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RESEARCH ARTICLE

NANOPARTICLES: PRIVILEGED SCAFFOLD FOR CANCER TREATMENT.

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Abstract

Nanotechnology is a regnant scientific field since itcombines knowledge from the various fields.It is a developing technological field with pronounced potential to lead in great breakthroughs so as to meet the escalating demands of man with curtailed side effect to the environment. Although nanotechnology has a number of applications but it has laid down new milestones in the treatment of the most deadly disease "CANCER". This review encapsulates the role that nanotechnology has played in improving cancer therapy through targeted delivery of drugs thereby reducing systemic toxicity.

Introduction:-

Nanotechnology is one of the leading technologies of the 21st century. Nanotechnology is the study of tremendously small structures. The prefix "nano" is a Greek word which means "dwarf". The word "nano" means very small or miniature size. Nanotechnology is the treatment of individual atoms, molecules, or compounds into structures to produce materials and devices with distinctive properties. Nanotechnology deals with materials in the size of 0.1 to 100 nm; however it is also vital that these materials should display different properties such as electrical conductance, chemical reactivity, magnetism, optical effects and physical strength from bulk materials as a result of their small size (Nikalje et al., 2015). Nanotechnology has gifted many applications for scientific knowledge from numerous disciplines in science and engineering to design, modify and monitor the properties of matter at nanoscale dimensions (Mousa et al., 2007). Nanotechnology holds colossal potential for overcoming many of the problems associated with conventional methods that faces difficulties in the detection, treatment, and diagnosis of cancer (Davis et al., 2008).

In recent years, substantial efforts have been devoted to develop nanotechnology to augment the delivery of anticancer drug to tumour tissue while minimizing its distribution and toxicity in healthy tissue. Many nanotechnology platforms, such as polymeric nanoparticles, liposomes, dendrimers, nanoshells, carbonnanotubes, superparamagnetic nanoparticles, and nucleic acid-based nanoparticles [DNA, RNA interference (RNAi), and antisense oligonucleotide (ASO)], have been applied to the delivery of specific anticancer drugs, including small molecular weight drugs and macromolecules (protein, peptides or genes) (Ahirrao et al., 2015).Pointless to say, the production and use of the tiniest particles invisibleto the naked eye are not a latter-day invention. Examples of the earlier use of nanomaterials are the Lycurgus Cup from the 4th century AD on display in the British Museum in London, some late medieval church windows and also the famous Damascene Swords: When light shines from the outside on the antique Roman cup the cup looks olive green, when illuminated from the inside it shines ruby red and the mythological king depicted on it turns lilac. Colloidal nanoparticles of silver and gold contained in the glass are responsible for this phenomenon. Ananalogous effect is seen in some late medieval church windows, which shine a

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luminous red and yellow because nanoparticles of gold and silver have been fused into the glass. In 2006 nanometersize particles of carbon were discovered in a Damascene Sword from the 17th century, these being responsible for the elasticity and resistance of the legendary swords (Reibold et al., 2006). These special properties of the colors and materials were already being produced intentionally many hundreds of years ago. Medieval artists and forgers, however, did not know the cause of these startling effects (Krukemeyer et al., 2015).

Currently used anticancer drugs have many disadvantages such as low aqueous solubility, a short half-life and non-selective targeting to cancer cells, which lower the therapeutic efficacy and escalate unwanted side effects. In order to overcome these curbs, nanoparticles were fabricated and validated as a potential tool. In this article emphasis has been made on use of nanoparticles which have revolutionized the field of medicine with promising cancer treatment and reducing relapse and metastasis.

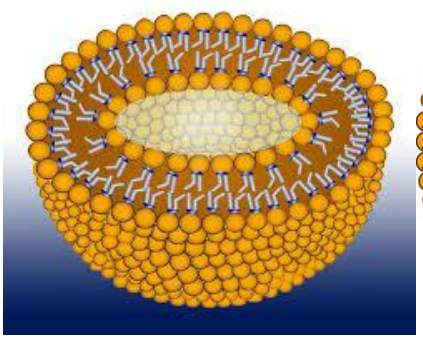
Types of Nanoparticles:-

Even thoughthe number of different type of nanoparticles (**Fig 1**) is increasing swiftly, they can be classified into following:

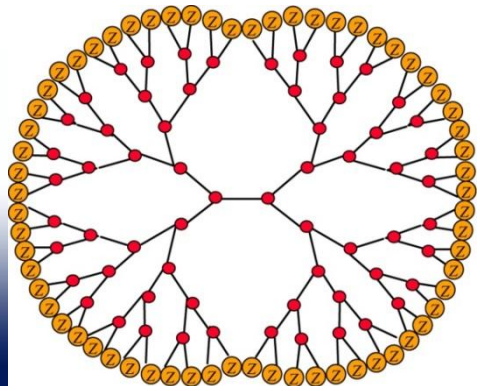
- Liposomes
- Dendrimers
- Carbon nanotubes
- Quantum dots
- Metallic nanoparticles
- Polymeric nanoparticles
- Magnetic nanoparticles
- Nanoshells
- Fullerenes

1. **Liposomes:** As closed spherical vesicles, liposomes consist of a lipid bilayer which encapsulates an aqueous phase to store drugs. These have been extensively explored and most developed nano carriers for novel and targeted drug delivery due to their small size. They have a size of 50-200 nm with good entrapment efficiency (Malam et al., 2009).
2. **Dendrimers:** They are hyper branched, tree-like structures with defined molecular weights and host-guest entrapment properties. They have size less than 10 nm and are used for long circulatory, controlled delivery of bioactive material, targeted delivery of bioactive particles to macrophages and liver targeted delivery (Nikalje et al., 2015).
3. **Carbon nanotubes:** These are well ordered, hollow nanotubes formed when single or multiple graphene sheets are rolled into a cylinder.Single- and multi-walled carbon nanotubes are the two types of carbon nanotubes. The surface of these nanotubes is functionalized for attaching drugs/ proteins/ ligands etc (Foldvari et al., 2008).
4. **Quantum dots:** Quantum dots are nanocrystals measuring around 2-10 nm with a structure consisting of an inorganic core, the size of which determines the color emitted, an inorganic shell and an aqueous organic coating to which biomolecules are conjugated. The biomolecule conjugation of the quantum dots can be modulated to target various biomarkers (Iga et al., 2007).
5. **Metallic nanoparticles:** In thecancer treatment, metallic nanoparticles have been playing a crucial role. Amongst various metals, silver and gold nanoparticles are of prime importance for biomedical use. Metallic nanoparticles have been used widely in drug delivery and also in biosensors (Nikalje et al., 2015).
6. **Polymeric nanoparticles:** A number of biodegradable or nonbiodegradable polymers have been used to prepare nanoparticles in order to achieve expected drug delivery performance and therapeutic effect. Polymeric nanoparticles can deliver not only small molecular weight drugs but also macromolecules such as genes and proteins. These have arisen as a versatile carrier system for targeted delivery of anticancer drugs (Wang et al., 2009).
7. **Magnetic nanoparticles:**The magnetic NPs (MNPs) are prepared by either entrapping drug into magnetic micro/nanosphere or embedding as a magnetically active disc. In magnetic targeting, the liberation of drug in blood circulation is controlled applying strong magnetic field. Different magnetic materials with a variety of magnetic properties are available, such as magnetite, iron, nickel, cobalt, neodymium-iron-boron, and samarium-cobalt. They have noteworthy applications as contrast agents for Magnetic resonance imaging, and can also be used in cancer thermal therapy (Akhter et al., 2015).

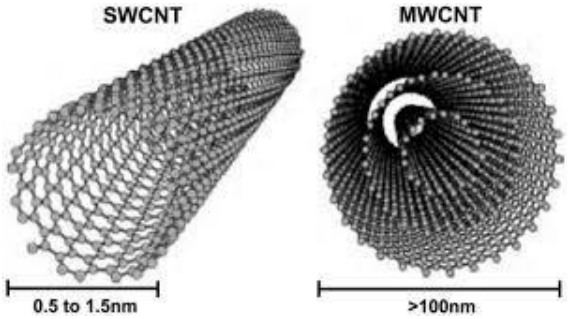
8. **Nanoshells:** Polymeric nanoshells (20-60 nm) of diblock copolymers can be made by self-assembly of oppositely charged polymers forming a core/shell structure. Gold nanoshells(10 to 300nm) are optically tunable nanoparticles comprising a dielectric core with a thin gold shell surrounded. Laser activated gold nanoshells thermal ablation is a selective and effective technique for the ablation of prostate cancer in an ectopic tumour model (Stern et al., 2008).
9. **Fullerenes:** Buckminster fullerene is the most common form of fullerene measuring about 7 Å in diameter with 60 carbon atoms arranged in a shape known as truncated icosahedrons. Fullerenes are being investigated for drug transport of antiviral drugs, antibiotics and anticancer agents (Tegos et al., 2005).



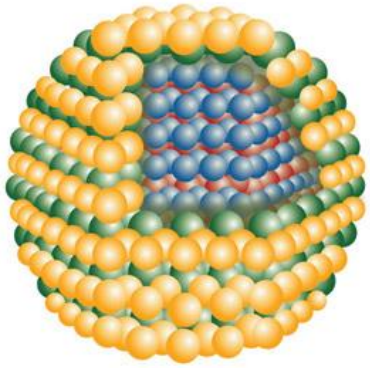
Liposome



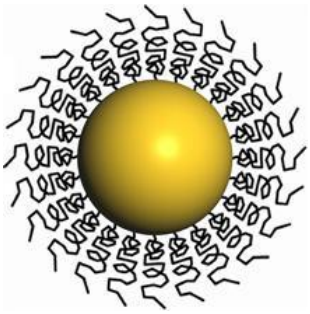
Dendrimer



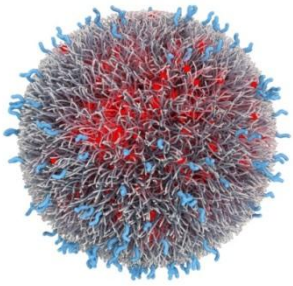
Carbon nanotubes



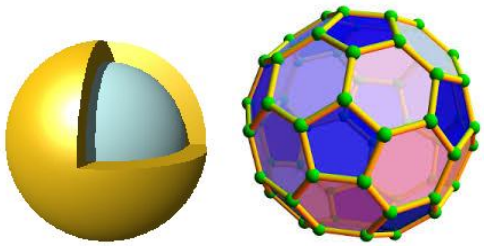
Quantum dot



Gold nanoparticle



Polymer nanoparticle



Gold nanoshell Fullerene

Fig. 1:-Different types of nanoparticle

Cancer: An inevitable disease:-

Cancer is a disease characterized by the unrestrained growth and spread of abnormal cells, and is still theleading cause of mortality worldwide. Cancer can be caused by a range of genetic or environmental factors, such as exposure to carcinogenic chemicals or radiation, or have a microbiological cause, including bacterial (eg, stomach cancer) or viral (eg, cervical cancer) infection. The characteristic behavior of the cancer is a process reflecting the complexity of malignant disease. This process includes promoter proliferative signaling, escape from growth suppressors, resistive cell death, replicative immortality, triggering of angiogenesis, and activation of invasion and metastasis. Genome instability, inflammation,and epigenetic changes are the underlying reasons for these. Regardless of the common features of neoplasms, there are a variety of types of cancer due to genetic diversity. Therefore, depicting each type of cancer is substantial to be able to develop an efficient and specific treatment without causing any damage to other tissues and organs (Altintas et al., 2015).

Cancers are classified by the type of cell that the tumor cell resembles and is thereforepresumed to be the origin of the tumor. These types include:

- **Carcinoma**

Cancers derived from epithelial cells. This group includes many of the most common cancers, particularly in the aged, and includes nearly all those developing in the breast, prostate, lung, pancreas, and colon.

- **Sarcoma**

Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develop from cells originating in mesenchyme cells outside the bone marrow.

- **Lymphoma and leukemia**

These two classes of cancer arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively. Leukemia is the most common type of cancer in children accounting for about 30%.

- **Germ cell tumor**

Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

- **Blastoma**

Cancers derived from immature "precursor" cells or embryonic tissue. Blastomas are more common in children than in older adults (Kumar et al., 2016).

Existing treatment for cancer embraces surgery, radiation, hormone therapy, and chemotherapy. Chemotherapy forms a major strategy for treating the disease. However, conventional chemotherapy is extremely nonspecific in targeting the drug to cancerous cells, making the normal healthy cells susceptible to the drug's undesirable effects. This significantly hinders the maximum allowable dose of the drug. Moreover, rapid elimination and specific distribution into targeted organs and tissues compels the administration of large dose of drug, which is not economical and often results in troublesome toxicity issues (Haley et al., 2008). Nanoparticles (NPs) are customized drug delivery vectors capable of preferentially targeting large doses of chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. NPs hold great potential of considerably changing the face of oncology by their ability of targeted delivery, and thereby, overcoming limitations of conventional chemotherapy, which include undesirable biodistribution, cancer cell drug resistance, and severe systemic side effects (Sinha et al., 2006).

Nanoparticle Use in Cancer Treatment:-

Since its discovery, nanotechnology has been likely to strengthen the current medical armament in clinical oncology. There are several nanoparticle systems currently being employed for cancer therapeutics. The properties of these systems have been modified to augment delivery to the tumor; for instance, hydrophilic surfaces provide the nanoparticles with stealth properties for longer circulation times, and positively charged surfaces can enhance internalization into the cancer cells. The types of nanoparticles currently explored for cancer therapeutic applications include dendrimers, liposomes, polymeric NPs, micelles, protein nanoparticles, lipid nanoparticles, ceramic nanoparticles, viral nanoparticles, metallic nanoparticles, and carbon nanotubes (Byrne et al., 2008).Nano particles have a special property of high surface area to volume ratio, which allows various functional groups to get attached to a nanoparticle and thus bind to certain tumor cells. Furthermore, the 10 to 100 nm small size of nanoparticles, allows them to preferentially accumulate at tumor sites as tumors lack an effective lymphatic drainage system (Nikhalje et al.,2015).

The delivery of an anticancer drug to the target tissue can be achieved by nanoparticles primarily in two ways: passive and active targeting**(Fig 2**).

A) Passive targeting:-

This type of targeting utilizes the pathophysiological conditions of the tumor microenvironment,such as leaky vasculature, pH, temperature, and surface charge surrounding the tumor for specific delivery of NPs.

Enhanced permeation and retention (EPR) effect:-

Nanoparticulate systems take advantage of unique pathophysiologicfeatures of tumor vessels for passive targeting. When the tumor volume reaches above 2 mm^3, diffusion limitation sets in, which eventually impairs nutrition intake, waste excretion, and oxygen delivery.Cancer cells growing in such a rapid manner recruit the generation of new blood vessels, a phenomenon called angiogenesis (or neovascularization). Irregular tortuosity, abnormalities in the basement membrane, and the lack of pericytes lining endothelial cells are the features of this process, resulting in leaky vessels with gap sizes of 100 nm to 2 μm, depending upon the tumor type.Furthermore, such tumors unveil poor lymphatic drainage due to the high interstitial pressure at the core of the tumor than at the periphery. This distinctive combination of leaky vasculature and poor lymphatic flow results in enhanced permeation and retention (EPR) effect. Nanoparticles can specially localize in cancerous tissues owing to their size being smaller than blood vessel fenestration and be entrapped in the tumor due to higher retention ability than the normal tissues (Maeda, 2001).

Tumor microenvironment:-

Passive targeting can also be achieved by taking advantage of the microenvironment surrounding tumor cells, which is distinct from the normal cells. Rapidly dividing cancer cells exhibit a high metabolic rate while tumor cells utilize glycolysis to maintain sufficient supply of nutrients and oxygen, thereby resulting in an acidic environment (Pelicano et al., 2006). The pH-sensitive nanoparticulate systems are designed to be stable at a physiologic pH of 7.4 but degraded to release active drug in target tissues in which the pH is less than physiologic values, such as in the acidic environment of tumor cells.

Surface charge:-

Passive targeting also entails the use of innate feature of the nanoparticles such as charge to target the tumor. Tumor cells bear relatively high negative surface charge than normal cells, thereby enabling favored binding by cationic NP systems. Targeting of cationic NP system is achieved by electrostatic binding to negatively charged phospholipid headgroups preferentially expressed on tumor endothelial cells (Krasnici et al., 2003).The cytotoxicity potential of polymeric NPs largely depends on cellular internalization and subcellular localization of the NPs, which is governed by the nature of polymeric surface charge (anionic, cationic, or neutral). Cationic NPs have been found to efficiently deliver small interfering RNA (siRNA) to silence target gene in cancer cells and also sensitize the cancer cells to the effect of paclitaxel (PTX) for improved anticancer activity (Beh et al., 2009).

B) Active targeting:-

In Active targeting, ligands are conjugated at the periphery of the nanoparticulate system to bind with appropriate receptors at the target tumor site. The targeting ligands can be categorized as proteins (antibody and its fragments), nucleic acids (aptamers), or other ligands (peptides, vitamins, and carbohydrates), which generally bind to the receptor uniquely overexpressed by tumor cells or vasculature (Peer et al., 2007). The targeting ligands play a vital

role in enhancing cellular uptake of NPs through the process of endocytosis. Long-circulating NPs enable their efficient delivery to the tumor site by the EPR phenomena, and internalization of the nanosystem results in improved therapeutic effect (Kobayashi et al., 2007). The cellular targets for this strategy have been identified on the tumor cell and endothelium.

Tumor cell targeting:-
This targeting approach involves targeting of cell surface receptors overexpressed by tumor cells in order to enhance the cellular uptake of the nanocarriers. The ligand-based targeting is more important for the intracellular delivery of macromolecular drugs such as DNA, siRNA, and proteins, whose site of action is located intracellularly. The cellular internalization of nanocarrier increases the antitumoral efficacy of ligand-targeted nanocarriers. The ability of the nanocarrierto be internalized post-binding to target cell receptor is requisite for proper selection of targeting ligands (Cho et al., 2008). The most widely studied targets are transferrin, folate, and epidermal growth factor receptors (EGFRs), and glycoproteins.

Transferrin receptors:-
Transferrin, a serum non-heme iron-binding glycoprotein, transports iron through the blood and into proliferating cells by attaching to the transferrin receptor. Once the transferrin is internalized, iron is released as a result of endocytosis in the acidic environment of the cell. The transferrin receptor is an important protein responsible for iron homeostasis and regulation of cell growth. Thus, the overexpression of transferrin receptors in metastatic and drug-resistant cancer cells in comparison to the normal cells due to increased requirement of iron makes this receptor a pertinent target for cancer therapy (Pastorino et al., 2006).

Folate receptors:-
The folate receptor is a 38 kDaglycosyl-phosphatidylinositol-conjugated glycoprotein, which is the most widely researched tumor marker. This receptor binds to the vitamin folic acid and folate–drug conjugates or folate-anchored nanocarriers with a high affinity and internalizes into the cells via receptor-mediated endocytosis. Folic acid is necessary for the synthesis of nucleotide bases, viz purines and pyrimidines. Moreover, normal cells transport folic acid only in reduced form such as 5-methyl-tetrahydrofolate and do not transport folate conjugates across their membrane. The major route of folate conjugate entry into the cancer cells is mainly via the folate receptors, as these receptors are significantly upregulated on cancer cells compared to normal cells. Functional folate receptors are majorly confined to the apical surfaces of polarized epithelia. A wide range of tumors overexpress folate receptors, including ovary, lung, brain, head and neck, renal cell, and breast cancers. The great utility of these folate ligands stems from the fact that they are inexpensive, nontoxic, and non-immunogenic. They also have high binding affinity, stability on storage and in circulation, and are easily conjugated to nanocarriers (Low et al., 2004).

Epidermal growth factor receptors:-
The EGFRs belonging to a family of tyrosine kinase receptors are highly upregulated on tumor cell surfaces. EGFR binds to six known endogenous ligands: EGF, transforming growth factor-α, amphiregulin, betacellulin, heparin-binding EGF, and epiregulin. Activation of EGFR by one of these ligands stimulates intracellular signaling processes involved in tumor growth and progression that include proliferation, angiogenesis, invasion, and metastasis. The EGFR is overexpressed in breast, lung, colorectal, and brain cancers (Lurje et al., 2009).

Glycoproteins:-
Lectins are proteins that can identify and attach specifically to the carbohydrate entity of glycoproteins expressed on tumor cell surface. Glycoproteins expressed on tumor cells are different from that of normal cells. Lectin targeting can be characterized as direct lectin targeting (lectins included in nanosystems as ligand to target cell surface glycoprotein) and reverse lectin targeting (conjugating nanosystem with carbohydrate moiety to target lectins). The lectin-based targeting has been applied majorly in targeting colon (Minko et al., 2004).

Tumor endothelium targeting:-
The growth of solid tumors can be inhibited by preventing angiogenesis, which is the production of new blood vesselsfor adequate blood supply mainly in the tumor core to provide oxygen and essential nutrients. Thus, designing of nanocarriers that actively target angiogenesis can prove to be very useful for regulating cancer growth and associated metastatic potential (Lammes et al., 2008). Targeting the tumor endothelium has following merits: (i) there is no need for the nanocarriers to cross endothelial barriers to reach their target site; (ii) nanocarriers have the ease of accessibility to bind to endothelial receptors post-intravenous injection; (iii) endothelial cells are less prone

to the risk of developing resistance to treatment than tumor cells because of high genetic stability; and (iv) this approach can be applied to all types of tumor as most of the markers are expressed on endothelial cells.

VEGF receptor:-

The vascular endothelial growth factors (VEGFs) induce tumor angiogenesis and neovascularization by virtue of their ability to bind and activate the VEGF receptor (VEGFR) signaling cascade (Shadidi et al., 2003). These receptors seem to be favorable strategy for angiogenesis-associated targeting of nanoparticle systems. Oncogenes and tumor hypoxia increases VEGF levels in the tumor cells, which leads to an overexpression of two types of VEGFRs, viz VEGFR-1 (fms-like tyrosine kinase) and VEGFR-2 (fetal liver kinase-1), on tumor endothelial cells. VEGFR-2 is the most widely explored among the VEGF class of receptors. Angiogenesis can be inhibited either by targeting VEGF to prevent ligand binding to VEGFR-2 or by targeting VEGFR-2 to reduce VEGF binding and activate an endocytic pathway.

αvβ3 integrin:-

The αvβ3 integrin, an endothelial cell receptor for extracellular matrix proteins, comprises von Willebrand factor, fibrinogen (fibrin), vibronectin, thrombospondin, osteopontin, and fibronectin. These proteins share a common structural feature of the presence of three-amino acid sequence (i.e., arginine-glycine-aspartic acid, RGD). The αvβ3 integrin is greatly upregulated on neovascular endothelial and tumor cells than on resting endothelial cells and other normal organs. It also plays a critical role in the calcium-dependent signaling pathway, thereby causing migration of endothelial cell. Derivatives of RGD (Arg-Gly-Asp) oligopeptides can bind and block the endothelial αvβ3 integrins which is also related intrinsically to the VEGFR-2 signaling. Blocking the αvβ3 integrin receptor binding is found to be associated with downregulation of VEGF, thereby inhibiting the tumor angiogenesis synergistically (Desgrosellier et al., 2010).

Vascular cell adhesion molecule-1:-

Vascular cell adhesion molecule-1 (VCAM-1), a transmembrane glycoprotein, is expressed exclusively on the surface of endothelial tumor cells. It promotes cell-to-cell adhesion during tumor angiogenesis and increased expression of VCAM-1 is usually found in leukemia, breast and lung cancer, renal cell carcinoma, melanoma, gastric cancer, and nephroblastoma (Dienst et al., 2005).

Matrix metalloproteinases:-

These metalloproteinases belong to a class of structurally related zinc-dependent endopeptidases. Matrix metalloproteinases (MMPs) are known to be acritical physiologic component involved in tissue repair, morphogenesis, and angiogenesis. Matrix metalloproteinase expressed on angiogenic endothelial tumor cells, including colon, cervical, and gastric carcinomas, and gliomas, melanomas, and malignancies of the lung are known as Membrane type 1 matrix metalloproteinase (MT1-MMP) which functions i) by degrading the extracellular matrix, ii) by playing a role in angiogenesis, metastasis, endothelial cell invasion, and migration,iii) in the formation of capillary tubes, and iv) in recruiting accessory cells. It also activates MMP-2 that hydrolyzes Type IV collagen, a cementing component of basement membrane. In addition, targeting the MT1-MMP limits the ligand binding to αvβ3 integrin, thereby suggesting it to be a valuable target (Vihinen et al., 2005).

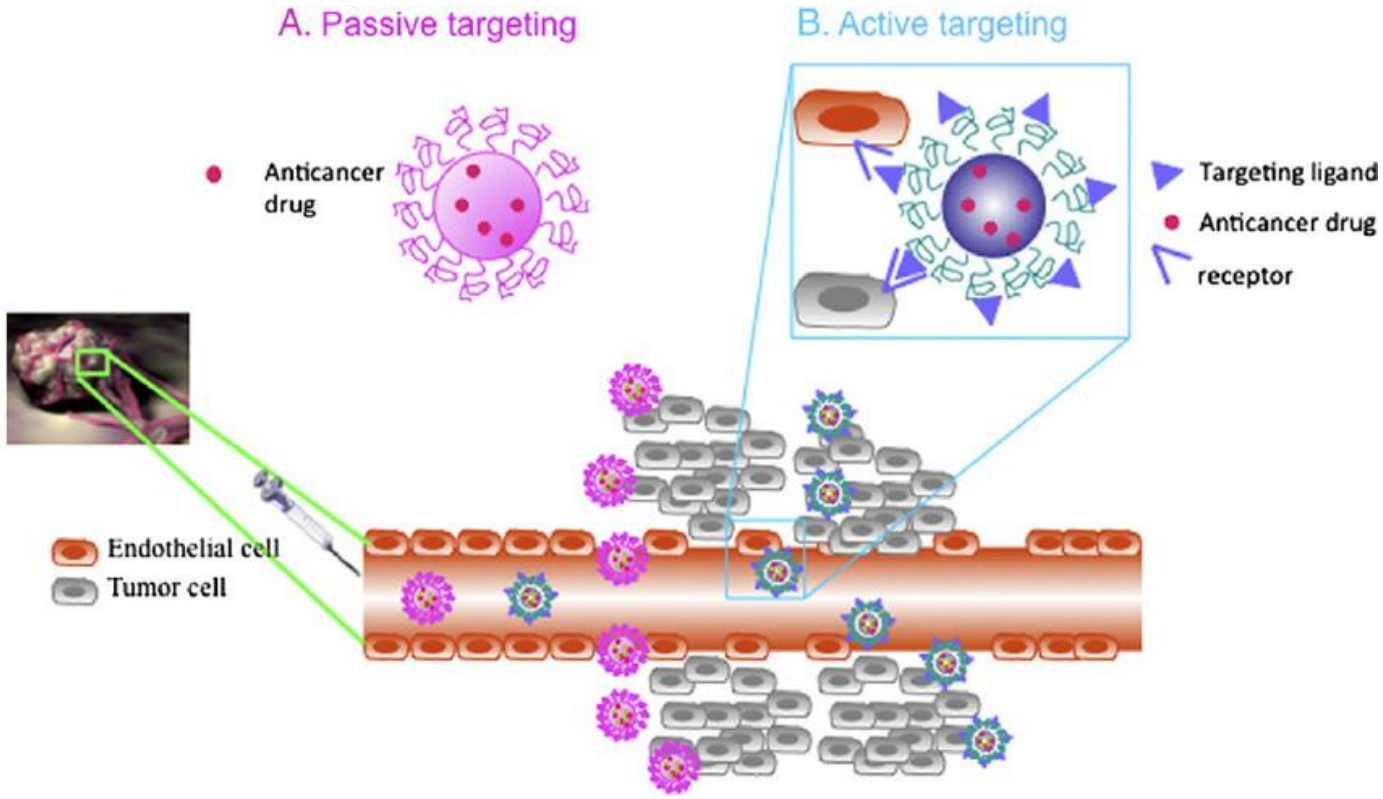


Fig.2 :- Delivery of an anticancer drug to the target tissue by nanoparticles through passive and active targeting.

Future Prospects:-

Nanomaterials have arousedas a significant treatment for therapeutic oncology due to their increased surface area and nano scale effects. They have turned out to be a propitious tool for the drug delivery, diagnostic biosensors and biomedical imaging with outstanding physicochemical and biologically important properties. The investigation for new molecular targets will advance their ability to improve drug delivery to the tumor cells with minimal toxicity to the normal cells. There is a very bright future for nanotechnology as it could lead to the generation of new complexes and hybrid technologies on blending with various other technologies in order to attain high therapeutic load and release control capacity with subsequentdurable implication on cancer treatment.

Conclusion:-

Nanotechnology is an emerging field with a critical role in the diagnosis and treatment of cancer.Nano materials have unique physicochemical and biological properties which greatly influence their interactions with bio molecules and cells, due to their peculiar size, shape, chemical composition, surface structure and charge.Because of their miniature size, NPs can be taken up very efficiently by cells forming a constant nanocomplex, thereby defending it from nuclease degradation and allowing successful delivery to the tumor site. In spite of the challenges restricting its application, it is promising that nanomaterials in the future would play a critical role in the detection and treatment of Cancer.

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