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State-of-the-art strategies in the development of cyclic peptide functionalized nanostructures for cancer chemotherapy

Muhammad Jahangeer[1], Zahed Mahmood[1], Sarmad Bashir[1], Sabahat Gulzar[1], Shoukat Hussain[1], Sarmad Ahmad Qamar*[2], Areej Riasat[1]

[1]*Department of Biochemistry, Government College University, Faisalabad, Pakistan*

[2]*Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan*

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Abstract

Nanobiotechnology is an emerging field in which nanoscale tools are developed for various functionalized biomedical and industrial applications including the targeted release of therapeutic drug molecules. These nanostructures are preferred as they can precisely attack the target site either actively or passively through metabolic barriers without affecting normal cells/tissues of living body. Cancer is a multifactorial disease which involves tissue malignancy and rapid cellular proliferation, leading towards the failure of normal pathophysiological functioning of tissues. Various types of cancers are being treated by chemotherapy, radiotherapy and debulking surgery (partial and/or complete removal of cancer cells). These methods have some limitations such as cancer resistance due to drug inactivation, apoptosis suppression (cell death inhibition), multi-drug resistance and modification in drug metabolism. Through the development of target specific functionalized particles, nanobiotechnology paved new road for cancer chemotherapy. Self-assembled peptides are less immunogenic and specific to their target site with ability to inhibit process of angiogenesis, hence, can be used for the engineering of functionalized nanostructures for cancer treatment. This review summarizes various cyclic peptides types (cediranib, abraxane, cilengitide, buserelin, cisplatin, cetrorelix, gemcitabine and triptorelin) that are being used for the treatment of various cancer types. Progress in nanotherapeutics will enhance the drug efficacy with tremendously reduced side effects due to cell-specific targeting leading to the better outcome in personalized oncology.

* **Corresponding Author:** Sarmad Ahmad Qamar ✉ sarmad_qamar@uaf.edu.pk

Introduction

Cancer is one of the globally leading causes of mortality and morbidity. According to global cancer statistics 2018, cancer is the second major cause of death due to diseases (Bray *et al.,* 2018). The incidences of cancer are increasing, with a decreased life expectancy and deterioration of the global ecosystem. It has been expected that the number of new cases would reach 23.6 million in 2030 (Stewart and Wild, 2015). In cancer, alteration of the cellular mechanisms that regulate cellular proliferation and gene expression take place mostly due to mutations and other epigenetic modifications. The tumor's growth rate, severity of disease and metastatic potential depends upon the specific cell types. However, other factors also involve in the development of cancer e.g., the hormonal imbalance or immunity characteristics and their complexities. The progress in future personalized oncology has not been explained into a prominent advancement of its incidence including potential side-effects which serve as major cause towards improper cancer treatment. This review aims to highlight the current trends and future perspectives in cyclic peptide functionalized nanostructures for cancer chemotherapy.

Self-assembled polypeptide chains that are arranged in the form of a ring are called cyclic peptides. This cyclic conformation can be obtained by joining both ends of the peptide chain by an ether, sulfide or amide linkage. Naturally occurring cyclic peptides include cyclosporin, gramicidin and vancomycin which are immunosuppressive and bactericidal agents. Various cyclic peptides can also be obtained from peptide hormones like somatostatin, oxytocin, vasopressin and calcitonin. Synthetic cyclic peptides can be obtained by organic synthesis or solid phase synthesis. These peptides initiate apoptosis of angiogenic blood vessels; hence, they facilitate tumor reversion.

Arginylglycylaspartic acid (RGD) peptide is a synthetic cyclic peptide. Improvements in the structure of cyclic RGD peptide were made by Mas-Moruno *et al.,* 2010. These improvements resulted into the formation of RGDfV. Then, cyclic (RGDf[NMe]V) was developed by N-methylation which increased its action and made it more stable (Zhou *et al.,* 2011). Peptides are preferred over small synthetic particles because they are not stored in tissues and are less toxic because they split into amino acid due to proteolysis. Due to this cyclic conformation, cyclic peptides are not affected by hydrolysis because amino and carboxyl termini are not present on outer surface resulting in the direct attach onto the target site. Cyclic peptides can easily cross the membranes as compared to the linear peptides (Joo, 2012). Cyclic peptides have a rigid structure, specific to the receptor and biologically stable substances. Due to these characteristics, peptides are best therapeutic agents. Scientists are trying to synthesize more cyclic peptides.

Cancer chemotherapy

Depending upon the tumor stage, treatment often involve chemotherapy or sometimes the chemotherapy combined radiotherapy and debulking surgery. Several important mutations such as epidermal growth factor receptor (EGFR), p53 and c-Myc that contribute to carcinogenesis were discovered (Hermeking and Eick, 1994). These have been extensively used as targets for the production of more selective drugs to tackle cancer prognosis. Though these drugs are much effective but, multidrug resistance has been increasing, which often results in low quality of life for patients and tumor deterioration (Miller *et al.,* 2016). As these methods spare surrounding normal tissue, through which ionizing radiation could easily cross, hence, these methods are challenging for the delivery of a therapeutic drug to tumor cells.

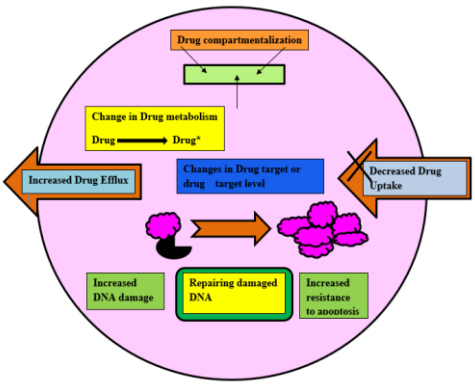

Fig. 1. General mechanisms of drug resistance in the cancer cells.

Development of resistance through different cancer treatment mechanism is the main difficulty in the treatment of cancerous cells. Several mechanisms include, drug inactivation, multi-drug resistance, apoptosis suppression, enhance DNA repair, epigenetic and drug targets, drug metabolism changes and amplification of gene that cause the resistance to the chemotherapy. General mechanism of drug resistance in cancerous cells has presented in Fig. 1. Cancer resistance can be categorized into intrinsic and acquired, depending upon the initial tumor response to a treatment:

(a) Intrinsic resistance: the resistance due to internal tumor structure before the therapy. The tumor will be resilient even before treatment.

(b) Acquired resistance: it produces in response to the particular therapy. In this case, the bulk of the tumor is eliminated, and its size is initially reduced. Until the treatment is finished some clones undergo evolution and resistance is developed in them as well as remain latent, and then are expanded to regenerate the tumor.

Intrinsic resistance is shown by some tumor types in Fig. 1. Moreover, attacking the tumor may train it as it will increase its resistance as well as will make it more robust, that is happened with bacteria when antibiotic treatment is disturbed before completeness (Livney and Assaraf, 2013).

Functionalization and cell-specific targeting

A current challenge in nanotherapeutics is the production of nanostructures that can selectively target the particular cell-types. This would decrease the potential side effects and would raise drug efficacy. Passive targeting relies on the fact that tumors have different pH, leaky vasculature with different local temperature, and have less efficient lymphatic drainage system (Upreti *et al.,* 2013). For instance, lipid-based nano vectors can passively enter lymphatic circulation and reach tumor sites efficiently as presented in Fig. 2(A). Passive targeting, although, have several limitations, such as difficulty in controling the process, which may lead to multi-drug resistance and non specific accumulation in spleen and liver (Barua and Mitragotri, 2014). Some of these drawbacks have been resolved by targeted drug delivery, permitting the transfer of drug to specific tumor cells. Qamar *et al.,* (2019) [in press] described the production of nanobiocomposites for sustainable and functional biomedical applications. This can be attained by the following two different methods i.e., triggered and active release of the drug as shown in Fig. 2 (B and C) (Martinelli *et al.,* 2019).

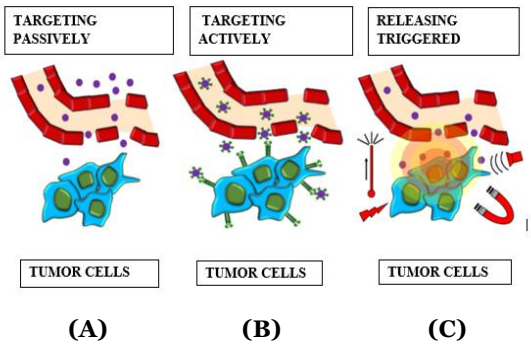

Fig. 2. Functionalization of nanocarriers (A) passive targeting (B) active targeting (C) Triggered release of therapeutic drug molecules.

Types of nanostructures for cancer-specific targeting

Nanoparticles comprise a number of materials that include metals, polymers and ceramics. Depending upon their development strategies and materials used, these particles can assume diverse sizes and shapes with well-defined properties. Nanocarriers that are used in chemotherapy are categorized into two major types that are designed for non-targeted or targeted drug delivery vehicles that use organic molecules as major building blocks and those that use inorganic elements (usually metals) as a core are inorganic. Organic nanocarriers include lipid nanoparticles, liposomes dendrimers, synthetic polymers and nanoemulsions. Inorganic nanocarriers have been extensively investigated in past few years for therapeutic treatments because they have great advantages such as large surface area, better bioavailability, tolerance towards most organic solvents, lower toxic side effects, better drug loading capacity and controlled drug release unlike polymer-based nanoparticles (Rani *et al.,* 2019). Inorganic nanocarriers include quantum dots, magnetic nanoparticles, layered double hydroxides, mesoporous silica nanoparticles and carbon nanotubes.

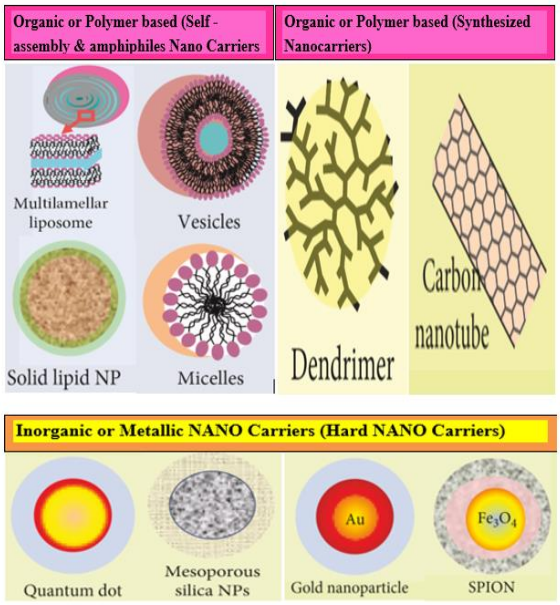

Fig. 3. Types of organic and inorganic nanocarriers for application in therapeutic drug delivery.

Inorganic nanocarriers

Quantum dots

Quantum dots have negligible photo bleaching, unique absorption and emission spectra, stable fluorescence and because of these characteristics they are ideal tool for cancer imaging. They have been combined with streptavidin-IgG for detection of intra- and/or extracellular compounds and are more photostable than classical fluorescent molecules. Anti-HER2 antibody and PEGylated quantum dots were conjugated and confined in particular cancerous cells (Malik *et al.,* 2013).

SPIONs

Super paramagnetic iron oxide nanoparticles (SPIONs) have intrinsic magnetism and can be visualized by MRI. Therefore, they have been used for diagnosis of cancer (Yu *et al.,* 2008). Dextran-coated SPIONs have been used as MRI contrast agents for *in vitro* and *in vivo* applications by functionalization with specific ligands (You *et al.,* 2014; Barrow *et al.,* 2015). Magnetic nanoparticles conjugated to chemotherapeutics and fluorophores are applied to visualize cancer cells and simultaneously kill them (Chinen *et al.,* 2015).

Gold nanoparticles

Gold nanoparticles are being studied to elevate the drug therapeutic effects (Pantiushenko *et al.,* 2015). Most studies suggest that DNA is indirectly damaged by free hydroxyl radicals and directly damaged by electrons. But recent *in vitro* and *in vivo* studies have demonstrated that the incorporation of gold nanoparticles into current radiotherapy protocols produces better results (Han *et al.,* 2006). Nanoparticles which are intravenously vaccinated can accumulate within the cancer cells by using its leaky vasculature and finally creep into the individual cancer cells (Lu *et al.,* 2006).

Carbon nanotubes

Carbon nanotubes (CNTs) are synthetic materials and structurally contain rolled sheets of graphene rings which are built from sp2 hybridized carbon atoms into hollow tubes. CNTs increase the temperature within tumors as a function of light intensity and CNT dose and are ideal for near infrared photothermal ablation therapy (Ji *et al.,* 2010; Khan *et al.,* 2012). Functionalized water-soluble CNTs can readily cross biological barriers and transport molecules into the cytoplasm effectively without any toxic effect and therefore they are being explored for their use in gene and drug delivery (Fadel *et al.,* 2014).

Organic nanocarriers

Dendrimers

A new and unique type of nanoparticles have been developed for carrying drugs to the target site are dendrimers which are manufactured in a step by step and repeated process. These have extremely branched globular structure. Dendrimer comprises coatings of branched chain repeating units, originator core and outer layer has functional end groups. Due to these characteristics dendrimers simultaneously transport both hydrophobic and hydrophilic drugs (Tucker, 2006). Water soluble drugs are attached on surface while water insoluble drugs are packed in a film inside the core. A well-known dendrimer is 5 poly(propyleneimine) in which all-trans retinoic acid (water soluble) and methotrexate (water insoluble) are transported collectively.

Polymer micelle

Micelle-like nanocarriers are obtained by the self-assembly of amphiphilic polymers and the micelles' hydrophobic core establishes a microenvironment for the fusion of lipophilic active compounds (drugs), contributing in significantly improved bioavailability at the same time, the hydrophilic shell replenishes a stabilizing interface between the hydrophobic core and the aqueous medium, inhibiting aggregation and unwanted interactions and enhancing the colloidal stability (Mikhail and Allen, 2009).

Table 1. Dendrimers for combination cancer therapy.

Formulation	Drugs	Indication	Status	References
Generation-3 poly(l-lysine) octa 3 (amiopropyl) silsequioxane dendrimer	Doxorubicin and siRNA	Glioblstoma	*In vitro*	Kaneshiro and Lu, 2009
Generation-5 poly(propyleneimine) dendrimer with ethylenediamine core	Methotrexate and all-trans retinoic acid	Leukemia	*In vitro*	Tekade *et al.,* 2009
Generation-4 polyamidoamine dendrimers	Methotrexate and all-trans retinoic acid	Leukemia	*In vitro*	Tekade *et al.,* 2009

Liposomes

Liposomes are self-assembled nanoparticles, consist of closed membrane structures. Their hydrophobic membranes and inner compartments are used for the incorporation of hydrophilic agents (Andresen *et al.,* 2005). Two distinct techniques are applied for encapsulation of drug into liposome. In the first method, hydrated lipid layers are obtained by liquefication of drug in liquid media and drug carrier multi-lamellar is produced that can be converted into uni-lamellar liposomes by passing through filters of fixed pore size (Batista *et al.,* 2015; Rani *et al.,* 2019). In second method, uni-lamellar liposomes are synthesized firstly and then allowed to cultivate in aqueous drug solution. The drug particles can pass through liposomal membrane inactively when aqueous cavity is concentrated. Then for separation of unpacked drug from drug carrier liposome solution, centrifugation, column chromatography, and dialysis are performed. According to their structural arrangement, hydrophilic drugs are packed in lipid bilayer membrane and hydrophobic drugs are carried out in aqueous core of liposome and are efficiently used for combined drug delivery (Zhang *et al.,* 2007).

Solid-lipid nanoparticles

These nanostructures are colloidal, spherical in shape, biocompatible, target specific, less toxic and have size range b/w 50 and 100 nm. They consist of a solid lipid core which is stabilized by an interfacial surfactant layer and can improve drug bioavailability and stability of the entrapped compounds. Several lipids such as highly purified triglycerides, fatty acids, waxes and complex glyceride mixtures can be used for the production of SLNs. Kuang and coworker produced targeted SLNs to tumor angiogenic vessels, which encapsulate the IR-780 iodide dye to monitor PTT by NIR imaging. Pre-clinical studies demonstrated their capability as efficacious drug carrier for paclitaxel in the treatment of lung cancer (Kuang *et al.,* 2017).

Polymeric nanoparticles

Improvements in the field of biomedical research have directed the development of decomposable and recyclable polymeric nanoparticles for carrying drug to the target site. Numerous artificial polymers are issued by FDA (USA) like polycaprolactone and poly lactic glycolic acid. Various natural polymers like polysaccharides and chitosan have been examined comprehensively for manufacturing nanoparticles. Polymeric nanoparticles usually have intense size delivery, continual and well-regulated drug deliverance, adaptable physiochemical characteristics, greater permanence and the drugs which are less soluble are greatly packed.

As polymer nanoparticles are synthesized artificially, they can be designed according to the requirement. Due to such outstanding features polymeric nanoparticles are widely used for biomedical and industry applications. Polymeric nanoparticles usually comprise of amphiphilic diblock copolymer which arrange automatically into nanoparticles in aqueous solution (Song *et al.,* 2009).

Table 2. Polymeric nanoparticles and polymer drug delivery conjugates for cancer therapy.

Formulation	Drugs	Indication	Status	References
HPMA-Gem-Dox	Gemcitabine and Doxorubicin	Prostate cancer and various cancer types	*In vivo*	Lammers *et al.,* 2009
Polyethylene glycol Poly (Aspartate hydrazide) block copolymer-Dox-Wor	Doxorubicin and phosphatidylinositol-3 kinase inhibitor	Breast cancer and various cancer types	*In vitro*	Bae *et al.,* 2017
Combretastatin-doxorubicin naocell	Combretastatin and doxorubicin	Lung carcinoma, Melanoma and various cancer types	*In vivo*	Sengupta *et al.,* 2005
Cationic core-shell nanoparticle	Paclitaxel and Bcl-2 targeted siRNA	Brest cancer	*In vitro*	Wang *et al.,* 2006
PDMAEMA-Bcl-based cationic micelles	Paclitaxel and VEGFs siRNA	Prostate cancer and various cancer types	*In vitro*	Zhu *et al.,* 2010
Nanoparticle-Aptamer bioconjugates	Doxorubicin and Docetaxel	Prostate cancer and various cancer types	*In vitro*	Zhang *et al.,* 2007
Poly(lactic-co-glycolic acid) nanoparticle co-encapsulating vincristine and verapamil	Vincristine and Verapamil	Breast cancer	*In vitro*	Song *et al.,* 2009
Polyalkylcyanocrylate nanoparticles co-encapsulating doxorubicin and cyclosporine A	Doxorubicin and cyclosporine A	Various cancer types	*In vitro*	Duan *et al.,* 2012

Cyclic peptides for cancer therapy

Peptides are the compounds which have less side effects so therapies involving the use of peptides are preferred in medical field. Peptides are less immunogenic than antibodies and specific to the target site. Due to these characteristics, peptide-based therapies are beneficial (Otvos and Wade, 2014). But only few peptide-based drugs are available in the market because peptides are less soluble and can become proteolytic. But problem can be overcome by using cyclic disulfide rich peptides. Cyclic disulfide peptides are assemblage of particles which are middle sized, highly stable and exactly attack the target site. Several cyclic disulfide rich peptides exist in nature for example sunflower trypsin inhibitor-1 (SFTI-1), kalata B1 (kB1) and *Momordica cochinchinensis* trypsin inhibitor-II (MCoTI-II). MCot-II and kB1 are stable because cyclic cysteine knot exists in their structure. While SFTI-1 is also stable due to the presence of wide spread network of hydrogen bonding. Cyclic disulfide rich peptide has recently entered the medical field because idea of grafting (biologically active substance induction into cyclic peptide structure) have been well known (Lammers *et al.,* 2009).

Presently several peptide-based therapies are being carried out to cure various types of cancer. Few of these peptides are described below:

Cyclic RGD peptide

A cyclic peptide known as Cyclo-RGDfV initiate apoptosis of angiogenic blood vessels, hence, it facilitates tumor reversion. Cyclo-RGD also helps in transport of nanoparticles, carrying drug, to the target site to inhibit tumor development (Joo, 2012). It is being used in the treatment of colon and prostate cancer (Cochran *et al.,* 2018).

Cediranib

Cediranib mainly blocks the activity of VEGFRs and its efficacy is found to be 14.0-17.0% in the treatmen of ovarian cancer (Matulonis *et al.,* 2009). Cediranib blocks the growth and reduces microvessel thickness in human umbilical vein endothelial cells where as it leads to epiphyseal zone hypertrophy in lab animals. Generally prescribed dosage for cediranib is 20-30 mg tablet one time a day which is enough to give best inhibitory concentration (IC50) for VEGFR 1, 2 and 3 (Brave *et al.,* 2011).

Abraxane

Abraxane was approved by FDA (USA) in 2005 for the treatment of lung and breast cancer (Bolukbas, 2017). Paclitaxel is used in the treatment of progressive non-small cell lung cancer (NSCLC). But this drug exhibits some limitations because it is less soluble and harmfulness is related to Cremophore EL (polyoxy ethylated castor oil), a lipid-based solvent that carries Taxol to its target (Moon *et al.,* 2000). Cremophore is related with Anaphylaxis, abnormal lipoprotein arrangement, histamine discharge, sensual neuropathy and accumulation of erythrocytes. Taxol needs more time for immersion usually 3-24 hours and it is pretreated with antihistamine and steroids to lessen the hazard of hypersenstive responses.

Micelles formed by cremophore disturbs the linear pharmacokinetics of Taxol. American Bioscience, Inc. has established a new molecule known as 'Abraxane' which is protein bound particle of paclitaxel and cremophore is absent in this molecule. This is developed to overcome all the drawbacks of Paclitaxel and its size is 130 nm. These are designed in such a way that albumin is used for carrying Taxol to the target site. In this method pretreatment with antihistamines can be skipped and immersion time can be minimized. Albumin can increase the transport of drug to the target site by starting receptor (gp60) mediated transcytosis in endothelial cells drug is stored in tumor cell because albumin form complex with NSCLC (Parodi *et al.,* 2019).

Integrins

An unusual type of receptor which are present external to the cell are called Integrins (Hynes, 2002). They also play role in mechanical adhesive interaction with cellular surroundings. Integrin is basically a heterodimer of α and β subunits. Alpha subunits exist in 18 different forms whereas β subunits exist in 8 homologous forms and these result in the formation of 24 αβ integrins which are found on several cells. RGD (Arg-Gly-Asp) is recognized by a subset of integrins. Integrins are involved in promoting the growth of tumor cells and its expansion in angiogenesis. Six integrins inhibitors are used in clinical trials named as Vitaxin, cilengitide, CNTO-95, ATN-161, volociximab and E7820. First three inhibitors attack αvβ3 while α2β1 and α5β1 are attacked by volociximab and ATN-161 respectively. The remaining inhibitor attack mRNA and changes its expression (Hurwitz and Mitragotri, 2019). The further explanation of these inhibitors is given below:

Table 3. Integrin inhibitor in clinical development evaluated as anticancer agents.

Name	Type	Target	Start of phase I	Indication	References
Vitaxin, MEDI-522	Humanized Monoclonal antibody	αvβ3	April 1997	Liver metastasis and prostate cancer	Patel *et al.,* 2001
Cilengitide EMD 121974	Cyclic peptide	αvβ3 and αvβ5	August 1998	Myeloid leukemia and prostate cancer	Eskens *et al.,* 2003
CNTO 95	Human Monoclonal antibody	αvβ5, αvβ3 integrins	Decembor 2003	Angiosarcoma	Trikha *et al.,* 2004
ATN-161	Peptide	α5β1 and αvβ3	January 2003	Angiogenesis and metastasis	Khalili *et al.,* 2006
Vlociximab, (Eos-200-4, M-200)	Humanized Monoclonal antibody	α5β1	May 2003	Metastasis of kidney cancer Used with dacarbazine	Ricart *et al.,* 2004
E7820	Aromatic sulfonamide derivative	Control expression of α2 integrin subunit	January 2004	Angiogenesis	Funahashi *et al.,* 2002

Buserelin

Buserelin, a nonapeptide-ethylamide, is a luteinizing hormone-releasing hormone (LH-RH) analogue. This was developed by Behringwerke AG.

It was used in the treatment of breast cancer for inhibition of estrogen and androgen hormone receptors and decreases the concentration of hormones, but it increases the level of estradiol.

Presently, LH-RH analogues have been industrialized. Prostate cancer and female breast cancer can be treated with prolonged infusion of follicle-stimulating hormone and synthetic LH-RH. When LH-RH is used in the treatment of prostate cancer, the level of androgen increases at first due to the burst of disease and patient suffer a bone pain. So, Flutamide is used along with Buserelin which acts as a pain killer and gives relief from pain. This is used in the treatment of prostate and breast cancer (Alliger, 2018)

Cetrorelix

Cetrorelix is a decapeptide which was initially manufactured at Tulane University, New Orleans, USA. Cetrorelix comprises a much-improved arrangement of LH-RH, consisting of 10 amino acids and 5 of these exist in non-natural D-configuration. This is stable due to the presence of C- and N-protective groups which are also important for its action (Ivy *et al.,* 2016). The examination of physiochemical properties of citrorelix revealed that its absorption and aggregation can be decreased by treating the peptide with acidic solution earlier to lyophilization for conversion of product. The constant use of agonist analogues inhibits the excretions of sex steroid and Gonadotrophin. This happen due to the down regulation of pituitary receptors and low sensitivity of gonadotrophin which results in hypophysectomy. Cetrorelix was applied for the first time as a single dosage. When used continuously, this decreased the level of testosterone in men. While it decreased the level of FSH and LH in women when it is used during menstrual cycle (Farris *et al.,* 2019).

Gemcitabine

Gemcitabine is an effective analogue of deoxycitidine which have a tolerable therapeutic index. The metabolism and mechanism of action of gaemciabie is well categorized. Gemcitabine is triggered by deoxycytidine kinase to dFdC-5 monophosphate (dFdCMP) and deoxycytidine deaminase is converted into 2, 2-difluorodeoxy uridine (dFdU) by deamination (Wang *et al.,* 2006). Difluorodeoxy uridine is inactive, whereas dFdCMP is converted into dFdC-5- diphosphate and dFdC-5-triphosphate which causes chain termination when merged into DNA. The structure and metabolism of Gemcitabine resemble with Ara-C. Beside this, Gemcitabine is more active against tumor cells (Lind, 2008). The tolerable dosage of Gemcitabine is generally prescribed 1000 mg/m^2 intravenously for about 3 weeks. Its action and antineoplastic activity can be increased by increasing the infusion time. An enzyme which is attained from 30 minutes of infusion known as deoxycytidine kinase by which Gemcitabine is phosphorylated into dFdC triphosphate (dFdCTP).

Paclitaxel

Paclitaxel was obtained in 1971 as an effective component from the bark of Pacific Yew, *Taxus brevifolia* which is a rare coniferous taken out from the timberlands of Pacific Northwest in 1963. At start paclitaxel sources were insufficient, Paclitaxel is an alkaloid ester in which oxeton ring is connected to texane ring at C-4 and C-5. Texane rings are also found on C-13 bounded with ester. Paclitaxel stimulates tubulin polymerization. So, microtubules designed by paclitaxel are inactive and highly stable that disturbs dynamic of normal microtubules which leads to cell death. On the other hand, apoptosis may also be initiated by taxane. Even low concentration of taxane causes DNA cleavage which also leads to cell death. Paclitaxel promotes the expression of TNF gene that is associated with cytokines which also inhibit the growth of tumor cells. Paclitaxel restricts the process of mitosis by inhibiting the disruption of microtubules (Xi *et al.,* 2011). This is used in the treatment of breast, head, lung, neck, ovarian sarcoma.

Triptorelin

Triptorelin pamoate is a decapeptide agonist analogue of LH-RH which have better effectiveness as compare to endogenous LH-RH. The amino-acid sequence for triptorelin is similar to endogenous LH-RH but difference is found at sixth position where L-glycine is substituted by D-tryptophan in case of triptorelin. This replacement enhances biological stability of compound hence it is not cleaved by proteolytic enzymes. Mechanism of action of LH-RH agonists involves the down-regulation of pituitary

gland thus repressing the excretion of LH and FSH from the hypothalamus which leads to the repression of secretions of testosterone from the testes. The LH-RH agonist triptorelin pamoate lowers the testosterone concentrations to the predefined levels for medical castration. It is widely used in the treatment of Prostate cancer (Schally and Rick, 2017).

Cisplatin

Cisplatin also known as cis-diamine dichloroplatinum, is a platinum-based molecule which have tetragonal shape. Cisplatin was the first compound issued by FDA for the treatment of cancer (Trikha *et al*., 2004). This resulted in increased importance of metal-based drugs which inhibit the growth of tumor cells. Cisplatin can be used for the treatment of various types of cancer like blood cancer, cancer of tissues and sarcomas (Dasari and Tchounwou, 2014).

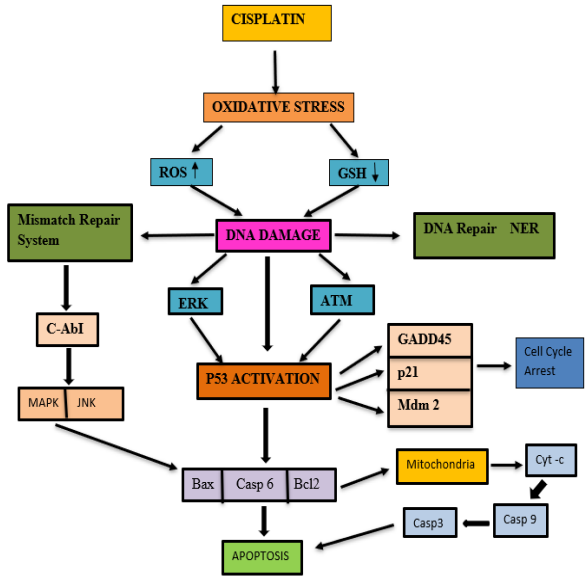

Fig. 4. Mechanism of action of Cisplatin in cancer treatment.

Cisplatin induced oxidative stress primarily on the mitochondria, causing the reduction of membrane potential, calcium uptake inhibition, loss of mitochondrial protein and sulfhydryl group (Saad *et al.,* 2004). Regular biological functions can be disturbed by exposing to oxidative stress. Upon immediate activation of numerous signaling pathways, cell death occurs but the definite pathways depend on the affected cell. Cisplatin can be used in the treatment of following types of cancer:

Cisplatin and lung cancer

Lung cancer is the major form of lethal malignant tumors. In all types of lung cancers, small cell lung cancer (SCLCs) exists 15% among cancer population. Cisplatin is used along with carboplatin in the treatment of small cell lung cancer. This treatment also has some side effects like vomiting and sickness, and kidney failure which can be overcome by controlling the dosage (Griesinger *et al.,* 2019).

Cisplatin and ovarian cancer

Patients suffering from ovarian cancer are mostly died because it can be identified at last stages due to insufficient examining techniques. The basic genetic of ovarian cancer is related to colon and breast cancer Such cancerous cells can be removed by operating and further treated with Cisplatin. But sometime cancerous cells are not affected by this treatment. So, ovarian cancer is treated by cisplatin in combination with Trichostati A and Apitoxin to obtain better results (Yadav *et al*., 2019).

Cisplatin and carcinomas

Head and neck squamous cell carcinoma (HNSCC) are affecting about 600,000 people/year all over the world. These tumor cells are not affected by Cisplatin when it is used as a single agent. So, Methotrexate or vinblastine are used along with cisplatin in the treatment of these cancerous cells (Matsuki *et al.,* 2013).

Cisplatin and breast cancer

Breast cancer is the major issue of women deaths all over the world. This can be treated only by chemotherapy. Cisplatin is used in the treatment of breast cancer which results in programmed cell death by blocking the process of replication. Cisplatin is also involved in the treatment of testicular, cervical, head, breast, ovarian and neck carcinoma (Dhar *et al.,* 2011).

Cisplatin and brain cancer

An invasive brain cancer is known as Glioblastoma which in few cases lead to the death of the patients. It can be treated surgically and also by chemotherapy which involve the use of Temodal. Cisplatin is involved in the treatment of anal cancer, gastric cancer and brain cancer in children (Ghosh, 2019).

Concluding remarks

Cancer is being treated by several methods like chemotherapeutic method, radiotherapy and debulking surgery. These methods have some limitations due to drug resistance. So, nanoparticles are preferred which are recently involved in cancer treatment and they specifically attack the target site. These nanoparticles mediated drug delivery to increase the efficacy or sometime the specific combination of drugs have increased the scope of nanobiotechnology. In this article, cyclic peptide functionalized nanoparticles are discussed for the treatment of cancer. Cyclic peptides are the peptides which have a cyclic ring in their structure and can inhibit the process of angiogenesis hence involved in the treatment of cancer.

These peptides initiate apoptosis of angiogenic blood vessels; hence, it facilitates tumor reversion. Various cyclic peptides e.g., Cediranib, Abraxane, Cilengitides, buserelin, Cispltin, Cetrorelix, Gemcitabine, triptorelin have been applied in the treatment of cancer. These peptides have less side effects, are less immunogenic and specific to the target site. Due to such characteristics, these peptides are preferred in the treatment of cancer. These peptides are being used now-a-days in the treatment of brain, breast, head and neck, prostate and lung cancer. Various improvements in such cyclic peptides which are used as nanocarrier can decrease the hazards of cancer to a much lower level and life span of patient can be increased.

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Abbreviations

EGFR: Epidermal growth factor receptor
EPR: Enhanced permeability and retention
LH-RH: Luteinizing hormone-releasing hormone
NIR: Near-infrared
NSCLC: non-small cell lung cancer
RGD: Arginylglycylaspartic acid
RGDfV: D-arginyl-L-alpha-aspartyl-glycyl-L-phenylalanyl-L-valyl
SLN: Solid-lipid nanoparticles
SPIONs: Super paramagnetic iron oxide nanoparticles

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