INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

CONJUGATES AS A CARRIER FOR CANCER DRUGS: AN UPDATE

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Accepted Date: 24/06/2016; Published Date: 27/06/2016

Abstract: The most significant challenges facing successful cancer therapy are general toxicity of cytotoxic drugs to the patients and their lack of tumor localizing and a steady distribution within the whole body. Besides, short half-lives and unwanted pharmacokinetics are the other drawbacks which inhibit potent cancer chemotherapy. Conjugation of very low molecular weight drugs with various carriers has been used as a way to tackle these problems and acts as an alternative tumor. Selective treatment approach and these systems will camouflage the undesirable properties of drugs. This review will focus on emerging techniques to further advance this exciting area of research.

Keywords: Chemotherapy, Conjugation, Drug carrier, Pharmacokinetics, Anticancer agents, Nanoparticles

PAPER-QR CODE

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Access Online On:

www.ijprbs.com

How to Cite This Article:

Adnan Ahmad, IJPRBS, 2016; Volume 5(3): 211-224

INTRODUCTION

Cancer is a broad term covering various type of cancer, such as lung cancer, colon cancer, skin cancer etc. Cancer is the major problem all over the world. In 2012 more than 14.1 million new cases of cancer were noticed globally [1]. Lung cancer is one of the most deaths causing cancer disease worldwide, almost 1.4 million deaths per year [2]. It accounts about 8.2 million deaths or 14.6% of all human deaths. According to a national cancer institute survey in 2014, an estimated 15,780 children and teenagers ages 0 to 19 were diagnosed with cancer. The most common cancers were categorized according to gender, in male lung, prostate, colon cancer and stomach cancer reported in increase number. In female, breast cancer and cervical cancer are the most common cancers. Due to high risk of breast and lung cancer, researchers have keen interest to develop the drug against these cancers.

Cancer itself very dangerous disease and also give birth to other illness and diseases. Malignancy of tumor is defined by movement of cancer cells from a primary site to another secondary site. It's also known as metastasis.

The discovery of novel anticancer agents along with the development of new molecular targets has led to new possibilities for anticancer treatment by using drug combination therapy. The combination therapy for the treatment of a disease refers to the simultaneous administration of more than two pharmacologically active agents with different types of therapy combinations (e.g. chemotherapy and radiotherapy). Multi-agent therapy can be combined with different type of signaling pathways in diseased cells, which maximize the therapeutic effect and, possibly unlike therapy based on single-agent to overcome resistance [3]. Several diseases are routinely cured with combination therapy, including cancer, HIV/AIDS and malaria. The Highly Active Antiretroviral Therapy (HAART) strategy that combines three or more anti-HIV drugs, for the treatment of HIV since first introduced in 1999 [4]. Thus, by administering combinations of drugs striking different molecular targets and the chances of success are maximized [5].In this sense, a clinical trial supported by Mount Sinai School of Medicine (CombiRx) is presently recruiting participants to establish the benefits of modulating interferon beta-1α (Avonex, Rebif®) and glatiramer acetate (Copaxone®) [6,7].

This is because of poorly foretelling preclinical models. To make therapy very convenient for patient use, therapeutic altitudes of the anti-tumor peptide are sustained for up to 3 months.

2. Protein Nanoparticle as a conjugate for cancer disease

Nanotechnology has given many new possibilities in medical sciences, like for drug delivery devices. Drug carrier systems are in the micro and nanometer size range and the number of products and patents and in the drug delivery field are increasing day by day. Nanoparticles

range in size from about 10 nm to 1000 nm and are solid colloidal particles. To design a nanoparticle as a delivery system several goals are kept in mind,these include controlled particle properties like size, surface and release of pharmacologically dynamic agents which helps to accomplish the site-specific act of drugs at a therapeutically ideal rate with required dosage[8-10]. Advantages of using Nanoparticle as a drug delivery systems includes, firstly, particle physical properties, i.e. the particle surface charge, morphology, and size of nanoparticles [11]. Secondly, drug delivery systems can carry a variety of therapeutic and diagnostic agents like small hydrophilic or hydrophobic molecules, peptides, proteins, nucleic acids etc The trapped molecules can be free from the nano-carriers in a precise manner over time or they can be activated to be free by some stimuli inimitable to the delivery site [12].These nano-carriers may also increase the stability and solubility of drugs which is encapsulated, providing a means to reuse drug candidates that were previously not used because of poor pharmacokinetics [13].Lastly, various routes of administration are used for site-specific drug delivery. The nanocarriers can have increased circulation time or enhanced cellular uptake and targeting abilities [14] .Factors to be considered while selecting Nanoparticl material includes-[a] the size of nanoparticle required, [b] intrinsic properties of the drug comparable aqueous stability and solubility, [c] drug release property preferred, [d] hydrophobicity and surface charge of nanoparticle, [e] nonmaterials biodegradability and biocompatibility, and [f] antigenicity and toxicity of the product. Biopolymer-constructed nanoparticles and protein nanoparticles have gained interest in recent years due to their usable properties like low toxicity and biodegradability, small size etc [15]. They are now developed for both nutraceutical and pharmaceutical delivery. Proteins have impending applications in both material and biomedical sciences [16]. The property of amphilicity make the nanoparticle as ideal delivery system which permits them to interact easily with both the solvent and drug [17].These are biodegradable, metabolizable, and can undergo surface alterations to permit attachment of targeting ligand to the drug [18]. They have been synthesized from various proteins naturally including water-soluble proteins (e.g., human serum albumin and bovine serum) and insoluble proteins (e.g., gliadin and zein) and daily consumable milk protein.

2.1. Albumin

Ovalbumin (Egg white), HSA (human serum albumin), and BSA (bovine serum albumin) are the sources of this protein. Albumin is a primary soluble protein of the circulating system, has a molecular weight of 66.5 kDa, maintains the osmotic pressure and transport nutrients to cells. Various drugs and endogenous molecules attached to albumin as it has multiple drug binding sites. Albumin also acts as a transporter protein [19, 20]. Albumin is now an ideal and most versatile protein carrier for targeting of cancer based drugs. The first drug involving albumin conjugate undergoing clinical trial was Methotrexate –albumin conjugate human serum

albumin (MTX-HSA) for targeting of cancer cells of rats. Followed by this a nanoparticle based drug, namely n*ab* Paclitaxel was developed by American Bioscience Inc. which is markedly approved. This NP encapsulates lipid drugs for treating breast cancer.[19] Another new technique is developed which involves the use of gold nanoparticle and thermal ablation for treatment of Hepatocellular carcinoma (HC) which is a most common liver cancer leading to high rate of mortality and is far better than chemotherapy and radiotherapy .Gold nanoparticle converts light energy into heat energy using Near infrared (NIR) laser irradiation for killing cancer cells without harming normal cells. Hepatocellular carcinoma (HC) cell exhibits high intracellular albumin levels. Albumin is internalized through endocytosis mechanism. Considering this internalization ,a albumin-GNP bionanosystem is developed for targeting Gp60 receptors and laser mediated necrosis of cancer using albumin and gold nanoparticle.This receptor is located on membrane of malignant liver cancer cells.The Alb-GNP treated cells were irradiated for 2 minutes using 808 nm laser,2 W/cm sq power and further with Dynamic light scattering(DLS),ATR-FT-IR and AFM measurements .This Alb–GNP photothermal treatment causes severe ER and GA morphological changes in HepG2 cells, which finally kills liver cancer cells.[21]

2.2. Milk Proteins

Milk contains several useful proteins with unique functional properties, making it capable of using it as drug delivery vehicles [22]. β-lactoglobulin (BLG) and casein are two milk protein.BLG preserve its native steady conformation at acidic pH so resists peptic and chymotryptic digestion. BLG has a very good gelling property and low cost, hence has wide drug delivery applications [23]. Casein does exists as micelles in the size of 100 to 200nm with no fixed three-dimensional structures which alters with any changes in temperature, pH, water activity, ionic strength, and hydrostatic pressure [24]. Caseins have two different hydrophilic and hydrophobic domains that support conformational changes in solutions according to environmental conditions. At the core, casein micelles have small aggregates of 10 to 100 casein molecules made with interaction with hydrophobic and through calcium phosphate nano clusters. Their surface is covered by -casein that results in a charged surface which stabilizes the casein micelles by steric and electrostatic repulsions [25]. Processing treatments like mechanical forces and heat does not effect casein molecules [26]. β-casein is an edible material and its micelles has been used for targeted oral-delivery system. Various hydrophobic chemotherapeutics have been entrapped in β-casein micelles like mitoxantrone, vinblastine, irinotecan, docetaxel and paclitaxel . Without prior simulated gastric digestion ,β-casein-paclitaxel nanoparticles were non-cytotoxic but with digestion of casein with pepsin, paclitaxel have its cytotoxic activity to human N-87 gastric cancer cells thus helpful for treating stomach cancer [27,28]

3. Peptide conjugates in the treatment of cancer diseases

In near future mortality from cancer will surpass that from cardiovascular diseases. Every year about 7 million people died from cancer-related diseases, and it is predictable that 16 million or more new cancer patient increased every year by 2020 [29,30]. Angiogenesis (growth of fresh blood vessels from existing vessels) is a common and essential process in growth and development; it is also a primary step in the transformation of tumors from a resting state to a malignant stage [31]. The discovery of numerous protein/peptide receptors and tumor-associated peptides and proteins is expected to discover a more potent and successful anticancer drug in the future [31, 32]. Monoclonal antibodies, protein and peptides are most useful biologic option for the treatment of cancer.

The use of such macromolecules has been limited to either vascular targets existing on the tumor vessel endothelium or hematological malignancies [33, 34]. Peptides possess several advantages, like small size, easy synthesis and ease of modification, tumor invasive ability, and excellent biocompatibility [35, 36].Peptide degradation by proteolysis can be prevented by chemical modifications like the incorporation of D-amino acids or cyclization [35]. Over the years peptides have been developed as potential therapeutic agents for the treatment of cancer, cardiovascular diseases, and diabetes. The application of peptides in a variety of different other therapeutic areas is growing rapidly. At the present time there are almost 60 approved peptide drugs in the market making a yearly sale of $13 billion. The peptide drugs entering in clinical trials is increasing gradually; in the year 1970 it was 1.2 per year, then increases up to 4.6 in the 1980s, after that in 2000 it come 16.8 every year. Several hundred peptide drugs are in clinical development. From the year 2000 onwards, peptides contributing in clinical study and they were widely used for better detection of cancer (18%) and metabolic disorders (17%) [37]. Many possible cancer treatment alternatives using peptides are outlined (Fig.1). Because of the ability to bind to various receptors and also involved in different biochemical pathways, peptides act as biomarkers in cancer progression and a potent diagnostic tool. There is an incredible progress in other area like peptide angiogenesis and inhibitors peptide-vaccine development.Various clinical trials are in progress which is expected to give good drug in the near future providing better alternatives to millions of cancer patients [38,39]

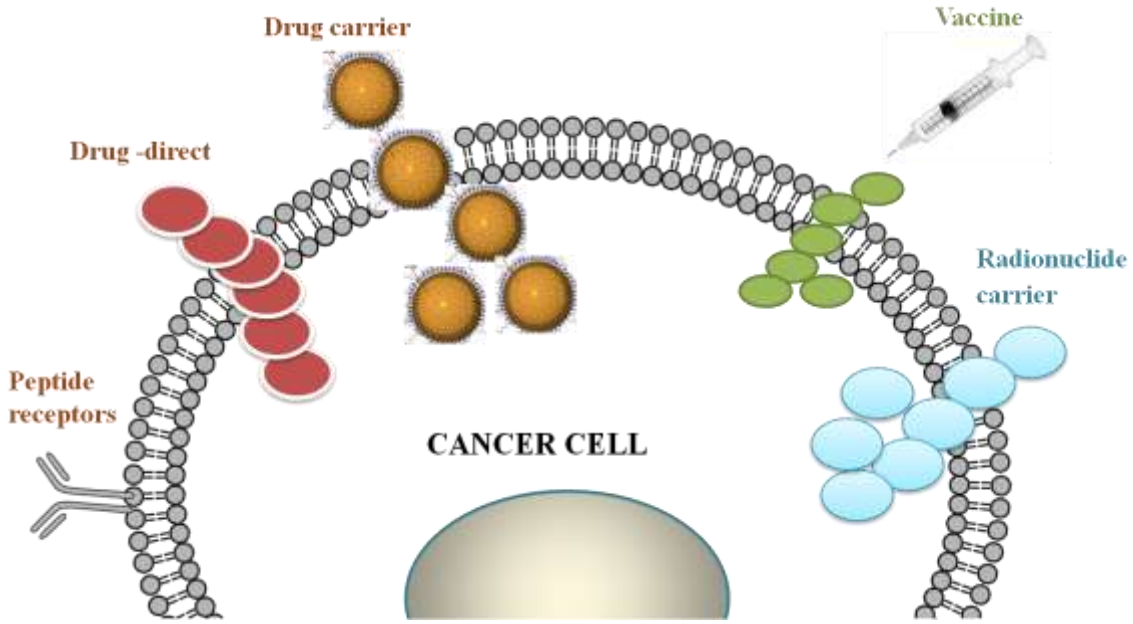

Figure.1. Differential potential alternative treatment of cancer utilizing peptides. Peptides can be used as an anticancer drug, vaccine, radionuclide carrier hormones, and cytotoxic drug carrier .

3.1. Peptide Hormones: LHRH

3.1.1. Agonists and Antagonists

Schally et al introduced LHRH (luteinizing hormone releasing hormone) as the best traditional example of the application of peptides in cancer treatment agonists to treat prostate cancer [40]. After this, many LHRH agonists such as buserelin, leuprolide, triptorelin and goserelin, have been developed for more convenient and more efficacious treatment of patients with prostate cancer [41]. LHRH receptors are down regulated because of these peptide administrations in the pituitary, causing the inhibition of follicle-stimulating hormone (FSH) and LH release, and associated decrease in testosterone production.Today, many potent LHRH antagonists are available for the clinical use in patients. The first LHRH antagonist available clinically is Cetrorelix undergone marketing approval and, thus, became usable. Subsequently, new generation LHRH antagonists for example abarelix and degarelix (Table1) have been approved for human use [42, 43].

Peptide	Sequence comparison	Indications
Agonists		
Goserelin	Pyr-His-Trp-Ser-Tyr-D-Ser(OtBu)-Leu-Arg-Pro-AzGly-NH2	In the prostate cancer; breast cancer
Leuprolide	Pyr-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt	In the prostate cancer; breast cancer
Nafarelin	Pyr-His-Trp-Ser-Tyr-2Nal-Leu-Arg-Pro-Gly-NH2	Treat symptoms of endometriosis, central precocious puberty
Antagonists		
Degarelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3_-pyridyl) Ala-Ser-4-aminoPhe(L-hydroorotyl)- D-4-Amino Phe(carbamoyl)-Leu-isopropylLys-Pro-D-Ala-NH2	In the prostate cancer
Ganirelix	Ac-D-2Nal-D-4-chloroPhe-D-3-(3_-pyridyl) Ala-Ser-Tyr-D-(N9, N10-diethyl)-homoArg-Leu-(N9, N10-diethyl)-homoArg-Pro-D-Ala-NH2	In fertility treatment

Table 1: LHRH agonists and new generation antagonists available in the market.

3.2. Peptide as Radionuclide Carrier

3.2.1. Somatostatin Analogues in Cancer remedy and Peptide Receptor Radionuclide Therapy (PRRT)

Radiolabelled somatostatin analogs make somatostatin receptors as important targets for delivery of radioactivity. Receptor agonist binds specifically and this binding is fast, efficient, and reversible after which the sst2 internalize into the cell [111In-DTPA]-octreotide (Octreoscan), the preliminary available radiolabeled somatostatin analog, quickly became the gold standard for detection of sst-positive Neuro Endocrine Tumors (NETs). Octreoscan and NeoTect (tc- 99m depreotide) are the barely radiopeptide tracers in the market approved by the Food and Drug Administration [44, 45].

3.3. Peptide Vaccines

Immune cells or immune molecules can treat cancer using active immunization and seems to be one of the capable strategies to treat cancer though many techniques. This plan of vaccinations against cancer has changed into clinical studies aiming to deliver vaccines based on particular antigens which induce anticancer immunity [46]. Active immunotherapy (vaccination) in host's immune system is either trigger de novo or re -stimulated to mount successful, tumor-specific

immune response which may be ultimately lead to tumor regression Vaccines consisting of peptides resulting from the protein sequence of applicant tumor-associated or specific antigens are used as a method of treating cancerous cells relies on host's immune system identifies antigens known as tumor-associated antigens (TAAs) expressed by tumor cells that can be recognized by the T cells [47,48] . These TAAs can be injected into cancer patients in a shot to induce a systemic immune response that may result in the devastation of the cancer growing in different body tissues. Most known TAAs are CTL (cytotoxic T lymphocyte another name is CD8+ T-cells or killer T cell) epitopes [49]. Peptide antigens are usually 8–10 amino acids long with 2-3 main anchor residues that attached with MHC class 1-molecules and its 2-3 residues which bind to T-cell receptor [49, 50]. CTLs directed against peptides presented with the help of MHC class 1 molecules comprise of powerful effectors of the immune system against tumor cells.

The T-cell antigen receptor (TCR) present on T cells recognizes the complex of a tiny peptide located in the antigen-binding groove present on MHC molecule. MHC molecules are subdivided into class I molecules and class II molecules, which are found on antigen presenting cells (APCs) like dendritic cells, B cells, macrophages, and epithelial cells or selected activated endothelial. CD4+ T cells identify antigens bound to MHC class II molecules, and class II molecules are also expressed on APCs that possess the ability of antigen incarcerate through phagocytosis or binding to surface antibody [51,52].To boost the immunogenicity and efficacy of the peptide Several strategies like epitope enhancement, use of different T-cell epitopes, adjuvants, assimilation of costimulatory molecules, *ex vivo* loading into APCs are also being explored as a vaccines [53].

4. Polymer conjugates in an anticancer nanomedicine

Polymer drug conjugates are administered intravenously as compared to polymer protein conjugates which are injected intramuscularly. Some of the linear polymers which have been explored includes *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, polyglutamic acid (PGA), polyethyleneglycol (PEG), polysaccharides (for example, dextran) [54]. Rapid advancement in polymer chemistry has now created many different hyperbranched polymers that are not linear like dendrimers and dendronized polymers[55] These polymers are bidegradable and hold controlled release of drug. For example for the treatment of prostrate cancer, many digferent shapes of polymers have been developed, few of them include rod shaped polymer(zoladez), microparticle polymer(leoprolide) etc. These are made from polylactide co-glycolide-entrapping leutinizing hormone releasing hormone (LHRH).slow degradation of polymer can retain anti tumor peptide for maximum 3 months, thus making it suitable to be used by patients [56]. Polyglutamate-paclitaxel, which is in phase3 trial and it will be used for the treatment of ovarian cancer, lung cancer etc.

The mechanism of action of the polymer drug conjugates is helpful to develop second generation level conjugates. Many factors influence anti-tumor property of tumor. Conjugation of hydrophobic chemotherapy to hydrophilic polymers improves solubility, and the manufacture of macromolecular prodrugs severely alters drug biodistribution. Moreover, the hydrolysis of conjugates and drug release during renal elimination can fetch unexpected toxicity, like dose-limiting cystitis seen for HPMA copolymer–camptothecin [57].

5. Conclusion and future prospects

The clinical achievement of various nano carriers constructs in cancer therapy has made these and similar systems promising drug delivery vehicles for upcoming work aimed to further improve their overall drug delivery efficiency. Because of the highest investment in antibody therapeutics and liposome for two decades, research in polymer therapeutics progressed is almost unseen. Paginated proteins and polymer combinations and the polymer–drug conjugates have been regularly used in the 1990s but this trend is rapidly changing, because of interest in nano diagnostics and nanomedicines, is bringing the essential investment to all category of polymer therapeutics. Because of the successful growth of first generation polymer–drug conjugates in the mid 1980s and 1990s, many new studies are done assessing their potential as drug delivery platforms for combination therapy. Nanoparticle drug delivery systems are utmost important and beneficial for the treatment of cancers and other severe diseases inspire of the existence of other drug delivery system (Fig. 2). We have to recognize nanoparticle materials that are effective and safe in delivering therapeutic agents near the target sites. Natural sources are used to build protein polymers and are auspicious materials for constructing the nanocarriers systems. Of the several proteins for drug delivery applications, albumin and gelatin are more broadly used, while milk proteins and plant proteins are now widely used in drug delivery applications, and they signify highly promising protein nonmaterial. The market success of albumin-based nanoparticles has made a great interest in other proteins. By wisely designing protein nanoparticles based on their effect in the tumor microenvironment, based on cancer cell biology, enhanced value and safety of cancer therapy can be accomplished. Additionally, multifunctional protein nanoparticles proficient of carrying both diagnostic agents and therapeutic are now being explored for extra effective cancer management. Although the application of protein nanoparticles for cancer therapy has previously made some exciting results and holds even greater promise in the future, comparison data on the therapeutic efficiency and performance of protein nanoparticles and other existing delivery systems are still lacking and represent a good needed area of research in the field.

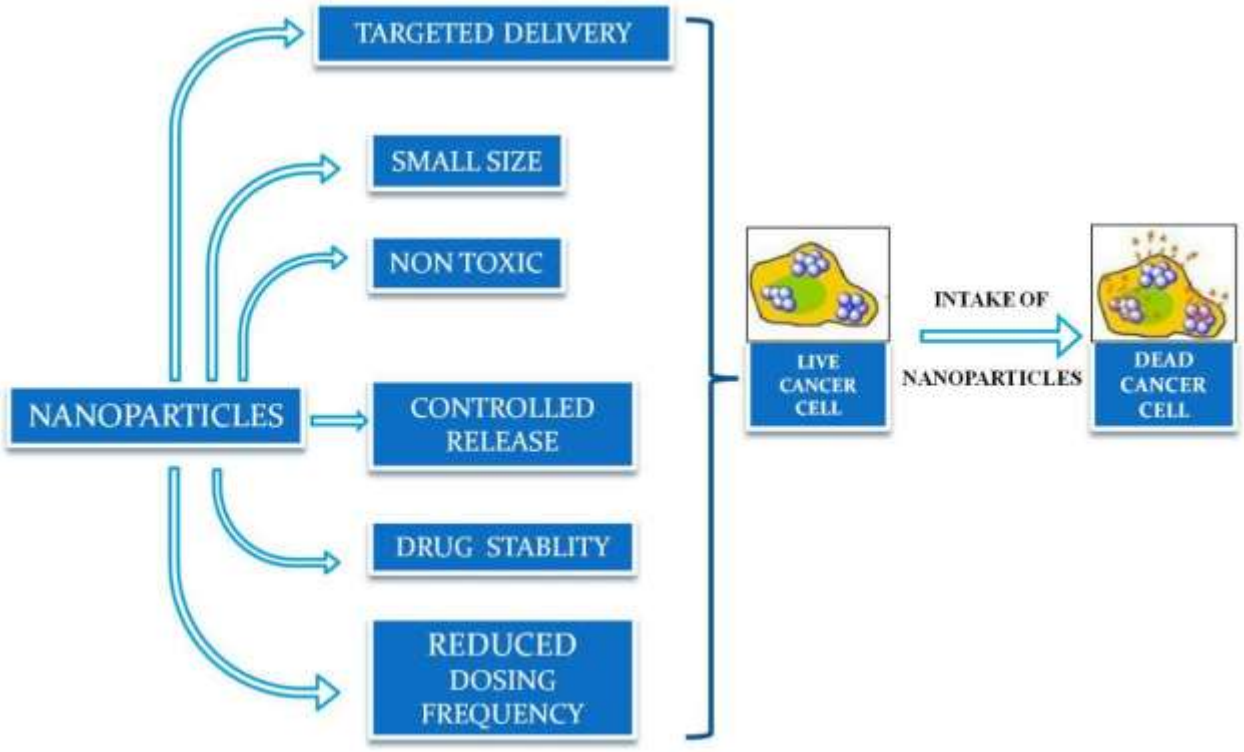

Figure.2. This diagram shows that when a nanoparticle with many advantages like small size, targeted drug deliver action, non toxicity, biodegradability, stability, reduced dosing frequency, controlled release etc, is administered into the live cancer cell, results in killing of cancer cell and achieves a site specific action of drug. All these properties makes NP an ideal drug carrier conjugate.

6. Acknowledgement

The authors acknowledge Integral University, Lucknow, India for providing the facilities required for the preparation of this review. We are thankful to Mr. Mohd Farhan for designing the figure 1 and figure 2. We are also grateful to Dr. Snober S. Mir of Dept. of Bio-Engineering, Integral University, for his valuable comments and critical suggestions on the manuscript.

7. Conflict of Interest: No conflict of interest exists for this Manuscript.

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