RECENT ADVANCES IN NANOTECHNOLOGY FOR CANCER THERAPY- A REVIEW

Adamu Abdullahi Abubakar[1], Shankaraiah Pulipaka[1], Rekha Sharma[2], Pavani Sriram[3]

Neeraj Choudhary[1], Ashish Suttee[1*]

[1]School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India
[2]School of Chemical Engineering and Physical Sciences, Lovely Professional University, Punjab, India
[3]Vaagdevi College of Pharmacy, Warangal, India.

ABSTRACT

One of the utmost serious threats facing people around the world is Cancer. Cancer occurrence and death are also elevated. Traditional methods of cancer treatment include chemotherapy, surgery or radiation therapy. Though the major treatments include surgery, chemotherapy and radiotherapy. Chemotherapy has been broadly applied in clinics due to its simple and suitable process, however, the therapeutic prospective of cancer chemotherapy is severely unsatisfactory owing to side effects and drug resistance, the distribution of non-specific medicines, multi-drug resistance; (RDM) and heterogeneity in cancer. To overcome these limits and attain better cancer therapeutic efficiency, it is essential to design a drug delivery system (DDS) to associate chemotherapy with supplementary cancer managements. In current years, nanotechnologies have presented high possibilities in cancer therapeutics due to the distinctive physicochemical and biological properties of nanomaterials. Nanotechnology in drug administration includes nanocarriers like nanodiamonds, quantum dots, high-density lipoprotein nanostructures, liposomes, polymer nanoparticles, Dendrimers, nanoconjugates and golden nanoparticles. Due to their physico-chemical and optical properties, their adaptableness, sub-cell size and their biocompatibility. They provide an adequate way to transport small molecules and bio macromolecules to diseased cells/tissues. It offers a unique approach and comprehensive technology in contrast to cancer over early diagnosis, prediction, prevention, personalized therapy, and medicine. Hence, combinational therapy based on chemotherapy facilitated by nanotechnology has been the tendency in clinical research at present, which can effect in a remarkably improved therapeutic efficiency with little side effects to normal tissues. The review concentrate on modern developments and approaches in nanotechnology in advancing cancer treatment.

Keywords: Cancer, nanoparticles; drug delivery, nanotechnology, nanocarriers, therapy, treatment

1. INTRODUCTION

Cancer is the second leading main cause of death following heart diseases: more than ten million people are analysed with the disease yearly. The speed at which cancer emerges only increases over time as a result of factors such as enlarged pollution, radiation, deficiency of exercise, and a balanced diet, amongst other variables such as genetics. Cancer is categorized by an unrestrained proliferation of cells and subsequent disappearance by apoptosis[1]. Cancer management has been very complex because of the

distinctive physiopathology of cancer cells, whose phenotypic and genetic levels show therapeutic resistance and clinical diversity. Any of these features can result in a mutation in the DNA of our cells such as oncogenes and grow into cancer[2]. The immortalization and durability of discrete cells that can reproduce at astounding rates, exceed all healthy functional cells, and ultimately cause death. Initially, cancers begin as confined to a small area, but they are prone to spread to remote sites throughout the body, making cancer incurable[3]. While our understanding of cancer biology has improved dramatically over the past 20 years, cancer remains a main health problem worldwide as the second foremost cause of death. Every year, there are over 10 million new cases and over 5 million deaths related to the disease[4]. A cancer analysis was earlier considered terminal, even if it is identified early, the prognosis is favourable. A substantial numeral of cancer patients is asymptomatic till they reach the final phases of the disease. The utmost common cancer treatments include chemotherapy, radiotherapy and surgery[5].Chemotherapy is extensively practiced and involves the systemic administration of cancer medications to patients to inhibit the growing of rapidly developing cancer cells. Most current chemotherapy medications are non-specific cell killers, they also produce similar toxicity in normal cells, producing serious side effects and unbearable pain for patients, which may cause tumor cells to resist chemotherapy medications and normal tissue cell damage[6]. Chemotherapeutics prompt cytotoxicity due to the high pharmacokinetic volume of distribution for low molecular weight active ingredients. Another most important limitation associated with chemotherapeutics is their primary clearance from the systemic circulation. Low molecular weight chemicals are excreted promptly. They are wash away from the body as being swallowed up by macro-phages. Therefore, they persist in the systemic circulation for a short duration of time and cannot interrelate with cancer cells, resultant in lower therapeutic effects. For this purpose, a higher concentration is requisite to attain a therapeutic impact that ends up in toxicity[7]. The low therapeutic index of chemotherapeutic suggests that the required concentration for the effective action is usually high resulting in general systemic dose-dependent side effects. Lower liquid solubility of antineoplastic medicine is additional issue that decreases their biological membrane penetration potential. Furthermore, a MDR macromolecule, P-gp, is overexpressed on cancerous cell surfaces, acting as an efflux pump and inhibiting the drug's accumulation within the tumors[8]. This ends up in the mediation of resistance to the drug and at last causing to the failure of chemotherapy. Formulating chemotherapeutic medication is difficult because of their poor liquid solubility. The low solubility makes the preparation of medicine tough because of the inclusion of oleophilic groups that show affinity toward the target receptor. Also, high degradation susceptibility mostly at the RES permits circumventing the employment of the preparation for oral drug administration and implies administration regimens, not in compliance with the patients. Thus, the variation may well be done in ways of administration of available chemotherapeutics by optimizing DDS. The poorly soluble drugs might cause embolization of blood vessels upon IV injection because of accumulation of the insoluble drugs, and sometimes lead to local toxicity as a outcome of high drug concentrations at the site of deposition[9].

Presently, thermodynamically stable polymeric micelles comprised of a lyophilic core encircled by a hydrophilic shell are examined and established as an efficient delivery system for poorly soluble

medicine[10]. Moreover, though the drug is with success delivered its effectuality is also restricted if the cancer cells have non-inheritable MDR. The typical feature of MDR is over-expression of the cell membrane P-gp that is able to medicine away from the cell. Numerous ways are extended to keep away fromP-gp-mediated MDR, as well as the encapsulation of antineoplastic medicine in nanoparticles and furthermore the co-administration of P-gp inhibitors. Efflux of the numerous lipophilic medication by means of drug effluence carriers coming in suboptimal therapeutic drug concentration at the situating of action is taken into record to be one among the hindrances behind the achievement of therapy[11].

Radiotherapy may cause damage of conventional tissue cells. Inferable from lacking treatments and clinical methods for defeating multi-drug safe malignant growth, new advances is significant that new advances arise for right early identification and treatment of this ailment owing to inadequate therapies and clinical procedures for overcoming multi-drug resistant cancer, new technologies is important that new technologies emerge for correct early detection and treatment of this malady. Current demonstrative and prognostic classifications are lean to create expectations for productive therapy and patient outcomes[12,13]. During this regard, numerous ligand-targeted therapeutic strategies, as well as immunotoxins, radio immunotherapeutic, and drug immunoconjugates, are being created to beat the issues identified with standard treatment, thereby providing further tools in cancer clinical aid. The principal objective of malignancy therapy should prompt increased therapeutic effectuality with low to least impacts thereby destroying cancerous cells whereas limiting mischief to conventional cells. In this manner, there's associate need to grow new and creative advances for the therapy of disease that would encourage to outline tumour margins, establish residual tumour cells and micro metastases, and affirm whether a tumor has been totally removed[14,15].

NANOTECHNOLOGY: a substitution and promising therapeutic tool

The latest advances suggest that designing science a multidisciplinary field (which includes the creation and control of materials at nanoscale levels to make the stock that show novel properties) can profoundly impact disease interference, analysis, and treatment[16]. Cancer nanotechnology is ascending as a substitution field of information area examination cutting across the controls of science, science, designing, and drug and is anticipated to manual for significant advances in disease discovery, conclusion, and treatment[17]. Nanotechnology can be characterized as the style and creation of devices in nanoscale to upgrade their physical, compound, and natural properties[15]. Nanomedicine (the medical application of nanotechnology) has amazing potential for revolutionizing cancer medicine and medicine by developing ingenious biocompatible nanocomposites for drug delivery functions that represent the foremost pertinent application of nanoparticles[17]. Recent years have seen remarkable utilization of Nano vectors (particularly within the size vary from ten nm to a hundred nm Fig1) in a minimum of one dimension as emerging category.

The nanoparticles are biocompatible and biodegradable and are created from a center, a particle that acts as a carrier, and one or more functional groups on the core that target specific sites[15,16]. The elementary advantages of nanoparticles are improved delivery of water-insoluble medication, targeted delivery, co-

delivery of 2 or a lot of medication for combination medical aid, and visual image of the drug delivery site by combining an imaging system and a therapeutic drug. As nanomaterials supply particular chemical, and biological properties, they need been appeared to significantly build the potency of drug-targeted medical aid. There are 2 basic approaches deal with nanotechnology-based cancer treatment. One is thru the utilization of nanomaterials as a drug carrier for cancer management, like anti-tumor medication, therapeutic genes, and antibodies. The inverse depends on the distinctive properties of nanoparticles like the photothermal effects from a number of the well-known nanomaterials: TiO2, gold, and carbon nanotubes[17,18].

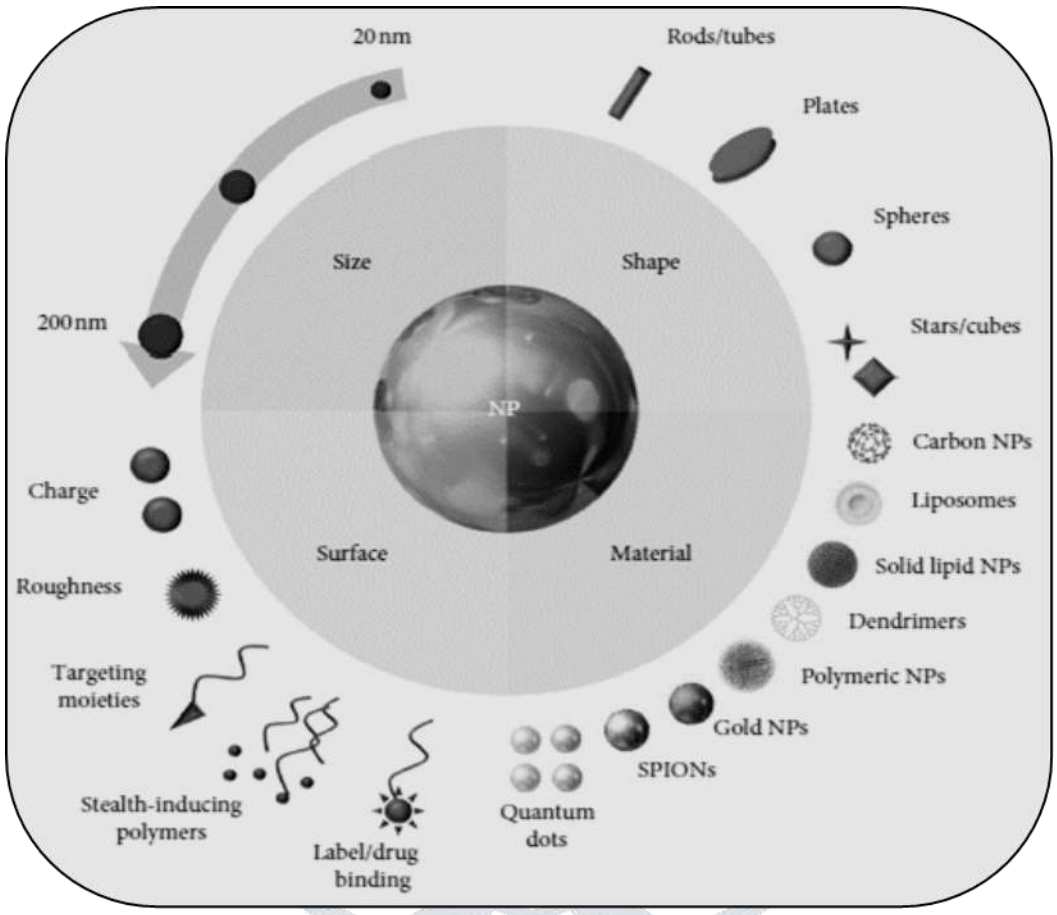

Figure1: Different features and design options of nanovectors used in the treatment of cancer[18]

These nanosystems have four distinct properties that recognize them from other cancer

Therapeutics: (i) the nanosystems will themselves have therapeutic or diagnostic properties (ii) nanosystems may be connected to multivalent targeting ligands, which yield high affinity and specificity for target cells (iii) nanosystems may be created to accommodate multiple drug molecules that simultaneously change combinatorial cancer therapy and (iv) nanosystems can bypass ancient drug resistance mechanisms. By utilizing both passive and active targeting ways, the nanocarriers canincreased intracellular concentration of therapeutic agents in cancer cells while minimizing toxicity in normal cells, simultaneously upgrading malignant effects and lessening systemic toxicity[15-18].

The most widely recognized nanocarriers for the delivery of chemotherapeutics include liposomes, polymeric nanoparticles, dendrimers, nano-shells, inorganic, nucleic acid-based, and magnetic nanoparticles[19]. Nanoparticular drug delivery systems supply important benefits for cancer treatment over free drug administration since NPs: improve the therapeutic index of the loaded chemotherapeutical agents

compared to the medication delivered via typical dosage forms, increase drug effectivity by achieving steady-state therapeutic levels of medicines over an extended period, lower drug toxicity because of controlled drug release and improve drug's pharmacokinetics by improving drug's solubility and stability, minimize their systemic clearance. Gives an opportunity to the applying of combination therapy by using chemotherapeutical and photothermal effects, or making magnetic nanostructures creating delivery of NPs easier with the application of an external magnetic field[20].

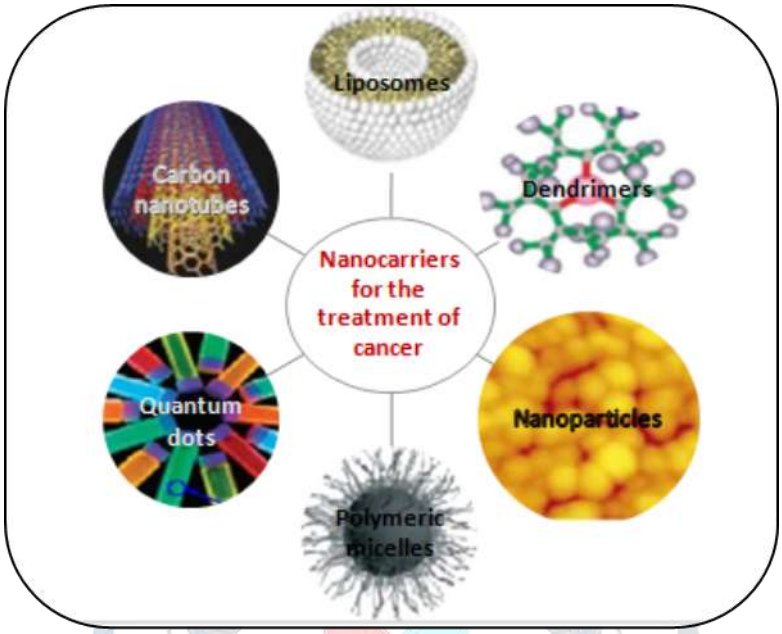

Figure2. List of Nano carriers used in cancer therapy

NANOMATERIALS/NANOCARRIERS AS NEW THERAPEUTIC AGENT FOR THE TREATMENT OF CANCER

Nanomaterials acted as transporters of medications to have the capacity to advance the specific distribution of macro-molecular substances in tumor tissues, accordingly improving medication adequacy and lessening side effects results through expanded penetration and maintenance. Nanomaterials go about as transporters of chemotherapeutics and qualities. A portion of the nanotechnology conveyances includes (Fig2, Table1)

Liposomes

Liposomes, round vesicles made out of a macromolecule bilayer with the capacity to diffuse across cell layers just to convey chemotherapeutics to cells, will convey hydrophilic and additionally hydrophobic agents and analytic specialists in the internal aqueous center of the structure or potentially inside the trans-film section[19]. Liposomes are self-gathered, uni-lamellar, or multi-lamellar circular vesicles essentially made out of phospholipids from one or the other plant or animal origins. Liposomes are presently being used, conveying treatment medications to tumor microenvironments. The particular quality that these nanostructures have is that, much the same as the cell wall, they will fuse almost something into their surface. Liposomal formulations of numerous chemotherapeutic agents, presently in pre-clinical and clinical with promising outcomes. One of the ways to deal with elimination of Cremophor EL and ethanol

was by the consideration of paclitaxel in liposomal formulation, which improved the medication's antitumor effectiveness[20,22].

Nanoparticles

Nanoparticles are a group of particles that can be noted as focusing on ligands that have the adaptability to limit in on chemical markers inserted in malignancy cells so they may tie to them (Fig3). These ligands incorporate aptamers, antibodies, various peptides, and cytokines. Antibodies and aptamers embedded on the skin of liposomes loaded up with anticancer medications can effectively target disease cells. Another part of nanotechnology utilized in the therapy of disease is gold nanoparticles (AuNP)[23]. Like liposomes, tumor-specific antibodies will connect to the outside of the gold particles to focus on the malignancy cells. Nanoparticles are submicron-sized colloidal particles with aa agent of interest inside their polymeric lattice or adsorbed or formed onto the surface. Nanoparticles are focused to explicit sites by surface changes, which give specific biochemical collaborations with the receptors communicated on target cells. Polymeric nanoparticles dependent on engineered polymers or common polymers have great biocompatibility with a high loading of medicine[23]. The numerous surface practical gatherings of polymeric nanoparticles may likewise be additionally altered with certain antibodies, peptides, and other focusing on ligands to accomplish active targetting. Likewise, the PEG-changed on the outside of the polymeric nanoparticles will shield them from the blood clearance by the mononuclear phagocytic framework (MPS). Polymer-drug nano-forms and dendrimers are completely based on polymer while they have distinctive novel properties. Polymer-drug nano-forms, as the name suggests, are formation that bond polymer with drugs covalently, that increase blood flow time by getting away from filtration from the kidneys. Of note, the increased blood circulation time permits anticancer forms to collect at the tumor[24-28].

Dendrimers

Dendrimers are polymeric nanocarriers with star-like or branch-like structures, allowing the conjugation of therapeutic and/or diagnostic agents on the surface to expand the results of malignancy treatments. Dendrimers are macromolecular compounds that includes a series of branches around an inner core, the size, and shape of which might be changed as desired, and consequently function as an attractive modality for drug delivery[27,28].

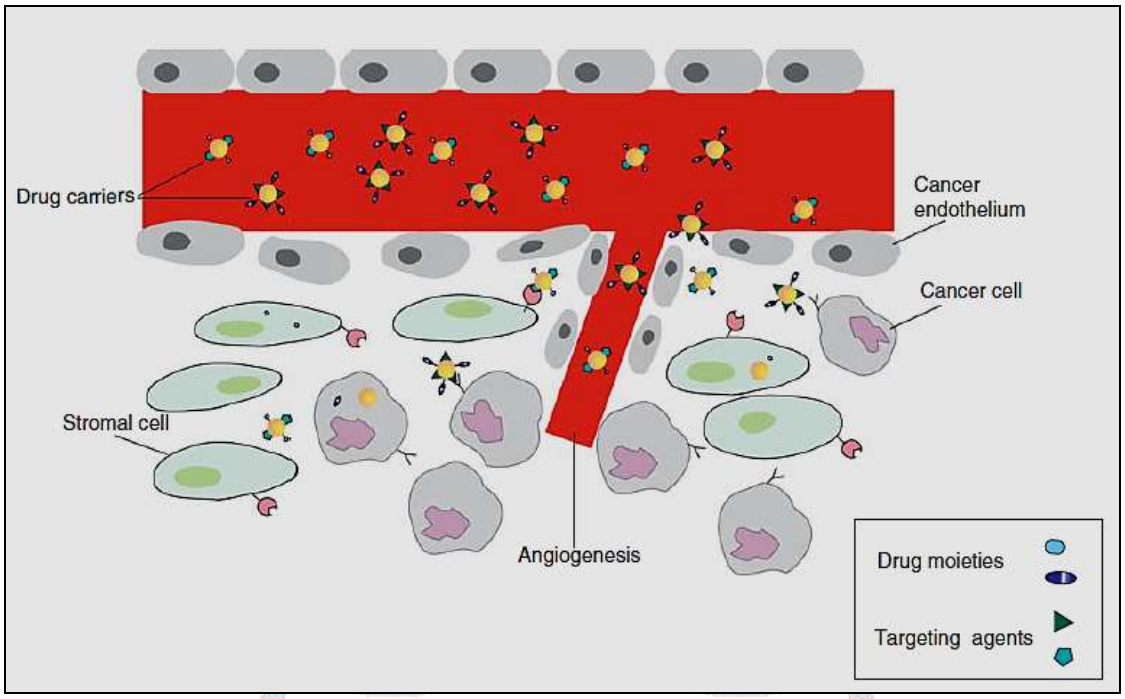

Figure3. Nanoparticle mediated targeted drug delivery to tumors[28]

Nanodiamond

Nanodiamond is carbon-based microscopic agents that need very high biocompatibility compared to other nanoparticles of their size with multiple biological applications. They can be loaded with doxorubicin and carried to metastatic tumour cells or used as biomarkers and tracers that label cancer.

Carbon nanotubes

Carbon nanotubes is a type of bio-marker nanodevice detection system. Carbon nanotubes are carbon cylinders made up of benzene rings used in biology as sensors for the identification of DNA and protein, as screening instruments for the discrimination of various proteins from serum samples, and as carriers for the delivery of drugs, vaccines or proteins. Carbon nanotubes (CNTs) can penetrate cells using a 'needle-like penetration' technique and deliver molecules to the cytoplasm. As drugs are specifically charged to CNT, CNT-coating polymers are released for conjugation with other functionalities, e.g. targeting molecules, antibodies, fluorescence molecules, or other multi-functional drugs.

Polymeric micelles

A micelle is known as a group of surfactant amphiphilic molecules, and it is a key element of therapeutics in the future. The first formulation of the polymeric micelle Paclitaxel, Genexol-PM (PEG-poly (D,L-lactide)-paclitaxel), is a cremophor-EL-free polymer-formulated paclitaxel.

Nanocantilever

Microarray approaches used to identify complex biomolecular associations are currently an important tool for cancer detection, gene testing and drug exploration. Small bars anchored at one end are also designed to bind to cancer-associated molecules. These molecules can bind to the modified DNA proteins that are found in certain cancer types. During detection procedures, if bio-specific interactions develop between the receptor immobilised on one side of the cantilever and the ligand in solution, the cantilever bends; if detected optically, it is possible to tell which cancer molecules are present and thus to observe early molecular events in the growth of cancer.

Quantum dots

The semiconductor quantum dots (QDs) gained the attention of many analysis teams due to their scientific and technical importance in microelectronics, optoelectronics and the cellular imagery. Semiconductor QDs are evolving as a new class of fluorescent labels for biology and drugs. The broad absorption and narrow emission properties of QDs make it possible to do multicolour imaging using a single excitation source. The high quantum fluorescence of the QDs, their resistance to photo bleaching and their distinctive physical, chemical and optical properties enable them attractive candidates for fluorescent tags for molecular and cellular imaging *in vivo*.

NANOTECHNOLOGY MEDIATED THERAPIES WITHIN THE TREATMENT OF CANCER

Cancer treatments are currently limited to surgery, radiation and chemotherapy. All three ways are at risk of damage to normal tissues or inadequate eradication of cancer. Nanotechnology provides a mechanism to target chemotherapy specifically and exclusively to cancer cells and neoplasms, to guide the surgical resection of tumours, and to improve the clinical effectiveness of radiation-based and complementary conventional care approaches (Fig4). All these will lead to a diminished risk to the patient and an increased chance of recovery. Study on nanotechnology cancer therapy expands beyond the delivery of medications to the development of novel therapeutics developed only through the use of nanomaterial properties. While small compared to cells, nanoparticles are wide enough to encapsulate a variety of tiny molecule molecules, which can be of several categories. At a similar time, the comparatively large surface area of nanoparticles is also compatible with ligands, as well as tiny molecules, DNA or RNA strands, peptides, aptamers or antibodies. These ligands are often used for therapeutic purposes or for direct *in vivo* fate of nanoparticles. These properties enable combination drug delivery, multi-modality therapy and integrated therapeutic and diagnostic intervention, known as "Theranostic." Physical properties of nanoparticles, such as energy absorption and re-radiation, can also be used to damage diseased tissues, such as laser ablation and hyperthermia.

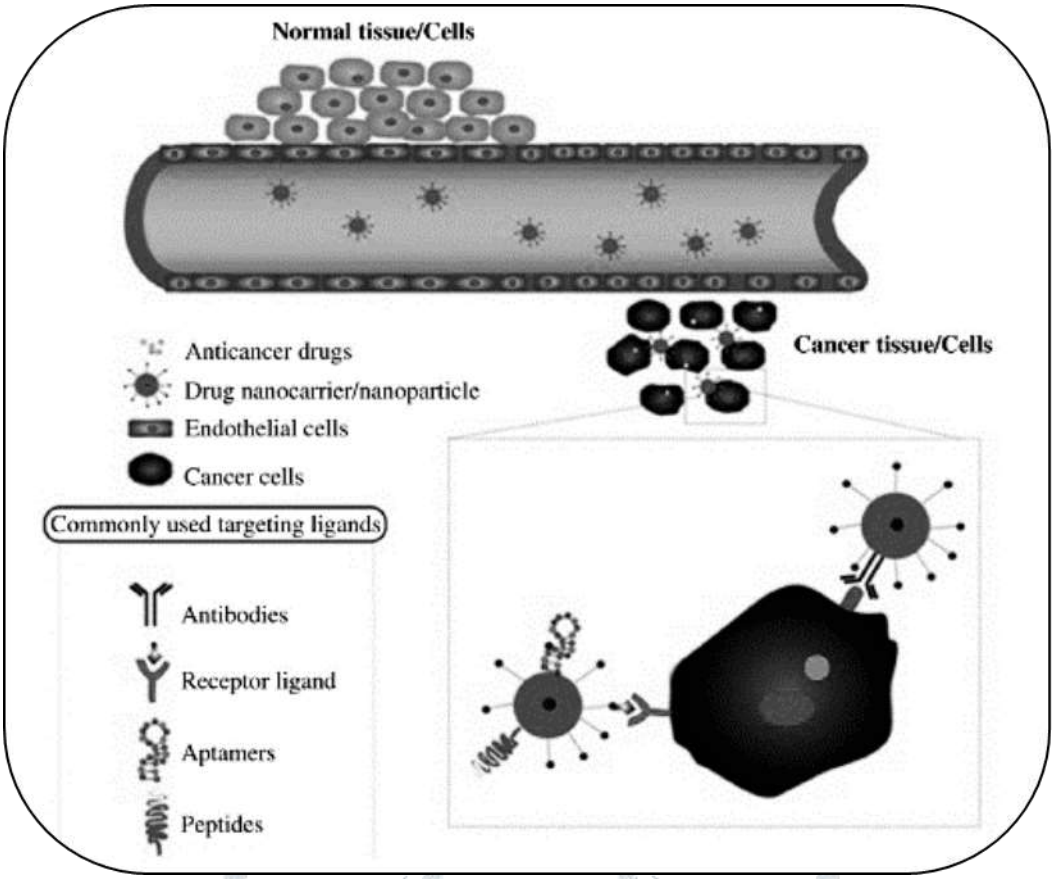

Figure4. Active cancer cell targeting by nanocarriers

Nanotechnology-mediated novel cancer therapy

Targeted chemotherapy – in which only cancer cells are destroyed and normal cells are not harmed – has been more desirable in cancer treatment. The field of nanotechnology has created new materials and methods for targeted cancer therapy. Designed nanoparticle properties open the door to new non-invasive cancer therapy techniques that were not currently available, including nanotechnology-based chemotherapy strategies such as photodynamic therapy (PDT), photothermal therapy, radiotherapy and radiofrequency therapy, theragnostics, immunotherapy, enhanced radiotherapy, synergistic therapy, gas therapy, gene therapy (Fig5).

Delivering Chemotherapy

The conventional application of nanotechnology in cancer medicine has been to promote the pharmacokinetics and reduce the general toxicity of chemotherapy by selective targeting and delivering these anticancer drugs to tumour tissues. The advantage of nano-sized carriers is that they can improve the overall therapeutic index of the drug distributed by nano formulations in chemotherapeutics that are either conjugated to the surfaces of nanoparticles. This capability is essentially due to their tunable size and surface properties. Size is a significant factor in the selection of nanotechnology-based drugs to tumour tissues. The targeted delivery of nanotherapeutic platforms relies mainly on the passive targeting of tumours by improved permeability and retention (EPR) effects. This development depends on tumour microenvironment-specific defects such as lymphatic drainage defect, along with enhanced tumour vasculature permeability to allow nanoparticles (<200 nm) to accumulate in the tumour microenvironment.

Nano-enabled therapy

Immunotherapy could be a new innovative front in cancer treatment that incorporates a variety of approaches, including check point inhibition and cell therapy. While the outcomes for a few patients are spectacular, only a limited percentage of patients being treated for a simple set of cancers had long-lasting reactions to these therapies. Expanding the benefits of immunotherapy requires a better understanding of tumor-host immune system interactions. New technologies for molecular and functional examination of single cells are being used to interrogate tumours and immune cells, and to elucidate molecular indicators and valuable immune responses to therapy. Nanotechnologies are now being studied for the delivery of immunotherapy. This involves the use of nanoparticles to provide immune suppression or immunomodulatory molecules in conjunction with chemotherapy or radiotherapy or as adjuvants of other immunotherapies. Standalone nanoparticle vaccines are also designed to improve adequate T cell response to eradicate tumours through co-delivery of antigens and adjuvants, the inclusion of multiple antigens to activate multiple dendritic cell targets, and the continuous release of antigens for sustained immune stimulation. Co-encapsulated nanoparticle vaccines can also be a molecular blocker of immunosuppressive factors generated to modify the immune background of tumours and enhance response.

Delivering or Augmenting Radiotherapy

Radiation therapy uses high-energy radiation to destroy cancers and kill tumor cells. Radiation therapy eliminates cancer cells by destroying their Deoxyribonucleic acid inducing cell apoptosis. Radiation therapy may either directly damage DNA or induce charged particles (atoms with an odd or unpaired number of electrons) inside cells that may successively damage DNA. Most kinds of radiations used for cancer treatment use x-rays, gamma rays, and charged particles. As such they are potentially cyanogenetic to all cells, not only cancer cells, and are delivered at doses that are as safe as possible without being excessively dangerous to the body or lethal.

Photodynamic therapy

Photodynamic therapy is another type of medical treatment that relies on external electromagnetic radiation (PDT). It is an efficient anticancer procedure for superficial tumours that depends on the tumour position of the photosensitizer accompanied by light activation for cytotoxic reactive oxygen species (ROS). Several nanotechnology platforms are currently being investigated. Typically made of lanthanide or hafnium-doped high-Z core, X-rays may be externally irradiated until absorbed, enabling the nanoparticle core to emit visible light at the tumour site. Particle photon emission after activation of a nanoparticle-bound or local photosensitizer to generate singlet oxygen (1O2) ROS for tumour destruction[58-60].

Photothermal therapy

Photothermal therapy (PTT) delivers photothermal nanoparticles to the tumour site in a targeted manner. A laser (near-infrared light energy) beam is used to illuminate the nanoparticles on the tumour site, which will develop enough heat to destroy the tissues of the tumour. Generally, the photothermal properties of these nanostructures can be controlled by varying their sizes and shapes. Gold nanoparticle conjugate [e. g.

Poly(ethylene glycol)-conjugated GNRs] will be produced systemically, leading to an occasional immunogenic response with a long-circulating half-life[61,62].

Photothermal therapy combined with photodynamic therapy

Owing to low energy absorption of PDT photosensitizers at near-infrared (NIR) wavelength and inadequate penetration into biological tissues, in-depth attempts have been made to incorporate PDT and PTT with improved therapeutic efficacy on malignant tumours. Gold nanorod(GNR)-AlPcS4 chemotherapy photosensitizer complex by combining photosensitizer with gold NPs. The results indicated that tumour growth declined by 79 percent with PDT alone and by 95 percent with PTT and PDT respectively. These distinctive materials can absorb a wide range of visible and near-infrared (NIR) wavelengths from 500 to 1000 nm, simultaneously generating substantial reactive oxygen species (ROS) and heat for combined PDT and PTT. Relative to single therapy, the combination of PDT and PTT has a synergistic effect on improved necrobiosis[60-62].

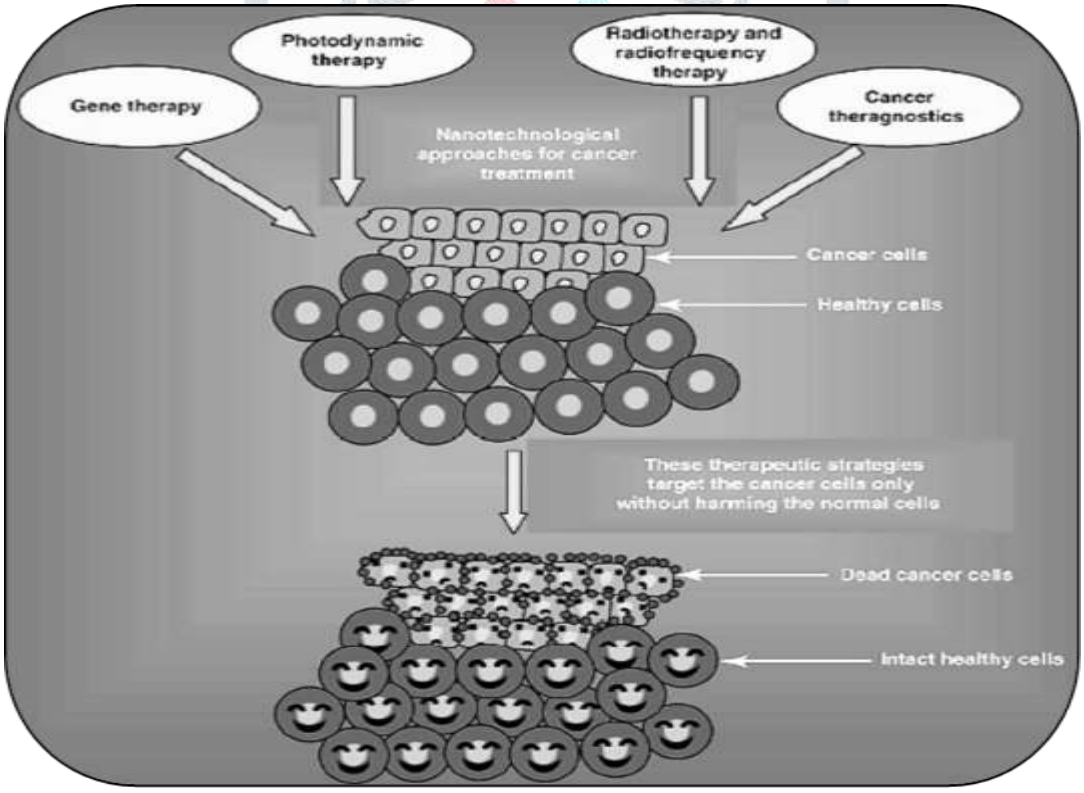

Figure5.Different approaches of nanotechnology[44]

Chemotherapy combined with photothermal therapy

The combination of chemotherapy and PTT has great potential in the treatment of tumours. There are several ways to treat chemotherapy and PTT in a synergistic manner. In order to achieve synergistic

therapy, multifunctional nanocarriers are developed with drugs and photosensitizers; or alternatively with photothermal materials as direct therapeutic agents[60-62].

Gas therapy combined with photothermal therapy

It is accepted that certain gases such as nitric oxide (NO), hydrogen sulphide (H2S) and carbon monoxide (CO) have a significant diffusion potential in tumour tissues due to their distinctive chemical properties. In addition, these gas molecules can regulate several physiological processes as second messengers. In order to minimize the issue of uneven heat transmission as well as the limited treatment accuracy of photothermal therapy[62,63].

Delivering Gene Therapy

Gene therapy is based on the concept that certain exogenous genes can be introduced into the tumour cell genome to provide a tumoricidal effect. The importance of nanomaterial distribution has become evident with improved varieties of therapeutics, such as those using nucleic acids, which are highly unstable in systemic circulation and are vulnerable to degradation. These comprise DNA and RNA-based genetic engineering, such as small interference RNAs (siRNAs) and microRNAs (miRNAs). Therapeutic silencing genes, siRNAs, have been reported to have substantially extended half-lives when transmitted either encapsulated or conjugated to the surface of nanoparticles. In a range of contexts, these medications are used to boot 'undruggable' cancer proteins. In addition, the enhanced stability of the genetic therapies delivered by nanocarriers, often combined with controlled release, has been shown to extend their effects[62,64].

Biomimetic nano cell membrane combined with photothermal therapy

Cell membrane coating can provide cells derived from nanomaterials with inherent functions and characteristics. Cell membranes (erythrocytemembrane, cancer cell membrane, NK cell membrane, etc.) are used to build a nano-drug-loading system that have the characteristics of mutually-derived cells *in vitro* and *in vivo*. Nanosponge Carbon Complex Red Blood Cell (RBC) membrane, which can be used as an invisible fibre carrier or as a means of transferring tumour penetrating agents and heat through radiation[64,65].

Nanotechnology-based radiotherapy and radiofrequency therapy

The increase in radiation dose by high atomic number (Z) materials has long been of concern. Loading high Z materials into the tumour have been recorded to result in more photoelectric absorption inside the tumour than in the surrounding tissues, thus enhancing the dose given to the tumour during radiation therapy. In order to be clinically helpful, a radiosensitizer and/or dose enhancer should notably improve the therapeutic ratio and be widely available, convenient to use and non-toxic[65].

Nanotechnology-based cancer theragnostics

The combination of identification and therapy in one step is an evolving medicinal approach referred to as theragnostics. The primary aim of theragnostics is to specifically target certain (diseased tissues or cells to improve diagnostic and therapeutic precision. With the aid of theragnostics, we can bring together main phases of medical services, such as diagnosis and therapy, to make treatment shorter, safer and more reliable. Several theragnostic approaches employed nanoparticles as they were carriers of diagnostic agents and drugs. Biocompatible nanoparticles are currently being developed as theragnostic agents for cancer that would enable non-invasive identification and precise cancer therapy. Such nanoparticle-mediated combination strategies promise to boost therapy, reduce treatment side-effects and increase cancer cure rates[60].

Radiofrequency ablation

Radiofrequency ablation is a well-established approach to tumour destruction that has generally involved the insertion of probes to tumours; however, nanotechnology facilitates the generation of non-invasive radiofrequency ablation of tumor cells. Gold nanoparticles have been developed *in vitro* and *in vivo* to promote cancer cell destruction in non-invasive radiofrequency fields. Eg. Gold nanoparticles for effective cancer cell targeting. A novel, non-invasive radiowave machine was used along with gold nanoparticle enhancer solutions to thermally dissolve tissue and cancer cells in both *in vitro* and *in vivo* systems[57].

CURRENT NANOTECHNOLOGY TREATMENTS CHEMO-CHEMOTHERAPY COMBINATION THERAPY

A number of combination therapies based on nanocarriers have currently been examined, including chemo-chemotherapy combination therapy, chemo-radiotherapy combination therapy, chemo-gene combination therapy, chemo-photothermal combination therapy, and chemo-photodynamic combination therapy[20].

Chemo-Chemotherapy Combination Therapy Based on Nano-Carriers

Research suggests that MDR hinders the therapeutic results of conventional chemotherapy. MDR is complex due to several cellular resistance mechanisms, including enhanced efflux pump function, activation of drug-induced DNA damage repair, rupture of apoptotic signalling pathways and activation of detoxifying proteins. New studies are developing nanoparticles that co-deliver chemotherapeutic drugs and MDR inhibitors to reverse MDR. For example, P-gp is one of the factors for MDR, which can reduce the anticancer potency of drugs due to reduced intracellular drug concentration by pumping drugs out of cancer cells rapidly[61-63].

Chemo-Chemotherapy Combination Therapy Based on Carrier-Free Nano-Medicine

Instead of using nanocarriers, a novel carrier-free drug delivery device with high drug loading capacity, no carrier-induced toxicity, and a quick and green method has recently attracted considerable attention. Carrier-free drug delivery mechanisms are basically focused on amphiphilic drug conjugate self-assembling in nanoparticles with increased therapeutic efficacy. For example, floxuridine (FUDR) is a hydrophilic therapeutic agent with high antitumor activity against cancer metastases, which can be paired with hydrophobic chemotherapeutic agents such as bendamustine (BdM) and camptothecin (CPT) by ester bonding to achieve dual-drug amphiphilic with the ability to self-assemble into stable nanoparticles[63-65].

Chemo-Radiotherapy Combination Therapy

Radiotherapy, as well as chemotherapy, is one of the most commonly used treatments currently used to eradicate cancer cells by radiation-induced DNA disruption and cell death. However the effectiveness of radiotherapy due to its toxic side effects is insufficient. In comparison, the simple combined procedure with chemotherapy and radiotherapy often deliberately increases the toxicity of patients. To overcome this constraint, a technique is to combines chemotherapy with local radiotherapy, synergistically focusing on biocompatible and biodegradable nano-platforms. The unique properties of nanoparticles, chemo-radiotherapy combined therapy, can achieve low doses of radiation and low toxicity[65,66].

Chemo-Gene Combination Therapy

Since several genetic variants contribute to tumorigenesis, genetic heterogeneity leads to MDR, t herapeutic genes, in addition to chemotherapeutic drugs, have developed in the treatment of cancer through precise control of complex gene expression, such as MicroRNAs (miRNAs), small interference RNAs (siRNAs), short hairpin RNAs (shRNAs), and so on. duMiRNAs are small non-coding RNAs, that produce

an effect on the translation of mRNA and various biological processes since the miRNA targets various mRNAs. Thus the miRNA technique can enhance cancer therapy outcomes by controlling complex cancer-related signalling pathways and proteins[67].

Chemo-Photodynamic Combination Therapy

Photodynamic therapy (PDT) is a non-invasive cancer treatment with three major factors, including light source, photosensitizer (PS) and oxygen. Specific PS for cancer PDT are chlorines, porphyrins and phthalocyanines, some of which are synthesised to enhance PDT activity. PS is delivered to tumour sites and is activated by a light source at a certain wavelength, producing ROS (1O2, H2O2, O2*, HO*) and subsequently by programmed cell death and tumour growth suppression. Generally, the way of cell death, either apoptotic or necrotic, is determined by the sort and concentration of PS, the localization of PS in cells, the kind of cell and the light portion. Moreover, during and after PDT, sickness cells can also be prohibited by inhibiting angiogenesis because that destruction of veins and leakage of liquid and macromolecular in vessels can cause hypoxia locally. To redesign the solvency of hydrophobic PSs, lessen side effects to normal tissues and control the release of PSs to keep up amplified helpful outcomes, the use of nanocarriers to immobilize or epitomize PSs is participating in the PDT treatment. Like chemotherapeutic agents, PSs can in like manner is loaded in organic (e.g., liposomes, polymeric nanoparticles, hydrogel) and inorganic nanocarriers (e.g., quantum spots, ceramic based nanoparticles, carbon materials, metallic nanoparticles)[68].

Chemo-Photothermal Combination Therapy

In various combination treatments dependent on nanotechnology, chemo-photothermal combination treatment is an intresting issue with regards to ongoing times, on a very basic level due to the fact that photothermal treatment (PTT) is ensured and non-invasive. Endless upon irradiation of near infrared laser, PTT doesn't convert light energy into thermal energy to rise the temperature of tumor sites to eliminate the tumors, yet also upgrade the chemotherapeutic effects through after points of view: (1) the expanded temperature improves the penetrability of the cell film, gathering nanoparticles in the disease cells more effectively;(2) hyperthermia can down regulate the statement of MDR-related characteristics, for instance, P-gp and MRP, in this manner diminishing or conquering MDR malignancy cells; (3) hyperthermia can hinder the maintenance of DNA damage produced by anticancer drugs in threatening development cells, elevating the impacts of chemotherapeutic agents[69].

Theranostic Nanoparticles Based on Combination Therapy and Multimodal Imaging

The uses of imaging methods in malignant growth recognizable and management can reflect the states of diseases and the bio distribution of helpful specialists progressively and in detail. Typical imaging modalities include computed tomography (CT), positron emission computed tomography (PET/CT), single photon emission computed tomography (SPECT), Magnetic resonance imaging (MRI), ultrasound imaging (USI), photoacoustic imaging (PA), and fluorescence imaging (FI).To increment the imaging contrast, specific agents are applied in various imaging methodology. To be specific, contrast agents with high electron thickness and nuclear number, for example, AuNPs, barium and iodine compounds are utilized

extensively as CT contrast specialists. Nanoparticles named with 18F, 124I and 64Cu or named with 125I and 125Cd can go about as PET or SPECT contrast agents to raise the picture contrast. Moreover, for MRI, paramagnetic agents (e.g., Gd3+, Mn2+, or Fe3+-based agents) and SPIONs improve the differentiation of T1 and T2 independently. Regular USI contrast agents are microbubbles which can encapsulate remedial specialists to acknowledge analysis and treatment[70].

Table1: Approved nanotechnology based Cancer drug therapy[21]

Nanomaterials	Drug	Used in the management of
Nanoparticles	Paclitaxel	Breast cancer, Pancreatic cancer, lung cancer
Liposomes	Daunorubicin	Kaposi's sarcoma
Liposomes	Cytarabine	Neoplastic meningitis
Liposomes	Doxorubicin	Kaposi's sarcoma, Ovarian and breast cancer
PEG-PLA polymeric micelle	Paclitaxel	Breast, lung and ovarian cancer
Liposomes	Vincristine	Acute lymphoid leukemia
Liposomes	Mifamuride	Osteosarcoma
Liposomes	Irinotecan	Pancreatic cancer

CONCLUSION

The use of nanotechnology inside the field of cancer technology has completely fledged exponential development within the previous few years. Various sorts of nanocarriers are examined that has permitted scientists to defeat constraints of standard chemotherapy by increasing the solubility of the free medication and diminishing the toxicity to the healthy tissues. As a result of the advancement inside the improvement of multifunctional nanocarriers, drug stacked in nanocarriers will explicitly be focused to the disease site by means of passive and active targetting. Reasonably designed nanocarriers could evade renal clearance, which permits them to circulate in the framework for an extended period. The limitation of antineoplastic medication has been improved by the utilization of nanocarriers, yet, new difficulties have emerged. Nanoparticles offer opportunities for planning and tuning properties that are not feasible with various types of remedial medicine and have demonstrated they need a splendid future as another age of malignant growth therapeutics. The multidisciplinary field of innovation holds the promise of delivering a mechanical advancement and is moving in a matter of moments from idea to the real world.

Conflicts of Interest

The authors declare that there are not any conflicts of interest relating to the publication of this paper.

References

1. Chakraborty M, Jain S, Rani V. Nanotechnology: emerging tool for diagnostics and therapeutics. Applied Biochemistry and Biotechnology 2011; 165: 1178-1187.
2. Nguyen K.T. Targeted Nanoparticles for Cancer Therapy: Promises and Challenges, J. Nanomed. Nanotechnol 2011; 2: 1-2.
3. Nie S, Xing Y, Kim G.J, Simons J.W. Nanotechnology applications in cancer. Annu. Rev. Biomed. Eng. 2007; 9: 257-288.
4. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. Cancer J Clin 2010; 60: 277–300.
5. Sahoo S, Parveen S, Panda J. The present and future of nanotechnology in human health care. Nanomed. Nanotechnol. Biol. Med. 2007; 3: 20-31.
6. Sutradhar K.B, Amin M.L. Nanotechnology in cancer drug delivery and selective targeting. ISRN Nanotechnol. 2014.
7. Bharali D.J, Mousa, S.A. Emerging nanomedicines for early cancer detection and improved treatment: current perspective and future promise. Pharmacol. Ther 2010; 128: 324-335.
8. Farokhzad O.C, Langer R. Impact of nanotechnology on drug delivery. ACS Nano 2009; 3: 16–20.
9. Vanna S, Nicolino P, Mario S. Targeted therapy using nanotechnology: Focus on cancer. Int. J. Nanomed. 2014; 9: 467–483.
10. Stewart BW, Coates AS. Cancer prevention: a global perspective. J ClinOncol 2005; 23(2): 392-403
11. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nat Rev Cancer 2005; 5(3): 161-71
12. Luo J, Solimini NL, Elledge SJ. Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 2009; 136: 823–37.
13. Ferrari, M. Cancer nanotechnology: opportunities and challenges. Nat. Rev. Cancer 2005; 5: 161–171
14. Siegel R, Miller K, Jemal A. Cancer statistics, 2018 CA: a cancer. J. Clin. 2017; 68: 7-30.
15. Cho K, Wang X, Nie S, Shin D.M. Therapeutic nanoparticles for drug delivery in cancer. Clin. Cancer Research 2008; 14: 1310-1316.
16. Davis M.E, Shin D.M. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nat. Rev. Drug Discov. 2008; 7: 771.
17. Torchilin V.P. Targeted pharmaceutical nanocarriers for cancer therapy and imaging. AAPS J. 2007; 9: 128-147.
18. Riccardo R, Sara G, Palol C, Salvatore P, Macro A. Nanovectors design for theranostic applications in colorectal cancer. Journal of Oncology. 2019; 2019:1-27.
19. Deshpande P.P, Biswas S, Torchilin, V.P. Current trends in the use of liposomes for tumor targeting. Nanomedicine 2013; 8: 1509-1528.

20. Kulshrestha P, Gogoi M, Bahadur D, Banerjee R. In vitro application of paclitaxel loaded magnetoliposomes for combined chemotherapy and hyperthermia. Colloids Surf, B: Biointerfaces 2011; 96: 1-7.
21. Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy:challenges, opportunities, and clinical applications. J Control Release. 2015; 200: 138-57.
22. Li X, Ding L, Xu Y, Wang Y, Ping Q. Targeted delivery of doxorubicin using stealth liposomes modified with transferrin. Int. J. Pharm. 2009; 373: 116-123.
23. Li N, Larson T, Nguyen H.H, Sokolov K.V, Ellington A.D. Directed evolution of gold nanoparticle delivery to cells. Chem. Commun. 2010; 46: 392-394.
24. Du H, Cui C, Wang L, Liu, H, Cui, G. Novel tetrapeptide, RGDF, mediated tumor specific liposomal doxorubicin (DOX) preparations. Mol. Pharm. 2011; 8: 1224-1232.
25. Pérez-Herrero E. Fernández-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. Eur. J. Pharm. Biopharm. 2015; 93: 52–79.
26. Davis M.E, Zhuo G.C, Dong M.S. Nanoparticle therapeutics: An emerging treatment modality for cancer. Nat. Rev. Drug Discov. 2008; 7: 771–782.
27. Jadia R, Scandore C, Rai P. Nanoparticles for Effective Combination Therapy of Cancer. Int. J. Nanotechnol. Nanomed. 2016; 1.
28. Shishu M.M, Maheshwari M. Dendrimers: the novel pharmaceutical drug carriers. IJPSR 2009; 2: 493-502.
29. Basile L, Pignatello R, Passirani C. Active targeting strategies for anticancer drug nanocarriers. Current Drug Delivery 2012; 9: 255-268.
30. Peer D, Karp JM, Hong S, et al. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2007; 2(12): 751-60
31. Peer D, Karp JM, Hong S. Nanocarriers as an emerging platform for cancer therapy. Nat Nanotechnol 2007; 2 :751–60.
32. Kwon GS. Polymeric micelles for delivery of poorly water-soluble compounds. Crit Rev Ther Drug Carrier Syst 2003; 20: 357–403.
33. Luo Y, Prestwich G. Cancer-targeted polymeric drugs. Curr Cancer Drug Targets 2002; 2: 209–26.
34. Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 2012; 64: 206–12.
35. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 2002; 54: 631–51.
36. Byrne J.D, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. Adv. Drug Deliv. Rev. 2008; 60: 1615-1626.
37. Cho K, Wang X, Nie S, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clin Cancer Res 2008; 14: 1310–16.
38. Parveen S, Sahoo, S.K. Polymeric nanoparticles for cancer therapy. J. Drug Target. 2008; 16: 108–123

39. Bharali, D.J. Nanoparticles and cancer therapy: a concise review with emphasis on dendrimers. Int. J. Nanomed. 2009; 4: 1–7
40. Shah M.R, Imran M, Ullah S. Chapter 8—Liposomes for targeted drug delivery in cancer therapy. Lipid-Based Nanocarriers for Drug Delivery and Diagnosis. William Andrew Publishing 2017.
41. Chen Q, Ke H, Dai Z, Liu Z. Nanoscale theranostics for physical stimulus-responsive cancer therapies. Biomaterials 2015; 73: 214–230.
42. Ardim G, Lima D, Valença W, Lima D, Cavalcanti B, Pessoa C, Rafique J, Braga A, Jacob C, da Silva Júnior E. Synthesis of Selenium-Quinone Hybrid Compounds with Potential Antitumor Activity via Rh-Catalyzed C-H Bond Activation and Click Reactions. Molecules 2017; 23: 83.
43. Gerber D.E. Targeted therapies: a new generation of cancer treatments. Am. Fam. Physician 2008; 77: 311-319.
44. Ranjita M, Sarbari A, Sanjeeb K. Cancer technology: application of nanotechnology in cancer therapy. Drug discovery today. 2010; 15:842-850
45. Liu D, Yang F, Xiong F, Gu N. The smart drug delivery system and its clinical potential. Theranostics 2016; 6: 1306.
46. Chow E.K, Ho D. Cancer nanomedicine: From drug delivery to imaging. Sci. Transl. Med. 2013; 5: 216
47. Zheng M.B, Zhao P.F, Luo Z.Y, Gong P, Zhang P.F, Sheng Z.H, Gao G.H, Cai L.T. The application of nanotechnology in cancer theranostics. Chin. Sci. Bull. 2014; 59: 3009–3024.
48. Xu X, Ho W, Zhang X, Bertrand N, Farokhzad O. Cancer Nanomedicine: From Targeted Delivery to Combination Therapy. Trends Mol. Med. 2015; 21: 223–232.
49. Ma, L.; Kohli, M.; Smith, A. Nanoparticles for Combination Drug Therapy. ACS Nano 2013, 7: 9518–9525.
50. Nehoff H, Parayath NN, Domanovitch L, et al. Nanomedicine for drug targeting: strategies beyond the enhanced permeability and retention effect. Int J Nanomedicine 2014; 9: 2539–55.
51. Hu C.-M.J, Zhang, L. Nanoparticle-based combination therapy toward overcoming drug resistance in cancer. Biochem. Pharmacol 2012; 83: 1104-1111.
52. Jabir N.R, Tabrez S, Ashraf G.M, Shakil, S, Damanhouri G.A, Kamal. Nanotechnology-based approaches in anticancer research. Int. J. Nanomed. 2012; 7: 4391.
53. Wang, X. Application of nanotechnology in cancer therapy and imaging. CA Cancer J. Clin 2008; 58: 97–110
54. Jere, D. Chitosan-graft-polyethylenimine for Akt1 siRNA delivery to lung cancer cells. Int. J. Pharm. 2009; 378: 194–200
55. Peng C.L. Development of pH sensitive 2-(diisopropylamino) ethyl methacrylate based nanoparticles for photodynamic therapy. Nanotechnology 2010; 21: 155103
56. Chang M.Y. Increased apoptotic potential and dose-enhancing effect of gold nanoparticles in combination with single-dose clinical electron beams on tumor-bearing mice. Cancer Sci. 2008; 99: 1479–1484

57. Cardinal, J. Noninvasive radiofrequency ablation of cancer targeted by gold nanoparticles. Surgery 2008; 144: 125–132
58. Lukianova-Hleb, E.Y. Tunableplasmonicnanobubbles for cell theranostics. Nanotechnology 2010; 21: 85102
59. Shubayev, V.I. Magnetic nanoparticles for theragnostics. Adv. Drug Deliv. Rev. 2009; 61: 467–477
60. Shim, M.S. Combined multimodal optical imaging and targeted gene silencing using stimuli-transforming nanotheragnostics. J. Am. Chem. Soc. 2010; 132: 8316–8324
61. Chen Yang Zaho, Rui Cheng, Zhe Yang, Zhong Min Tian. Nanotechnology for cancer therapy based on chemotherapy. Molecules 2018; 23: 826, 1-29
62. Tian, L,Chen Q, Yi X, Wang G, Chen, J Ning P, Yang K, ,Liu, Z. Radionuclide I-131 Labeled Albumin-Paclitaxel Nanoparticles for Synergistic Combined Chemo-radioisotope Therapy of Cancer. Theranostics2017; 7: 614–623.
63. Zulkifli A.A, Tan F.H, Putoczki T.L, Stylli S.S, Luwor R.B. STAT3 signaling mediates tumour resistance to EGFR targeted therapeutics. Mol. Cell. Endocrinol. 2017; 451: 15-23.
64. Zhou L, Wang H, Li Y. Stimuli-responsive nanomedicines for overcoming cancer multidrug resistance. Theranostics 2018; 8: 1059.
65. Chen F, Zhao Y, Pan Y, XueX, Zhang X, Kumar A, Liang X.-J. Synergistically Enhanced Therapeutic Effect of a Carrier-Free HCPT/DOX Nanodrug on Breast Cancer Cells through Improved Cellular Drug Accumulation. Mol. Pharm. 2015; 12: 2237–2244.
66. Mi Y, Shao Z, Vang J, Kaidarperson, O Wang, A.Z. Application of nanotechnology to cancer radiotherapy. Cancer Nano 2016: 7, 11.
67. Zhang M, Liu E, Cui Y, Huang Y. Nanotechnology-based combination therapy for overcoming multidrug-resistant cancer. Cancer Biol. Med. 2017; 14: 212–227.
68. Rajesh S, Koshi E, Philip K, Mohan A. Antimicrobial photodynamic therapy: An overview. J. Indian Soc. Periodontol. 2011; 15: 323–327.
69. Wang Xu, H Liang, C Liu, Y, Li, Z Yang, G Cheng, L Li, Y, Liu Z. Iron Oxide @ Polypyrrole Nanoparticles as a Multifunctional Drug Carrier for Remotely Controlled Cancer Therapy with Synergistic Antitumor Effect. ACS Nano 2013; 7: 6782–6795.
70. Elgqvist J. Nanoparticles as Theranostic Vehicles in Experimental and Clinical Applications-Focus on Prostate and Breast Cancer. Int. J. Mol. Sci. 2017; 18: 1102.
71. R Bashary, M Vyas, SK Nayak, A Suttee, S Verma, R Narang, G. K. An Insight of Alpha-amylase Inhibitors as a Valuable Tool in the Management of Type 2 Diabetes Mellitus. *Curr. Diabetes Rev.* **16**, 117–136 (2020).
72. N Choudhary, GL Khatik, A. S. The possible role of Saponin in Type-II Diabetes-A review. *Curr. Diabetes Rev.* (2020). doi:DOI: 10.2174/1573399816666200516173829
73. Subba Rao Chamakuri, Ashish Suttee, P. M. AN EYE-CATCHING AND COMPREHENSIVE REVIEW ON PLUMERIA PUDICA JACQ.(BRIDAL BOUQUET). *Plant Arch.* **20**, 2076–2079 (2020).

74. Neeraj Choudhary, Kirti. S. Prabhu, Shyam Babu Prasad, Amritpal Singh, Udai Chand Agarhari, A. S. PAST ISSUES EDITORIAL BOARD FOR AUTHORS MORE NEWS Search search Submit Article Phytochemistry and Pharmacological exploration of Chenopodium album: Current and future perspectives. *Res. J. Pharm. Technol.* **13**, (2020).
75. Shukla, A. *et al.* Ecotoxicology and Environmental Safety Global trends in pesticides : A looming threat and viable alternatives. *Ecotoxicol. Environ. Saf.* **201**, 110812 (2020).
76. Choudhary, N. *et al.* Phytochemistry and pharmacological potential of *Operculina turpethum*. *Plant Arch.* **20**, 683–692 (2020).
77. Khanna, V., Sriram, P., Singh, A., Singh, G. & State, T. Novel drug delivery system for herbal drugs- AND. 293–306 (2019).
78. Singh G., Suttee A., Barnwal RP. , Singla N. , Sharma A. , Chatterjee M., Kaura G., C. V. and M. V. INVESTIGATION OF IN VITRO ANTHELMINTIC ACTIVITY OF CAESALPINIA PULCHERRIMA LEAVES. *Plant Arch.* **19**, 4527–4530 (2019).
79. Manishaben Jaiswal, "COMPUTER VIRUSES: PRINCIPLES OF EXERTION, OCCURRENCE AND AWARENESS ", International Journal of Creative Research Thoughts (IJCRT), ISSN:2320-2882, Volume.5, Issue 4, pp.648-651, December 2017, http://doi.one/10.1729/Journal.23273 Available at http://www.ijcrt.org/viewfull.php?&p_id=IJCRT1133396
80. Mishra, V., Chanda, P., Tambuwala, M. M. & Suttee, A. Personalized medicine : An overview. *Int. J. Pharm. Qual. Assur. 2019;* **10**, 290–294 (2019).
81. Mishra, V. *et al.* Biomedical Potential of Graphene oxide based Nanoformulations : An Overview. *Int. J. Drug Deliv. Technol.* **9**, 109–113 (2019).
82. Suttee, A. & Singh, A. Siegesbeckia orientalis- valuable but less known ethno medicinal plant. *Jouranal Herb. Med. Toxicol.* **4**, 115–116 (2010).
83. Amini, M. H. *et al.* Phytochemical screening and antioxidant activity of *Heracleum afghanicum* Kitamura leaves. *Res. J. Pharm. Technol.* **10**, 3498–3502 (2017).
84. Amini, M. H., , Vandna Kalsi , Barinder Kaur, R. L., Singh, G. & , Anupam Sharma , Manish Vyas1, A. S. Assessment of Assessment of in vitro anthelmintic activity of *Heracleum afghanicum* Kitamura. *Int. J. Green Pharm.* **11**, 86–88 (2017).
85. Singh, A., Duggal, S., Singh, J. & Katekhaye, S. Eclipta alba Linn. ancient remedy with therapeutic potential. *Int. J. Phytopharm.* **1**, 57–63 (2010).
86. Ashish Suttee1, Gurpal Singh2, Nishika Yadav1, Ravi Pratap Barnwal3, Neha. Singla3, Kirti. S. Prabhu4, V. M. A Review on Status of Nanotechnology in Pharmaceutical Sciences Ashish. *Int. J. Drug Deliv. Technol.* **9**, 98–103 (2019).
87. Manishaben Jaiswal "Big Data concept and imposts in business" International Journal of Advanced and Innovative Research (IJAIR) ISSN: 2278-7844, volume-7, Issue- 4, April 2018 available at: http://ijairjournal.in/Ijair_T18.pdf
88. V, S. *et al.* Antimicrobial Evaluation of *Caesalpinia decapetala*. *Int. J. Pharmacogn. Phytochem. Res.* **9**, 1421–1424 (2018).

89. Kaur, G., Prabhakar, P. K., Lal, U. R. & Suttee, A. Phytochemical and biological analysis of *Tinospora cordifolia*. *Int. J. Toxicol. Pharmacol. Res.* **8**, (2016).
90. Choudhary, A. *et al.* EGCG: The shield against genotoxicity caused by Cisplatin. *Int. J. Pharmacogn. Phytochem. Res.* **8**, (2016).
91. Kaur, H., Amini, M. H., Singh, A. & Sutte, A. Phytochemical Screening and Antimicrobial Activity of *Caesalpinia sappan* L. Leaves. *Int. J. Pharmacogn. Phytochem. Res. 2016; 8(6); 1040-1045* **10**, 512–518 (2011).
92. Manishaben Jaiswal " SOFTWARE QUALITY TESTING " International Journal of Informative & Futuristic Research (IJIFR) , ISSN: 2347-1697 , Volume 6, issue -2 , pp. 114-119 ,October-2018 Available at: http://ijifr.com/pdfsave/23-12-2019214IJIFR-V6-E2-23%20%20OCTOBER%202018%20a2%20files%20mergeda.pdf
93. Harjit, K., Amini, M. H. & Suttee, A. Evaluation of antioxidant and anthelmintic properties of *Caesalpinia sappan* L. Leaves. *Int. J. Pharmacogn. Phytochem. Res.* **8**, 362–368 (2016).
94. Singh, A., Duggal, S. & Suttee, A. *Acanthus ilicifolius* Linn.-Lesser Known Medicinal Plants with Significant Pharmacological Activities. *Int. J. Phytomedicine* **1**, 1–3 (2009).
95. Sharma, A., Kalsi, V., Suttee, A., Mukhtar, H. M. & Kaur, B. Standardization of an Ayurvedic Formulation-Maharasnadi Kvatha Churna. *Res. J. Pharm. Technol.* **11**, 1220 (2018).
96. Kishore, H., Kaur, B., Kalsi, V. & Suttee, A. Effect of Ethanolic Extract of Spondias pinnata on Ischemia- Reperfusion Injury and Ischemic Preconditioning of Heart. *Int. J. Pharmacogn. Phytochem. Res.* **8**, 865–870 (2016).
97. Disha Arora, Richa Shri, Sourav Sharma, A. S. Phytochemical and Microscopical Investigations on. *Int. J. Curr. Pharm. Rev. Res.* **3**, 54–59 (2012).
98. Rana, S. & Suttee, A. Phytochemical investigation and evaluation of free radical scavenging potential of *Benincasa hispida* peel extracts. *Int. J. Curr. Pharm. Rev. Res.* **3**, 43–46 (2012).
99. Sharma, V. *et al.* Biological and Phytochemical Studies on the leaves of *Caesalpinia decapetala* (Roth) . *Res. J. Pharm. Technol.* **10**, 4005 (2018).
100. Singh, A., Ashish, S. & Katekhaye, S. Rajpatha Ethno medicine of Controversial Origin. *Int. J. Curr. Pharm. Rev. Res.* **3**, 86–90 (2012).
101. Ashish Suttee, Geeta Kaura, Anupam Sharma, D. A. In vitro Anthelmintic study of *Caesalpinia bonduc*. *Can. J. Pure Appl. Sci.* **5**, 1505–1507 (2017).
102. Ashish Suttee, Geeta Kaura, Anupam Sharma, Disha Arora, Mandeep Singh, Saurabh Sharma, S. R. Phytochemical screening of *Caesalpinia bonduc*. *Can. J. Pure Appl. Sci.* **5**, 1631–1636 (2011).


JETIR