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A Vitamin Drug Conjugates Like Folic Acid for Anticancer Activity

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ABSTRACT

Cancer, after cardiovascular diseases, stands as the second most prevalent cause of death globally. Chemotherapy serves as the established and effective method for treating cancer. However, traditional chemotherapy has certain limitations, including low solubility in water, short duration of action in the body, development of resistance to multiple drugs, and lack of specificity or potential toxicity to healthy cells. The development of a precise drug delivery system to target cancer cells and achieve the desired anticancer effect remains a formidable challenge.

Keywords: Cancer, chemotherapy, anticancer drug and vitamin, folate, chemotherapy, folate receptors

Introduction

Cancer is an illness distinguished by the unregulated proliferation of cells within the human body, which, if not appropriately controlled, can disseminate to other regions of the body. It is a multifaceted ailment that can arise from any cell or organ, with numerous factors playing a role in its progression. Presently, cancer ranks as the second most prevalent cause of mortality globally, trailing behind cardiovascular disease.9,10,11)

The primary methods of treating cancer consist of surgery, radiotherapy, immunotherapy, hormonal therapy, laser therapy, and stem cell therapy. Surgery and radiotherapy are particularly effective in treating localized tumors and nonmetastatic cancers. Conversely, drugs like chemotherapy, biological therapy, and hormonal therapy are utilized for metastatic cancer. These medications can reach all body tissues via the bloodstream. Among these treatment choices, chemotherapy is regarded as the preferred approach because of its capacity to impede the rapid growth of cancer cells. Nevertheless, the precise targeting of cancerous cells with anti-cancer drugs continues to pose a challenge in cancer research. (12)

To address this challenge, various strategies can be considered. One commonly used method involves utilizing efficient drug delivery systems. Among these, polymeric drug carriers stand out for their adaptability and ease of chemical modification. These carriers can either passively accumulate in different organs based on their elimination pathway or actively target specific organs. Moreover, targeting agents like vitamins, antibodies, peptides, magnetic particles, or hormones can be incorporated into the carrier to enhance the precision of drug delivery. 13,14)

Vitamin-drug conjugates

A drug is connected directly or via a spacer to a targeting moiety to create a new pharmacologically active compound known as a vitamin-drug conjugate.

Benefits: Vitamin-drug conjugates are non-toxic, selectively internalize into cancer cells, and release anticancer drugs with full efficacy. They also reduce systemic toxicity by remaining stable in the bloodstream and exhibit target-specific activity, sparing normal cells and minimizing potential side effects.(15)

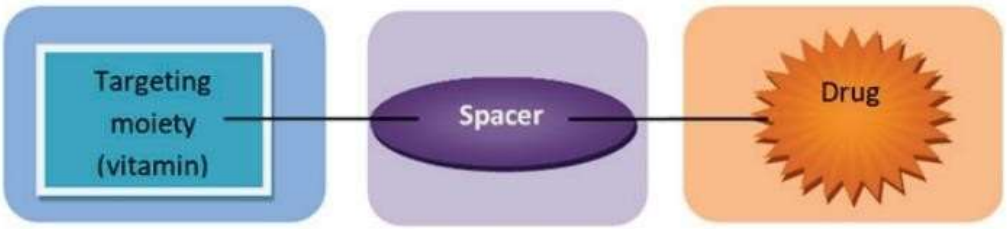


Figure 1. Vitamin drug conjugate.

Folic acid

Folic acid, also known as vitamin B9, is a crucial water-soluble vitamin that is converted to tetrahydrofolic acid within the body. This conversion is vital for normal erythropoiesis, the synthesis of purines and thymidylates, the metabolism of amino acids like glycine and methionine, as well as the metabolism of histidine (Hillman, 1995). Folic acid is recommended for the prevention and treatment of folic acid deficiency conditions, including megaloblastic anemia and anemias of nutritional origin during pregnancy, infancy, or childhood. It is often prescribed to women planning to conceive and during the early stages of pregnancy to decrease the risk of neural tube defects and other birth defects (Product Information Folic acid tablets, 1998). Folic acid, a water-soluble micronutrient, is sometimes referred to as pteroylglutamic acid or vitamin B9. It is the naturally occurring form of folate found in high concentrations in leafy greens like spinach, lettuce, broccoli, okra, asparagus, fruits such as bananas, melons, and lemons, beans, yeast, mushrooms, and meat. Medically, folic acid is utilized to treat various conditions resulting from folate deficiency, such as low blood pressure or anemia. It is an essential vitamin crucial for cellular growth and regeneration, yet often overlooked. Some of the key functions of folic acid in the body include nucleotide biosynthesis in cells and providing Red blood cell formation, epigenetic control of gene expression, and the prevention of anemia are all crucial functions of folic acid. It plays a key role in promoting normal fetal growth and development, particularly in the brain. Folic acid, along with calcium and iron, is often referred to as the essential trio for prenatal health. Deficiency of this vitamin in expectant mothers can have detrimental effects on the brain development of their unborn babies. It is important to note that while folic acid and folate are commonly used interchangeably, they are biologically distinct. Folate is the natural form of vitamin B9 found in various plant and animal sources, while folic acid is the synthetic form commonly found in supplements and fortified foods (16)

Chemical composition and molecular structure

Folic acid, also known as (2S)-2-[[4-[(2-amino-4-oxo-1H-pteridine-6-yl) methylamino]benzoyl]amino] pentanedioic acid, possesses an odorless orange-yellow hue. Its molecular weight is approximately 441.404 g/mol. Folic acid exhibits a melting point of 482°F and its molecular formula is C19H19N7O6. This compound is hydrophilic and exhibits slight solubility in organic solvents such as methanol, ethanol, and butanol. (Fig2.(16)

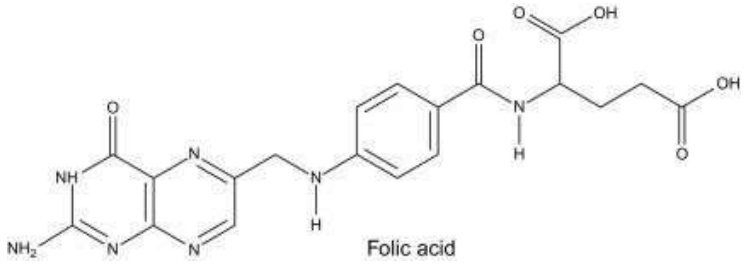


Fig.no.2

Sources

Dark leafy green vegetables such as spinach, collard greens, turnip greens, mustard greens, and romaine lettuce are widely known for their high folic acid content, making them an important source of folate. Asparagus is another vegetable that is rich in folic acid, providing up to 262 µg per serving. Additionally, it is a good source of vitamin K, vitamin C, vitamin A, and manganese. Avocado/butter pea is also worth mentioning, as it contains up to 110 µg of folate per cup. Brussels sprouts, in addition to their abundance of vitamin C, vitamin K, vitamin A, manganese, and potassium, can fulfill 25% of the daily requirement of folic acid in just one cup. Lastly, beans, peas, and lentils, including pinto beans, lima beans, green peas, black-eyed peas, and kidney beans, are all excellent sources of folic acid.

Molecular targets

Insufficient levels of folic acid in humans, below the recommended daily intake of 400 µg, can result in an elevated risk of different types of cancers, such as colorectal, breast, ovarian, pancreas, brain, lung, cervical, and prostate cancers. To address this issue, patients are prescribed methotrexate, a medication that hinders the production of active tetrahydrofolate from inactive dihydrofolate and helps alleviate its side effects, including inflammation. Additionally, a supplement called leucovorin, which contains folinic acid, is administered to provide sufficient folate for maintaining normal cell functions in cells that divide at a slower rate. Depletion of folate has been observed to increase the expression of tumor suppressor genes p16INK4A, p21WAF1, and p53, which play vital roles in signaling DNA damage, inhibiting cell cycle progression, and promoting apoptosis. The folic acid receptor acts as a high-affinity receptor responsible for facilitating the absorption of folic acid and its derivative in eukaryotic cells. It is notably overexpressed on the surfaces of numerous cancer cells, including those found in ovarian, cervical, breast, lung, kidney, colorectal, pleura, endometrium, bladder, and brain cancers. Conversely, it is rarely detected on healthy tissues and cells. To enhance the targeted delivery of drugs to specific therapeutic sites while minimizing delivery to other areas, ligands are conjugated with polymeric micelles for active targeting of tumor cells. Examples of these polymeric micelles include chitosan, MPEG, PLGA, PEG, carboxymethyl chitosan, alginates, and bovine serum albumin. These micelles can be used individually with a ligand or in combination with each other.

Vitamin-9 (Folic Acid)-Drug Conjugates

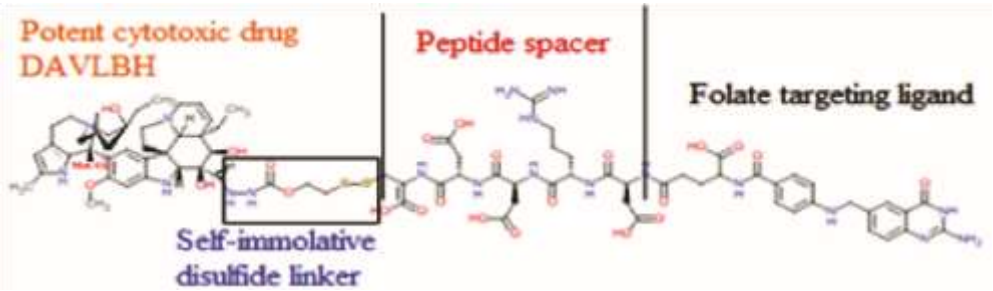
Folic acid is closely associated with folate receptors. A membrane folate receptor linked to glycosylphosphatidylinositol (GPI) plays a role in the absorption of folate-based chemotherapeutic drugs through receptor-mediated mechanisms. This membrane protein, connected to GPI, gathers ligands from the extracellular matrix and transports them to the intracellular space via the recycled endosomal pathway. Folate receptors are identified as tumor antigens or biomarkers because they are typically not found in normal tissues. As a result, therapeutic and diagnostic approaches have been developed for cancer treatment. Molecular payloads, ranging from radionuclides to large DNA and liposome constructs, have been effectively delivered through the folate receptor pathway in cancer cells (1-2)

Folic acid-DAVLBH conjugates

Vintafolide, formerly identified as EC145, is a potent FA-SMDC that has been developed as a water-soluble conjugate with the purpose of specifically targeting the delivery of desacetyl vinblastine monohydrazine (DAVLBH) to tumors that exhibit overexpression of FRalpha. Research carried out by Leamon et al. has demonstrated that vintafolide exhibits a greater affinity for binding to FRa, leading to a robust and selective response against FRa-positive xenografts in comparison to non-targeted DAVLBH.(17)

Vintafolide consists of four components: an acid moiety that targets FRa, a hydrophilic peptide spacer, an autoimmolative disulfide linker, and a DAVLBH microtubule-stabilizing compound (Figure 3). In a study conducted by Leamon, the impact of altering three of the constituent elements of vintafolide was examined. It was observed that changing the compositions of the spacer, as long as it remained hydrophilic, had minimal effect on the potency of vintafolide. However, the use of a bioreleasable linker such as glutathione (GluSH) in the endosomal environment was found to be crucial for the action of the conjugate. This is because the linker is cleaved by intracellular thiols, resulting in the release of the activated drug within the cell. (17)

Figure 3. Chemical structure of folic acid-based SMDC vintafolide.



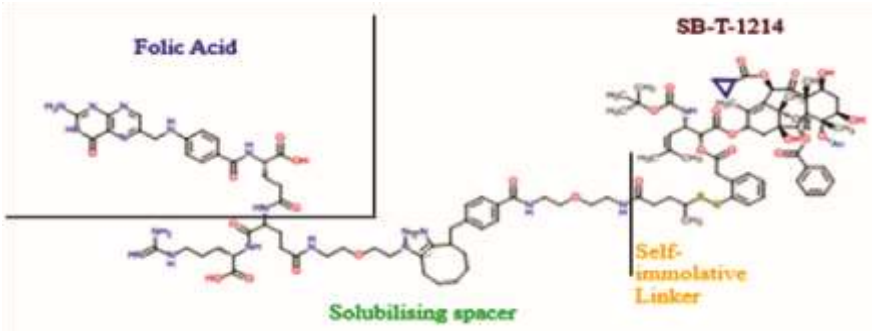
Folate-taxoid conjugates

Seitz (2015) created a fusion of folate and taxoid which has demonstrated significant effectiveness against drug-sensitive and drug-resistant cancer cells. The conjugate, illustrated in Figure 4 .consists of a powerful taxoid, resembling the chemotherapy medication Taxol, along with a folic acid component. It is structured with a hydrophilic PEGylated dipeptide spacer and an autoimmolative disulfide linker, akin to vintafolide.(4)

In order to compare the behavior of the free taxoid and the taxoid conjugate in FRa-positive and FRa-negative cells, in vitro research was conducted. As anticipated, the free taxoid SB-T-1214 displayed strong effectiveness in both cell lines. Moreover, the taxoid conjugate showed notable cytotoxicity against the FRa-positive cell lines. Furthermore, the taxoid conjugate demonstrated a remarkable decrease in toxicity to normal cells, with over a 1000-fold reduction compared to the free drug. (3)

The folate-taxoid conjugates, which employ a disulfide linker for the release of cytotoxic drugs, are part of a diverse array of conjugates. It is important to highlight that folate is attached to a variety of other drugs, including camptothecins, tubulysins, mitomycins, and maytansinoids. All of these conjugates were synthesized and tested using a disulfide linker. (5,19)

Fig no .4



Folic acid-paclitaxel conjugate

Researchers conducted a study in which they developed folic acid-peptide-paclitaxel conjugates (FA-P3/P7-PTX) to address drug resistance, achieve targeted delivery to tumors, enhance cellular absorption, and create water-soluble conjugates. The synthesized conjugate (FAP3/P7-PTX) included folic acid and lytic peptides I-3 and I-7, serving as molecular carriers and cell-disrupting peptides. The effectiveness of these conjugates was assessed by the researchers, revealing higher anti-proliferative activity compared to free paclitaxel in MCF-7/PTX cells. Additionally, FA-P3-PTX showed increased cellular uptake in MCF-7/PTX cells in comparison to P3-PTX, attributed to the presence of folate receptors. FA-P7-PTX displayed more pronounced effects on cell toxicity, apoptosis, and membrane disturbance behavior in MCC. Similar to FA-P3-PTX, FA-P7-PTX exhibited superior tumor growth suppression compared to PTX. Researchers have also documented related findings in this area. (6,7,)

Folic acid- trimethyl chitosan- paclitaxel conjugates

A revised edition of trimethyl chitosan (TMC-PTX) linked paclitaxel (PTX) named folic acid (FA)-TMC-PTX was presented. This alteration was created to facilitate the oral and intravenous administration of PTX. Additionally, adjustments were made to FA in order to minimize the absorption of conjugate proteins, as demonstrated in prior research. (18)

Folic acid coupled to the pegylated-liposomes of 5-fluorouracil

Pegylated-liposomes linked with folic acid were created, leading to an impressive 11-fold rise in in vitro absorption when compared to pegylated liposomes without folic acid. The tumor-suppressing impact of FA-SL (stabilized liposome) was notably better than that of free 5-FU and SL. Therefore, this innovation shows promise in efficiently transporting 5-FU to cancer cells. (20)

Folate as Targeting Ligand

Recent research has honed in on the significance of folate in chemotherapy, given its prevalence in cancer cells and its crucial function in cell division(21)The folate receptor (FR) has been identified as being prominently present in specific cancer cells, which necessitate high levels of folate for DNA repair in the initial phases of tumor growth(21,22). By employing folate as a targeting ligand in chemotherapy, the adverse effects of chemotherapeutic drugs can be reduced(22,23,24) Folate selectively attaches to cancer cells that exhibit elevated FR levels, while displaying a lower binding affinity to normal human cells. Consequently, medications targeting FR have been explored as a potential treatment for various cancer types, including breast cancer.

Distribution of folate receptors in normal and cancer

There exist three subtypes of folate receptors present in both normal and cancer cells: FRα, FRβ, and FRγ. FRα is mainly found in different types of carcinoma cells, particularly in breast cancer, with lower levels in normal human cells. The overexpression of FRα plays a crucial role in the uncontrolled and rapid growth of tumor cells. Due to its increased presence in cancer cells, FRα is recognized as the main receptor that folate-conjugated drugs target in chemotherapy. (23,24,25)

Structural basis for binding of folic acid to folate receptors

FR has a distinct relationship with folate and demonstrates a high affinity for facilitating the absorption of folate into the cell from the bloodstream. Version 1: FR has a unique connection with folate and shows a robust affinity for assisting in the absorption of folate into the cell from the circulatory

system..(21,23,25) The spherical shape of FR consists of 4 lengthy α-helices, 2 brief α-helices, 4 β-strands, and a loop area. Research has shown that folate creates a strong hydrogen bond and hydrophilic interaction with FRα in the loop region. These crucial bonds and interactions play a key role in emphasizing the increased attraction of folate towards FRα. (21,25,24)

Mechanism of folate conjugates uptake by folate receptors

It has been theorized that delivery systems linked with folate can specifically bind to the FR, found on the exterior of cancer cells, and enter the cells via clathrin-mediated endocytosis. Chemotherapeutic carriers conjugated with folate in the blood attach to FRs on the surface of carcinoma cells, resulting in invagination, internalization, and vesicle formation. (26,23,25)

When the pH decreases inside the vesicle, the chemotherapeutic agent linked with folate is released into the cytosol. This results in the intended pharmacological effect within the cancerous cells, either by stopping cell division or triggering apoptosis. Folate ligand conjugates display varying behaviors when attaching to different cancer cells. Upon the entry of the folate-conjugated chemotherapeutic agent into the cell, the internalized folate receptors (FRs) reassemble on the cell surface, enabling further endocytosis of folate-targeted drugs or free folates. The recycling of FRs back to the tumor cell surface ensures continuous internalization of folate-conjugated carriers by the cancer cells. Extensive research is therefore necessary to establish folate as the targeting ligand for chemotherapy drug delivery systems, aiming to enhance the efficacy of anticancer drugs on tumor cells while minimizing their impact on healthy human cells. The subsequent part of this review offers a synopsis of current data on the use of folate-conjugated nanoparticles in experimental breast cancer models.

Folate targeted nanoparticles in breast cancer treatment

Recent research has placed emphasis on the focused administration of medications using nanocarriers as a result of the adverse reactions linked to potent chemotherapeutic agents.

Folate conjugated nanoparticles loaded with doxorubicin

Various nanocarriers have been extensively researched for targeted drug delivery, responding to stimuli like temperature, redox, and sensitivity. In a specific study, a multiblock copolymer nanocarrier was created for breast cancer treatment. This nanocarrier was modified with folate and trastuzumab, targeting ligands, and loaded with DOX. The drug release was highly pH-responsive, with 72% released at pH 5.5 and only 18% at pH 7.4. Cellular uptake studies revealed higher uptake and increased apoptosis in the MCF-7 cell line with the ligand-conjugated nanocarriers compared to the control group. In vivo studies demonstrated minimal toxicity and a 91% tumor regression rate in Ehrlichascites tumor, surpassing free DOX efficacy. Another research team developed a biodegradable triblock copolymer with dual targeting strategies for breast cancer treatment, attaching AS1411 aptamer and folate to the nanocarrier. The drug release profile also showed pH responsiveness, with 70% release at pH 5.0 and 25% release at pH 7.4 due to the acid-sensitive hydrazone linkage.(29,30)

Folate conjugated nanoparticles loaded with Paclitaxel

PTX has become the favored initial medication for breast cancer therapy due to its remarkable efficacy and tolerability. In a research conducted by Nazli et al, they devised folate-conjugated amphiphilic β-cyclodextrins that were loaded with PTX to specifically deliver it to the breast cancer site. Through the encapsulation of PTX within hydrophobic chains, the resulting nanoparticles (NPs) demonstrated greater stability in comparison to alternative nanoparticulate systems. This formulation holds promise for prolonged drug release and exhibits superior attributes when compared to traditional dosage forms. (31)

Folate conjugated nanoparticles loaded with other drugs

The use of 5-FU, a cytotoxic agent with broad effectiveness, is limited due to its non-specific distribution, short duration of action, and the potential for tumor cells to develop resistance to the drug. To address these challenges, Mazen et al. have created poly (D, L-lactide-co-glycolide) NPs that are PEGylated and decorated with FA (FOLPEG-PLGA NPs) for treating breast and colon cancer. These NPs exhibit a sustained (biphasic) release pattern, high hemocompatibility, and minimal cytotoxicity, making them an efficient method for drug delivery. In vitro studies have shown that FOL-PEG-PLGA NPs loaded with 5-FU have a 4-fold lower half maximal inhibitory concentration compared to PLGA NPs loaded with 5-FU . Another promising approach in cancer therapy involves the use of magnetic NPs (MNPs) that target the tumor site with an externally applied magnetic field. Gunduz et al. have been investigating this method for breast cancer treatment. These MNPs were conjugated with the targeting ligand FA and loaded with the anticancer drug idarubicin. Successful internalization and accumulation of MNPs in MCF-7 cells were observed through light and confocal microscopy. Empty MNPs showed no toxicity on MCF-7 cells within the concentration range of 0-500 mg/mL. However, idarubicin-loaded PEG coated NPs exhibited concentration-dependent toxicity. Additionally, idarubicin-loaded MNPs were more toxic than free idarubicin. XTT cell proliferation assay results indicated that when idarubicin was administered as FA conjugated PEG coated MNPs, the IC50 value of free idarubicin decreased from 2.48 µM to 1.25 µM. In vitro studies also demonstrated that idarubicin-loaded MNPs had significantly higher cytotoxicity compared to free idarubicin on the MCF-7 cell line. furthered this research by developing bifunctional NPs (BF-NPs) that were simultaneously modified with two ligands, specifically the c. (32)

Theranostic applications of folate targeted nanoparticles in breast cancer

. Nanotechnology has become a valuable tool in the diagnosis and treatment of breast cancer. It offers targeted drug delivery and theranostic properties, making it a promising approach. Researchers have investigated different nanocarriers that respond to stimuli for precise targeting, cell imaging, and drug transport .One example is the encapsulation of luminescent Mn:ZnS quantum dots (QDs) with chitosan and FA, which allows for targeted drug transport and cell imaging. Chitosan acts as a stabilizer and provides a binding site for cancerous cells when combined with QDs. Furthermore, the inclusion of FA as a targeting agent results in orange-red fluorescence emission at approximately 600nm, enhancing stability at various pH levels. The synthesized composites have been proven to be non-toxic to human breast cell lines MDA-MB-231, MCF-10, and MCF-7 at a concentration of 500 µg/mL. The conjugated Mn:ZnS QDs serve as fluorescence markers in studies on cellular uptake, improving the internalization and binding affinity of the nanocarrier to cells that overexpress the folate receptor. (33)

Conclusion:

Vitamin-Drug Conjugate techniques were identified as the most suitable methods among all the other documented methods and can be utilized for the current treatment of cancer. In most types of cancer, folate receptors are highly overexpressed on the surfaces of malignant cells, making them an advantageous target for drug delivery. Various polymers have been effectively used to prepare folate conjugates. Vitamin-drug conjugates possess the ability to differentiate and manipulate the morphological and physiological variances between normal cells/tissues and cancerous ones. Cancer cells, for example, exhibit an increased expression of cancer-specific receptors to enhance their uptake of nutrients and vitamins. These receptors can be targeted for the delivery of cytotoxic drugs to cancer cells through receptor-mediated endocytosis (RME). In our review, we primarily focus on the conventional treatment of cancer and discuss its pros and cons. It has been observed that numerous innovative approaches are being developed to overcome these drawbacks. Among the various formulation therapies being explored, methods such as conjugation with metal ions or different vitamins have shown promise. The use of Vitamin Drug conjugates has emerged as an effective therapy. The advancements in Vitamin-drug conjugates include the development of recent conjugates that utilize the vitamin-receptor mediated endocytosis mechanism for targeted delivery, thereby reducing toxicity to healthy cells. Additionally, we provide information on vitamin-metallodrug conjugates that are utilized for both therapeutic and diagnostic purposes in cancer treatment.

REFERENCES

1. Dai, Y., Cai, X., Bi, X., Liu, C., Yue, N., Zhu, Y. … Qian, H. (2019). Synthesis and anti-cancer evaluation of folic acid-peptide-paclitaxel conjugates for addressing drug resistance. European Journal of Medicinal Chemistry, 171,104–115. http://dx.doi.org/10.1016/j.ejmech.2019.03.031..
2. Bartouskova, M., Melichar, B., & Mohelnikova-Duchonova, B. (2015). Folate receptor: A potential target in ovarian cancer. Pteridines, 26(1), 1–2. https://doi.org/10.1515/pterid-2014-0013
3. Fernandez, M., Javaid, F., & Chudasama, V. (2018). Advances in targeting the folate receptor in the treatment/imaging of cancers. Chemical Science, 9(4), 790–810. https://doi.org/10.1039/C7SC04004K.
4. Seitz, J. D., Vineberg, J. G., Herlihy, E., Park, B., & Melief, E. (2015). Design, synthesis and biological evaluation of a highly potent and cancer cell selective folatetaxoid conjugate. Bioorganic & Medicinal Chemistry,2187–2194. http://dx.doi.org/10.1016/j.bmc.2015.02.057.
5. Henne, W. A., Kularatne, S. A., Hakenjos, J., Carron, J. D., & Henne, K. L. (2013). Synthesis and activity of a folate targeted monodisperse PEG camptothecin conjugate. Bioorganic & Medicinal Chemistry Letters, 23(21), 5810–5813. http://dx.doi.org/10.1016/j.bmcl.2013.08.113.
6. Yuxuan, D., Xingguang, C., Xinzhou, B., Chunxia L., Na, Y., Ying, Z., Jiaqi, Z., & Mian, F. (2019). Synthesis and anti-cancer evaluation of folic acid-peptide- paclitaxel conjugates for addressing drug resistance. European Journal of Medicinal Chemistry, 171, 104–115.doi: 10.1016/j.ejmech.2019.03.031
7. Wang, X., Li, J., Wang, Y., Koenig, L., Gjyrezi, A., Giannakakou, P. Shin, D. M. (2011). A folate receptor-targeting nanoparticle minimizes drug resistance in a human cancer model. ACS Nano, 5(8), 6184–6194. http://dx.doi.org/10.1021/nn200739q.
8. Gaspar, V. M., Costa, E. C., Queiroz, J. A., Pichon, C., & Sousa, F. (2015). Folatetargeted multifunctional amino acid-chitosan nanoparticles for improved cancer therapy. Pharmaceutical Research, 32(2),562–577. http://dx.doi.org/10.1007/s11095-0141486-0.
9. Davis, C. (2019, September 18). Cancer [Web log post]. Retrieved from http://www.medicinenet.com/cancer/article.htm#.
10. Baskar, R., Lee, K. A., Yeo, R., & Yeoh, K. W. (2012). Cancer and radiation therapy: Current advances and future directions. International Journal of Medical Sciences, 9(3), 193. http://dx.doi.org/10.7150/ijms.3635.
11. Padma, V. V. (2015). An overview of targeted cancer therapy. Bio-Medicine, 5(4). http://dx.doi.org/10.7603/s40681-015-0019-4.
12. Pérez-Herrero, E., & Fernández-Medarde, A. (2015). Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. European Journal of Pharmaceutics and Biopharmaceutics, 93, 52–79. http://dx.doi.org/10.1016/j.ejpb.2015.03.018.

13. Pawar, S. K., Badhwar, A. J., Kharas, F., Khandare, J. J., &Vavia, P. R. (2012). Design, synthesis and evaluation of N-acetyl glucosamine (NAG)–PEG–doxorubicin targeted conjugates for anticancer delivery. International Journal of Pharmaceutics, 436(1-2),183–193. http://dx.doi.org/10.1016/j.ijpharm.2012.05.078.

14. Cavallaro, G., Maniscalco, L., Campisi, M., Schillaci, D., & Giammona, G. (2007). Synthesis, characterization and in vitro cytotoxicity studies of a macromolecular conjugate of paclitaxel bearing oxytocin as targeting moiety. European Journal of Pharmaceutics and Biopharmaceutics, 66(2), 182–192. http://dx.doi.org/10.1016/j.ejpb.2006.10.013.

15. Ojima, I., Zuniga, E., Berger, W., & Seitz, J. (2012). Tumor-targeting drug delivery of new-generation taxoids. Future Medicinal Chemistry, 4(1), 33–50. http://dx.doi.org/10.4155/fmc.11.167.

16. Megha Bansal, ... Kausar Mahmood Ansari, in Advances in Molecular Toxicology, 2018

17. Leamon, C. P., Vlahov I. R., Reddy, J. A., Vetzel, M., Santhapuram, H. K., You, F. … Westrick, E. (2014). Folate-vinca alkaloid conjugates for cancer therapy: A structure- activity relationship. Bioconjugate chemistry, 25(3), 560–568. http://dx.doi.org/10.1021/bc400441s.

18. He, R., & Yin, C. (2017). Trimethyl chitosan based conjugate for oral and intravenous delivery of paclitaxel. Act Biomaterial, 53, 355–366. http://dx.doi.org/10.1016/j.actbio.2017.02.012.

19. Bartouskova, M., Melichar, B., & Mohelnikova-Duchonova, B. (2015). Folate receptor: A potential target in ovarian cancer. Pteridines, 26(1), 1–2. https://doi.org/10.1515/pterid-20140013.

20. Gupta, Y., Jain, A., Jain, P., & Jain, S.K. (2007). Design and development of folate appended liposomes for enhanced delivery of 5-FU to tumor cells. Journal of Drug Targeting, 15(3), 231–240. http://dx.doi.org/10.1080/10611860701289719.

21. C. Chen, J. Ke, X.E. Zhou, W. Yi, J.S. Brunzelle, J. Li, E.-L. Yong, H.E. Xu, K. Melcher, Structural basis for molecular recognition of folic acid by folate receptors.SI, Nature. 500 (2013) 486–9. https://doi.org/10.1038/nature12327.

22. A.K. Bakrania, B.C. Variya, S.S. Patel, Novel targets for paclitaxel nano formulations: Hopes and hypes in triple negative breast cancer, Pharmacol. Res. 111 (2016) 577591. https://doi.org/10.1016/j.phrs.2016.07.023.

23. M.W. Amjad, M.C.I.M. Amin, H. Katas, A.M. Butt, P. Kesharwani, A.K. Iyer, In VivoAntitumor Activity of Folate-Conjugated Cholic Acid-Polyethylenimine Micelles for the Codelivery of Doxorubicin and siRNA to Colorectal Adenocarcinomas, Mol. Pharm. 12 (2015) 4247–4258. https://doi.org/10.1021/acs.molpharmaceut.5b00827

24. B. Gorain, H. Choudhury, M. Pandey, C. Kokare, R.K. Khurana, A. Sehdev, Polyester, Polyhydroxyalkanoate Nanoparticles as a Promising Tool for Anticancer Therapeutics, Polym. Nanoparticles as a Promis. Tool Anti-Cancer Ther. (2019) 101–121. https://doi.org/10.1016/B978-0-12-816963-6.00006-6.

25. L. Xu, Q. Bai, X. Zhang, H. Yang, Folate-mediated chemotherapy and diagnostics: Anupdated review and outlook, J. Control. Release. 252 (2017) 73–82. https://doi.org/10.1016/j.jconrel.2017.02.023.

26. H. Choudhury, B. Gorain, M. Pandey, S.A. Kumbhar, R.K. Tekade, A.K. Iyer, P. Kesharwani, Recent advances in TPGS-based nanoparticles of docetaxel for improved chemotherapy, Int. J. Pharm. 529 (2017) 506–522. https://doi.org/10.1016/j.ijpharm.2017.07.018.

27. A. Kumar, S. V. Lale, M.R. Aji Alex, V. Choudhary, V. Koul, Folic acid and trastuzumab conjugated redox responsive random multiblock copolymeric nanocarriers for breast cancer therapy: In-vitro and in-vivo studies, Colloids Surfaces B Biointerfaces. 149 (2017) 369–378. https://doi.org/10.1016/j.colsurfb.2016.10.044.

28. P. Kesharwani, A.K. Iyer, Recent advances in dendrimer-based nanovectors for tumor-targeted drug and gene delivery, Drug Discov. Today. 20 (2015). https://doi.org/10.1016/j.drudis.2014.12.012.

29. S. V. Lale, A. R. G., A. Aravind, D.S. Kumar, V. Koul, AS1411 Aptamer and Folic Acid Functionalized pH-Responsive ATRP Fabricated pPEGMA?PCL?pPEGMA Polymeric Nanoparticles for Targeted Drug Delivery in Cancer Therapy, Biomacromolecules. 15 (2014) 1737–1752. https://doi.org/10.1021/bm5001263.

30. P. Kesharwani, R.K. Tekade, V. Gajbhiye, K. Jain, N.K. Jain, Cancer targeting potential of some ligand-anchored poly(propylene imine) dendrimers: A comparison, Nanomedicine Nanotechnology, Biol. Med. 7 (2011) 295–304. https://doi.org/10.1016/j.nano.2010.10.010.

31. N. Erdoğar, G. Esendağlı, T.T. Nielsen, M. Şen, L. Öner, E. Bilensoy, Design and optimization of novel paclitaxel-loaded folate-conjugated amphiphilic cyclodextrin nanoparticles, Int. J. Pharm. 509 (2016) 375–390. https://doi.org/10.1016/j.ijpharm.2016.05.040.

32.] J. Chen, S. Li, Q. Shen, Folic acid and cell-penetrating peptide conjugated PLGA-PEG bifunctional nanoparticles for vincristine sulfate delivery, Eur. J. Pharm. Sci. 47 (2012) 430– 443. https://doi.org/10.1016/j.ejps.2012.07.002.

33. M.S. Muthu, D.T. Leong, L. Mei, S.-S. Feng, Nanotheranostics - application and further development of nanomedicine strategies for advanced theranostics., Theranostics. 4 (2014) 660–77. https://doi.org/10.7150/thno.8698.

34. Fasehee, H.; Dinarvand, R.; Ghavamzadeh, A.; Esfandyari-Manesh, M.; Moradian, H.; Faghihi, S.; Ghaffari, S.H. Delivery of disulfiram into breast cancer cells using folatereceptor-targeted PLGA-PEG nanoparticles: In vitro and in vivo investigations.J. Nanobiotechnol. 2016, 14, 32. [CrossRef] [PubMed]