Review Article

THERANOSTICS NANOMEDICINE: RECENT ADVANCEMENT, APPLICATIONS AND CHALLENGES

ABSTRACT:

Many advancements have been made in diagnosis and treatment tools with the progress in modern medicine and technology. Theronostics are multifunctional nanomaterials that combine therapeutic and diagnostic functions in a single nanostructured system. Theranostic nanomedicines are highly suitable systems for monitoring drug delivery, drug release and drug efficacy.The incorporation of diagnostic and therapeutic agents within a single system provides the target site localization and accumulation of nanomedicines in organs.It provides a transition from conventional medicine to personalized medicine. It Many different types of nanomedicines have been evaluated over the years. Theragnostics approach includes personalized medicine, pharmacogenomics, and molecular imaging to develop efficient new targeted therapies which will help in better and optimize drug selection along with monitoring the therapy response to increase drug saafety and efficacy This review summarizes the various nanocarriers developed until now for nanotheranostics, such as Polymeric, drug polymer conjugates, dendrimers, micelles, liposomes, metallic, inorganic nanoparticles, and carbon nanotubes.

Keywords:Theranostics, Nanomedicine, Nanoparticles, Personalized therapy, Liposomes, Targeting

1. INTRODUCTION:

The past decade witnessed a tremendous progress in the field of diagnostics and treatments due to the advancement in medicinal and pharmaceutical area.Theranostic is an emerging therapeutic system which combines therapy and diagnostic strategy in a nanostructure entity for developing targeted personalized therapy**[1]**Theranostic obtained when a single particle (nanoparticle), is fabricated which contain a combination of therapeutic element (drug) and diagnostic/ imaging element. In the scientist community, there is increase in the interest for theranostic drug delivery systems for the management of diseases such as, inflammatory and cancer**[2]**Recent Innovations in nanodelivery system have led to the escalating research work and advancement on nanotheranostics due to various advantages of nanoparticles such as site-specific targeting, thermo stimulation, phototherapy and delivery of combination of drugs **[1].**

The therapeutic agents in theranosticnanocarriers include therapeutic drugs, proteins, peptides and genetic materials. Diagnostic/imaging agents used in theranosticnanocarriers include gadolinium, fluorescent dyes, quantum dots, radionuclides, superparamagnetic iron oxides and heavy elements (iodine) for optical imaging, magnetic resonance imaging (MRI), nuclear imaging and computed tomography**[3]**For theranostic applications, various combinations of therapeutic and imaging combinations are possible.

Several drug delivery systems reported to use clinically such as, liposomes, micelles and nanoparticles etc.**[4,5]**Imaging agents along with therapeutics can be incorporated into such nanocarrier system, which helps in providing valuable diagnostic information and thus can be used as theranostic agents, which can be employed to non-invasively monitor drug delivery, drug release and drug efficacy, and which therefore hold significant potential for personalizing nanomedicine treatments**[1]**In the present Review article, we discussed the possible use of nanocarrier system for drug delivery and imaging purposes, andalso the applications and challenges of Theronostics in Pharmaceutical drug delivery development.

2.TheranosticNanomedicine:

Due to multifunctional and intrinsic molecular characteristics, nanomaterials have emerged as one of the promising tool in theranostics and biomedical science **[6-8]**Recently, nanotechnology has been vastly utilized for the diagnosis and treatment of many diseases including cardiovascular diseases, diabetes as shown in Figure 1.

Figure 1: Role of Theranostic in Various Diseases

Nanotheranostics is a rapidly developing field for monitoring distribution of drug, drug release, and therapeutic efficacy through a single nano carrier system**[9-13]**Nanoparticles can be chemically modified to incorporate various bioconjugate moieties for precise detection and therapy**[14-17]**Various nanoparticle-basedtheranostic agents have been designed that involves carbon nanotubes,magnetic nanoparticles, gold nanoparticles, silica nanoparticles, **[2,18,19]**,and quantum dots**[20-22]**.
The variety of Theronostic platforms are explored such as in therapy, formulation design, diagnostics, imaging,drug deliver as shown in figure 2.

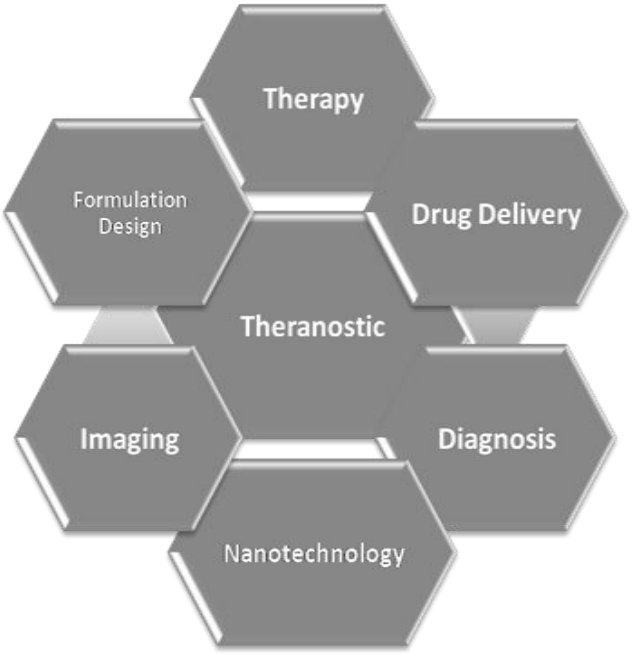

Figure 2: Interdisciplinary Applications of Theranostics.

Theronostics nanoparticles can be composed of organic and inorganic materials such as polymeric nanoparticles, nano capsules, , micelles, liposomes, dendrimers, quantum dots , and carbon nanotubes as depicted in Figure 3.

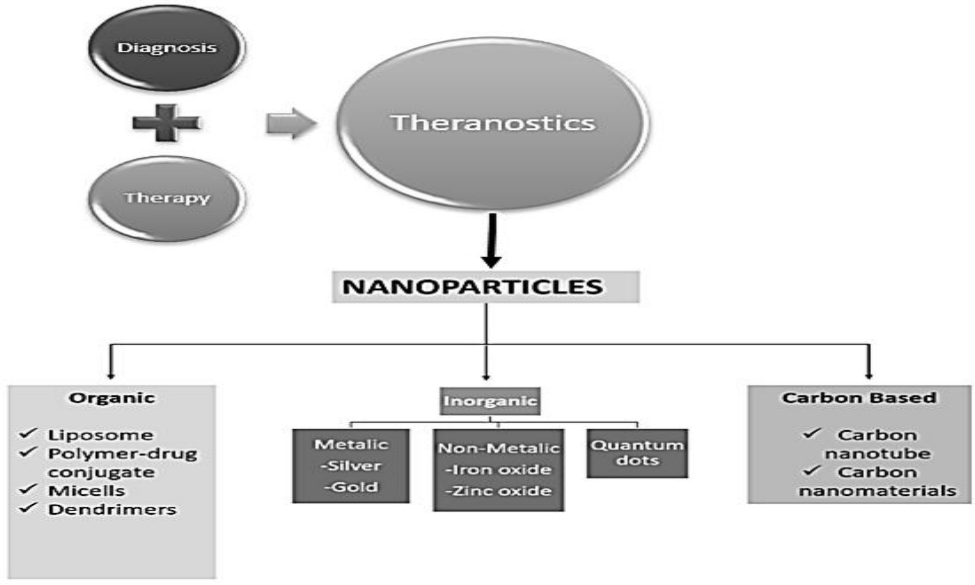

Figure 3: Theronostics Nanoparticles

2.1 Metallic Nanoparticles ForTheranostics:

There are various nanoparticle formulations which can be used as theranostics including both organic and inorganic nanoparticles. Common materials used to synthesize or form nanoparticle systems include proteins, polymers, lipids, gold, and iron oxides.

2.1.1 Gold Nanoparticles:

Gold Nanoparticles (AuNPs) designed from gold cores are biocompatible and are usually prepared as spheres, wire, rods, cubes, and cages**[23-26]**. Unprepared with core size from 1.5 to 10 mare conjugated with drug and targeting ligand as that specifically recognizes the target receptor for active targeting**[27-29]**AuNPs showed promising results in treating MDR tumors by targeted photothermal treatment in combination with a chemotherapeutic agent **[30]**A theranostic system for cancer treatment, which was able to reduce the cytotoxic effect on normal cells, has been developed based on the use of Unsurfaced-functionalized with a paclitaxel drug and biotin receptor. AuNPs were also investigated for their peculiar interaction with cancer cells and found to be more efficient and improve the treatment of gliomas**[31, 32]**Recently, matrix metalloproteinase-2- sensitive gold-gelatin nanoparticles were developed; RGD and octarginine were used as targeting ligands to pass through the BBB, allowing a pH-triggered release to the glioma-specific area**[33]**

2.1.2 Silver Nanoparticle :

Metallic NPs have this capacity to be attached to biological compartments to target specific receptors on tumor cells**[34]**Silver nanoparticles (AgNPs) have several characteristics that make them suitable for cancer diagnosis and therapy**[34]** Many researchers have developed nanocomposite particles using Silver with other metals or polymers for cancer theranostics**[35]** developed biocompatible AgNP with chitosan, labeled with a p-aminothiophenol**[36]**developed AgNP using Olaz scandens leaf extracts that showed anticancer activity against different cancer cells**[35, 36]**.

2.2 Polymer Based Nanoparticles:

The most common materials used to make polymeric nanoparticles are poly(lactic acid)/poly(lactic-co-glycolic acid) PLA/PGLA,block copolymers, and chitosan. Polymeric nanoparticles are utilized in Theronostics due to their biocompatibility, better physiochemical characteristics, easy surface modification nontoxicity, storage stability, protection of loaded drug/diagnostic agent and controlled/ sustained release**[37, 38]**.

The glycol chitosan (GC) has gained interest owing to solubility in aqueous media, biodegradability, and bio-compatibility. fluorescent polymeric nanoparticles (FNPs) were researched as theranostic agents for cancer detection and treatment. These are fabricated by employing fluorescent proteins, inorganic quantum dots, commercial organic dyes, and biocompatible biopolymers**[39, 40]**.
Polymer based magnetic nanoparticles (PMNPs) have applications in targeted drug delivery, cell tracking, tissue engineering and bio separation**[15,41]**PMNPshaving targeting moiety which possesses a magneto-responsive therapeutic agent found to be an efficient nanotheranaostic system for diagnostics as well as drug delivery **[41,42]**.
Dendrimers, highly branched macromolecules, with a low density interior and a high density exterior have found many applications in theranosticnanomedicine. Many researchers havedeveloped dendrimers for cancer theranostics including PAMAM (poly(amidoamine)), Bis¬MPA (2,2¬bis(hydroxymethyl) propionic acid), PPI (polypropylene), PEG (poly(ethylene glycol)), 5¬ALA (5aminolevulinic acid), and TEA (triethanolamine)**[43]**.

2.2.1 Drug-Polymer Conjugates:

Drug-polymer conjugates include protein conjugates and drug conjugates with appropriate polymers. HPMA (N-(2-hydroxypropyl) methacrylamide)based conjugates are used for theranostics since they're stable, non-toxic and biocompatible for in vivo applications**[44, 45]** There are many studies showing the applications of HPMA polymer together with diagnostic agents. as an example, a passive targeted HPMA-doxorubicin (DOX) conjugate labeled with I-131 has been studied in run phase I clinical trial**[46]** Yuan et

al synthesized poly(HPMA) based theranostic copolymers loaded with Cu-64 (i.e., intrinsic theranostic agent) and RGD was used as targeting ligand for targeting tumor angiogenesis**[47]**.

2.2.2 Chitosan Nanoparticles:

Chitosan (CS) could be a biodegradable polymer of cationic polysaccharide generated by partial deacetylation of chitin. Several researchers have conducted studies on chitosan nanoparticles for carcinoma drug delivery for therapeutic purposes evaluated the effect of chitosan coated doxorubicin loaded nanocarrier in cancer of the liver where it showed excellent inhibitions of cell growth of cancer of the liver**[48]**Loutfy et al, (2016) synthesized chitosan nanoparticle (CS-NPs) for evaluation of the in vitro human carcinoma cell model (HepG2). They investigated that the cytotoxic effect of CS-NPs towards carcinoma cells is comparatively good and that they suggested that CS-NPs are suitable for drug delivery proposes for cancer of the liver **[49]**.

2.3 Based Nanoparticles:

The lipid-based NCs provide an option in the development of a specific nanotheronostic delivery system for different liver cancer drugs. A nanostructured lipid carrier was synthesized by Bondì et al, (2015) for the controlled release of sorafenib drug to see the anticancer activity compared to free drug. They suggest that lipid based nanocarrier can be a good delivery agent for liver cancer for therapeutic application**[50]**Furthermore, Zhao et al, (2015) developed a lipid nanocarrier that delivers the doxorubicin and curcumin drug in mice model and they found that lipid nanocarrier has the excellent inhibitory effect on tumor growth with its high encapsulation efficacy, uniform particle size and sustained release profile**[51]**.

2.3.1 Solid Lipid Nanoparticles:

Solid lipid nanoparticles are a secure and effective alternative colloidal matrix carrier to traditional emulsions, liposomes, and polymeric nanoparticles**[52]**.They are made of solid hydrophobic core containing dissolved or dispersed drug. Solid lipid nanoparticles are nanomedicine made from biocompatible lipids (e.g., triglycerides) which are solid at temperature. Solid lipid nanoparticles gain access to the blood compartment easily due to their small size and lipophilic surface. the size range of less articles for intravascular delivery than 100 nm allows solid lipid nanoparticles to cross tight-endothelial cells of barrier for brain targeting**[53-55]**Bae et al. reported quantum dots loaded solid lipid nanoparticles for anti-cancer theranostics with synergistic/multimodal therapeutic effects of paclitaxel and siRNA**[56]** Recently, lymphatic delivery of solid lipid nanoparticles emerged as a technology to provide better transport into the lymphatics resulting in enhanced oral bioavailability of therapeutic agents**[57]**Bae et al. reported quantum dots loaded solid lipid nanoparticles for anticancertheranostics with synergistic/multimodal therapeutic effects of paclitaxel and siRNA**[56]**.

2.3.2 Liposomes:

Phospholipids, the dominant component of cell membranes, naturally become a category of promising candidates to create the platforms for nanomedicine due to their wide availability and excellent biocompatibility. Lipid nanoparticles within the style of vesicles and micelles are widely applied to drug delivery systems, and are developed with many successful products of nanomedicine on the market and within the clinical trials **[58]**.

Liposomes are composed of natural or synthetic phospholipids, and other stabilizing components like cholesterol, which assemble into vesicles with their sizes varying from tens to many nanometers. Basically, liposomes are obtained through the rehydration of a lipid film and further physical extrusion or sonication **[59]** and theranostic liposomes is produced by adding functional agents into the starting materials during the preparation. For liposomes, their aqueous chamber can encapsulate hydrophilic payloads, and therefore the lipid bilayer may accommodate hydrophobic molecules. Therefore, liposomal drug formulations have succeeded in many chemotherapeutic compounds, including doxorubicin (DOX), paclitaxel, cisplatin, irinotecan, mitoxantrone, annamycin, topotecan and vinorelbine.

The liposomes can successfully protect the functional components from the external environment, prolong the systematic circulation time, and enhance their tumor accumulations**[58]**Many researchers have worked on liposomal formulations that have applications in targeting, therapeutic, and imaging functionalities**[60]**Besides liposomes, other varieties of lipid-based drug carriers are developed for the delivery of theranostic agents **[61]** including nano emulsions, and solid-lipid nanoparticles. for example, an oil-in-water nanoemulsion encapsulating iron oxide nanoparticles (IONPs), Cy7 near infrared (NIR) dye and glucocorticoid prednisolone acetate valeranate is utilized to look at the uptake of the nanoparticles and therapeutic effectiveness through resonance imaging (MRI) with high spatial resolution and fluorescent imaging with high sensitivity**[62]**.

The lipid drug conjugates have also been demonstrated with an enhanced anticancer activity against solid cancers for squalene based anticancer prodrugs**[63, 64]** Solid lipid nanoparticles with a solid lipid core matrix are developed to boost the physical stability that hurdles the appliance of liposomes, and are utilized to deliver both of paclitaxel and Bcl¬2 targeted siRNA into human lung carcinoma cells**[56, 65]** Cell membranes are considered to be an ideal disguise for drug carriers to avoid immune clearance**[66]**.

2.3.3 Micelles:

Polymeric micelles are self-assembling colloidal structure with a hydrophobic core and hydrophilic shell were tested as theranostic carriers and imaging probes**[67]**Therapeutic/ diagnostic agents is loaded into hydrophobic core of micelles and also the outer hydrophilic layer with targeting agent, which might then be administered intravenously**[68- 71]**

2.3.4 Dendrimers:

Dendrimers are hyperbranched nanostructures with controlled functionality and are vehicles which will be efficiently tailored for the spatial distribution of varied functionalities on their surface. These versatile functions, which permit stimuli–response ability and also the ability to self-assembly, make dendrimers excellent candidates for theranostic applications**[72]**Dendrimers used in nanotheranostics are usually 10 to 100nm **[73]**Saad and coworker designed, and evaluated a theranostic dendrimer for in vitro and in vivo. These nanocarriers delivered the paclitaxel and diagnostic agent **[74]**.
Taratula et al. developed a novel dendrimer-based theranostic platform for tumor- targeted delivery of phthalocyanines. The study revealed the significant potential of dendrimers as an efficient theranostic agent**[75]**.

2.4 Carbon Nanomaterials:

2.4.1 Nano Carbons:

Nano carbons, such as carbon nanotubes (CNTs), graphene derivatives and carbon dots (Cdots) show inherent optical properties which makes them useful contrast agents in optical imaging and sensing**[76-78]**Carbon nanotubes (CNTs) are composed of various layers of graphene sheets, which form a cylindrical shape. CNTs are considered as allotropes of carbon with poor biocompatibility and slow biodegradation**[87]** CNTs are useful for theranostic applications since they will ameliorate the effect of chemotherapeutic drugs and are adaptable to clinical applications**[86, 87]**CNTs are potentially considered excellent nano-vehicles for the delivery of different therapeutic agents due to their small size and mass, high electrical, strong mechanical potency and thermal conductivity**[89-92]**Chen et al., reviewed the applications of functionalized fullerenes in tumor theranostics**[93]**Xu and co-workers investigated the influence of oxidized multiwalled CNTs on macrophages and reported novel approach of using CNTs in cancer immunotherapy**[94]**Shen H and co-workers**[95]**reported the applications of graphene and graphene derivatives in the field of biomedicine such as, drug and gene delivery, cancer therapy, biomedical imaging, biosensing and tissue engineering.

3. Recent Advancement of Theranostic Nanoparticles:

The Table 1 summarized the recent applications and advancement of Theranostic Nanoparticles.

Table1 : Recent Advancement of Theranostic Nanoparticle

Types of theranostic nanomaterials	Theranostic advancement	References
Liposomes	Co-delivery of docetaxel and quantum dots	**[79]**
Gold Nanoparticles	❖ AUNPs improve the treatment of glimos ❖ Stimulus responsive drug release ❖ Diazirine-decorated gold NPs	**[80]** **[81]**
Magnetic Nanoparticles	Useful tool for magnetically enhanced accumulation in brain tumors and non-invasive MRI screening	**[82]**
Drug-polymer conjugates	Cancer imaging and radio chemo-therapy	**[47]**
Solid lipid Nanoparticles	Multimodal Therapy	**[83]**
Polymeric nanoparticles	Co-delivery of docetaxel and quantum dots	**[84]**
Dendrimers	Delivery of single theranostic agent	**[75]**
Micelles	Delivery of single theranostic agent	**[85]**

Carbon Nanotubes	They can ameliorate the effect of chemotherapeutic agent and translatable to clinical application	**[86, 87]**
Carbon nanomaterials	Self photolumines-cent and photothermal property	**[88]**

4. Challenges:

One of the major challenges associated with theranostic nanomedicine is interaction and compatibility between nano material and biological components which can show immunoreaction, inflammation and related side effects**[96]**Many researchers reported acute adverse immune reaction caused by many nanoplatforms . Another challenge is the safety profile of nanotheranostics in humans, and for this more advanced clinical trial are needed to established the safety concern. The major challenge associated with thetheranostic nanomedicines is the difficulty in control and reproducibility of the formulation process. Since theranostic nanoparticles are multifunctional unit, more accurate formulation approach and control along with good manufacturing practice are needed. Also, more stringent regulatory steps are needed to bring theranostic nanomedicine from research laboratories to clinical use **[97]**.

5. Conclusion:

Nano theranostics is a promising field that conglomerates the advantages of diagnosis and therapy. These novel nanocarriers not only deliver the drug but also simultaneously monitor and diagnose therapy response. The theranostic nanomaterials are fabricated based on the concept of combining therapeutic agents, imaging agents, and targeting moieties. The NP-based theranostic involves gold-, magnetic-, carbon-, silica-NPS and carbon nanotubes. These nano-drug delivery systems have shown potential outcome in cancer and other diseases. This technology will help to save time and decrease costs and better patient compliance.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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