



Use of prodrugs in cancer therapy - A Review

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ABSTRACT

A prodrug is a medicine that is primarily used after administration, that is metabolized into a pharmacologically active drug. A prodrug is generally a precursor form of a drug. A prodrug is used to selectively improve the drug that directly interacts with cells used in any form of treatment like chemotherapy. The drug, when taken separately, does not have much effect, whereas, a drug taken in after the administration of prodrug acts very effectively. Prodrugs are often used in the pharmaceutical field. Prodrug alters certain properties of prodrugs, such as physicochemical properties to enhance their efficacy and reduce their toxicity. The cancer cells are first injected with a gene that expresses an enzyme that has the ability to convert a non-toxic prodrug into its active cytotoxic form. Various applications of prodrugs include improving drug penetration through biological membranes, increasing site-specificity of a drug; it mainly improves patient's acceptance. Prodrugs stabilize the active drug and prevent drug metabolism. This review was written with an aim to highlight the important aspects of prodrugs and its use in cancer therapy.



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INTRODUCTION

Prodrugs are biologically inactive compounds that are metabolised in the body to produce a drug. Prodrugs are known for their efficiency in cancer treatment. Antibody-drug conjugates are one of the clinical uses of a prodrug that is most commonly used.

In spite of its potential uses, it shows limited prodrug uptake, difficulty in selective targeting and gene expression (Souza *et al.*, 2019). They are usually inactive and are derivatives of drug molecules that undergo a chemical transformation to form active compounds. Recombinant technology in prodrugs acts as an important component that is mainly focused on attacking complex Molecular phenotypes in relevant cancer (Giang *et al.*, 2014). Prodrugs are the best combination of products of nanotechnology and aptamer conjugated nanomaterials. This combination of prodrugs is one of the best strategies used for many treatments (Souza *et al.*, 2019). Prodrugs generate multipurpose function and reduce the toxicity of conventional anti-cancer drugs that is done by masking as a cleavable marker. Enzyme activatable prodrugs are used in the design of anti-cancer prodrug and can be used as a cancer treatment strategy.

Prodrug therapy is a step-by-step procedure. The first step in prodrug therapy is the drug activating enzyme, that is the target enzyme gets expressed on the tumor. The second step of prodrug therapy is the non-toxic drug that is an exogenous enzyme in nature and is expressed in the tumors that are administered separately. The activation of selective prodrugs in tumor tissues is used by this exogenous enzyme, that is done in several ways (Xu and McLeod, 2001). Prodrugs also have some drawbacks, which includes low conversion of prodrugs to drugs, the low transduction efficiency of vectors, non-specific toxicity in the delivery system of the enzyme in the prodrugs. Gene directed enzyme prodrug therapy (GDEPT) is one of the targeted approaches that is used for cancer treatment in recent years. This treatment mainly relies on three important components - enzyme, prodrug and gene delivery system or vector (Malekshah et al., 2016). Further studies were done in the department of biochemistry in Saveetha dental college on topics like cancer biology, endocrinology, phytochemistry. Quercetin showed maximum protection against non-alcoholic steatohepatitis or NASH by increasing the levels of adiponectin, when compared to pioglitazone and hydroxy citric acid (Mohan et al., 2015). Childhood obesity causes illnesses like high cholesterol, diabetes and also social problems (Shukri et al., 2016).

The aim of this is to study the use of prodrugs in cancer therapy by studying various salient features of prodrugs and its uses in cancer treatment, its application in cancer therapy.

Prodrugs - A Review

Prodrugs are usually found to be used in a number of applications. Prodrugs were first introduced into medicinal chemistry by a scientist named Albert in the Year 1951. Prodrugs are mainly of two types - the carrier - linked prodrugs and precursor prodrugs. Prodrug approaches are used for many reasons such as - It improves the drug water solubility, it enhances the absorption of substances and improves the membrane permeability, and most importantly it reduces the side effects (Abet et al., 2017).

Prodrugs are substances that are irreversible derivatives which undergo a chemical transformation in vivo condition and release an active parent drug. The components inside the prodrug are of immense help by which it notices the tumor sites. Some advantages of Prodrugs are that it converts normal or conventional drug administration, whereas prodrugs do not have any odour, irritation or pain (Valecha and Dubey, 2014).

Cancer and its types

Cancer is a disease in which there is an uncontrolled growth of abnormal cells anywhere in the body. Certain causative agents of cancer can be due to chemical compound exposure, certain pathogens, human genetics, ionizing radiation. 6-shogaol is used successfully as a healing agent that provides defence against UVB-induced provocative and oxidative skin reimbursement that can potentially lead to skin cancer (Chen et al., 2019). There are over 200 types of cancer present. Cancer types include carcinoma, sarcoma, leukemia, lymphoma, myeloma, central nervous system cancer, gliomas. These gliomas are the primary cause of cancer and are joined by death, mostly in adolescent people and account for about 80% of all malignant tumors (Li et al., 2020). Meningiomas, pituitary adenomas, vestibular schwannomas, liver cancer, The curative groups have been used by G. Mangostana Linn fruit extract (GME) that has an anticarcinogenic effect on the development of liver cancer (Jainu et al., 2018). Primary CNS lymphomas, primitive neuroectodermal tumors, thyroid cancer. A study reveals that signal transducer and activating transcription (STAT-3), which is an oncogenic transcriptional factor, is deactivated by sesame. This, therefore, reduces the elevated expression of cyclin-D1, Bcl-2. The sesame initiates the thyroid cell expansion and apoptosis of thyroid cancer cells (Ma et al., 2019). Common cancers seen in women are breast cancers, the anticancer effect of Zingiber officinale or commonly called ginger acts on dimethylbenz(a)anthracene (DMBA) - induced mammary cancer in Sprague-Dawley (SD) rats as a foundation of 7 mammary cancer cells (Gan et al., 2019). Lung cancers. Common cancers seen in men are prostate, lung and colorectal and common cancer seen in children leukemia, brain tumors and lymphoma (Blackadar, 2016). Cancer cells arise due to the imbalance of body functions and invade the normal infected cells. Other types of Cancer that affect other body parts are blood, lungs, colon, rectum, prostate, skin, breast, uterus, thyroid, lymphatic system. All these types of cancer have various treatments such as chemotherapy, precision medicine, radiation therapy, surgery, stem cell transplant, hormone therapy, immunotherapy and targeted therapy (Koul, 2019).

Different Cancer Treatments

The cancer treatments in recent years include surgery, chemotherapy, radiation therapy, immunotherapy. New strategies, therapies are being developed to decrease drug toxicity in health issues and to promote the use of nanostructures for therapeutic purposes (Arruebo et al., 2011). The

different types of cancer treatments in development are nanomedicine, extracellular vesicles for cancer diagnosis therapy, natural oxidants (antioxidants) in cancer therapy, targeted therapy, immunotherapy, gene therapy, radiomics and pathomics (Pucci *et al.*, 2019). A recent study shows that the Siberian ginseng gold nanoparticle (SG-GNPs), which are biosynthesised induces apoptosis or the death of cells in melanoma cells and shows anticancer properties (Wu *et al.*, 2019). Astray also infers that biosynthesised morphologically synthesised Zinc oxide nanoparticles are an effective anticancer agent that induces cell death in the laryngeal cell line and also for various cancer treatments (Wang *et al.*, 2019). Fruits like pineapple extract are used as an effective treatment of oral cancer (Menon *et al.*, 2016). A mace extract of myristica fragrans was also used in which it exhibited cytotoxicity and anticancer effect against carcinoma KB cell lines and it also suppressed the growth of cancer cells (Rengasamy *et al.*, 2018). Proteases are also used in tumor growth and progression that highly depends on nutrient and oxygen supply (Eatemadi *et al.*, 2017). Such Alkaline proteases are also used in one of the most important industrial enzymes that are mainly extracted from the intestine of fish. These are widely used in laundry detergents for the degradation of the protein (Rengasamy *et al.*, 2016).

Uses of Prodrugs in Cancer Therapy

Prodrugs improve the selectivity of cancer therapy. This is done by targeting abnormal markers on cancer cells. Antibody-drug conjugates (ADCS) is used widely, major drawbacks of the use of prodrugs are the lack of relevance in vivo models, the complexity of human metabolism, economic limitations, dis-organised development of new Prodrugs. Combinations of prodrugs with nanotechnology is a new strategy approach for the treatment that can overcome a lot of these drawbacks or limitations (Souza *et al.*, 2019). Catharanthus roseus (CR) AuNP nanocomplexes are used as drug delivery systems and are of immense help in human cancer treatment and diagnosis (Ke *et al.*, 2019).

Prodrugs - Advantage or Disadvantage

Prodrugs are used both for pharmacological and clinical purposes. The use of drugs become more efficient after the intake of a prodrug rather than the intake of a drug alone. This is depicted by a curve. The area under the curve of the elimination phase is found to be limited for Prodrug compared to a drug (Hammerstein, 1990). The effect of Prodrug solubility in chemical stability long duration and inaction of the target site is effective for different diseases as well (Valecha and Dubey, 2014).

DISCUSSION

Prodrugs are first introduced in the field of medical chemistry by Albert. These prodrugs are actually molecules that do not have any intrinsic biological factors that are capable during different phases, where the metabolism generates biologically active drugs (Abet *et al.*, 2017). Cancer begins due to genetic interfere in an orderly process. Cancer cells start growing uncontrollably. These cells form a mass in the body called a tumor. The primary site of storage used for excess energy as triglycerides that helps in synthesizing many biologically active compounds is the group of cells forming Adipose tissue. The cells forming tumors are not of any good use, but rather it invades the nearby cells and tissues and grows to form secondary tumors (Ponnulakshmi *et al.*, 2019). Tumors are mainly of two types - malignant and benign. Malignant cancer occurs when the tumor spreads to other parts of the body. Benign tumors grow but do not spread throughout the body. Cancer can affect different parts of the body like lungs, rectum, skin, breast, etc. (Koul, 2019). The treatment for cancer ranges from chemotherapy, radiotherapy to cell-based immunotherapy (Abbas and Rehman, 2018). Prodrugs are administered in an inactive form; one of the common prodrug used is tamoxifen. This is metabolised in the liver by active metabolites. Prodrugs harness the process and selective activation. Cancer cells divide rapidly and overpress an enzyme called topoisomerase II, which activates small Prodrugs (Utku, 2011). Chemotherapy improves cancer treatment. Bacteria express enzymes for selective prodrug activation. These bacteria are non-invasive in tumors. The intensity of luminescence of CFU in Beta- G increases the time for bacterial replication occurring in tumors. Tumor targeted prodrug activating bacteria is useful in selective cancer chemotherapy (Cheng *et al.*, 2008). Activated prodrugs are designed in the knowledge of the structure and function of tumor tissue. Presence of antigens on the receptors targets the selective delivery of activation of prodrugs within the tumor (Stańczak and Ferra, 2006). Cancer can also be treated using strawberries as it has cytotoxicity effects on oral cancer due to the presence of beneficial anticancer constituents in the strawberries (Ramya *et al.*, 2018).

Chemical series of pharmacodynamic properties are called lead chemicals. The derivatives of lead chemical having intrinsic activity are converted into an active drug. This active drug is called prodrugs. This is used extensively as a medicine (Connors, 1999).

The targeted prodrugs depending on the presence of unique cellular activity, the desired target has

availability of enzymes, transporters, the target site for antibodies. This is called enzyme prodrug therapy. This approach does not require enzyme catalyze prodrug interconversion (Horani *et al.*, 2015). Activation of prodrugs makes the enzymes to be delivered to the tumor cells by the DNA constructs to the corresponding gene. The activating mechanism uses a small proportion of the tumor cells competent to activate prodrugs (Denny, 2004).

CONCLUSION

The review highlighted the possible advantages and some disadvantages of prodrugs. The prodrug concept is, therefore utilized in cancer therapy as a recombinant approach. Combination of prodrugs with cancer nanotechnology can be an efficient strategy towards the treatment of cancer.

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Conflict of Interest

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