International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

Nanotheranostics as an Emerging Strategy for Cancer Therapy

Divya Sharad Borse
SHASTRY INSTITUTE OF PHARMACY
Palasdal, Near Anjani MadhyamPrakalpa, Gat No. 4/1, Besides AH 46, Tal. Erandol, Dist. Jalgaon.

Submitted: 01-01-2023 Accepted: 08-01-2023

ABSTRACT

Worldwide, there is still no cure for cancer, which is a public health problem. Recent advancements in the treatment of cancer have led to the development of theranostics, which combines a therapeutic medicine and an imaging agent in a single formulation. The last ten years have seen a significant increase in interest in the use of nanotheranostics as novel characteristic and healing agents for a variety about illnesses, including cancer. To present, a number of strategies have been used to create smart nanotheranostics, which combine bioactive targeting on particular tissues and diagnostic capabilities. The nanotheranostics can provide therapeutic chemicals while concurrently tracking the therapy's outcome in real-time.The field of nanotheranostics, which combines therapeutic and bioimaging functions at the single nanoparticle level, has grown significantly in recent years. The nanotheranostics platform is made in a way that it can efficiently target the payload to the intended locus, overcome a variety of biological obstacles, and support planning, monitoring, and verification of therapy delivery at the same time to show increased therapeutic efficacy. A nanotheranostic platform may therefore help with patient stratification, medication targeting, image-guided focused therapy, drug release and distribution monitoring, and treatment response prediction. This study focuses on the methods for building chemically based theranostics systems and emphasises their usage in the treatment of cancer, which might serve as important references for future research.

I. INTRODUCTION:

1.1 Cancer (malignancy)

The top cause of death in the world is cancer. Cancer starts when genetic alterations disrupt this systematic process. Uncontrollable cell growth starts to occur. These cells could aggregate into a lump known as a neoplasm. A tumour may be benign or cancerous. A cancerous neoplasm is malignant, which implies it will spread to various parts of the body as it develops. A benign tumour will continue to growstill noscatter. A fewmalignancy do not develop into tumours. Lymphoid, the majority of lymphoma varieties, and Kahler disease are among them (30).

1.1.1 Types of cancer

There are four primary cancer types:

- **Carcinomas**

The skin or the tissue that covers the surface of internal organs and glands is where a carcinoma first appears. Solid tumours called carcinomas are the norm. They are the most prevalent cancer type. Prostatic adenocarcinoma, breast cancer, lung cancer, and colorectal cancer are a few examples of carcinomas.

- **Sarcomas**

The tissues that support and link the body are where cancer first develops. Fat, muscles, nerves, tendons, joints, blood vessels, lymph vessels, cartilage, or bone can all develop cancer.

- **Leukemias**

A cancer of the blood is leukaemia. Once normal blood cells start to change and proliferate out of control, leukaemia has started. Acute lymphocytic leukaemia, chronic lymphocytic leukaemia, acute myeloid leukaemia, and chronic myeloid leukaemia are the four main kinds of leukaemia.

- **Lymphomas**

Cancer that starts in the lymphatic system is called lymphoma. The vascular system could consist of a network of glands and vessels that helps the body fight infection. Hodgkin lymphoma and non-Hodgkin lymphoma are the two main forms of lymphomas (30).

The habitat that a growing tumour or cancer develops for itself is referred to as the tumour micro environment (TME). As knowledge of cancer development advances, it emphasises the quality of the malignancies characterised by inter-tumor and intra tumour heterogeneity between cancer forms of completely different or an equivalent anatomical region. The TME is thought

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

to supply differentiation niches for being development that results in tremendous cancer heterogeneity (1).

A tumour grows larger and occupies more body space. Pressure from the cancer may then be placed on nearby structures. It may potentially develop into neighbouring bodily parts. It is referred to as local invasion. It is unclear exactly how a cancer spreads into the tissues around it.

A cancer may spread from its initial location in any direction. However, scientists are aware that some tissues are easier than others for tumours to invade. For instance, tumours find it difficult to spread through major blood arteries with thick walls and tough tissues like cartilage. Tumors so typically develop along the "route of least resistance." This implies that they probably choose the quickest option (37).

- Cancer risk elements include:

-Smoking
-excessive alcohol use
-Unhealthy body weight
-Active inactivity
-Poor nutrition
Other cancer-causing factors cannot be avoided.

The onset of cancer may be effect by congenital cause. The genetic coding in human determines when bothunits will cut upwith burn. Gene swap may result under incorrect instructions, which may cause malignancy.Certain genes alter the proteins that would typically mend harmed cells. This might result in cancer.

The changed instructions could be passed on to a child if a parent carries these genes. Some genetic alterations take place after birth, and risks might be increased by things like smoking and sun exposure. Other alterations that can lead to cancer occur in the chemical signals that control how the body uses, or "expresses," particular genes (40).

Despite being exposed to substances that can cause cancer (including X-rays, sunshine, and secondary smoking) throughout their period, some people don't get the disease. Additionally, some people carry the genes linked to cancer but never get it. It is evident that the higher the quantity or level of cancer-causing materials to which an individual is exposed, the greater the likelihood that the individual will develop the disease, even though researchers may not be ready to provide a satisfactory account of each individual (42).

Additionally, those with genetic predispositions to cancer may not get it for the same reasons as others (lack of enough stimuli to allow the genes function). Additionally, some individuals may have a very strong immune response that regulates or destroys cells that are or may develop into cancer cells. There is evidence that even eating habits may have a significant impact on whether tumour cells can survive or not while working with the immune system. Due to these factors, it is challenging to identify a single cause of cancer in many people (42).

II. LITERATURE REVIEW:

2.1. Nanotheranostics

The term "theranostics" itself denotes the fusion of diagnostic and therapy, a young and dynamic area of medicine with significant potential to treat a wide range of disorders thatwere previously exceedingly challenging to treat. A superior treatment plan that is both subject-specific and enhanced in prognosis is provided by the combined functions of diagnosis and therapeutic strategy. An advanced theranostic method known as nanotheranostics uses "nanotechnology" for the detection and treatment of several diseases with dismal out looks.To create a family of nanomedicines, such as polymer conjugates, dendrimers, micelles, liposomes, metal and inorganic nanoparticles (NPs), carbon nanotubes (CNTs), silica-based nanoparticles, etc. Innovative approaches to combat this TME have been provided by nanomedicine, which also provides for biodistribution and/or action assessment at the same time(2).

Nanotheranostics systems are often multi-functional nanosystems that can carry and distribute active component to the target and supply medicinal capabilities, enabling it to be detected early and destroy cancer cells in a highly additional selective manner. The development of multifunctional, responsive nanomedicines suitable for combining medical help and theranostics has been prompted by the physio-chemical features of supported gold nanoparticles, which are among the most promising multifunctional nanosystems. These nanostructures are the main blessings for medical specialty applications because they are small, on a scale comparable to that of biomolecules, and they have a higher space-to-volume ratio, allowing for the multiplication of the interphase area in a very small area(3).

Theranostics is a natural extension of individualized medicine (PM), which combines treatment and diagnostic picturing in a one system. At the site ofmargeatomic picturingwith atomic treatment, nanomedicine used under a variety about

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

individualized therapy settings, like untimely disease discernment, malady presenting, the choosing of the most effective therapy, treatment planning, spotting side effects in the earliest step of therapy, with scheduling check out treatments. The cancer nanomedicineprocess would be able to first determine the partabout malignancy, then pictureof multiplicity about cancer, then administer the appropriate therapy based on the results of the imaging and diagnostic procedures, and finally monitor how well the therapy worked. Using nanoscale particles to diagnose and treat diseases, nanotechnology is a major player in theranostics, which led to the creation of nanosensors and nanomedicine, respectively(4).

2.1.1. Advantages:

Nanotheranostics uses systems based on nanotechnology to identify and treat a particular ailment. This method is especially pertinent for personalised medicine since it allows for the early detection of cancer, the targeting of an appropriate therapy found on the atomicaccount of the altered constitution, and the facilitation of disease monitoring and post-treatment care. A customised approach also makes it possible to lower the unintended side effects of general treatments and enhance the safety profile of a specific medication (5).

Nanoparticles' propensity to naturally collect between tumours due to greater porousness retention is a major benefit for cancer treatment. The primary methods of enhanced permeability and retention (EPR) are impaired liquid body substance voidance, hyperpermeability of the growth vasculature to large particles, and retention of the particles into the growth's opening area (enhanced retention). As a result, nanomaterials passively gather at tumour locations, where they will eventually provide their therapeutic or diagnostic effects (6). Nanoparticles should be between ten and one hundred nm in sizeand, preferably, have a neutral or anionic charge to extend the duration of action and minimise nephritic filtration and liver capture (7),(29).

2.1.2 Disadvantages:

- Most common disadvantages of nanotheranostic preparations are as follows:
- Acute toxicity
- Biomaterial and cytostatic limitations
- Not biodegradable
- High price of big scale production
- Absence of uniform agreement for practice in medical center
- Drug load efficacy is low
- Batch-to-batch manufacturing variance
- Limited instability and leakage of loaded material
- minimum solubility
- expedited expulsion
- Limit the release of relevant bioactive substances
- Demanding surface modifications (thiol groups) (5).

2.2 Two-dimensional nanomaterials used for cancer nanotheranostics (2DNMs):

Due to its high mortality and significant morbidity, cancer represents the largest global health burden. The overall five-year survival rate for cancer patients is still low despite the enormous efforts that have been made to treat cancer, which calls for the use of more efficient treatment and prevention methods.

Diagnostic imaging and therapeutic intervention combined to form a new term known as nanotheranostics. As a result, newly developed, intricately engineered nanomaterials present unheard-of prospects for treating cancer patients in a tailored way. 2DNMs stand out among them as prospective options for both cancer detection and treatment. Nanomaterials with one dimension smaller than 100 nm are referred to as 2DNMs. 2DNMs have exceptional thermal, mechanical, chemical, and optical properties due to their distinctive structure.The applications of 2DNMs in energy storage, energy transfer, and electronic and mechanical devices are highly researched due to these favourable properties. Personalized cancer nanotheranostics, such as sensing, imaging, gene and drug delivery, and therapy, offer great potential for use of 2DNMs due to their wide range of strengths in biomedical applications, including high drug and gene loading capacity, great light heat conversion efficiency, and photodynamic properties (8).

It still has a long way to go before 2DNMs are actually used in clinics. Their toxicity and pharmacokinetics continue to raise questions.

- In physiological media, some 2DNMs, like graphene, are simple to aggregate, which could potentially be harmful in vivo.
- Impurities (such heavy metals or metal oxides acquired during the manufacturing process) may exceed human tolerance levels.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

- Slow metabolism can cause primary toxicities and accumulation in the body's major organs.

The following benefits are available when cancer nanotheranostics are combined into a single nanoparticle as opposed to using them separately.

- Imaging and therapy coordination could deliver more in-depth data for precise treatment with great sensitivity and little interference.
- For effective therapy, a synergetic impact could be strengthened.
- During the course of treatment, the combination makes it possible to keep an eye on the location, size, and metastasis of various tumour stages.

2.2.1.Applications of 2DNMs

Following are the applications of 2DNMs:

- 2DNMs Multimodal imaging is optimised and functionalized.
- Phototherapy
- Delivery of genes and drugs (8).

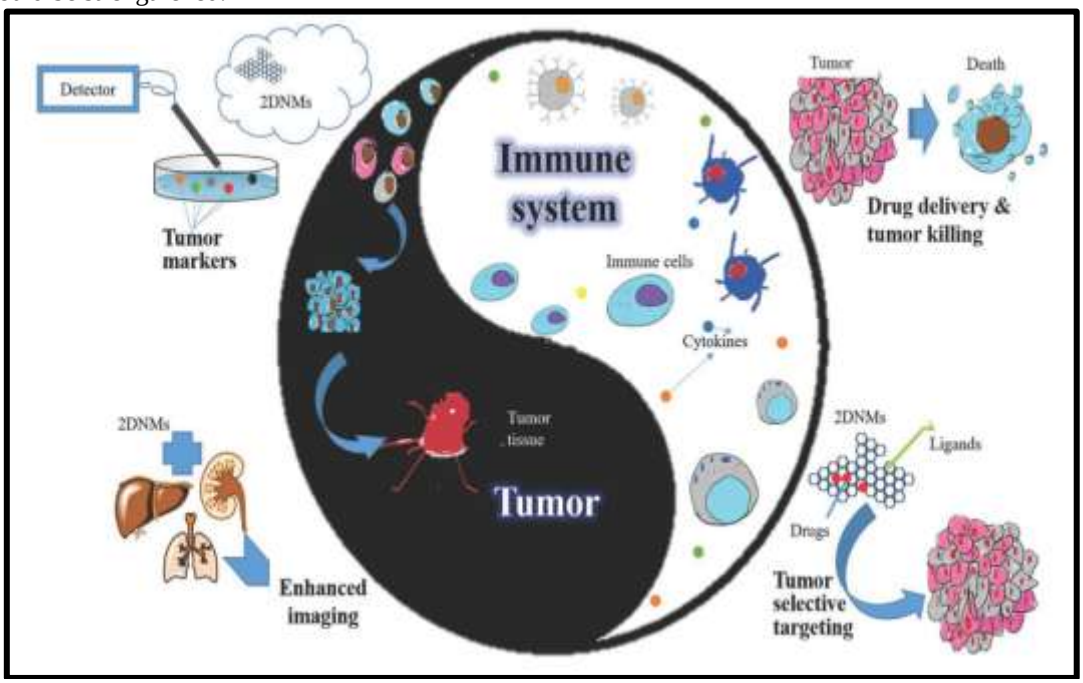

Figure 1: Mechanism of action of 2DNMs (41)

2.3 Recent trends in cancer theranostics:

Recent developments in biomaterials and nanotechnology have created unique nanosystems with increased complexity and a variety of features that can react to the various pathways involved in the development of cancer.

Multicomponent individual particles referred to as hybrid nanotheranostic systems, fabricated from living and non living substance, are effective of each charecteristics and medicinal actions, comparable to drug or cistron delivery, laser-assisted medical care , and imaging methods. so as to supply the prospect of human action every growth , drug unleash, withvarious methods on the simplest doable therapy, the individual agents' associationwith a nanoparticles process enlargeand redoubled the accessible nanomedicine device.Frequently, biocompatible compound layers and/or targeted moieties, such as distinction ants, are used to functionalize these nanosystems. Furthermore, the discharge of medicine is usually triggered by an out of doors stimulus, comparable to ultrasonograpy,brightness , heat, or pH changes, letting prosperous interaction between the therapeutic and imaging functions of nanoparticles.

This observe specializes in polymer-, metallic- and lipid-based nanosystems to be used in solid tumors because of the rapid changes within the area of nanomedicine and the need for non-stop updates on product improvements.

The maximum promising (and hard) techniques of nanomedicine are nanoprocess, which can be commonly able to combining a couple of compound cloth right into a center-shell shape. but, the floor functionalization of those nanosystems allows for active focused on of cancer

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

cells and/or a aggregate of mild-primarily based methods. Making sure in vivo balance is important inside the fabrication of these nanoplatforms as they may be exposed to detrimental conditions inside the tumor microenvironment. therefore, the structure and optimized formula of these multifunctional nanoplatforms are required for the efficient transport of medicine or diagnostic markers to biological targets in most cancers (9).

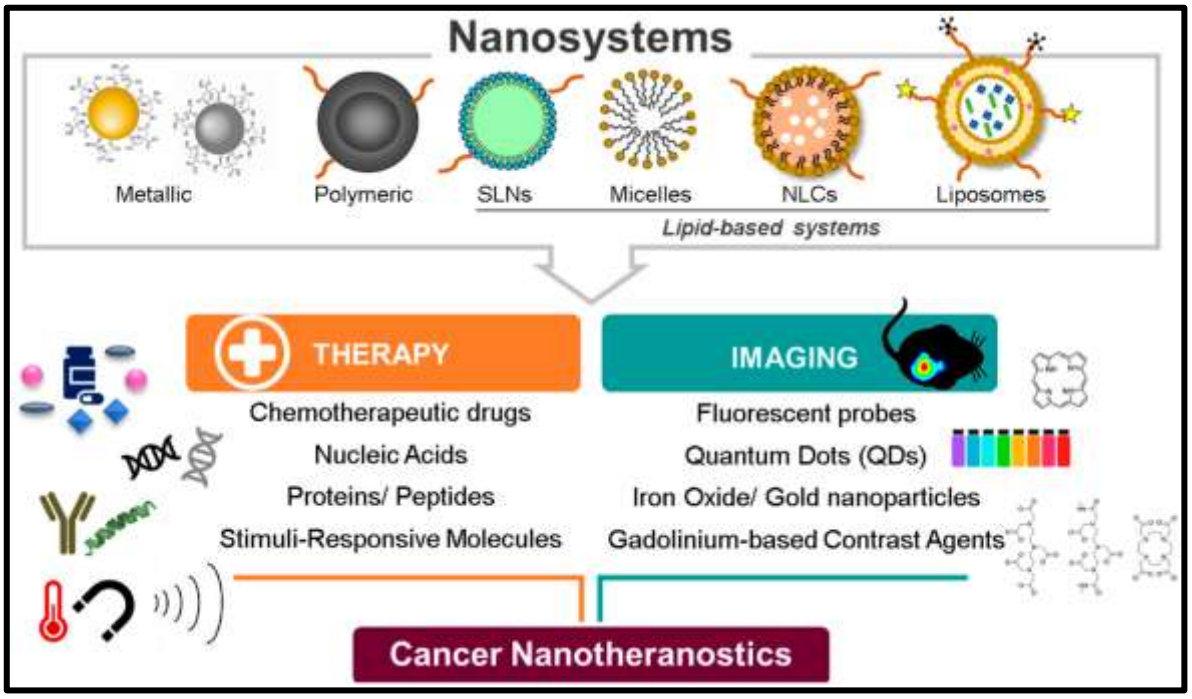

Figure 2: Nanotheranostics: polymeric, metallic, and lipid-based nanosystems for cancer management (42)

As interactions between nanomaterials and biomolecules, tissues (healthy and cancerous cells), and biologic organisms are enormous and complex, integrated nanotheranostic systems can include ways to measure those dynamics, for example, by real-time imaging. Hyaluronic acid (HA) is macromolecule and a polysaccharide which is most commonly found in the tumor micro environment, has been extensively studied as a tumor target. It is a natural ligand for the CD44 receptor and is overexpressed in many types of cancers.

In addition, as a polymer, HA presents several advantages for functionalization of both polymeric and metallic nanoparticles due to the possible linkage by amine groups, and features such as its improved stability, biodegradability, biocompatibility, low toxicity, and low immunogenicity. Thus, HA has been studied as a multiple conjugate (i.e., targeting, imaging, and therapy), with aanti-neoplastic agent (gemcitabine) and, separately, a probe (tris hydroxypyridinone (THP), which is a gadolimium chelator) for in vivo imaging by single photon emission computed tomography/computed tomography (SPECT/CT)(9).

2.4. Types of nanomaterials

2.4.1. Gold-based nanomaterials

When compared to the emanation from a fluorescent colour, the cross sectional area of light emitted by gold nanoparticles is more than 1,000,000 times larger. By using dull field dissipating microscopy, gold nanoparticles with a width of more than 10 nm can be visualised. When compared to a fluorescent color, gold nanoparticles are photostable and their light dissipates steadily. Due to these advantages, gold nanoparticle imaging tests for optical imaging arepromising(10).

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

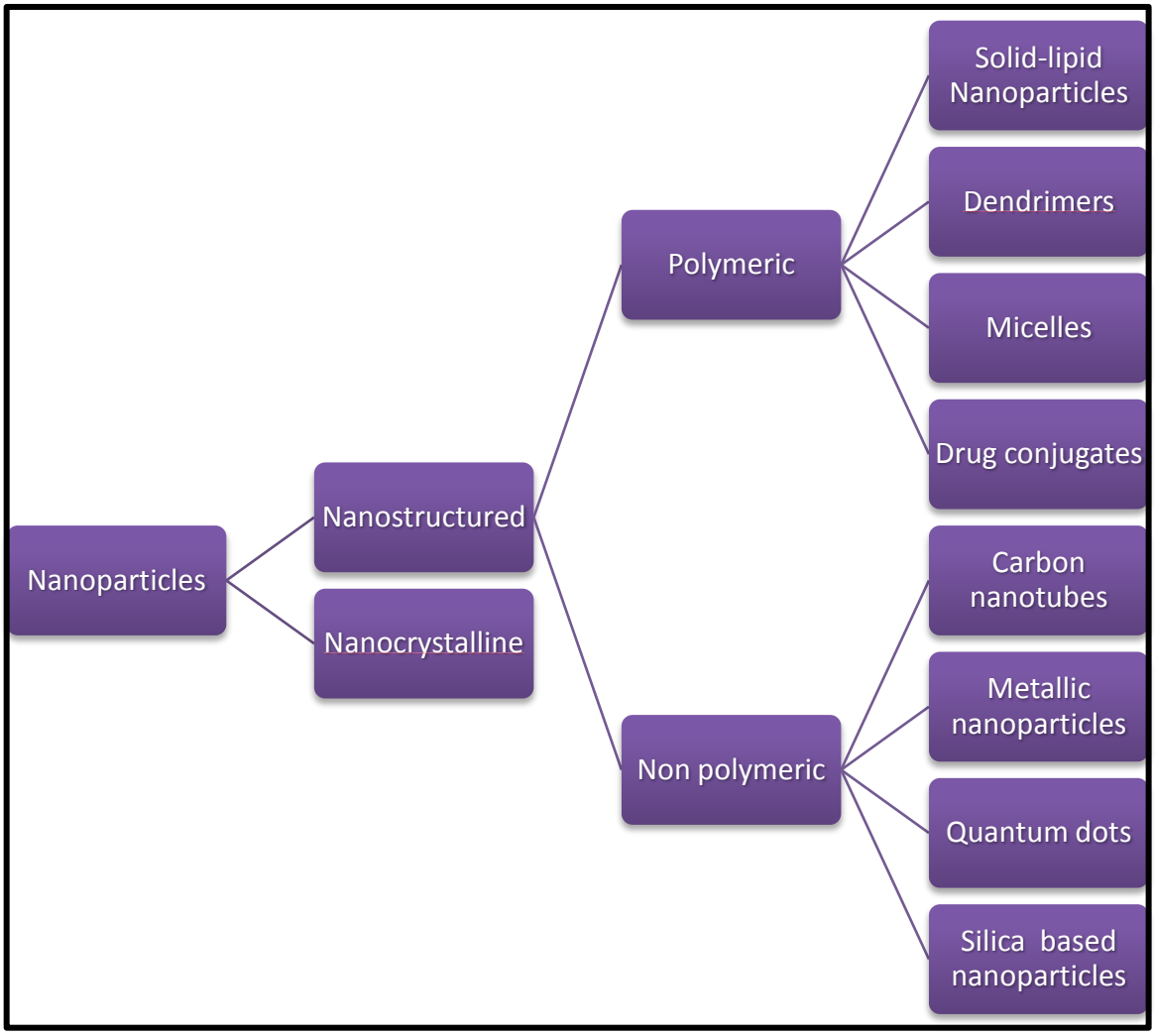

Figure 3: Classification of nanoparticles

Gold-based nanomaterials are being looked into as multifunctional probes because of their superior biocompatibility and well-established methods for surface modification (such as gold-thiol bonding). Gold nanoparticles' unique optical and photothermal properties enablethem to be used not only as sensing tools but also to create photothermal effects for medicinal purposes.

Gold (Au) nanoparticles (NPs), nanorods (AuNR), nanocapsules, and nanocages exhibit distinct optical and thermal properties that could immediately make gold nanomaterials potentialtheranostics. That is carried out through calibrating the localized floor plasmon resonance of the yellowish nanoparticles. via binding yellowish to the thiol, the gold nanomaterial gives a flexible surface for drug shipping (8).

2.4.2. Magnetic nanoparticles

Magnetic nanoparticles with surface modifications are frequently utilised as vectors, enabling drug directional movement under the applied magnetic field, resulting in tailored drug delivery. These have a lot of applications in MRI because they are magnetic field sensitive (11).

Due to the noninvasive nature of magnetic resonance imaging, magnetic nanoparticles will serve as nanotheranostics. With the right nanoformulation, they may also serve as a platform for drug delivery. The Food and Drug Administration has approved magnetic resonance imaging distinction agents based on T1 Gd3+.The most often used magnetic nanoparticles with inherent imaging capabilities for T2 distinction are

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

iron oxide nanoparticles (IONPs). Additionally, IONPs benefit from an enlarged area to volume quantitative ratio, have the ability to load a variety of medications, and are used as a nanotheranostic (12). However, formulations of nanoparticles like liposomes or micelles that incorporate such gold-bearing particles are also more common for use in research as imaging agents and drug delivery agents for theranostic capabilities (4).

2.4.3. Polymeric nanoparticles

Non-metallic nanoparticles, and more specifically polymer-based nanoparticles, are the most commonly used nanoplatform in clinical settings. Because they can target specific tissues and organs, polymer-based NPs outperform liposomes.

Most of the development of nanotechnology has been PEGylated to reduce the lipopolysaccharide of the nanoparticles and to increase the circulating lifetime in bioabsorbable. Composite nanomaterials, often composed of amphipathcompound, provide an outer shell for the conjugation of matter to detect indicators of certain diseases, while providing internalcentral for aquaphobic compounds like as chemotherapeutic or seeing agents (14). PEG has the ability to prevent the deterioration of the nanoparticle core through steric hindrance. By increasing the fluid mechanics of the PEG-carrier conjugate and thus in more itsemulsifiable due to hydrophilicity, renal clearance is reduced (11).

2.4.4. Silica-based nanoparticles

Dental fillings, implants, contact lenses, and dietary supplements have all been made using silicon-based compounds. Because of their size, optical features, high surface area, low density, adsorption capacity, capacity for encapsulation, biocompatibility, and low toxicity, silicon dioxide (silica)-based nanoparticles are particularly appealing inert solids in a variety of biomedical applications (15).

Potential options for fully developed theranostic nanoparticles (NPs) are mesoporous silicon oxide nanoparticles (MSNs). MSNs' ultrahigh surface area makes it possible to functionalize a larger area with the necessary ligands (16). MSNs are modified to provide cistern for supplying, distributing,associating sufficient amount of medication because to their increased surface area and porous interior. In order to increase MSNs' usefulness in theranostics, the exterior of the devices may be functionalized with various materials (11).

2.4.5. Carbon nanoparticles

The cylindrical shape of Carbon Nanotubes (CNTs) is a result of the layers of graphene sheets that make up each one of them. CNTs can be thought of as carbon allotropes with a sluggish rate of biodegradation and a low level of biocompatibility. They possess unique mechanical and electronic properties that are appropriate for theranostic use (3).

Based on their bonding patterns, carbon nanomaterials can be classified as zero-dimensional fullerenes (sp2 or sp3).

•Dot of carbon
•Micro diamond
•Carbon nanotubes with only one dimension
•Graphene in two dimensions.

They every have one of a kind bodily and chemical characteristics. For instance, carbon dot and nano diamond are capable of show off herbal fluorescence emission because of their optoelectronic characteristics. SWNT cannot handiest emit photoluminescence withinside the 1.0-1.four m vicinity for in vivo tumour imaging, however it may additionally act as an powerful NIR absorber and heater for photothermal ablation of tumours whilst injected at low dose.Carbon nanotubes are ten instances greater a success in putting off tumours than AuNPs, and additionally they require decrease injection doses and radiation powers (11).

2.4.6. Composite nanoparticles

Theranostic drugs are predicted to address the drawbacks of conventional cancer detection and treatment because of their multifunctional features (including targeting, imaging, and therapy). The majority of nanomaterials do, however, have a special property that might be useful for either medicinal or diagnostic purposes. Recent research has looked into hybrid or composite nanomaterials, made up of several nanomaterials, as viable platforms for medicinal, imaging, and diagnostic uses. Here, composite nanomaterials that are made up of more than two nanoparticles without polymer encapsulation are chosen. The activity is known to be higher when two or more nanomaterials are involved. It may be argued that its applications have a wide range (11).

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

2.4.7. Other nanoparticle

Notwithstanding the normal nanomaterials (AuNP, SPIO, and SINPs), there is expanding interest in utilizing higher transformation nanoparticles (UCNPs) for theranostic applications. UCNPs are lanthanide-doped nanocrystals that go through an upconversion interaction to invigorate lower energies of light (978 nm) and afterward emanate higher energies of light (apparent). Electromagnetic NIR wavelengths have no biological tissue absorption. Therefore, the combination of UCNP with photosensitise can help with the main difficulty of PDT, namely that the photosensitise itself can only be stimulated by electromagnetic spectrum and can hardly penetrate into biological tissues (11).

Semiconductor nanocrystals, so-called quantum dots (QDs), have an intense and constant fluorescence. Its optical properties can be altered by varying the size and composition of the particles. When QDs of different sizes are synthesized using CdSe, CdTe, InAs, and ZnSe, chip nanoparticles emerge that absorb the entire electromagnetic and NIR spectrum. However, less research has been done on QD-based nanomaterials, mainly due to their inherent toxicity and instability(11).

In either the core or the shell, silver nanoparticles (AgNPs) are used as imaging distinction agents. so as to make a gold colloid nanoplatform with tall and widevisual attenuation at NIR observation that may be used for optoacousticsimaging, a porous silver covering was created around silicon oxide cores (180-520 nm) (11). at the side of AuNPs, it's ofttimes utilized as a theranostic agent. the thought of victimization elite nanoparticles' optical characteristics as a purposeful part in varied product and sensors is gaining popularity. Not like several dyes and pigments, silver nanoparticles have a color that depends on the scale and form of the particle and are improbably effective at each riveting and dispersing light-weight. This oscillation ends up in outstandingly potent scattering and absorption properties (32).

The majority of solid lipid nanoparticles (SLNs), whose mean diameters range from fifty nanometers to a thousand nanometers for mixed drug delivery applications, are made up of lipids that are solid at room temperature and surfactants for emulsification. Intriguing for their potential to improve the performance of medicines, neutraceuticals, and other materials, SLNs offer unique qualities such small size, enormous surface area, high drug loading, and the interaction of phases at the interfaces.

SLNs came into sharp attention in drug delivery studies. They are common composite to use in drug carrier systems due to their high level of biocompatibility, physiochemical characteristics, and capacity to improve lymphatic uptake of hydrophobic medicines. SLNs allow for significantly greater control over drug distribution since they permit less formulation-based drug mobility than liquid oil solutions (3).

Liposomes are sac-like structures with liquid at their core and a hydrophobic bilayer around them that was made by the phospholipids being forced out of their pores. Because phospholipids are GRAS (generally acknowledged as safe) substances, the possibility of negative consequences is reduced. The hydrophobic bilayer prevents solutes, such as medication, from passing through it. However, hydrophobic molecules are absorbed into the bilayer, allowing the vesicle to hold both deliquescent and hydrophobic molecules (17). Liposomes are valuable for medication delivery and cosmetic distribution applications because the lipid bilayer of these particles can fuse with other bilayers, such as the cell membrane, to facilitate the release of their contents. Nanoliposomes are another name for liposomes with vesicles in the nanometer range (18).

Hetrostructuremicromolecules Carriers are made from a combination of solid and liquid lipids, however at body temperature, the particles are solid. Lipids are adaptable molecules that can build variously structured solid matrices, such as the lipid drug conjugate nanoparticles (LDC) and nanostructured lipid carriers (NLC), which have been developed to increase drug loading capacity (18).

Nanoshells, also known as core-shells, are characterised by spherical cores of a certain compound (concentric particles) that are encircled by an outer layer or shell made of a different substance that is only a few 1–20 nm nanometers thick. When compared to their single component counterparts or other nanoparticles of the same size, nanoshell particles, which are highly functional materials, exhibit modified and improved features (18). Changing either the constituent materials or the core-to-shell ratio will change the properties of these structures.

They are about 20 nm in size. A focal moiety or core, layers of branched repeat units coming from the core, and functional end groups on the outer layer of repeat units make up the three

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

distinct architectural sections that make up dendrimers. They are known to be sturdy, covalently fixed, three-dimensional structures with a homogeneous external surface functioning and a solvent-filled inside core (nanoscale container) (18).

Due to its well-known 3D structure, numerous surface functional groups, and capacity to load drug molecules both internally and onto the surface groups, dendrimers can serve as drug transporters. Numerous reactive functional groups are plentiful on their surface, making conjugation loading of various medicinal drugs easier (19). They frequently exhibit benefits in size uniformity, reduced macrophage absorption, quick cellular entrance, target ability, and more widespread transit across biological membranes by transcytosis when compared to other delivery strategies (3)

2.5. Enhanced permeability and retention (EPR)

Since its initial description in 1986 by Maeda et al., This is(EPR) has garnered a lot of attention in connection with the advancement of nanomedicine. The widespread fenestration of blood vessels and compromised vessel structure in the neovasculature of tumour tissues are the results of the fast and erratic angiogenesis in expanding tumour tissues. Contrary to healthy endothelial layers, the tumor's leaky vasculature makes it simple for nanoparticles to extravasate into the interstitium (20). As a result of this improved permeability, tumour tissues accumulate nanoparticles far more than other organs do.

Uneven distribution and particle size dependency are well understood today, yet there are still some challenges. EPR has demonstrated that the formation of nanoparticles in tumour tissue occurs significantly more quickly than in normal tissues (7).

The significant level of interest in the development of nanoparticle medicines as cancer treatments has been largely attributed to EPR. Preclinical research on the EPR effect, however, has recently produced conflicting results. Some studies support preferential, EPR-mediated accumulation of nanomedicines within tumours, while others demonstrate that the EPR effect is strongly influenced by the tumour model. EPR is still a contentious issue in nanomedicine today (7).

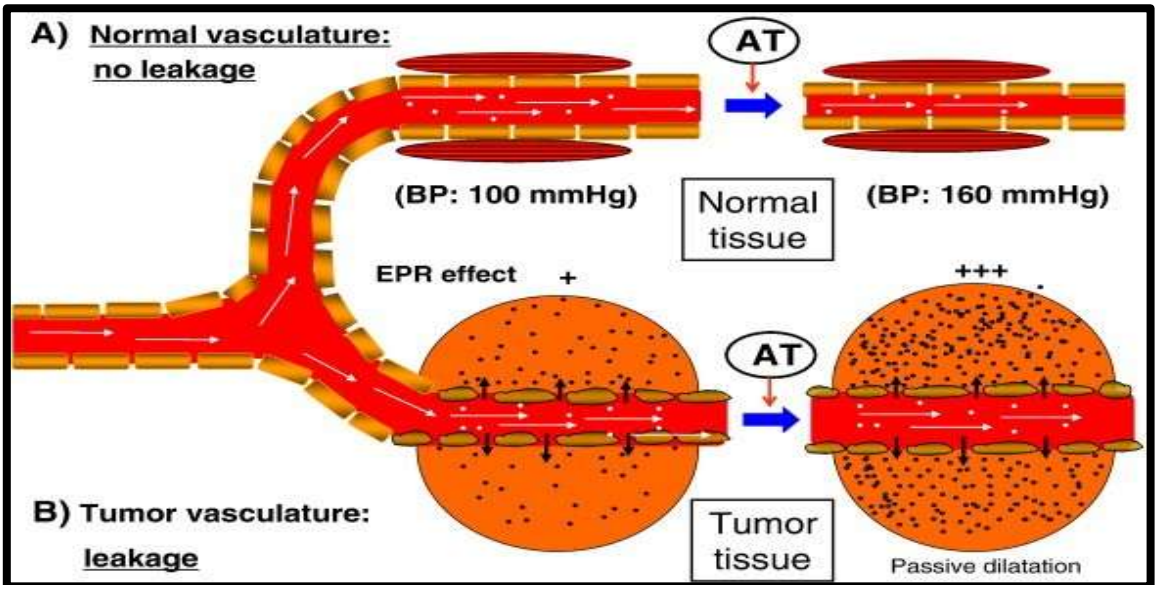

Figure 4: The EPR effect for macromolecular drug system(36)

2.6. Mechanism of action

Drug encapsulation using nanoparticles (NP) has a number of benefits for developing efficient localization and drug delivery systems. Effective NP delivery systems are made possible by NP characteristics such particle size, surface charge, and shape, which work through a variety of methods (21). Figure 4 illustrates the fundamental concept underlying the nanoparticles' activity mechanism. As a result of these nanoparticles' binding to cancer cells, aptamers, antibodies, and other peptides are produced. As a result, these nanosystems reach malignant cells, releasing drugs

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

that have anti-tumor properties and causing cell death.

2.7. Factors affecting the mechanism of action of nanoparticles

Following are the various factors on which mechanism of action of nanoparticles depends:

2.7.1. Effect of particle size

The effectiveness, volume of distribution, and cellular absorption of different nanoparticle systems can all be impacted by particle size. It is believed that size factors may have a substantial impact on which NPs interact with cells and adhere to them. In the processes of NPs' removal and degradation, size can also be a crucial factor.

The rate of clearance increases along with the size of NPs. According to studies, NPs with hydrophilic surfaces and particles smaller than 100 nm can successfully evade the mononuclear phagocytic system (MPS). In physiological systems for the removal of foreign chemicals, MPS is a crucial component. Opsonin proteins found in blood serum effectively bind to bigger NPs and mark them for MPS destruction (21).

2.7.2. Effect of particle charge

The effectiveness of NP distribution to and through cellular membranes depends heavily on NP charge. A NP system's stability is aided by the level of surface charge on the NPs. The degree of repulsion between identically charged particles is substantially stronger in a highly charged system. Inhibiting NP aggregation and stabilising NP are the effects of this net repulsive force.

It has been demonstrated that NPs with high surface charges can stabilise NP suspension and stop particle aggregation. As it has been discovered that NPs with highly positive charges can interact with the anionic polyelectrolyte properties of mucus, resulting inimproved muco-adhesion and retention of NPs inside the mucus layer, surface charge features can determine the degree of NP absorption (21).

2.7.3. Effect of particle shape

The biological characteristics of NPs can be significantly impacted by particle form. Shorter polymer micelles demonstrated a longer total blood circulation duration after intravenous (i.v.) injection, according to research by Geng et al. Shorter spheres effectively carried the medicine, paclitaxel, to targeted tumour cells and underwent a higher degree of cell absorption in comparison to longer micelles.Additionally, it was discovered that as particle length grew, the following binding of NPs reduced, providing further evidence that cellular length influences attachment and adhesion. These results point to the significance of NP shape in connection to therapeutic drug delivery and design. Characterization and design for NP development must take into account more factors than only particle size and surface charge. It is equally important to take shape effects on targeted NP outcomes into account (21).

2.7.4. Cell targeting

Large complicated molecules like membrane receptors are among the numerous biological targets for nanomedicines. Through polyvalent contact between these targeted receptors and its suitable ligand, biological processes are started. There is evidence that several formulations, including dendrimer and polymer-based NPs, target polyanionic receptors in order to work.

Large complicated molecules like membrane receptors are among the numerous biological targets for nanomedicines. Through polyvalent contact between these targeted receptors and its suitable ligand, biological processes are started. There is evidence that several formulations, including dendrimer and polymer-based NPs, target polyanionic receptors in order to work.

Targeted viral and cellular contacts have been shown using dendrimer-based NP systems through polyvalent interactions with various surface proteins. It has been demonstrated that folate-formulated polymer-based NPs bind to tumour cells' overexpressed folate receptors and start cellular entrance.

It has been shown that polymeric micelles can target cancer cells and start cellular uptake while preventing excessive uptake in healthy epithelial cells. The NP differentiation of the endocytosis machinery that each cell type shares is assumed to be the cause of this variation in cellular uptake. Caveolae-mediated endocytosis, which is lacking in normal cell lines, initiates the uptake of carcinogenic substances by cancerous cells. Drug uptake into malignant cell lines is made possible by the caveolae targeting capacitance of polymeric micelles, which prevents drug uptake in healthy cells. As a result, cytotoxic medications can be created in polymer-based micelles to treat cancer without harming healthy, functional cell types (21).

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

III. APPLICATIONS

3.1 Gold-based nanoparticles

In a recent study, it was found that AuNP changeaccompanied by various molecules, including PEG, vitamin H,with Tetraet hylrhodaminecyclomaltoses of the outside, exist an effective theranostic agent for treating cancer without having an adverse effect on normal cells (22).

However, the viability of AuNP as a distinguishing agent in X-radiation computed tomography (CT) imaging was investigated due to its higher number and X-ray coefficient of absorption than iodine. Additionally, unique multifunctional AuNP was produced and investigated for decidon atomic CT seeing and treatment of prostate malignancy (23).

The tumor tissue was damaged by the photothermal effect caused by the model metalloprotease (MMP)-sensitive yellowish nanorod , which could increase the temperature of the medium to 60 °C (23).

Drugs can be released from yellowish nanoparticles in response to external stimuli like light. After mixing at room temperature for 24 hours, You et al. reported successful loading of Doxorubicin on gold nanoparticles and gold nanoshells. It was discovered that higher drug loading (up to 70%) was accomplished in gold nanoshells than in gold nanoparticles (around 20%). It was thought that nanoparticles' hollow interiors enhanced their effective surface area for higher drug loading (11).

3.2 Magnetic nanomaterials

Propenoic acid has been used to increasefusion to an ferricoutside and also to adjust temperature, which is important due to its hydrophilic nature.NIPAAM served as the climate-reactive tochemical for hyperthermic ability. The PEG methacrylate also provided a top layer, extended circulation time, and allowed for reagent (OH) sets for vitamin B coupling. When tested on ghost agar gels, these composite nanocomposites showed approximately 200 nm in size and in size a cross-sectional time constant (T2). weighted picture darker than the manage. Using the thermal responsiveness of NIPAAM has resulted in the prolonged release of DOX only at hyperthermic climate (total 72 5), which is almost 2.5 times more than under usual anatomical conditions (11).

An intelligent nanoplatform of pH-sensitive, pH-modified herceptin (antibody of HER2), medication delivering magnetic NPs is intended for efficient cancer therapy that is guided by molecular imaging (11).

In order to treat tumours, Jordan et al. first used magnetic nanoparticles, and subsequently they created magnetic fluid thermotherapy (MFH). A liquid magnetic substance with both magnetic and water-soluble characteristics is known as magnetic fluid. The nanoparticle core of the magnetic fluid converts the magnetic energy into thermal energy when a magnetic field is applied. This raises the temperature of the tumour tissue steadily, which inhibits tumour growth or may cause tumour cell apoptosis (24).

3.3 Polymeric nanoparticles

Extensive research has been conducted to identify polymer-based theranostic drugs that take advantage of the beneficial encapsulation abilities of polymers. A successful prototype was created in a multifunctional polymeric micelle system, where the micelle surface is functionalized with a lung cancer targeting peptide (LCP) and the micelle core encapsulates superparamagnetic IONPs and DOX for MRI and healingconviction, respectively (14).

To confirm intratumoral accumulation, single-photon emission computed tomography imaging of 123I-labeled NPs was performed. The nanocarriers had outstanding anticancer activity and a high rate of apoptosis in tumorcells in vivo, and for the length of the 80-day treatment, neither DOX nor polymeric materials significantly damaged the heart, liver, or kidneys.

Chitosan has also been utilised in the creation of theranosticnanocarrirers as a polymeric material. theranostic chitosan nanoparticles (NPs) containing paclitaxel and Cy5.5 for real-time imaging of cancer. In these studies, hydrophobic 5-cholanic acid was added to glycol chitosan NPs to give them a localised patch of nanoparticles for there recapitulation hydrophobic compound (11). (25).

3.4 Nanomaterials based on silica

Future potential theranostic nanoparticle (NP) candidates include mesoporous silica nanoparticles (MSNs). A greater variety of regions can be functionalized with desired ligands thanks to the submicronoutside of MSNs. A multifunctional SiNP, known as hematoporphyrin, was designed and synthesised in a study. It has a nonporous dye-doped silica core and a mesoporous silica shell that contains photosensitizer molecules. The mesoporous silica nanovehicle served as a nanoreactor to speed up the photo-oxidation

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

reaction in addition to serving as a carrier for the photosensitizers. Additionally, the hematoporphyrin's photooxidation efficiency was greatly increased (11).

In a recent study, a new strategy to combat multidrug resistance was tested on cancer cells. This strategy involved delivery of siRNA that suppresses efflux transporter expression along with an appropriate anticancer drug to drug-resistant tumor cells (11).

Cancer-selective multimodal silica nanoparticles labelled with 124-iodine and encapsulated with Cy5 fluorophore have been described by Benezra et al. for optical and PET imaging in vivo. Clinical trials on humans with their nanoprobe have been authorised. A multifunctional nanoprobe potential for cell tracking with MRI and positron emission tomography was disclosed by Patel et al (PET). They created PET imaging-capable superparamagnetic iron oxide nanoparticles in their research by encapsulating them in a porous silica shell and performing additional surface modification (15).

3.5 Carbon based nanoparticles

Due to its strong optical absorbance in the NIR region, single-walled carbon nanotubes (SWNT) are one potential candidate for us as theranostic agents. SWNT can not only emit photoluminescence in the 1.0-1.4 m region for in vivo tumour imaging but also act as an efficient NIR absorber and heater (SWNT increases the local temperature of tumour as high as 60°C under 5 minutes of 808-nm laser irradiation) for photothermal ab (11) (26).

SWNTs conjugated to placitaxel PTX have demonstrated potential for in vivo cancer treatment. The ability of SWNT administration of PTX to significantly outperform clinical Taxol (Bristol-Myers Squibb Co.) in terms of therapeutic efficacy is demonstrated by its capacity to inhibit tumour development at low PTX doses (27).

A study is developing a graphene oxide (GO)-based theranosticnanohybrid fortumor detection and treatment. A matrix metalloproteinase-2 (MMP2)-cleavable peptide bond chemically links DOX to PEI-PEG-grafted GO. Under typical circumstances, GO quenched the intrinsic fluorescence of DOX.Overexpression of the MMP2 enzyme in the tumor led to cleavage of the peptide, releasing DOX for tumor therapy. The simultaneous DOX fluorescence signal was used to image tumor cells in situ. Here, the positively charged theranostic GO showed efficient transfection for nanotherapy. With a combination of diagnosis and therapy of the pathological response, this study offers an entry into theranostictumor treatment. Here, CNTs have been shown to be effective in transmitting therapeutic and diagnostic information at the preclinical level for future use(28).

3.6 Composite nanoparticles

Mesoporous silica was used to modify the surface of AuNP-linked magnetic nanoparticles instead of amorphous silica, creating a brand-new photothermal sensitizer as a result (AuNP-MMSNEs) The functions in MRI, PTT, and drug-loading capabilities were provided, respectively, by the magnetic core, AuNP, and mesostructure of the silica shell. Chemotherapy, MRI, PTT, IR, thermal, and optical imaging were all combined into onesystem with the hybrid AuNP-MMSNE. Under acidic conditions, 50% of the loaded drug might be released according to the drug's release profile (DOX) in under 5 hours (pH 5.5). Additionally, the combination of PTT with chemotherapy was found to have a synergistic effect on the rate of tumour inhibition (14).

Magnetic guidance was used to transport and silence genes in cells and tumours in mice using the LipoMag formulation, which consists of an oleic acid-coated magnetic nanocrystal core and a cationic lipid shell (11).

3.7 Other nanoparticles

UCNP should be multipurpose in both picturing and treatment by combining it with other nanomaterials. IONPs adsorb onto the outside of a NaYF4-based UCNP to generate a multifunctional probe, which is then followed by the development of a thin yellowish layer induced by nucleation reduction. like multi rolesupconversion nanoprobes have been shown to be practical in PTT and in vivo imaging using MRI or NIR irradiation (11).

The synthesis of QDs of various sizes using CdSe, CdTe, InAs, , and ZnSe has produced semiconductor nanoparticles covering the entire glow and emission. QD-based theranostic carriers have received relatively little research interest, mainly due to their inherent instability and toxicity.Thiolated ligands have been used to bind to the outer surface of QDs (or the ZnS shell) through a disulfide bond, giving the QDs their enhanced solubility and stability. Lipid-conjugated QDs have

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

better uptake and retention of tumor cells and lower toxicity. Whereanswerscoming outof creature experiments indicated that QD-loaded micelles exhibited increased near-IR antitumor activity (resulting in a 77.3-fold increase in cancer volume) and acumen harmful, more distantinspection are needed to elucidate the method of anticancerpursuit and this To demonstrate QD loading. Near-IR micelles are a superior therapeutic agent (11).

Dendrimer-associated drug molecules can be used to cure cancer, improve drug solubility and permeability (dendrimer-drug conjugates), and transport drugs intracellularly. A polyamidoamine dendrimer compound with methotrexate as the therapeutic drug and folate antagonist (FA) as the targeted agent was reported by Myc et al (30). Cells expressing FA receptors and cells lacking FA receptor expression were used to investigate cytotoxicity and specificity. Results from both in vitro and in vivo experiments demonstrated that the target cells were preferentially cytotoxic to the dendrimer compound (27).

IV. FUTURE PERSPECTIVES

Several viewpoints can be established with regard to theranostics' ultimate goal of satisfying the need for individualised medicine: One of the key sectors delivering an all-in-one nanosystem with complete features is nanotheranostic platforms, which harness great capability permitting many methods, either curative or indicative, or the couple. To be high piontdown with more distant research into ability and understandings labeling long-term assuming of nanoparticales are the system's rising complexity, safety, and stability of nanoparticles. The in vivo investigations are quite important and necessary. Additionally, it has been possible to use fluorescent dyes and QDs to monitor treatment and follow-up responses at the cellular level; nevertheless, body imaging presents more challenges in this regard.

High-resolution imaging must be made possible in order to reduce background fluorescence and photoleaching. However, using near infrared (NIR) dye to produce moreresolve and repeatable pictureperhaps a more alluring different method for bioscience pictures.

Liposomal and polymeric nanoparticle formulations own a significant collision on the standard of wellness program and therapies, as well as customised, preventative, and anticipating medicine. Nanomedicine may provide the appropriate medication at the appropriate amount to the appropriate sick person at the appropriate hour. Pharmaceutical corporations should become increasingly interested in this research in the very near future for the creation of customised nanomedicine platforms and the future release of these cutting-edge nanomedicine on the sell.Chemical compound, iorn, and phospholipid-based nanosystems that combine medicinal and diagnostic capabilities are predicted to have a promising future. For it to be successful, pharmaceutical companies must be motivated to mangementexperimentation & continue to sell new nanomedicines.

V. CONCLUSION

The scientific research community has worked very hard to get these novel nanomedicines into field test. The biodivision of nanomaterials and pharmaceuticals supplied by imaging techniques, as well as understanding how these nanomaterials interrelatewith living systems, are currently the main areas of concern. There are distinctions between them in terms of agile and acquiescentshipment, that may connected to the matter utilised to create the nanoplatform and its inherent ability to interact with the tumour microenvironment.

To evaluate specificity receptor binding and internal tumour cell processes (such endocytosis) of the nanosystems, non-invasive imaging approaches are critical. To do this, a thorough comprehension of their interlinkage, as well asprotection evaluation, have completed taking a natural position into consideration. There are many ways to understand the role of nanotheranostics, particularly in the context of cancer treatment.

Despite significant development, there is still no nanomedicine representative or piece such is complex enough to connectexperimental requirements. The price of yellowish nanoparticles, the inadequate responsivenessof inorganic nanoparticles (IONP) acting as magnetic resonance imaging differenceforce, the complication of complex carriers, the bigsize of crystal NPs, and the deathless power of carbon materials are some of the weaknessesand challenges faced by the majority of nanotheranostic platforms. Due to these problems, serious efforts must be made to implement specific remedies.

REFERENCES

[1]. Roma-rodrigues C, Pombo I, Raposo L, Pedrosa P, Fernandes AR, Baptista P V.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 227-241 www.ijprajournal.com ISSN: 2249-7781

Nanotheranostics Targeting the Tumor Microenvironment. 2019;7(August):1–18.
[2]. Sharma M, Dube T, Chibh S, Kour A, Mishra J, Panda JJ. Nanotheranostics, a future remedy of neurological disorders. Expert Opinion Drug Delivery. 2019;16(2):113–28.
[3]. Sonali, Viswanadh MK, Singh RP, Agrawal P, Mehata AK, Pawde DM, et al. Nanotheranostics: Emerging Strategies for Early Diagnosis and Therapy of Brain Cancer. Nanotheranostics. 2017;2(1):70–86.
[4]. Mura S, Couvreur P. Nanotheranostics for personalized medicine. NanotheranosticsPers Med. 2016;1–337.
[5]. Arms L, Smith DW, Flynn J, Palmer W, Martin A, Woldu A, et al. Advantages and limitations of current techniques for analyzing the biodistribution of nanoparticles. Front Pharmacol. 2018;9(AUG):1–17.
[6]. Zhang L, Webster TJ, Zdrojewicz Z, Waracki M, Bugaj B, Pypno D, et al. Nanotechnology in therapeutics : a focus on nanoparticles as a drug delivery system R eview. CarbohydrPolym [Internet]. 2016;1(1):71–88.
[7]. Ngoune R, Peters A, Elverfeldt D Von, Winkler K, Pütz G. Accumulating nanoparticles by EPR : A route of no return. J Control Release [Internet]. 2016;238:58–70.
[8]. Chen Y, Wu Y, Sun B, Liu S, Liu H. Two-Dimensional Nanomaterials for Cancer Nanotheranostics. Small. 2017;13(10):1–14.
[9]. Silva CO, Pinho JO, Lopes JM, Almeida AJ, Gaspar MM, Reis C. Current trends in cancer nanotheranostics: Metallic, polymeric, and lipid-based systems. Pharmaceutics. 2019;11(1).
[10]. Wang S, Lu G. Applications of Gold Nanoparticles in Cancer Imaging and Treatment. Noble Precious Met - Prop Nanoscale Eff Appl. 2018;
[11]. Wang LS, Chuang MC, Ho J an A. Nanotheranostics - A review of recent publications. Int J Nanomedicine. 2012;7:4679–95.
[12]. Santra S, Kaittanis C, Grimm J, Perez JM. Drug/dye-loaded, multifunctional iron oxide nanoparticles for combined targeted cancer therapy and dual optical/magnetic resonance imaging. Small. 2009;5(16):1862–8.
[13]. Cooper DL, Conder CM, Harirforoosh S. Nanoparticles in drug delivery: Mechanism of action, formulation and clinical application towards reduction in drug-associated nephrotoxicity. Expert Opinion Drug Delivery. 2014;11(10):1661–80.
[14]. Rozenberg BA, Tenne R. Polymer-assisted fabrication of nanoparticles and nanocomposites. Prog Polym Sci. 2008;33(1):40–112.
[15]. Shirshahi V, Soltani M. Solid silica nanoparticles : applications in molecular imaging. 2015;(May 2014).
[16]. Lu J, Liong M, Li Z, Zink JI, Tamanoi F. Biocompatibility, biodistribution, and drug-delivery efficiency of mesoporous silica nanoparticles for cancer therapy in animals. Small. 2010;6(16):1794–805.
[17]. Wu W, Zhou T, Berliner A, Banerjee P, Zhou S. Smart core-shell hybrid nanogels with ag nanoparticle core for cancer cell imaging and gel shell for pH-regulated drug delivery. Chem Mater. 2010;22(6):1966–76.
[18]. Mudshinge SR, Deore AB, Patil S, Bhalgat CM. Nanoparticles : Emerging carriers for drug delivery. Saudi Pharm J [Internet]. 2011;19(3):129–41.
[19]. Nanjwade BK, Bechra HM, Derkar GK, Manvi F V., Nanjwade VK. Dendrimers: Emerging polymers for drug-delivery systems. Eur J Pharm Sci. 2009;38(3):185–96.
[20]. Maeda H, Tsukigawa K, Fang J. A Retrospective 30 Years After Discovery of the Enhanced Permeability and Retention Effect of Solid Tumors: Next-Generation Chemotherapeutics and Photodynamic Therapy—Problems, Solutions, and Prospects. Microcirculation. 2016;23(3):173–82.
[21]. Cooper DL, Conder CM, Harirforoosh S. Nanoparticles in drug delivery : mechanism of action , formulation and clinical application towards reduction in drug-associated nephrotoxicity. 2018;(September).
[22]. Heo DN, Yang DH, Moon HJ, Lee JB, Bae MS, Lee SC, et al. Gold nanoparticles surface-functionalized with paclitaxel drug and biotin receptor as theranostic agents

for cancer therapy. Biomaterials [Internet]. 2012;33(3):856–66.
[23]. Wang S, Lu G, Lu G. Applications of Gold Nanoparticles in Cancer Imaging and Treatment Applications of Gold Nanoparticles in Cancer Imaging and Treatment.
[24]. Guo T, Lin M, Huang J, Zhou C, Tian W, Yu H, et al. The recent advances of magnetic nanoparticles in medicine. J Nanomater. 2018;2018.
[25]. Na JH, Koo H, Lee S, Min KH, Park K, Yoo H, et al. Real-time and non-invasive optical imaging of tumor-targeting glycol chitosan nanoparticles in various tumor models. Biomaterials [Internet]. 2011;32(22):5252–61.
[26]. Sobhani Z, Behnam MA, Emami F, Dehghanian A, Jamhiri I. Photothermal therapy of melanoma tumor using multiwalled carbon nanotubes. Int J Nanomedicine. 2017;12:4509–17.
[27]. Bamrungsap S, Zhao Z, Chen T, Wang L, Li C, Fu T, et al. Nanotechnology in Therapeutics A Focus on Nanoparticles as a Drug Delivery System. 2012;7(8):1253–71.
[28]. Muthu MS, Leong DT, Mei L, Feng S. T h e r a n o s t i c s Nanotheranostics - Application and Further Development of Nanomedicine Strategies for Advanced Theranostics. 2014;4(6).
[29]. Homan K. Silver nanosystems for photoacoustic imaging and image-guided therapy. J Biomed Opt. 2010;15(2):021316.
[30]. Najlah M, Freeman S, Attwood D, D'Emanuele A. In vitro evaluation of dendrimer prodrugs for oral drug delivery. Int J Pharm. 2007;336(1):183–90.
[31]. URL:https://stm.sciencemag.org/content/7/294/294ec112 (accessed on 20/10/2019).
[32]. URL:https://www.cancer.net/navigating-cancer-care/cancer-basics/what-cancer (accessed on 21/10/2019).
[33]. URL:https://www.wcrf.org/dietandcancer/cancer-trends/data-cancer-frequency-country (accessed on 21/10/2019).
[34]. URL:https://www.sigmaaldrich.com/technicaldocuments/articles/materialsscience/nanomaterials/silver-nanoparticles.html (accessed on 21/10/2019).
[35]. URL:https://www.sciencedirect.com/science/article/abs/pii/S0169409X12003201 (accessed on 20/10/2019).
[36]. URL:https://link.springer.com/chapter/10.1007/698_2017_143(accessedon07/11/2019)
[37]. URL:https://www.researchgate.net/figure/Fig-1-Cancer-cell-targeting-strategiesutilizedby-nanoparticles-NPs-encapsulating_fig1_295246666(accessedon07/11/2019).
[38]. URL:https://www.sciencedirect.com/science/article/abs/pii/S0169409X12003201 (accessed on 20/10/2019).
[39]. URL: https://www.medicalnewstoday.com/articles/323648.php#causes (accessed on 16/11/2019).
[40]. URL:https://www.cancerresearchuk.org/about-cancer/what-is-cancer/how-cancers-grow (accessed on 16/11/2019).
[41]. URL:https://www.materialsviewschina.com/2017/04/24768/(accessedon16/11/2019).
[42]. URL: https://www.mdpi.com/1999-4923/11/1/22 (accessed on 16/11/2019).
[43]. URL: https://www.medicinenet.com/cancer/article.htm (accessed on 17/11/2019).