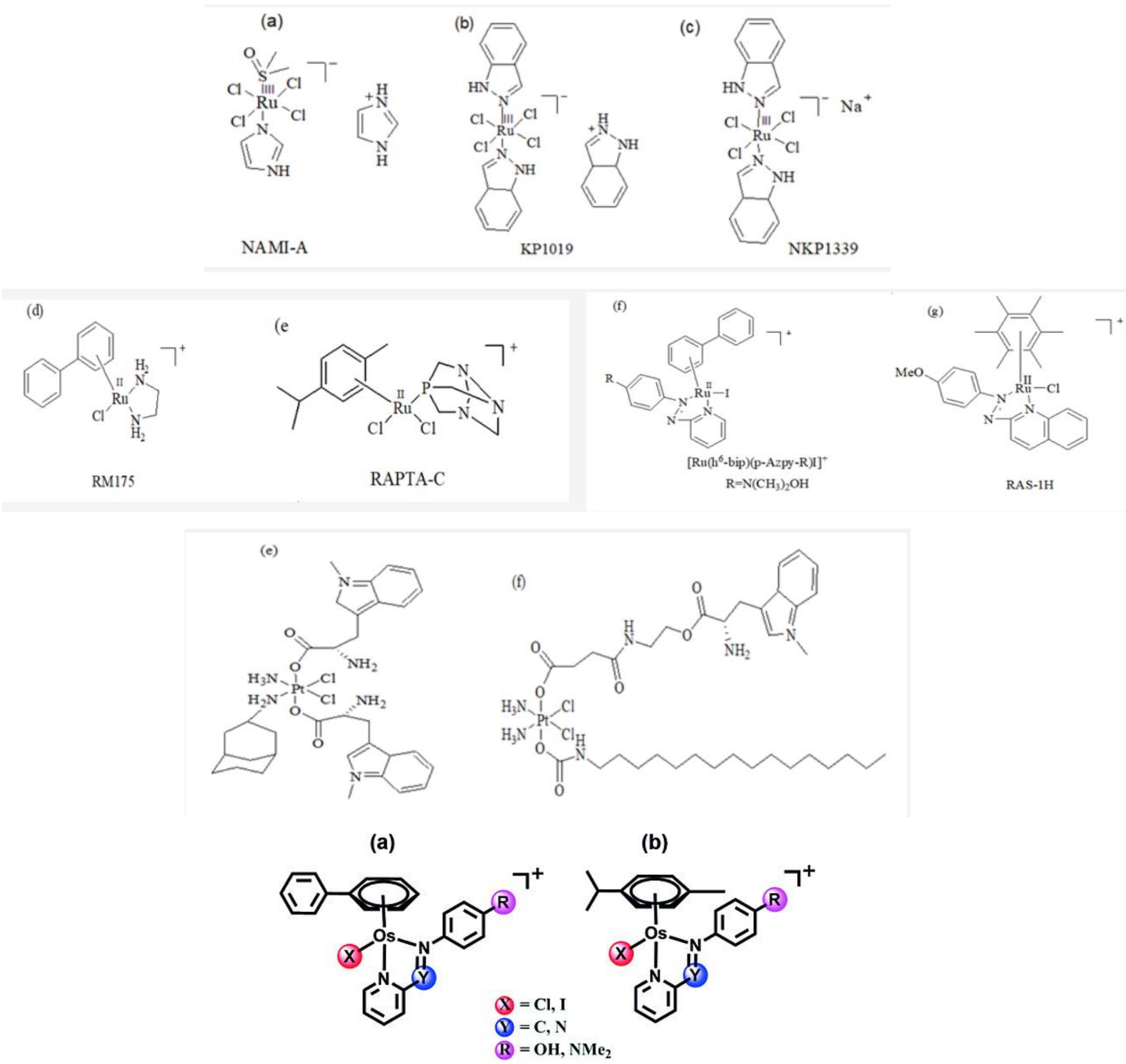


Figure 1: X-Ray crystal structure of [Au III(TPP)]+.Figure 2: Some Co, Ru, Pt and Os metal complexes exhibiting redox mediated anticancer activity.

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E. Silver: Silver has been **accustomed** prevent infection at the burn site for burn wound patients.
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Gallium (III) complexes present a special activity in anticancer therapy because of the analogy of the Ga (III) ion with the Fe (III) ion in ionic radius, electron affinity, electro-negativity, co-ordination geometry, and Lewis base affinity. Di-nuclear and tetra-nuclear organometallic gallium (III) compounds containing heterocyclic thiolato ligands were synthesized by Gomez-Ruiz et al (Figure 4). These compounds were synthesized by a straightforward protonolysis reaction of trimethylgallium and also the thiol group of mercapto-substituted imidazole, tetrazole, benzothiazole or phenyl-oxadiazol heterocycles. The heterocyclic thiolate poly-nuclear gallium (III) derivatives showed improved anticancer activity [25]. Alzheimer’s disease (AD) is currently an incurable neurodegenerative disorder that affects variant people round the world. Various Amyloid β-targeted metal complexes have exhibited promising potential as anti-AD agents because of their fascinating physicochemical properties over the past 20 years (Figure 5) [26].

Numerous other studies are reported for metal complexes as medicinal agents. The utilization of zinc applied topically to push the healing of wounds dates to around 1500 B.C., and silver is now commonly applied to forestall infection in bum patients. Osmium carbohydrate polymers are reported to possess anti-arthritic activity. Transition metal complexes have a protracted history of use as antibacterial and antiviral agents; as an example, Zn is employed to treat herpes, possibly by inhibiting the viral DNA polymerase. Early transition-metal (e.g., tungsten) polyoxoanions are employed to treat AIDS patients. Deficit of essential metal ions ends up in various deficiency syndromes which will often be fatal. Malnutrition is treated temporarily or over longer time periods using dietary supplements consisting of 1 or more metal ions. Iron deficiency is that the most prevalent and over 2 billion people are plagued by it worldwide. Certain metal deficiencies arise from genetic metabolic disorders (acrodermatitis enteropathica, Menkes disease) while others occur thanks to complications in cases of gastric atrophy or chronic nephropathy. Acrodermatitis enteropathica is an autosomal recessive disorder affecting the uptake of zinc that patients depend lifelong on zinc supplements to survive. Similarly, Menkes Disease is caused by a mutation on the gene encoding Cu2+ transporting ATPase that ends up in the dysfunction of the many copper dependent enzymes and acute copper deficiency. Immediate treatment can prevent brain damage.

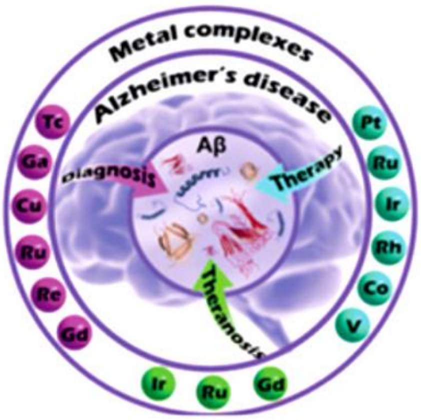

Figure 5: Metal complexes for potential applications in Alzheimer's disease.

Medical Use of Metal Nanoparticles

Nanotechnology has greatly enhanced drug delivery system to an oversized extent, thereby reducing the unwanted effects by limiting the drug effect to specific site and leaving other tissues untouched. Therefore, the chance provided by nanoparticles to selectively target cancer cells and leave behind healthy cells untouched has gained interest within the design of metal-based cytotoxic drugs. Metal-based NPs are of various shapes and sizes and are investigated for his or her role in diagnosis and drug delivery system. most ordinarily available metal-based NPs include nickel, gold, silver, iron oxide, gadolinium and titania [27]. Metal-based NPs provide an oversized expanse that allowed incorporation of huge drug dose. to enhance the specificity within the diagnosis of cancers, various styles of highly specific and sensitive NP-based optical imaging platforms are being investigated [28]. They provide a significant advantage compared with other agents. They'll be functionalized to specifically target tumor cells, allowing the imaging and therapeutic agent to be specifically delivered to those cells.

Metal nanoparticles (silver and gold) are widely utilized in cell imaging, DNA hybridization detection, proteins interaction, and photothermal therapy because of their extremely strong absorption and light-weight scattering within the plasmon resonance [29]. Among every type of noble metal-based nanoparticles, gold nanoparticles (Au NPs) have shown a good capacity to be used as potential drug delivery carriers (Figure 6). It's relatively easy to get Au NPs with various sizes (1–100 nm) and shapes (spherical, rod-like, cage-like, etc.) [30].

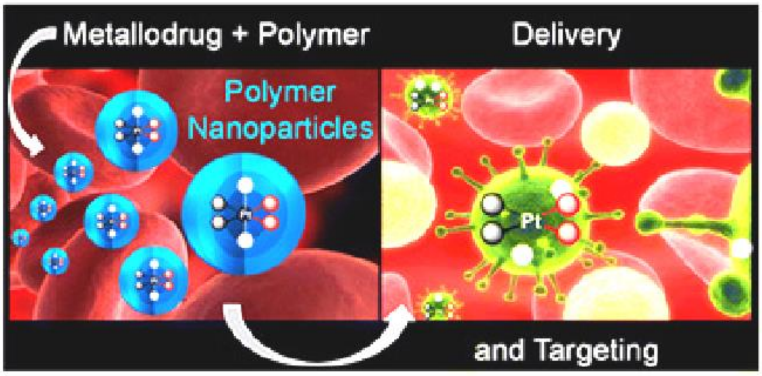

Figure 6: Various applications of Au nanoparticles as carriers.

Encapsulation of the platinum (IV) prodrug mitaplatin in block copolymer nanoparticles increases drug circulation time within the blood and reduces accumulation within the kidneys, as reported by Lippard and colleagues (Figure 7) [31]. Importantly, controlled drug release from the nanoparticles produces long-term anticancer efficacy, with the prospect of reduced side effects. Metal coordination complexes offer the prospect of novel mechanisms of activity on account of their unique architectures, in addition as potential activation mechanisms, including ligand substitution and metal- and ligand-cantered redox properties.

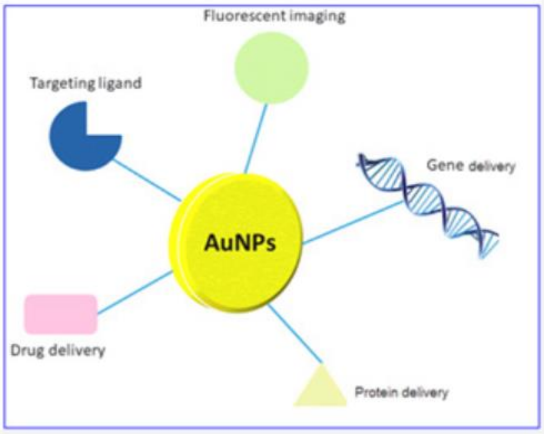

Figure 7: Encapsulated Platinum(IV) prodrug mitaplatin in block copolymer nanoparticles.

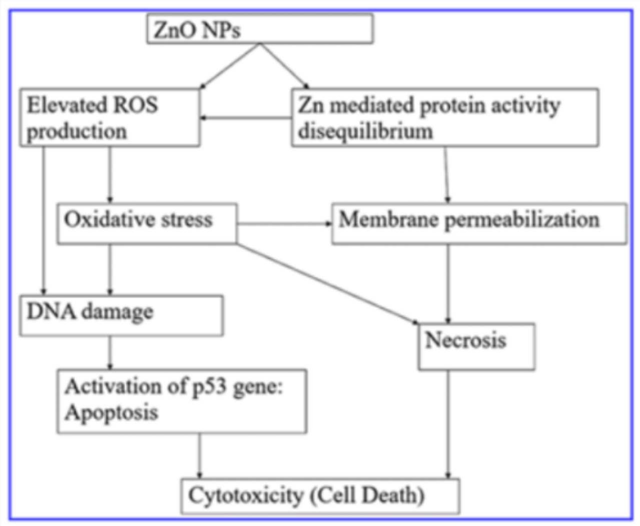

Figure 8: The use of magnetic nanoparticles embedded into PLGA nanoparticles for diagnosis and treatment of diseases.

In a recent study, antibody-conjugated magnetic poly (D, L-lactide-co-glycolide) (PLGA) nanoparticles with doxorubicin (DOX) were synthesized for the simultaneous targeted detection and treatment of carcinoma. DOX and magnetic nanoparticles were incorporated into PLGA nanoparticles, with DOX serving as an anticancer drug and Fe2O3 nanoparticles used as an imaging agent (Figure 8) [32].

Research has shown that low zinc concentration in cells results in the initiation and progression of cancer and high zinc concentration shows toxic effects. The selective localization of ZnO nanoparticles towards cancer cells thanks to enhanced permeability, retention effect and electrostatic interaction show that ZnO nanoparticles can selectively target and kill cancer cells, making them a promising anticancer agent (Figure 9). The standard organic drugs alone might not be complete without a parallel exploration of metal pharmacology as many organic drugs require interactions with metals for activity. Metal compounds offer new properties that can't be found amongst purely organic agents.

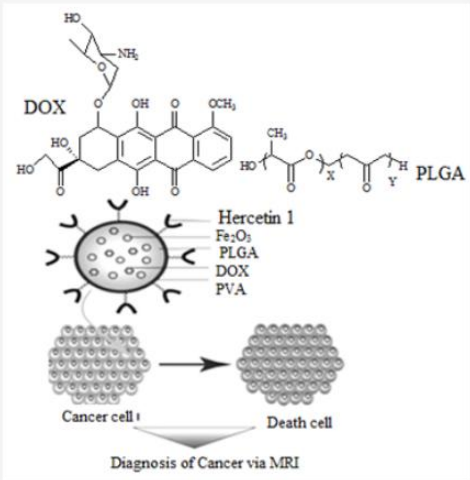

Figure 9: A schematic representation of the overall cytotoxicity of ZnO nanoparticles, leading to cell death

Conclusion and Future Prospective

Since metals are endowed with unique properties that are absent in conventional carbon-based drugs, the positive trend in drug discovery may be continued for the planning of recent metal-based drugs. The therapeutic application of metal complexes remains an unexplored area of research and should be useful to develop novel therapeutic agents. The exploration of transition metal complexes, still as targeting and activation strategies, should result in future generations of medication which may overcome a number of the disadvantages related to present drug therapies, including the reduction of side-effects, widening the spectrum of activity, and resistance. The sphere of medicinal chemistry and interdisciplinary researches related with metallodrug should, therefore, be exploited with a rapid acceleration to resolve the biological and pharmacological profiles and molecular activity mechanisms of metallodrugs within the complex biological systems. Thus, metallodrugs will definitely take a key a part of drug development to enhance the standard of lifetime of patients.

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