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STUDIES OF PRODRUG APPROACH IN ANTICANCER DRUGS

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ABSTRACT

A prodrug is pharmacologically inactive, meaning it needs to be converted into an active drug by enzyme or chemical processes that are metabolized in the body that are designed to increase the amount of active drug at the site of action. Prodrugs in anticancer treatment can help to reduce side effects and limitations of conventional anticancer treatment because conventional drugs have high systemic toxicity and lack tumor selectivity. Natural products can also address cancer, but because of systemic toxicity or lack of tumor selectivity, a prodrug strategy will help in overcoming these limitations. To get a more effective outcome in cancer therapy, try combining nanoparticles or photouncaging methods with a prodrug. Human carcinogenesis is caused by CYP1A1, therefore inhibition of its activity may result in chemoprevention. Lipophilic prodrugs combined with nanotechnology can be used to design liposomes that overcome drawbacks. We will provide a summary of recent research article reports on anticancer prodrugs.

KEYWORDS: Anticancer drug, Amphiphilic nano theranostic, Curcumin, Camptothecin, Emetine, Gene-directed enzyme prodrug therapy.

INTRODUCTION

Anticancer drugs have various limitations when it comes to chemotherapy. Cancer, as we know, causes the uncontrolled growth of abnormal cells. Prodrugs from natural sources are also used to treat cancer, but very few are used in clinical practice due to their poor water solubility, poor bioavailability, and lack of tumor specificity.[1] It is necessary to convert a prodrug to its active form to make it active. The barrier can be its solubility or bioavailability. Therefore, promoiety is added so that the drug will be in the active form is released and

promoiety is released in the inactive form.[2] By using the prodrug approach, various anticancer drugs can be modified to eliminate the limitations or side effects of conventional treatments for cancer.[3].

Prodrugs in anticancer therapy

- **Camptothecin-11**

ACETYLCHOLINESTERASE (AcChE) is the enzyme involved in degrading acetylcholine. Consequently, when anticancer prodrug CPT-11 is administered, it inhibits Acetylcholinesterase. However, this prodrug causes rapid catalysis by butyl cholinesterase to create SN-38 (7-ethyl-10-hydroxycamptothecin), which inhibits topoisomerase 1, an enzyme that is involved in the cutting of one of the two strands of double-stranded DNA so, by this way, there will not form new tumor cells. But due to inhibition of the AcChE enzyme, there are more chances of the cholinergic syndrome in which excess acetylcholine is formed, so in this condition, atropine is given to reduce this effect.[1].

- **Doxorubicin and Cephalosporin**

Prodrugs have very much capacity to give active drugs having higher potential than alone drugs this can see from CCM and C-DOX prodrugs. These prodrugs are useful in anticancer treatment. C-DOX is Cephalosporin doxorubicin and CCM is 7-(4-carboxybutanamido)-cephalosporin mustard. The bacteria *Enterobacter cloacae* β lactamase (bL) is gram-negative bacteria that is responsible for the catalytic conversion of CCM and C-DOX to the active drug. The active drug released is doxorubicin and phenylenediamine mustard. To explain this prodrug activity anti-melanoma monoclonal antibody (mAb)- β -lactamase conjugate used for activation of prodrug and binding with the cell surface of cancer cell should have high affinity so mAb 96.5 have this property to bind with melanotransferrin antigen (p97). So, to know prodrug ability towards anticancer property an experiment is done as follows i) C-DOX prodrug and 96.5-bL is administered to mice having 3677tumor cell and the observed recovery of the cell is not found. ii) CCM prodrug with 96.5- bL when administered to mice it recovers 3677 tumor cells. iii) C-DOX and CCM with 96.5 bL combination cured 3677 tumor cells and in addition to that no toxicity side effects. By considering the above points we can say that CCM prodrug shows more effectiveness than C-DOX.[4]

- **SN-38 glucuronide**

In the above point, we have seen CPT-11 prodrug require enzymatic hydrolysis to convert into SN-38. And also saw how this enzyme causes an antitumor effect by blocking topoisomerase 1 in S-phase. When SN-38 is metabolized it produced inactive SN-38 glucuronide (SN-38G) which decreases the activity of SN-38. Here they considered that when SN-38G is administered in the body its hydrolysis will increase the anticancer activity of CPT-11. For selective hydrolysis of SN-38G to SN-38 the carcinoma cells of human bladder EJ and EJ/mβG (membrane-tethered β-glucuronidase) had been used. EJ/mβG cells show more sensitivity to SN-38G invitro. When systemic administration of CPT-11 was done there is accumulated SN-38G and hydrolysis of SN-38 in the EJ/ mβG tumor located site. By the systemic administration of CPT-11, there is no increased systemic toxicity is observed, and also delayed growth of EJ/ mβG xenografts. Hence, the anticancer activity of CPT-11 can enhance by the conversion of endogenously generated SN-38G to SN-38 in tumors at a high level. In the patients who have been treated with CPT-11, the concentration of SN-38G is high in serum so the response can be increased by raising β-glucuronidase activity in tumors.[5].

- **Human cytochrome P450 1A1**

Human cytochrome P450 1A1 with bergamottin and erlotinib show active site modifications for binding of diverse ligands. Cytochrome P450 monooxygenases which are known as a superfamily of enzymes have functions in the metabolism and detoxification of a large variety of drugs and environmental toxins. Because CYP1A1 has a role in human carcinogenesis if inhibited its activity might potentially help in cancer chemoprevention, whereas utilizing CYP1A1's oxidative activity could help selectively activate anticancer prodrugs. To have such capacity for therapeutic purposes requires detailed knowledge of interactions of CYP1A1's with potential ligands. CYP1A1 ligands also differ substantially in size and it has not been seen from a single existing CYP1A1 structure how larger, structurally very different ligands are accommodated within the enclosed active site. Natural product furanocoumarin bergamottin and the lung cancer drug erlotinib show binding orientations are consistent with the formation of non-harmful metabolites and toxic metabolites, respectively. Local changes on the active site enlarge the active site and ultimately form a channel to the protein exterior. Although further structural modifications would be required to accommodate the largest CYP1A1 ligands knowing which components of the active site easily provides the

right information for those who are trying to use computational approaches to estimate compound binding and substrate metabolism by this clinically relevant monooxygenase[6].

- **Acyloxymethyl esters of isophosphoramide mustard**

Carboxylesterase causes activation of prodrugs so the synthesis of ester analog iPAM using oxy methyl as a linker can be activated by using carboxylesterase. So, by use of ester as a prodrug changes the lipophilicity of the drug and as a result, there was an increase in adsorption and distribution. Two prodrugs have been obtained in the reaction of isophosphoramide mustard. To gain better selectivity of cytostatic drugs, they synthesized new ester analogs of iPAM with oxy methyl linker, which may be activated with the aid of using carboxylesterase. with the corresponding acetoxymethyl halides and show antitumor activity. By studying various linkers for iPAM we can do progress for better selectivity.[7]

- **(Pt(DACH)(mal)2)**

To get the desired compound studied nine novel compounds shown in (Fig.1). The most promising drug candidate, 4b (Pt(DACH)(mal)2) established low in vivo toxicity however profound anticancer activity against both L1210 leukemia and CT-26 colon carcinoma models and they observed the determined anticancer and specifically antileukemic activity blended with low systemic toxicity in animal experiments shows that compound 4b probably a promising candidate for further preclinical development. The obtained results for the 4b compound are as follows: 1) Stability in Aqueous media-Maintain under physiologically relevant conditions and seen as it is stable in aqueous media within 1 hour and also in phosphate buffer saline (PBS) at PH 7.4 and 6.0 and in 0.05 M HCl. After 24 hours no decomposition occurs in the 4b compound having bidentate amine. 2) Lipophilicity: By measuring logKw and logK30 using RP-HPLC and mobile phase used water/ MeOH. So logKw value obtained is -0.11 ± 0.01 and logK30 is -0.65 ± 0.02 these values show lower logK values. 3) In vitro study: Faster hydrolysis and reduction were seen in the 4b compound which means higher toxicity for cancer cells. 4) In vivo study: 4b shows the most promising drug candidate, 4b (Pt(DACH)(mal)2) and also low in vivo toxicity and found great anticancer activity against both L1210 leukemia and CT-26 colon carcinoma models specifically. So 4b can be considered for future study.[8]

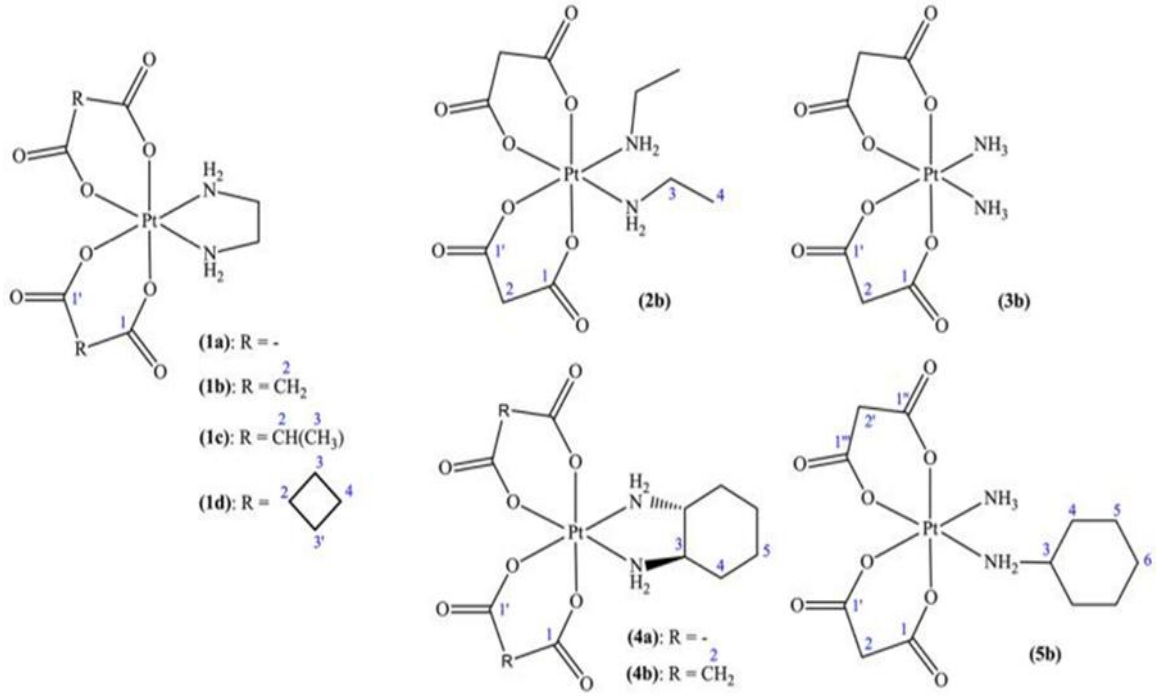


Fig. 1: Chemical structures of novel diam(m)inebis (dicarboxylate) platinum (IV) complexes 8.[8]

- **Sulforaphane**

Sulforaphane (SF) has chemoprotective properties derived from cruciferous vegetables. And it is having the property to increase the antioxidant effect. Dinitrobenzamide mustard have pre-prodrug PR-104 and prodrug metabolite PR-104A.To see this effect the Aldo-keto reductase 1C3 (AKR1C3) protein is obtained by treating a low concentration of SF to HT29 colon cancer cells. For identification proteins modulated via a low concentration of SF, they treated HT29 colon most cancer cells with 2.5 μM SF. Protein abundance modification had been detected by stable isotope labeling of amino acids in cell culture. 18 proteins were found which are up-regulated noticeably so in that Aldo-keto reductase 1C3 (AKR1C3) and bioactivated the DNA cross-linking prodrug PR-104A which is further characterized by Preconditioning HT29 cells with SF and there is a decrease in EC50 of PR-104A 3.6- fold. The increase in PR-104A cytotoxicity was linked to AKR1C3 abundance and activity, both induced each prompted via means of SF in a dose-dependent way and this impact change was reproducible in a second colon cancer cell line SW620, however not seen in other colon cancer cell lines wherein AKR1C3 abundance and activity were absent or slightly detectable and couldn't be improved by SF. SF had no such influence on PR-104A cytotoxicity on normal cells. In conclusion, the response of PR-104A after preconditioning with SF was seen

only in cancer cells and AKR1C3 is expressed, while non-cancerous cells did not show such a response.[9]

- **Puromycin [Boc-Lys (Ac)-Puromycin]**

They formerly studied and developed a prodrug approach for selective cancer therapy by use of a masked cytotoxic agent puromycin [Boc-Lys (Ac)-Puromycin], which may be sequentially activated through histone deacetylases (HDACs) and cathepsin L (CTSL) to kill cancer cells and expresses high levels of both enzymes. Although the promise as a selective cancer therapy, its requirement of relatively excess dosage might be having the capacity to develop difficulty in the clinical setting to cope with this difficulty, they aimed addition to enhance the overall efficacy of our prodrug approach. As the proteolytic cleavage through CTSL is the rate-limiting step for the drug activation, they attempt to enhance the substrate structure for CTSL activity by modification in the α-amino protecting group of lysine Show that protection with Fmoc [Fmoc-Lys(Ac)-Puromycin] (Fig. 2) exhibits a marked development in overall anticancer efficacy as compared to the original Boc-Lys(Ac)-Puromycin and that is mainly because of the highly efficient cellular uptake apart from its improved substrate structure. Furthermore, to cope with the difficulty that the improved drug efficacy might attack high toxicity to the normal cells, they confirmed that Fmoc-Lys (Ac)-Puromycin nevertheless has amazing cancer cell selectivity in vitro and no apparent systemic off-target toxicity in vivo. Thus, their preclinical assessment data reveal that the Fmoc-Lys (Ac)-Puromycin has significantly improved anticancer efficacy.[10]

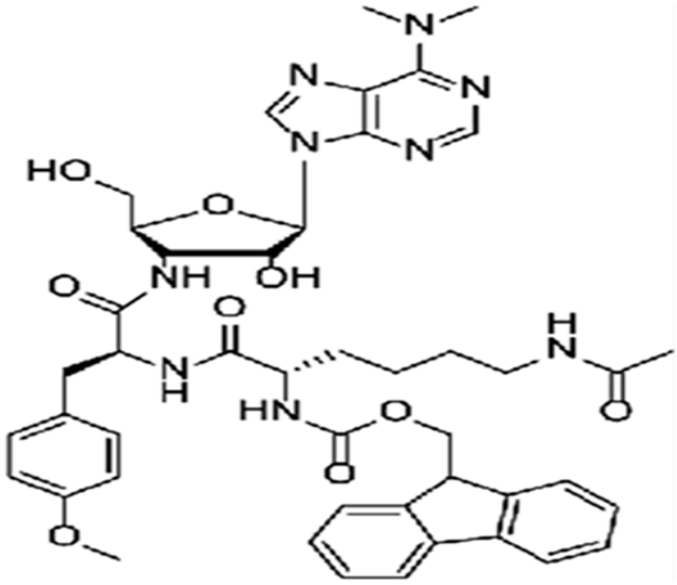
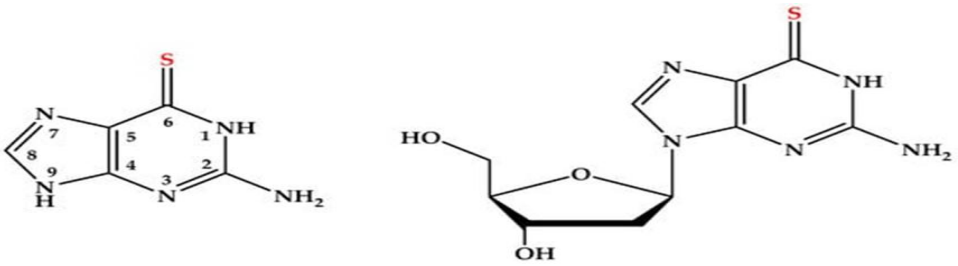


Fig. 2: Chemical structure of Fmoc-Lys (Ac)-Puromycin.[10]

- **6-Thioguanosine**

Sulfur-substituted purine nucleobases have long been prescribed to deal with inflammatory bowel disease, arthritis, and numerous cancers. 6-Thioguanosine (6tGuo) is produced and integrated into DNA following extensive metabolization of 6-thioguanine (6tGua), 6-mercaptopurine, or azathiopurine and the only structural difference among 6tGua and 6tGuo is N9-glycosidic substitution (Fig. 3), recent work has shown that the sugar substituent can play important role in the excited-state properties of sulfur-substituted DNA bases.[11]



6-Thioguanine (6tGua) 6-Thio-2'-deoxyguanosine (6tGuo)

Fig. 3: chemical structures of 6-Thioguanosine and 6-Thioguanosine.

- **Devd-S-Dox/DCK Therapy**

This new therapy with an anticancer prodrug approach can be alternative for treating cancer for the long-term attributed to its oral availability and low-toxicity profile in addition to the effective anticancer effect. Radiotherapy-assisted orally available metronomic apoptosis-targeted chemotherapy can be used to overcome changing behavior of cancer and also not have success in cancer treatment. Doxorubicin can be released continuously and selectively to only radiation-given cells with sufficient oral bioavailability and this can be possible by using this method with minimum toxicity. This prodrug was not active by itself but showed great impact in anticancer activity when given with radiotherapy. As a result, the daily oral administration of DEVD-S-DOX/DCK in combination with the low-dose radiotherapy effectively suppressed the growth of tumor in vivo with no significant systemic toxicities no matter that the accumulated dose of doxorubicin passed 150 mg/kg.[12]

- **YD0171 as an inhibitor**

Colorectal cancer cells contain high levels of cystathionine-β-synthase (CBS) so for its inhibition synthesized methyl ester derivative of aminooxyacetic acid (AOAA) called YD1071. YD0171 prevents the action of mitochondrial respiration and glycolytic function and taken approximately G0/G1 arrest, but did not show tumor cell apoptosis or necrosis. The

efficacy of YD0171 as an inhibitor of tumor growth was examined in nude mice bearing subcutaneous HCT116 cancer cell xenografts. A 5-d safety observation in mice proved that YD0171 at 20 mg/kg/d (given in two divided doses) the results obtained are i) does not enhance plasma markers of organ injury ii) does not show histological changes in the liver or kidney iii) Give rise to moderate rise in plasma homocysteine levels which is an amino acid produced when proteins are breakdown. So, from these results we can say that the prodrug technique enhances the pharmacological profile of AOAA; YD0171 which exhibits a prototype for CBS inhibitory anticancer prodrugs. By targeting colon cancer an emerging approach illustrates may offer excellent opportunities.[13]

- **Camptothecin (CPT)**

A natural alkaloid from Camptotheca acuminate has very good anticancer properties against a variety of cancers by the mechanism of inhibition of the DNA enzyme topoisomerase I (topo I). It is having active lactone ring instability, lack of target specificity, poor aqueous solubility, and high lipophilicity. A 750-amino acid type II transmembrane peptidase enzyme is a prostate-specific membrane antigen (PSMA) that is encoded by the folate hydrolase 1 (FOLH1) gene. A series of PSMA activated CPT prodrugs were synthesized and prepared by coupling water-soluble pentapeptide, a PSMA hydrolyzing substrate, to CPT through an appropriate linker. PSMA was administered within tumor having sites and the cytotoxicity of CPT prodrugs had been blocked for some time until they were hydrolyzed by the PSMA. To see in vitro selective cytotoxic activities of the prodrugs are evaluated against PSMA-expressing human prostate cancer cells which are LNCaP-FGC and non-PSMA-expressing cancer cells HepG2, Hela, DU145, PC-3 MCF-7, and normal cells MDCK, LO2 by standard methyl thiazole tetrazolium (MTT) assay. The cellular uptake experiment had been done and the PSMA-targeting ability of the CPT-HT-J-ZL12 was greatly accumulated in LNCaP-FGC (PSMA+) while it was accumulated minimum in HepG2 (PSMA−) cells. LNCaP-FGC (PSMA+) cell also shows induced cell multiplication of cancer cells than in HepG2 (PSMA−). Cell cycle analysis indicated that CPT-HT-J-ZL12 may cause cell cycle arrest at the S phase.[14]

- **Emetine**

Emetine is a small molecule located in the root of the plant species Carapichea ipecacuanha (Brot.) L. Anderson but now recently this plant species named as Psychotria ipecacuanha (Brot.) Stokes. Structure-activity relationship (SAR) studies have shown that the N-20

position of emetine is essential for its inhibition of protein synthesis and it has to be a secondary amine. This strategy can help target cancer tumor cells without killing normal cells. To overcome steric hindrances and enhance protease-specific cleavage PSA activatable peptide prodrugs of emetine were synthesized. A 2-stage prodrug activation process is needed for the release of emetine in infected cells (cancer cells). In this 2-stage process to obtain full prodrug emetine, prodrug intermediates are coupled to the PSA peptide substrate (Ac-His-Ser-Ser-Lys-Leu-Gln). The prodrug intermediates are 10 (Ala-Pro-PABC-Emetine) and 14 (Ser-Leu-PABC Emetine). These were examined for kinetics of hydrolysis to emetine and potency [Where PABC = p-aminobenzyloxycarbonyl]. Both intermediates liberated emetine when incubated under appropriate conditions, upon coupling of PSA substrate to give the full prodrugs. in vivo toxicity studies are done on those prodrugs and other derivatives of emetine. The only prodrug 16 obtained from 14 was hydrolyzable by PSA. Cytotoxicity research in PSA generates LNCaP and CWR22Rv1 to confirm the activation of the prodrug by PSA. The noticeable cytotoxicity of prodrug16 had been seen to be reduced in cancer cells that do not produce PSA. From the results, we can see results show the importance of conformational modulation in emetine prodrugs in which modification at the N-20 causes emetine to become significantly less cytotoxic (i.e., up to 300-fold reduction). Thus, the N-20 position of emetine represents a potential cytotoxic ‘‘molecular switch” that would be turned ‘‘OFF” in an N-20 modified emetine prodrug and then turned ‘‘ON” when the prodrug is activated in the cancerous tumor microenvironment to release emetine.[15]

- **Chitosan-1-acetic acid-5 fluorouracil**

Drugs like oxaliplatin, 5-fluorouracil (5-FU), folinic acid, methotrexate, bevacizumab (Avastin), and celecoxib (Celebrex) are used to treat colon cancer. However, most of these drugs have few limitations, due to the fact they may be ingested through the mouth and they have a short half-life and nonspecific selectivity. A prodrug for colorectal cancer should be non-toxic, biocompatible, and stable in the small intestine and stomach. Chitosan CS (Fig. 4) is a polysaccharide containing repeated units of glucosamine and N-acetyl glucosamine units linked by β-(1,4)-glycosidic bonds. CS is a fully or partly deacetylated form of chitin and it is a very abundant natural resource. Due to its biodegradable, non-toxic properties and biocompatibility chitosan is good for use in the fabrication of prodrugs, which might be bonded covalently to a carrier macromolecule (polymer). Chitosan (CS) was extracted from local fish scales using a recognized method. 5-FU converted to 1-acetic acid-5-fluorouracil (FUAC) and reacted with this CS to prepare chitosan-1-acetic acid-5-fluorouracil (CS-

FUAC) conjugates as a colon-specific prodrug. The synthesized compound was subjected to a chemical stability study in phosphate buffer (0.2 M, pH 7.4) and KCl/HCl buffer (0.2 M, pH 1.2) at different time intervals (0–240 min) and incubation at 37 °C. These studies discovered significantly greater stability and a longer half-life for the CS-FUAC than for FUAC. The cytotoxicity research of the conjugates has been also evaluated on the human colorectal cancer cell line (HT-29), which confirmed that the conjugates are more cytotoxic than the free drug. So, CS-FUAC conjugates may be taken into consideration to represent potential colon-specific drug delivery agents, with minimal undesirable side effects, for colon cancer therapy.[16]

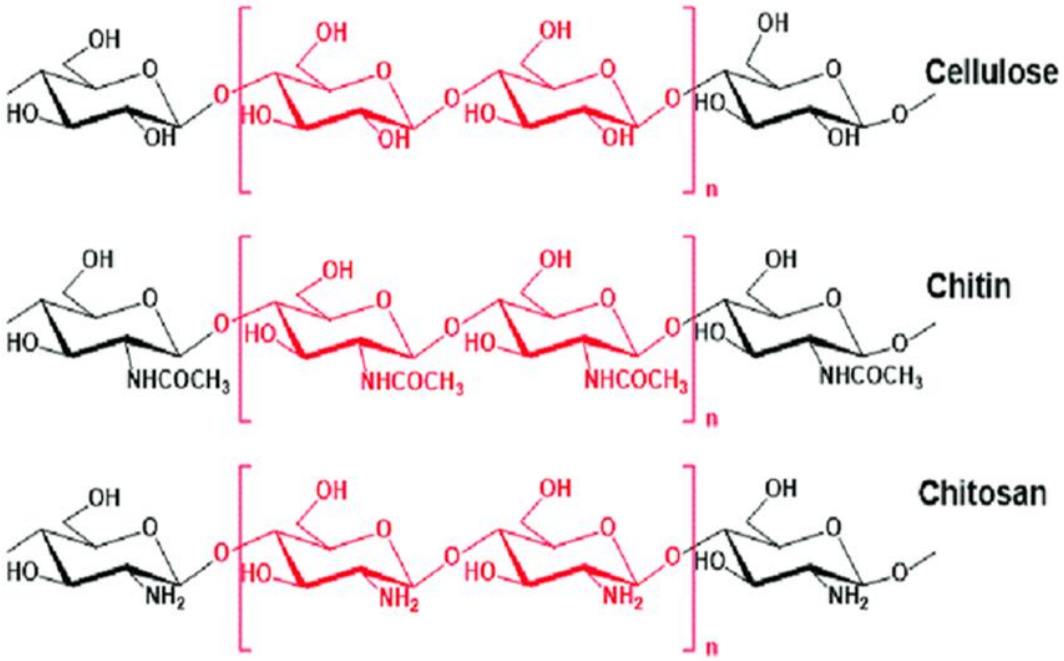


Fig. 4: structures of cellulose, Chitin and Chitosan.[16]

- **Amphiphilic nano theranostics**

This method involves bringing together a structurally homogenous prodrug in one unit and are reproducible. Which has synergistic targeting ability, and integrates the advantageous features of small molecular theranostics and polymer-drug conjugates. Camptothecin (CPT) serves as a hydrophobic disulfide-bridged anticancer drug and the hydrophilic PEG oligomer-bridged biotin segment serves as an active targeting unit focused on optimizing the hydrophilic fragment length to construct stable, well-defined nanostructured assemblies. These are made up of PEGn-biotin units as the controllable hydrophilic fragments and the covalently linked hydrophobic DCM-S-CPT moiety as the fluorescent reporter. Most stable, uniform, and reproducible core-shell micellar nanostructures' structural homogeneity, fixed

drug loading efficiency, real-time drug release tracking, and synergistic targeting could only form by BP20-DCM-S-CPT. To facilitate cellular internalization the shell surface having biotin which is directly exposed to the receptor on melanoma cell can facilitate this process. They describe the strategy of molecularly precise self-assembly of monodisperse nanotheranostics for BPn-DCM-S-CPT with fixed drug loadings and constant release capacities, permitting in vivo real-time targeted therapy. Activatable near-infrared (NIR) fluorophore is taken as a bis-condensed dicyanomethylene-4H-pyran (DCM) derivative and it uses two-terminal conjunctions. The active target is the hydrophobic disulfide-bridged anticancer prodrug camptothecin (CPT) and the hydrophilic oligomer-bridged biotin segment. BP20-DCM-S-CPT showed excellent tumor-specific (target-specific) drug release in HeLa tumor-bearing nude mice, in which there was enhanced in vivo antitumor activity and almost destroy the tumor and have few side effects.[17]

- **SN38-PA liposomes**

SN38 is a very good antitumor analog of camptothecins (CPTs) but has drawbacks like poor water solubility, and low plasma instability. As Compared to CPT-11, SN38-PA liposomes are more stable in close lactone form, more efficient in conversion rate to SN38, and have maximum potency in cytotoxicity against cancer cells. Pharmacokinetic studies show SN38-PA liposome has a very good improved plasma half-life (t1/2) value of SN38 and increased area under the curve (AUC) of SN-38 was 7.5-fold higher as compared to CPT-11 and SN38 is a more active metabolite in each tissue seen in biodistribution study. The pharmacodynamic study revealed that SN-38 liposomes had a higher antitumor effect and antitumor inhibition rate of 1.61 times that of CPT-11. As SN38-PA liposomes show significantly higher drug loading, more stable lactone form, more effective conversion rate, and improved in vivo pharmacokinetics and hence drawbacks are eliminated, compared to CPT11.When further studies are done SN38-PA liposomes show excellent anticancer activity against large cultured cancer cells, and mice having S180 tumors show favorable therapeutic effects in S180 tumor-bearing mice. Therefore, considering all these results, the SN38-PA liposomes show a good ability to bind the target site and potential for further clinical use.[18]

- **Irinotecan**

It is a prodrug that requires its hydrolysis by the carboxylesterase CES2 for conversion into the active compound 7-ethyl-10-hydroxycamptothesin (SN-38). carboxylesterase CES2 enzyme has 60-fold better hydrolytic performance against irinotecan than CES1.CES1is

another human carboxylesterase isozyme and have the ability of colorectal tumors to hydrolyze but irinotecan correlates with their expression of CES2, but not CES1. CES2 has been approved for the treatment of many types of solid tumors, including colon cancer. CES2 expression in the cell is regulated by the tumor suppressor protein p53. p53 is a tumor suppressor that is activated by several cellular stresses such as DNA damage, oxidative stress, and hypoxia. The relationship between the TP53 gene and CES2 expression in colon cancer is not seen. In most colorectal cancer specimens 70% had lower CES2 mRNA levels than the adjacent normal tissue, and only 30% had higher CES2 mRNA levels. TP53 gene sequencing shows no relationship between CES2 downregulation and TP53 mutational status, while colorectal cancer cells expressing wild-type p53 show p53-dependent upregulation of CES2. This means that CES2 mRNA expression is lowered in human colorectal cancer without depending on p53.[19]

- **Ruthenium anticancer prodrugs**

Photodynamic therapy (PDT) and photoactivated chemotherapy (PACT) use poorly penetrating high energy photons which is a blue or green light for their activation and this is the drawback of these therapies. Upconverting nanoparticles (UCNPs) b produce high-energy light under near-infrared (NIR) excitation, which may solve this issue if the coupling between the UCNP surface and the Ru prodrug is rearranged to produce stable nanoconjugates with efficient energy transfer from the UCNP to the ruthenium complex. There are two structurally related ruthenium (II) polypyridyl complexes. First is [Ru(bpy)2(5)](PF6)2 ([1](PF6)2) and it is photolabile but nonselective and slow photosubstitution of one of its three ligands, making it a poor PACT compound. Second complex is [Ru(bpy)2(6)](PF6)2 ([2](PF6)2) and it is efficient and photostable PDT photosensitizer.(bpy = 2,2-bipyridine, 5 is 5,6-bis(dodecyloxy)-2,9-dimethyl-1,10-phenanthroline, and 6 is 5,6-bis(dodecyloxy)-1,10-phenanthroline). The water-dispersible, negatively charged nanoconjugate UCNP@lipid/ [2] produces reactive oxygen species (ROS).[20]

- **Piperine (Pip)**

Like camptothecin alkaloid, piperine is also a natural plant-derived alkaloid and prodrug. Pip is an amide alkaloid extracted and isolated from the fruits of the black pepper plant (*Piper nigrum Linn*). A novel DDS comprising hydroxyapatite nanoparticles with phosphonate groups (HAPs) at pH 7.2 and 9.3 as nanocarriers loaded with Pip and coating of gum Arabic (GA) and conjugation of folic acid (FA) prolonged the release effect on the surface as active

targeting ligands for cancer selectivity. The synthetic HAPs are structurally identical to the hydroxyapatite found in human bones because it is suitable as a drug carrier. The nanoformulations full inhibition that is~60% seen in monolayer HCT116 colon cancer cells but less in Caco2 colon cancer and MCF7 breast cancer cells after 72 h and free Pip had a weaker effect. The longer release was observed at pH 7.4 and a higher release rate was obtained at pH 6.8 and pH 5. So, this DDS for pip is effective for HCT116 colon cancer cells.[21]

- **Curcumin**

Curcumin when administered through the oral route the concentration of curcumin in the blood is so low to have a maximum antitumor effect. After oral administration of curcumin, it produces metabolite curcumin β-D-glucuronide (curcumin monoglucuronide, CMG) so, this metabolite had been synthesized in vivo which is water-soluble and can be injected intravenous. From (fig.10) the conversion of the free form of curcumin by synthetic CMG (intravenously) in presence of β-glucuronidase might give more than 1000 times higher plasma curcumin levels as compared to oral administration.[22]

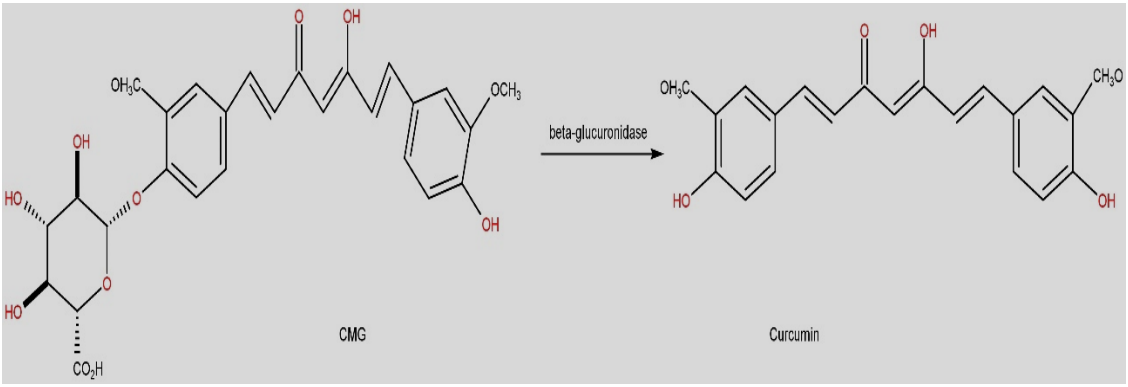


Fig. 10: curcumin β-D-glucuronide (CMG) converted to curcumin by β glucuronidase.[22]

- **Gene-directed enzyme prodrug therapy**

(GDEPT) it is a two-step process for cancer treatment. In the first step, a gene expressing the enzyme is delivered. In the second step, a prodrug is administered that can be activated to a toxic drug by the enzyme that has been expressed in the tumor. A single polymeric micellar carrier is developed that contains both prodrug GCV and its activating HSV-tk gene for establishing a one-step approach for GDEPT in which both gene and prodrug were delivered at the same time by incorporating them with polymeric micellar nanovectors. The polymeric

nanocarrier is composed of a hydrophobic inner core formed by Poly(ε-caprolactone) (PCL) which is linear resorbable and has a hydrophilic outer shell. GCV had been an initiator in the ring-opening polymerization of ε-caprolactone (ε-CL) for the synthesis of hydrophobic GCV-poly(caprolactone) (GCV–PCL), then it was further inserted with hydrophilic chitosan to obtain an amphiphilic polymer (GCV–PCL– chitosan) for the fabrication of self-assembled micellar nanoparticles. To check anti-cancer effectiveness HT29 colorectal cancer cells cultivated with Polymeric prodrug micelles incorporated with HSV-tk encoding plasmids. In one step there is the delivery of prodrug GCV and HSV-tk cDNA encoded plasmid incorporated in GCV–PCL–chitosan polymeric nanocarriers to HT-29 cells and started high cytotoxicity. So, they gain a one-step process with GCV–PCL–chitosan/HSV-tk nanovectors as potent carriers for cancer therapy.[23]

- **Doxorubicin and Daunorubicin**

Drugs from the anthracycline class **are** used in chemotherapy for anticancer treatment but this class of drugs has systemic toxicity and also cardiovascular risk. Anthracyclines are used widely in chemotherapy and belong to anticancer drugs. doxorubicin (DOX) and daunorubicin (DAU) are anthracyclines that are given with antibiotics in chemotherapy. Here they prepared new prodrug conjugates which are formed by ester bond, Polyhedral oligosilsesquioxanes [POSS(OH)32] as nanocarrier which is water-soluble, Polyethylene glycol (PEG), biotin and succinic anhydride-modified (SAMDOX and SAMDAU) with carboxylic function had been used and form the POSS-anthracycline conjugates (fig. 12). These conjugates increased the active drug release time so lower dose administration can give high potency in addition that these conjugates are having large sizes so there will be less harm to a normal cell. So, this system is useful for anticancer therapy.[24]

CONCLUSIONS

We can conclude that there is very much enhancement in anticancer drugs by using the prodrug approach and also research is still going on to make more improvements for a better future. Many drugs produce metabolites and these can be used as a prodrug for better target delivery of an active drug. So, if more progress is done on this approach surely, we will gain success for a better future.

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REFERENCES

1. Christopher LM, Randy MW, Mary K D, Philip MP. The Anticancer Prodrug CPT-11 Is a Potent Inhibitor of Acetylcholinesterase but Is Rapidly Catalyzed to SN-38 by Butyrylcholinesterase. Cancer Res J, 1999; 59(7): 1458-1463.
2. Alicia JS, Jun Z, Sarah P, Esmael MA, and Ching-An P. Polymeric Nanovectors Incorporated with Ganciclovir and HSV-tk Encoding Plasmid for Gene-Directed Enzyme Prodrug. Molecules, 2021; 26(6): 1-15.
3. Abdulilah DB Y. Computational Study on the Mechanism of the Photouncaging Reaction of Vemurafenib: Toward an Enhanced Photoprotection Approach for Photosensitive Drugs. Molecules, 2021; 26(7): 1-15.
4. David EK, George JS, Vivekananda MV, Hakan PS, Inegerd H, Karl EH, and Peter DS. Regressions and Cures of Melanoma Xenografts following Treatment with Monoclonal Antibody β-Lactamase Conjugates in Combination with Anticancer Prodrugs. Cancer Res J, 1995; 55(16): 3558-3563.
5. Zeljko MP, Kai CC, and Steve RR. Local enzymatic hydrolysis of an endogenously generated metabolite can enhance CPT-11 anticancer efficacy. AACR J, 2009; 8(4): 940-946.
6. Aaron GB and Emily ES. Structures of human cytochrome P450 1A1 with bergamottin and erlotinib reveal active-site modifications for binding of diverse ligands. J Bio Chem, 2018; 293(50): 1-24.
7. Joanna C, Konard M, Beata FS and Joanna W. ACYLOXYMETHYL ESTERS OF ISOPHOSPHORAMIDE MUSTARD AS NEW ANTICANCER PRODRUGS. Acta Polo Pharma, 2013; 70(3): 481-487.
8. Hristo PV, Simone G, Petra H, Sarah T, Alexander R, Frank J, Michael AJ, Walter B, Markus G, Bernhard KK. A Novel Class of Bis- and Tris-Chelate Diam(m)inebis (dicarboxylate)platinum(IV) Complexes as Potential Anticancer Prodrugs. J Med Chem, 2014; 57(15): 6751-6764.
9. Melanie ME, Cédric B, Katrin M H, Sabine S, Pascale W, Nadine S, Simona C, Niko B, Jerry WS, Giancarlo M, Bernd W, Shana JS. Sulforaphane Preconditioning Sensitizes Human Colon Cancer Cells towards the Bioreductive Anticancer Prodrug PR-104A. Plos One J, 2016; 11(3): 1-17.
10. Nobuhide U, Wei W, Cooper S, Caroline MN, Nicole SS, and Michael JH. Synthesis and Preclinical Evaluation of a Highly Improved Anticancer Prodrug Activated by Histone Deacetylases and Cathepsin L. Theranostics J, 2016; 6(6): 808-816.

11. Brennan Ashwood, Steffen Jockusch and Carlos E. Crespo-Hernández. Excited-State Dynamics of the Thiopurine Prodrug 6-Thioguanine: Can N9-Glycosylation Affect Its Phototoxic Activity?. Molecules, 2017; 22(3): 1-15.
12. Seung WC, Seho K, Beom SL, Gui CK, Foyez M, Hanul L, Young SC, Jeong Uk C, Ok-Cheol J, Ji WK, Seong WK, In-San K, Sang YK, and Youngro B. Radiotherapy-assisted tumor-selective metronomic oral chemotherapy. Int J Cancer, 2017; 141(9): 1912–1920.
13. Celia C, John RZ, Ye D, Ciro C, Amy AM, Nadiya D, Paul J, Haiying C, Judy LH, Antonia A, Kazunori Y, Gabor O, Petra S, Gabor T, Fredrick JB, Minal C, Rachel L, David E, Akbar A, Katalin M, Ashley U, Bartosz S, Andreas P, Jia Z, Mark RH, and Csaba S. Cystathionine-a-Synthase Inhibition for Colon Cancer: Enhancement of the Efficacy of Aminooxyacetic Acid via the Prodrug Approach. Mol Med J, 2016; 22: 361-379.
14. Bing X, Fei Z, Meng-Meng Y, De-Sheng C, Wen-Bo G, Yu-Qin Y, Xiao-Hui J, Wen-Xi Z, Tong L, Tao M, Peng-Long W and Hai-Min L. PSMA-Oriented Target Delivery of Novel Anticancer Prodrugs: Design, Synthesis, and Biological Evaluations of Oligopeptide-Camptothecin Conjugates. Int J Mol Sci, 2018; 19(10): 1-21.
15. Emmanuel SA, Marc DR, Oladapo B, Samuel RD. Anticancer activities of emetine prodrugs that are proteolytically activated by the prostate-specific antigen (PSA) and evaluation of in vivo toxicity of emetine derivatives. Bioorg Med Chem, 2017; 25(24): 6707-6717.
16. Mohsin OM, Kameran SH and Nadia QH. Preparation and Bioactivity Assessment of Chitosan-1-Acetic Acid-5-Fluorouracil Conjugates as Cancer Prodrugs. Molecules, 2017; 22(11): 1-12.
17. Chenxu Y, Zhiqian G, Yanyan S, Yi C, He T, and Wei-Hong Z. Molecularly precise self-assembly of theranostic nanoprobes within a single-molecular framework for in vivo tracking of tumor-specific chemotherapy. Chem Sci, 2018; 9: 4959-4969.
18. Chan W, Yang Z, Daoqiu Y, Jinfeng Z, Juanjuan M, Dan C, Jianming C, Li D. Novel SN38 derivative-based liposome as an anticancer prodrug: an in vitro and in vivo study. Int J Nanomaterials, 2018; 14: 75-85.
19. Momoko I, Hyeon-Cheol L, Hirofumi N Hajime O, Toshiyuki K, Konomi M, Mikumi E, Ituro I, Koichi S, and Takehiko Y. The Relationship between TP53 Gene Status and Carboxylesterase 2 Expression in Human Colorectal Cancer. Dis Markers, 2018; 2018: 1-7.

20. Michael SM, Victorio ST, Michiel FH, Roxanne EK, Albert MB, Marta MN, and Sylvestre B. NIR-Light-Driven Generation of Reactive Oxygen Species Using Ru(II)-Decorated Lipid-Encapsulated Upconverting Nanoparticles. Langmuir, 2019; 35: 12079-12090.
21. Khaled A, Agata S, Iman MH, Magdalena J, Anna SS, Agnieszka C, Jacek W, Urszula S, Samar AS, Ahmed M. A-E, Faten A-E, Stanislaw G, Tomasz C and Witold L. Effective Targeting of Colon Cancer Cells with Piperine Natural Anticancer Prodrug Using Functionalized Clusters of Hydroxyapatite Nanoparticles. Pharmaceutics, 2020; 12(1): 1-28.
22. Hitomi O-U, Atsuhiro K, Atsushi I, Tadashi H, Tadashi A, Hideaki K, Masashi K. Curcumin β-D-glucuronide exhibits anti-tumor effects on oxaliplatin-resistant colon cancer with less toxicity in vivo. Cancer Sci, 2020; 111(5): 1785-1793.
23. Alicia JS, Jun Z, Sarah P, Esmael MA and Ching-An P. Polymeric Nanovectors Incorporated with Ganciclovir and HSV-tk Encoding Plasmid for Gene-Directed Enzyme Prodrug Therapy. Molecules, 2021; 26(6): 1-5.
24. Kinga P, Jan K and Wlodzimierz AS. Novel Polyhedral Silsesquioxanes [POSS(OH)32] as Anthracycline Nanocarriers—Potential Anticancer Prodrugs. Molecules, 2021; 26(1): 1-15.