Nanomed. J. 9(2): 95-106, Spring 2022

REVIEW PAPER

Layered double hydroxide nanostructures as drug-carriers in treatment of breast cancer

Kamran Hosseini [1, 2]†, Saiedeh Razi Soofiyani [3, 4]†, Reza Eghdam Zamiri [5], Afsaneh Farjami [6, 7], Azita Dilmaghani [8], Mehri Mahdavi [3], Vahideh Tarhriz [3]*, Vahid Yousefi [3]*

[1]Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Molecular Medicine, Faculty of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Molecular Medicine Research Center, Biomedicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Clinical Research Development Unit of Sina Educational, Research and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Radiation Oncology, Tabriz International Hospital, Tabriz, Iran
[6]Food and Drug Safety Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[7]Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[8]Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

ABSTRACT

Breast cancer is a public health problem globally and is the most frequent cancer world wide. Currently, anti-inflammatory and anti-cancer drugs are of prime interest in treating some cancers especially breast cancer and have become an exciting challenge for researchers. The use of layered structures consisting of anions and cations called layered double hydroxides (LDHs) has attracted the attention of many researchers in the field of biomedical and pharmaceuticals. LDHs-nanostructures can be used as drug carriers, especially anti-inflammatory and anti-cancer drugs to treat cancers. Thus, the LDHs should have a number of physicochemical properties to act as a desirable drug carrier. Among the primary factors to increase the efficiency of LDHs are their surface characteristics and size, number and type of ions, rapid clearance from the body after drug release, and non-toxicity. All of these properties make LDHs nano-carriers for carrying anti-inflammatory and anti-cancer drugs to treat a variety of cancers. Therefore, we focus on reviewing the nature of LDH nano-carriers and evaluating the desirable properties for drug delivery, drug loading methods into LDH and anti-inflammatory drug delivery methods, their potential applications in biomedical and their toxicity and antimicrobial effects in breast cancer.

Keywords: *Anti-inflammatory drugs, Breast cancer, Cancer therapy, LDH nanostructures, Nano-carriers*

How to cite this article
Hosseini K, Razi Soofiyani S, Eghdam Zamiri R, Farjami A, Dilmaghani A, Mahdavi M, Tarhriz V, Yousefi V. Layered double hydroxide nanostructures as drug-carriers in treatment of breast cancer. Nanomed J. 2022; 9(2): 95-106. DOI: 10.22038/NMJ.2022.63097.1661

INTRODUCTION

Cancer is one of the major causes of death worldwide and stays a challenging medical condition that affects millions of individuals over the world. As a critical threat in the healthcare system, cancer led to about 9 million deaths each year globally [1, 2]. Breast cancer is the most frequently occurring malignancy in women, accounting for about 570,000 deaths in 2015. Breast cancer is an invasive neoplasia and can commonly metastasis to distant organs (Heat/pH-boosted release of 5-fluorouracil and albumin-bound paclitaxel from Cu-doped layered double hydroxide nanomedicine for synergistical chemo-photo-therapy of breast cancer). About 90-95% of cancers happen following genetic mutations from environmental/lifestyle factors such as and just 5–10% of cases of cancers are due to inheritance [3]. To increase the survival rate of patients suffer from cancers, early diagnosis and timely treatment are so important. The various strategies, including surgery, chemotherapy, immunotherapy, nanotechnology, precision medicine, radiotherapy, and hormonal therapies, are used alone or in combinations with each other for cancer treatment [4, 5]. Because these approaches non-

* *Corresponding authors: Emails: tarhrizv@tbzmed.ac.ir; vahid.yousefi@chemist.com*
Note. This manuscript was submitted on January 1, 2022; approved on March 13, 2022
† These authors contributed equally to this work

specifically target cancer cells, they are not significantly effective in the patients. In addition, targeting cancer cells non-specifically limit the application of the greater drugs doses to reach the tumor site [6]. Nanotechnology is a multidisciplinary field that uses very tiny particles for diagnosis of cancers, drug delivery specifically and effectively into tumor cells [6, 7]. The drug-delivery application of nanoparticles (NPs) is so valuable, since nano-carriers decreases the non-specific accumulation of anti-cancer agents, also lessen the side effects of anti-cancer drugs into non-cancerous cells in cancer therapy. Therefore, the application of NPs in cancer drug delivery suggests a specific and effective cancer treatment strategy [8]. The lack of efficiency of conventional treatments in targeting cancer cells justifies the increasing application of NPs in drug-delivery. Recently, micelles, dendrimers, liposomes, polymeric/solid lipid, viral, gold and magnetic carriers) are used as nano-drug delivery systems [7, 9-12]. The NPs used in cancer therapy are indicated in Table 1. The main benefit use of NPs, as anti-cancer agent's carriers, is overcoming of the problems of solubility, stability, resistibility, and the feasibility of targeted delivery to the tumor [13]. The diagnostic/treatment agents depend on the NPs analyzed by clinical analytic methods such as Abraxane, Daunoxome, Doxil, Depocyt, and Oncaspar. The food and drug administration approves these agents and demonstrates their effective treatment in various cancers particularly in breast cancer [14-17]. Among the various NPs, Layered double hydroxide (LDH)-nanoparticles or nanostructures, are known as a suitable drug carrier with ability to protect the loaded drug from environmental modifications and bio-degradation. Layered double hydroxides, recognized as anionic clays or brucite-like compounds, are two main sub-classes of ionic layered materials. LDHs are represented with the general formula of $[M(II)_{1-x}M(III)x\cdot(OH)_2]^{x+}\ [A^{n-}]_{x/n.}mH_2O$, where M^{2+} and M^{3+} are respectively di- and trivalent metal cations, and A is n-valent interlayer guest anion. The primary constituents of LDHs are the charged layers that provide diverse chemical compounds with versatile usability, for example, biocompatibility, adsorption, intercalation and ion exchange [7, 8, 18]. In contrast to former drug delivery methods, which suffering low circulation stability, poor bioavailability, and drug degradation; LDH acts as a novel drug nano-carriers which are relatively cost-effective with low toxicity for the target cells or organs beside ease of synthesis, and great drug loading capacity for efficient drug transportation [9, 19]. These nanostructures have the high level of loading capacity, stability, and penetration aptitude of the cargoes. Several studies confirmed that LDHs nanostructures can infiltrate lightly into the cells and stabilize the anti-inflammatory or cancerous drugs within the interlayer [20-23]. It has been showed that in previous studies LDHs containing magnesium and aluminum have potential antacid, antipepsin and antimicrobial properties as extra beneficial features of drug delivery in-vivo condition [20, 21, 24]. Considering the ability of LDH nanostructures in loading density, chemicophysical stability, and targeted penetration into the cells, in this review, we focus on novel delivery methods of anti-inflammatory and anti-cancer drugs using LDH nanostructures for improvement of breast cancer therapy.

Table 1. Various types of NPs which used in cancer therapy

	NPs
Hybrid NPs	Lipid-Polymer hybrid NPs (64)
	Organic-Inorganic hybrid NPs (86)
	Cell- membrane coated NPs (87)
Organic NPs	Liposomes- based NPs (88)
	Polymer based NPs (89)
	Dendrimer (90)
	Carbon nanotubes (91)
Inorganic NPs	Gold NPs (92)
	Silica NPs (93)
	Magnetic NPs (94)
	Quantum dots (95)
	Clay NPs (66)
	Hydroxide nanoparticles like LDH (96)

Size and surface characteristics of LDHs

One of the important functions of LDH nano-carriers is to control the timing and distribution of carried drugs. They must also kill neurons before they could reach the target tissue, such as tumors. One of the functions of the reticuloendothelial system is to trap foreign matter. Hence, unmodified nano-materials or conventional carriers are trapped by this system before entering the target tumor tissue because the reason could be a non-uniform distribution in terms of size, type and size of nano-materials [25]. For these reasons, we can pay special attention to a number of parameters, including the type of raw material, design and modification of the NP surface, and the synthesis method used based on the desired shape and size.

Surface characteristics

One of the important parameters to determine the lifespan of LDH and its stability in the body's circulatory system, due to the presence of macrophages, is the surface properties of NPs. Because NPs are not trapped by immune macrophages, they have a hydrophilic surface. By doing so, they can escape from macrophages. In practice, two methods are used to prevent NPs from being trapped by macrophages: 1- Using Peg hydrophilic polymer to cover the surface of NPs; 2- Protection of the opsonization process by plasma protein.

Biomedical applications of Layered double hydroxide

In the field of pharmaceuticals, the use of LDH NPs is widely used and due to their interesting properties, they are used as drug delivery tools to treat a variety of diseases [26]. Early in the development of LDH, it was used as an antacid and anti-pepsin agent. LDHs have also been found to reduce hyperphosphatemia by removing phosphate from gastrointestinal juice. In the field of medicine, the properties of LDHs in terms of biocompatibility, type of chemical composition, high drug loading capacity, thermal stability and High anion exchange capacity and have been studied so that it can be used for controlled mixing and release of drugs [27-29]. In the inner layer of LDH, there are areas called microvessels where the drug can be stored, its integrity and nature preserved, and protected from the effects of oxygen and light [26, 30-33]. In the 1842s, a Swedish geologist named Carl Hochstetter discovered a natural mineral called hydrotalcite. Several years later, this mineral substance, called Talcid (Mg-Al-CO_3), was sold commercially by pharmaceutical companies. The main application of this synthetic LDH is the symptomatic treatment of problems related to the stomach (antacid properties) and heartburn. Hydrotalcite has a sandwich-like layered structure and releases a network of layers depending on the pH. Talcid is able to remain stable at pH around 3-5 and exert its effects. Stomach acid can be neutralized by active compounds that are bases alkalis such as calcium carbonate, aluminum hydroxide, magnesium hydroxide, sodium hydrogen carbonate, aluminum phosphate, magnesium trisilicate, magnesium carbonate, and magnesium oxide [34], for example Talcid releases active compounds very slowly so that accelerates wound healing and restores the gastric mucosa to its normal state. Tarnawski et al. found that expression of growth factors such as EGF (Epidermal Growth Factor) and its receptor (EGFR) could be affected in gastric ulcers and normal stomachs by Talcid. By expressing EGF and EGFR, cell proliferation, migration, epithelialization, angiogenesis and wound healing are accelerated, eventually they concluded that Talcid provided a mechanism for healing stomach ulcers and restoring mucus to its normal state [35, 36]. There is a type of layered double hydroxide called Mg/Al LDH, which has previously been used as a carrier of anti-inflammatory drugs such as indomethacin [37] and fenbufen [38]. The purpose of using these LDHs is to store these compounds and other anti-inflammatory drugs in it and transport them to the desired parts of the body. LDHs have long been used as carriers of anti-cancer drugs. Due to the poor solubility and instability of anti-cancer drugs, drug delivery systems such as LDHs are used to increase the stability and efficiency of the transported drug and that the drug can be easily delivered to the desired tumor tissues (Fig. 1). Using an anion exchange process, Dong et al. were able to load the anti-cancer drug camptothecin (CPT) into Mg/Al LDH. This increases the solubility of CPT and due to the decomposition of the LDH layer, the drug is released at a pH of about 4.8 [31]. A similar study was performed by Qin et al. On the anti-cancer drug podophyllotoxin (PPT), and the PPT-Mg/Al LDH composite readily entered the cervical cancer cells (Hela) and reduced tumor growth [39]. In this regard, Wang et al. used etoposide drug into glioma cells using Mg/Al LDH composite and inhibited the growth and proliferation of tumor cells [40]. Chakraborty et al. also used the Mg/Al-LDH composite to load the

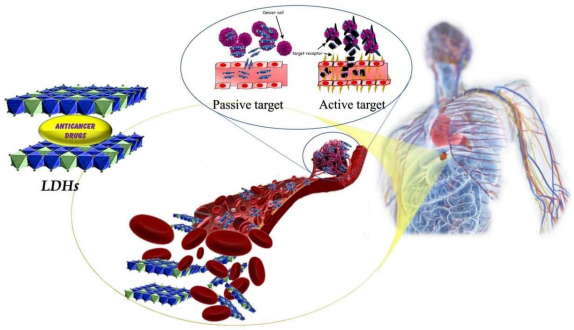

Fig. 1. Schematic representation of the application of LDHs as anti-cancer drugs carriers

anti-cancer drug methotrexate (MTX) into colon cancer cells (HCT-116), which reported an efficacy of 13.1%. The best MIC of drug-LDH composite was reported in 48 hours and slow release of drug at pH about 7.4 was reported [41].

In another study, Barahuie et al. were able to load chlorogenic acid into the Zn/Al LDH composite using the ion exchange method. This complex increases the thermal stability of the drug and the drug-containing complex has the potential for cancer therapy [42]. Using another method called co-precipitation, which involves adding drugs while synthesing LDH, the researchers were able to incorporate the drugs into LDH. For example, Yamini et al. used the chemotherapeutic drug Dacarbazine (DAC), which is used to treat melanoma, to load the drug into the NaCa LDH composite through a co-precipitation process, which has anti-cancer efficacy. DAC-LDH was increased in melanoma and breast cancers, and this complex inhibited the growth of cancer cells [43]. Gans et al. also used the Mg/Al LDH composite containing the anti-cancer drug doxorubicin (DOX). In this way, the drug-LDH composite is well delivered to the tumor tissue and is easily absorbed into the tissue. After the absorption process, the drug is slowly released into the tumor. Due to the nature of the drug, which is damage to the DNA of cancer cells, cardiac toxicity was reduced by using the drug-LDH composite [44].

Targeted drug delivery and the factors affecting LDHs in it

In the treatment of breast cancer through nano-carriers, to deliver the drug, much attention should be paid to the body's physiological barriers such as the blood-brain barrier, blood, gastrointestinal tract, and etc. In other words, since the drug to be able to bind to its intended target and exercise its therapeutic efficacy on only tumor tissue, it must cross these barriers, following the passage of nano-carriers, its activity or volume may decrease [45]. This procedure has a number of benefits that should be considered, such as reducing the dose of the drug, increasing the half-life of the drug in the body, and reducing unwanted side effects in the patient. Given the above explanations [46], LDHs can be considered as a suitable candidate for the delivery of cancer drugs (Table 2).

Drug-loading methods into interlayers of LDHs

The drug can load between the LDH layers and firmly attaches. There are several ways in which the drug can be loaded into the LDH, including (a) co-precipitation, (b) ion exchange, (c) purification-regeneration, and (d) exfoliation-

Table 2. Examples of LDH structures in cancer therapy

LDH or LDH containing carrier	Method for drug delivery	The type of cell	The name of drug	Refs.
(LDHs), $Mg_2Al(OH)_6(NO_3)\cdot 0.1H_2O$	*in vitro*	Bone cancer	methotrexate (MTX)	(97)
CMC/LDH(Zn/Al)-5-Fu hydrogel beads	*in vitro*	oral colorectal cancer	5-fluorouracil (5-Fu)	(98)
zinc iron LDHs embedded in poly(ε-caprolactone) (PCL) matrix	*in vitro* *In vivo*	cancer	raloxifene hydrochloride (RH)	(99)
LDH	*in vitro*	cervical adenocarcinoma cancer	MTX and 5-FU	(100)
LDH@Au	*in vitro*	gastric cancer cell	Doxorubicin	(101)
magnetic Fe_3O_4@MTX-LDH/Au nanoparticles	*in vitro*	cancer	MTX	(102)
MSP@LDH	*in vitro*	Hela cells	doxorubicin (DOX)	(103)
albumin-stabilized –LDH nanoparticle (BLDH)	*in vivo*	colorectal cancer	5-fluorouracil (5FU) and albumin-bound PTX (Abraxane, ABX)	(104)
LDH-NCO-TCS/AuNp*	*in vitro*	breast cancer	Doxorubicin (DOX)	(83)
CaAl-LDH nanoparticle	*in vitro*	lung carcinoma	etoposide (ETO)	(105)
Fe_3O_4@CaAl-LDH	*in vitro*	melanoma cancer cells(skin cancer)	l-Dopa	(106)
(LDHs)	*in vitro*	breast cancer	Co-delivery of siRNAs and 5-fluorouracil (5-FU)	(107)
Dox-PAA-LDH*	*in vitro*	lung adenocarcinoma	doxorubicin (DOX)	(108)
Gal*-Cur/LDH	*in vitro*	hepatocellular carcinoma	curcumin (Cur)	(109)
GdDy*-LDH	*in vitro*	Hela* cells	Doxorubicin	(110, 111)
MTX-LDH	*in vitro*	mouse colon carcinoma	methotrexate (MTX)	
ZnPc*-DOX/LDH	*in vitro*	KB cells	Dox	(112)
AGN*-LDH hybrids	*in vitro*	Hela cells	AGN	(113)
LDHs	*in vitro*	cervical adenocarcinoma	MTX and 5-FU	(100)
Ca/Al-NO_3-LDHs	*in vitro*	prostate cancer	Epigallocatechin-3-Gallate (EGCG)	(114)

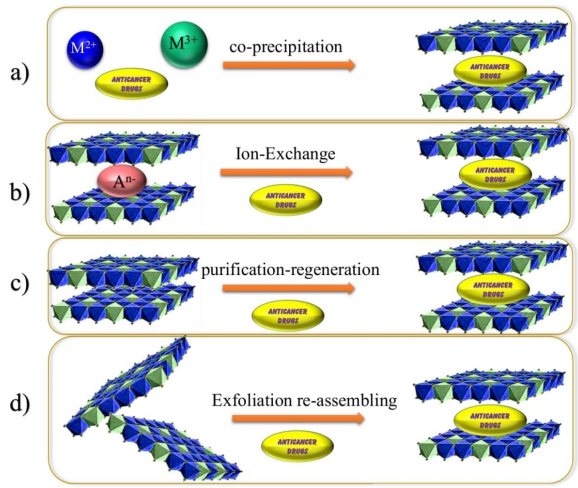

Fig. 2 Methods of drug loading into LDH layers (a) co-precipitation, (b) ion exchange, (c) purification-regeneration, and (d) exfoliation-re-assembling

re-assembling, which are summarized in Fig. 2. Under special hydrothermal conditions, chemical synthesis of NPs can be performed, the purpose of which is to modify and improve the size of LDH nano-carriers, done at the nanoscale and the crystallization process is better. [24]. Therefore, the replacement of interlayer anions with other compounds with negative charge (such as organic matter or biomolecules) can be done through the common ion-exchange reaction method to LDH nanohybrids. [20]. One of the pathways for the introduction of biomolecules or drugs into LDHs is the exfoliation reassembly pathway. Therefore, a suitable and efficient method must be adopted for the synthesis of nanohybrid-drugs, which are necessary for the steric effect and the size of the guest molecules [47, 48].

Passive and active targeting

Targeting LDHs has two important advantages: increasing therapeutic efficacy and reducing systemic toxicity. In general, targeting mechanisms are divided into two categories 1-Passive targeting, associated with the increased retention and permeability (EPR), which in turn increases vascular permeability and poor lymphatic drainage of cancer cells. Uses and persuades NPs to passively target cancer cells; 2- Active targeting associated with interaction between ligand and receptor. Receptors on the surface of cancer cells include the following: transferrin receptors, folate receptors, glycoprotein, and epidermal growth

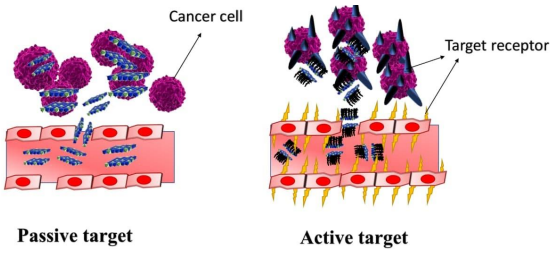

Fig. 3. Targeting mechanisms by LDH-nanomaterials

factor receptor. According to recent studies, active methods have attracted a lot of attention (Fig. 3).

Evaluation of toxicity and antimicrobial properties of LDH

In order to potentially use LDH in biology and medicine, great attention should always be paid to its toxicity. One of the causes of abnormal LDH side effects is that they are internalized through energy-dependent endocytosis. In A549 cell lines, HeLa cells, HOS cells, and normal L-132 cells, LDH-induced toxicity has been demonstrated [49). LDH with a concentration of 250-500 µg/ml and a maximum incubation time of 72 hours induces membrane degradation, oxidative stress, and inflammation. To prove this, the levels of LDH, ROS, and IL-8 can be measured. In general, the development of cytotoxicity depends more on the cell type, and among these cell lines, A549 shows the highest toxicity, i.e. LDHs on A549 cause membrane degradation, ROS production and IL-8 production. The production of IL-8 by this NP has been shown to have a more severe cytotoxic effect on A549 but has no effect on normal cells. Therefore, it can be concluded that LDHs cause toxicity on cancer cells [50]. Some studies have shown that LDH has cytotoxic properties. For example, Li et al. Examined the cytotoxic effects of ZnAl/LDHs on HeLa cells and found that these NPs cause oxidative stress [49]. As a result, the researchers found that zinc-containing LDHs had stronger toxic effects than other elements [51]. Alkhafaji synthesized the Ag NPs/Ni-Al-LDH composite using the ion exchange method and found that this complex has antibacterial and antimicrobial properties and prevents the formation of biofilms in nutrient solutions [52]. Koba-Ucun et al. synthesized the Zn-Fe LDH hybrid complex using co-precipitation method and its structural validation was performed by XRD, FTIR, SEM and other methods. Toxicity of this complex

Table 3. The various LDHs with antimicrobial properties

Structure	Properties	Bacteria	Investigation method	Refs.
ZnAl/LDH	Causes oxidative stress	-	-	(49)
Ag NPs/Ni-Al-LDH	antibacterial and antimicrobial	-	ion exchange	(52)
Zn-Fe LDH	Toxic effects on plants, animals, algae and bacteria	*Vibrio fischeri*, *Pseudokirchneriella subcapitata*, *Daphnia magna* and *Spirodela polyrhiza*	co-precipitation	(53)
CuAl-LDH and MnAl-LDH	antimicrobial activity	*E. coli*	broth dilution method	(23)
MnAl-LDH and CoAl-LDH	antimicrobial activity	*S. aureus*	Broth dilution method	(23)
MgFeAl-pipemidic acid	antibacterial	*E. coli* and *S. typhi*	anion exchange	(55)
polyacrylic nitrile-ZnAl-LDH	antibacterial	*B. subtilis*, *P. Aeruginosa*, *E. coli* and *S. aureus*	in situ polymerization	(22, 56)

was performed on a variety of aquatic organisms such as *Vibrio fischeri*, *Pseudokirchneriella subcapitata*, *Daphnia magna* and *Spirodela polyrhiza*. Among these organisms, *P. subcapitata* is the most sensitive and *S. polyrhiza* is the least sensitive to the Zn-Fe LDH composite. Finally, they found that severe toxicity depended on the time of exposure and the type of organism being tested [53]. Yan et al. investigated whether accumulations of LDHs stimulate systemic toxicity. They observed accumulation when LDH was mixed with saline solution or erythrocytes. Following intravenous injection, one hour later, and these accumulations occurred in the lungs of mice, which caused severe deposits in the lungs and congestion, and eventually death of the mice. They further found that lipid-coated LDH prevents the formation of aggregates and ultimately the death of mice [54]. Li et al. were able to remove Mg ions from the MgAl-LDH composite and instead inserted Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Mg^{2+} ions using the facile method, thus changing the structure and characteristics of the LDH composite and its antimicrobial activity increases. They found that synergistic factors could contribute to its antibacterial mechanism, such as its environment, surface interactions, NP morphology, ROS, and ions [23]. Santana-Cruz and colleagues were able to synthesize the MgFeAl-pipemidic acid complex using the anion exchange method. This complex contains pipemidic acid anions, along with carbonate and chloride in the inner layers. The MgFeAl-Cl matrix completely inactivates both *E. coli* and *S. typhi*, but the MgFeAl-PIP matrix kills all *E. coli* colonies after 90 min and all *S. typhi* bacteria after 120 min [55]. Barik et al. Synthesized polyacrylic nitrile-ZnAl-LDH composite using in situ polymerization method. They confirmed the structure and properties of the complex by XRD, FESEM, HRTEM and other techniques. With the formation of the PAN-LDH composite, the thermal decomposition of PAN increased. The increase in thermal stability with achieving antibacterial behavior of nano-complex due to dispersion of LDH .platelets may enable the material in packaging and textile industries. They evaluated the antibacterial activity of PAN and the PAN-LDH composite against bacteria such as *B. subtilis*, *P. aeruginosa*, *E. coli* and *S. aureus*. Among these bacteria, PAN-LDH composite had the greatest effect on *B. subtilis* but had no inhibitory effect on other bacteria [22, 56] (Table 3).

Enhanced permeability and retention effects

The vasculatures of tumors are different from the normal tissues. These vasculatures usually have leaky walls and deviated branching [57]. This leakiness is created by the decrease in the frequency of pericytes and the fast proliferation of endothelial cells. These features cause to create big pores in the tumor vasculatures, ranging from 100 nm to 1000 nm in diameter, as compared to a normal vessel (5–10 nm) [58]. The big pores facilitate the hydraulic conductivity and passing of NPs to vascular of tumors [57]. In addition, there is a stronger lymphatic system in normal tissue for clearance of the macromolecules. However, in tumor tissues, the rapid proliferation of cancerous cells compress lymphatic vessels and smash most of the vessels, particularly in the middle of tumors [59]. The inefficient lymphatic system in tumor tissues with along high permeability of tumor vasculature leads to the EPR effect. Therefore, it seems that NPs by extending retention times in tumors can increase their concentration in tumor tissues rather than the plasma and normal tissues. In other words, NPs can achieve intelligent

targeting to tumor cells by the EPR effect [45].

NPs clearance by the MPS (mononuclear phagocyte system)

For the high efficiency of EPR, NPs must be have ability to remain in circulation until accumulating with tumor cells. The important problem is the capture of NPs by the mononuclear phagocyte system. MPS is the main corresponding of the immune system for the clearance of macromolecules [60]. The MPS include bone marrow progenitors, blood monocytes and tissue macrophages, spleen macrophages and Kupffer cells of the liver, which have duty to clear macromolecules from circulation. Currently, the main research has concentrated on the prevention of clearance NPs by MPS cells because the fast elimination of them from circulation cannot allow them to accumulate in tumors.

Breast cancer treatment using LDHs

The surgery was historically the principal method of cancer treatment [61]. For the first time, Emile Grubbe used X-rays for treatment recurrent breast cancer in 1896. After that surgery and radiotherapy are introduced as the main types of cancer therapy. IIn 2003, the completion of the Human Genome Project provided advances in understanding many human diseases especially cancer. The complete wide genome analysis of tissues from patients specimens, investigators get strong understanding of the development, susceptibilities, and prognosis of cancers, and gain the knowledge how to plan treatment strategies which are patient specific. Subsequently, the rates of cancer cause of death rate for breast cancer is reduced due to development of new treatment strategies [62]. The five year survival for cancers has enhanced to 66.7% in 2013. In spite of these hopeful advances, cancer accounts the second leading cause of mortality in the United States. These numbers will grow with the expected aging of the people [63]. Nanotechnology provides the way to improve drug solubility /stability, enhance drug half-lives in plasma, reduce off target effects of the drugs, and concentrate the drugs at a amid site. Nanotechnology uses submicron sized molecular devices or NPs by the sizes ranging from 5 to 500 nm. Previous research effort resulted in methods to combine therapeutic agents into biocompatible nano-devices such as polymer NPs, liposomes, micellar systems, inorganic NPs, nanotubes, and dendrimers [48, 64-66]. Nano-carriers target the cancer cells via passive targeting or enhanced permeability and retention (EPR) effect. The nano-carriers are able to carry more than one drug and also they can be loaded with high doses of drugs . A targeting moiety supports active targeting of the tumor cells via targeting the molecules which are specially expressed by tumor cells. Targeting tumor cells by nano-carriers is more efficient cancer treatment method which not affects non-cancer cells [67]. The point that nano-carriers can target disease tissue while preserve normal cells from its side effects opens new areas for improving drug loading of nano-carriers with the goal of decreasing the doses of drugs. In traditional treatment, the high doses of drugs have been used because drugs become metabolized in the body. Moreover, targeting of cancer cells increase the rate of bioavailability and intracellular delivery of the drug, which means that smaller dose of drug could be loaded onto the nano-carriers [68]. One of the most invasive diseases in which the growth of breast tissue cells is out of control is breast cancer [69]. Epidemiologically, the disease is common in women around the world and affects approximately one in seven women [70]. Risk factors for the disease include alcohol and obesity [71], old age [72], abnormal hormone levels [73, 74], and genetic predisposition [75]. Breast cancer treatment strategies depend on several factors, including the patient's age and the type of stage of the breast tumor. Therapies include surgery, hormone therapy [76, 77], chemotherapy, radiation therapy [78, 79], and medication [80]. Recently, researchers using modern sciences such as nanotechnology have been able to conjugate many drugs with nanoparticles and treat breast cancer with target therapy. In this way, the side effects of anti-cancer drugs are reduced. In this regard, many studies have been conducted by researchers that will be discussed below.

Using LDH-Au nanoparticles, Komarala et al. were able to fluorescently image cancer cells MCF-7 (breast cancer), HeLa (cervical cancer), and L929 (mouse fibroblast cells). They found that a concentration of 1 mg/ml of the LDH-Au complex was compatible with these cells and could act as a photothermal agent (in the presence of a laser with a wavelength of 808 nm for 10 min), 70% of MCF-7 cancer cells destroy [81]. In general, curcumin has a low solubility, and if the drug is conjugated to LDHs, its solubility is increased and it also shows phototoxic properties against many types of tumor cells. In this regard, Khorsandi et al. studied the response of MDA-MB-231 cells to LDH-curcumin complex after photodynamic treatment

(PDT) and found that following treatment with PDT complex, cell survival in the dark was 90% (Concentration was 100 µg/ml), cell proliferation was inhibited and cell cycle was arrested in G0/G1 phase, autophagy (25 µg/ml) and apoptosis (25 and 100 µg/ml) as well as ROS production were induced [82]. Anirudhan et al. designed an LDH-chitosan nanocomposite capable of delivering drug to target areas of breast tumor cells. They showed that the presence of gold nanoparticles increases the high temperature resistance caused by NIR radiation and increases photothermal therapy. They also loaded doxorubicin into Au/TCS-NCO-LDHs and found that in MCF-7 cells, this complex arrest the cell cycle in the G0/G1 phase and shows little hemolytic activity [83]. Liu et al. report a new nanomedicine for the treatment of breast cancer. The nanodrugs were used as LDH-Cu complexes containing 5-fluorouracil (5-FU) and paclitaxel (PTX) bound to albumin (nAb-PTX). The release of the 5-FU/Cu-LDH@nAb-PTX complex was depend on pH and heat and induced apoptosis in 4T1 cells (breast cancer cells) through synergy with photothermal therapy and chemotherapy. They also concluded that the nanodrug removed 4T1 tumors in the presence of 808 nm irradiation (in two course) at doses of 0.25 and 0.5 mg/kg of 5-FU and nAb-PTX [84]. Guo et al. designed two-dimensional nanoparticles for diagnostic-therapeutic purposes. They inserted ferrous ions into the LDH-Mg-Al-doxorubicin complex and performed magnetic resonance imaging through synergy with chemotherapy and photothermal therapy. This complex, together with ferrous ions, increases the ability of light-induced heating, which can be combined with doxorubicin to synergistically kill 4T1 tumor and inhibit tumor growth rate [85] (Table 4).

CONCLUSIONS

Today, due to advances in pharmaceutical sciences and nanotechnology, many incurable diseases particularly variety of cancers have been recovered. The use of LDHs to deliver anti-cancer

Table 4. Studies of LDH structures in breast cancer therapy

LDH or LDH containing carrier	Method for drug delivery	Cell lines or animals	Drug and chemical substances	Application	Refs.
	In vitro	MCF-7 cell ine	Co-delivery of CD-siRNAs and 5-fluorouracil (5-FU)	drug resistance and enhance cancer treatment	(107)
	in vitro	L929, HeLa and MCF-7 cell lines	Au	photothermal therapy, optical and fluorescence imaging of cancer cells	(81)
LDH	*In vitro* and *in vivo*	4T1 or MCF-7 cancer cell lines and Balb/c mice	Doxorubicin (Dox) and Indocyanine green (ICG), and CpG	Inhibition of tumor recurrence and metastasis	(115)
	In vitro and *in vivo*	MCF7/mot cell line and balb/c mice	methotrexate (MTX)	High distribution efficiency and inhibition of tumor proliferation and induction of apoptosis	(116)
	In vitro	MCF-7, MCF-7/ADR, HepG2, HEK293, Hs68, MCF-10A cell lines	selenium (Se) and siRNA	Microtubule stabilizer, Gene silencing and reducing gene expression, and Overcoming drug resistance	(117)
	In vitro	MCF-7 cell line	methotrexate (MTX)	Increase drug delivery efficiency	(118)
LDH-NCO-TCS/AuNp*	*In vitro*	MCF7 cell line	Doxorubicin (DOX)	chemophotothermal therapy	(83)
Cu-doped LDH	*In vitro* and *in vivo*	4T1 cell line and Balb/c female mouse	5-fluorouracil (5-FU) and albumin-bound paclitaxel (nAb-PTX)	Increase treatment efficiency	(84)
Mn-LDH	*in vivo*	mouse subcutaneous MDA-MB-468 tumor	Perfluoropolyether (PFPE)	Helps to image cancerous tissue	(119)
Fe-LDH	*in vitro* and *in vivo*	4T1 cell line and 4T1 bearing mice	doxurubicin (DOX)	Diagnostic-therapeutic application	(85)
MgMnAl-LDH	in vitro and in vivo	L929 cell line and Female Balb/C mice	Iron Oxide (IO)	Contrast enhancer for tumor imaging	(120)
Mg/Al-LDH	*In vitro*	MCF-7, HeLa, and 3T3 cell lines	protocatechuic acid	Enhancement of drug release	(121)
nanoclays or LDH	*In vitro*	MDA-MB-231 cell line	curcumin	photodynamic therapy	(82)
MgAl-LDH	*In vitro*	MCF7 and L929 cell line	doxorubicin (DOX)	Delivery of pH-dependent anticancer drug	(122)
mesoporous silica layer (LDH@MS)	*In vitro* and *in vivo*	MCF-7 cell line and H22 tumor bearing mice	curcumin	Rational release of the drug into the tumor microenvironment	(123)
N-GQDs/$CoFe_2O_4$/LDH	*In vitro*	MCF-7 and L929 cell lines	paclitaxel (PTX)	theranostic candidate for anticancer drugs delivery	(124)
Layered gadolinium hydroxychloride (LGdH)	*In vitro*	MDA-MB-231 and MCF7 cell lines	anti-miRNA oligonucleotides (AMO)	Application of miRNA in diagnosis, treatment, and imaging	(125)

drugs for treating cancers has been extensively studied. In this study, we first investigated the structural properties of LDH as a carrier of anti-cancer drug and then its applications in the field of biomedical, factors involved in its function, simultaneous delivery of LDH with several drugs, toxicity and its antimicrobial properties were discussed. Therefore, the multi-functional nano-medicine with controled drug release potential is a promisising formulation to remove the breast tumor masses with the fewer side effects.

ACKNOWLEDGEMENTS

The authors acknowledge Molecular Medicine Research Center, Bio-medicine Institute, Clinical Research Development Unit of Sina Educational, Research and Treatment Center, Tabriz University of Medical Sciences.

FUNDING

This work was supported by Tabriz University of Medical Sciences of Iran. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

CONFLICTS OF INTEREST

All other authors declare no conflict of interest.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a cancer journal for clinicians. 2016;66(1):7-30.
3. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68(1):31-54.
4. Jahanafrooz Z, Baradaran B, Mosafer J, Hashemzaei M, Rezaei T, Mokhtarzadeh A, et al. Comparison of DNA and mRNA vaccines against cancer. Drug discovery today. 2020;25(3):552-560.
5. Bhatia K, Das A. Combinatorial drug therapy in cancer-New insights. Life Sciences. 2020:118134.
6. Sudhakar A. History of cancer, ancient and modern treatment methods. J Cancer Sci Ther. 2009;1(2):1.
7. Mfouo Tynga I, Abrahamse H. Nano-mediated photodynamic therapy for cancer: Enhancement of cancer specificity and therapeutic effects. Nanomaterials. 2018;8(11):923.
8. Khodabandehloo H, Zahednasab H, Hafez AA. Nanocarriers usage for drug delivery in cancer therapy. Iran J Cancer Preve. 2016;9(2).
9. Cho K, Wang X, Nie S, Shin DM. Therapeutic nanoparticles for drug delivery in cancer. Clinical cancer research. 2008;14(5):1310-1316.
10. Majidinia M, Mirza-Aghazadeh-Attari M, Rahimi M, Mihanfar A, Karimian A, Safa A, et al. Overcoming multidrug resistance in cancer: Recent progress in nanotechnology and new horizons. IUBMB life. 2020;72(5):855-871.
11. Zorkina Y, Abramova O, Ushakova V, Morozova A, Zubkov E, Valikhov M, et al. Nano Carrier Drug Delivery Systems for the Treatment of Neuropsychiatric Disorders: Advantages and Limitations. Molecules. 2020;25(22):5294.
12. Farjami A, Salatin S, Jafari S, Mahmoudian M, Jelvehgari M. The Factors Determining the Skin Penetration and Cellular Uptake of Nanocarriers: New Hope for Clinical Development. Current pharmaceutical design. 2021;27(42):4315-4329.
13. Hua S, De Matos MB, Metselaar JM, Storm G. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. Frontiers in pharmacology. 2018;9:790.
14. Pillai G. Nanomedicines for cancer therapy: an update of FDA approved and those under various stages of development. SOJ Pharm Pharm Sci 1 (2): 13. Nanomedicines for Cancer Therapy: An Update of FDA Approved and Those under Various Stages of Development. 2014.
15. Aghebati-Maleki A, Dolati S, Ahmadi M, Baghbanzhadeh A, Asadi M, Fotouhi A, et al. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. J Cell Physiol. 2020;235(3):1962-1972.
16. Wakaskar R. Cancer therapy with drug delivery systems. J Pharmacogenomics Pharmacoproteomics. 2017;8:e158.
17. Shukla S, Shukla SK, Govender PP, Giri N. Biodegradable polymeric nanostructures in therapeutic applications: opportunities and challenges. RSC advances. 2016;6(97):94325-94351.
18. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, et al. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Frontiers in Molecular Biosciences. 2020;7.
19. Lotfipour F, Shahi S, Farjami A, Salatin S, Mahmoudian M, Dizaj SM. Safety and Toxicity Issues of Therapeutically Used Nanoparticles from the Oral Route. BioMed Research International. 2021;2021.
20. Yousefi V, Tarhriz V, Eyvazi S, Dilmaghani A. Synthesis and application of magnetic@ layered double hydroxide as an anti-inflammatory drugs nanocarrier. J Nanobiotechnolog. 2020;18(1):1-11.
21. Mansouri E, Tarhriz V, Yousefi V, Dilmaghani A. Intercalation and release of an anti-inflammatory drug into designed three-dimensionally layered double hydroxide nanostructure via calcination–reconstruction route. Adsorption. 2020:1-8.
22. Geoprincy G, Gandhi N, Renganathan S. Novel antibacterial effects of alumina nanoparticles on Bacillus cereus and Bacillus subtilis in comparison with antibiotics. Int J Pharm Pharm Sci. 2012;4:544-548.
23. Li M, Li L, Lin S. Efficient antimicrobial properties of layered double hydroxide assembled with transition metals via a facile preparation method. Chinese Chemical Letters. 2020;31(6):1511-1515.
24. Yazdani P, Mansouri E, Eyvazi S, Yousefi V, Kahroba H, Hejazi MS, et al. Layered double hydroxide nanoparticles as an appealing nanoparticle in gene/plasmid and drug delivery system in C2C12 myoblast cells. Artificial cells, nanomedicine, and biotechnology. 2019;47(1):436-442.
25. Delgado RR, Vidaurre MA, De Pauli C, Ulibarri M, Avena M. Surface-charging behavior of Zn–Cr layered double hydroxide. J Colloid Interface Sci. 2004;280(2):431-441.

26. Del Hoyo C. Layered double hydroxides and human health: an overview. Applied Clay Science. 2007;36(1-3):103-21.
27. Li F, Duan X. Applications of layered double hydroxides. Layered double hydroxides. 2006:193-223.
28. Ookubo A, Ooi K, Hayashi H. Hydrotalcites as potential adsorbents of intestinal phosphate. J Pharm Sci. 1992;81(11):1139-1140.
29. Xu ZP, Zeng QH, Lu GQ, Yu AB. Inorganic nanoparticles as carriers for efficient cellular delivery. Chemical Engineering Science. 2006;61(3):1027-1040.
30. Figueiredo MP, Cunha VR, Leroux F, Taviot-Gueho C, Nakamae MN, Kang YR, et al. Iron-based layered double hydroxide implants: Potential drug delivery carriers with tissue biointegration promotion and blood microcirculation preservation. Acs Omega. 2018;3(12):18263-18274.
31. Dong L, Yan L, Hou W-G, Liu S-J. Synthesis and release behavior of composites of camptothecin and layered double hydroxide. J Solid State Chem. 2010;183(8):1811-1816.
32. Chen W, Zuo H, Zhang E, Li L, Henrich-Noack P, Cooper H, et al. Brain targeting delivery facilitated by ligand-functionalized layered double hydroxide nanoparticles. ACS applied materials & interfaces. 2018;10(24):20326-20333.
33. Barahuie F, Hussein MZ, Fakurazi S, Zainal Z. Development of drug delivery systems based on layered hydroxides for nanomedicine. Int J Mol Sci. 2014;15(5):7750-7786.
34. Maton PN, Burton ME. Antacids revisited. Drugs. 1999;57(6):855-870.
35. Tarnawski AS, Tomikawa M, Ohta M, Sarfeh IJ. Antacid talcid activates in gastric mucosa genes encoding for EGF and its receptor. The molecular basis for its ulcer healing action. J Physiol Paris. 2000;94(2):93-98.
36. Meneses CCF, de Sousa PRM, Pinto LC, Coelho GM, da Silva TF, Ferreira LO, et al. Layered double hydroxide–indomethacin hybrid: A promising biocompatible compound for the treatment of neuroinflammatory diseases. J Drug Deliv Sci Technol. 2021;61:102190.
37. Del Arco M, Cebadera E, Gutierrez S, Martin C, Montero M, Rives V, et al. Mg, Al layered double hydroxides with intercalated indomethacin: synthesis, characterization, and pharmacological study.J Pharm Sci. 2004;93(6):1649-1658.
38. Li B, He J, Evans DG, Duan X. Inorganic layered double hydroxides as a drug delivery system—intercalation and in vitro release of fenbufen. Applied Clay Science. 2004;27(3-4):199-207.
39. Qin L, Xue M, Wang W, Zhu R, Wang S, Sun J, et al. The in vitro and in vivo anti-tumor effect of layered double hydroxides nanoparticles as delivery for podophyllotoxin. Int J Pharm. 2010;388(1-2):223-230.
40. Wang Z, Liang P, He X, Wu B, Liu Q, Xu Z, et al. Etoposide loaded layered double hydroxide nanoparticles reversing chemoresistance and eradicating human glioma stem cells in vitro and in vivo. Nanoscale. 2018;10(27):13106-13121.
41. Chakraborty J, Roychowdhury S, Sengupta S, Ghosh S. Mg–Al layered double hydroxide–methotrexate nanohybrid drug delivery system: evaluation of efficacy. Materials Science and Engineering: C. 2013;33(4):2168-2174.
42. Barahuie F, Hussein MZ, Arulselvan P, Fakurazi S, Zainal Z. Drug delivery system for an anticancer agent, chlorogenate-Zn/Al-layered double hydroxide nanohybrid synthesised using direct co-precipitation and ion exchange methods. J Solid State Chem. 2014;217:31-41.
43. Asiabi H, Yamini Y, Alipour M, Shamsayei M, Hosseinkhani S. Synthesis and characterization of a novel biocompatible pseudo-hexagonal NaCa-layered double metal hydroxides for smart pH-responsive drug release of dacarbazine and enhanced anticancer activity in malignant melanoma. Materials Science and Engineering: C. 2019;97:96-102.
44. Hakeem A, Zhan G, Xu Q, Yong T, Yang X, Gan L. Facile synthesis of pH-responsive doxorubicin-loaded layered double hydroxide for efficient cancer therapy. Journal of Materials Chemistry B. 2018;6(36):5768-5774.
45. Shi Y, Van der Meel R, Chen X, Lammers T. The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. Theranostics. 2020;10(17):7921.
46. Natfji AA, Ravishankar D, Osborn HM, Greco F. Parameters affecting the enhanced permeability and retention effect: the need for patient selection. J Pharm Sci. 2017;106(11):3179-3187.
47. Wang Q, O'Hare D. Recent advances in the synthesis and application of layered double hydroxide (LDH) nanosheets. Chemical reviews. 2012;112(7):4124-4155.
48. Lin G, Mi P, Chu C, Zhang J, Liu G. Inorganic nanocarriers overcoming multidrug resistance for cancer theranostics. Advanced science. 2016;3(11):1600134.
49. Choi S-J, Oh J-M, Choy J-H. Toxicological effects of inorganic nanoparticles on human lung cancer A549 cells. J Inorg Biochem. 2009;103(3):463-471.
50. Dikalov SI, Dikalova AE, Mason RP. Noninvasive diagnostic tool for inflammation-induced oxidative stress using electron spin resonance spectroscopy and an extracellular cyclic hydroxylamine. Archives of biochemistry and biophysics. 2002;402(2):218-226.
51. Lanone S, Rogerieux F, Geys J, Dupont A, Maillot-Marechal E, Boczkowski J, et al. Comparative toxicity of 24 manufactured nanoparticles in human alveolar epithelial and macrophage cell lines. Particle and fibre toxicology. 2009;6(1):1-12.
52. Alkhafaji EN, editor Synthesis and characterization of Ag nanoparticle inter Nickel/Aluminum-layer double hydroxide nano hybrids compounds. IOP Conference Series: Materials Science and Engineering; 2020: IOP Publishing.
53. Koba-Ucun O, Ölmez Hanci T, Arslan-Alaton I, Arefi-Oskoui S, Khataee A, Kobya M, et al. Toxicity of Zn-Fe Layered Double Hydroxide to Different Organisms in the Aquatic Environment. Molecules. 2021;26(2):395.
54. Yan M, Yang C, Huang B, Huang Z, Huang L, Zhang X, et al. Systemic toxicity induced by aggregated layered double hydroxide nanoparticles. Int J Nanomedicine. 2017;12:7183.
55. Santana-Cruz A, Flores-Moreno JL, Guerra-González R, Martínez-Ortiz MdJ. Antibacterial activity of pipemidic acid ions-MgFeAl layered double hydroxide hybrid against *E. coli* and *S. typhi*. J Mex Chem Soc. 2016;60(2):62-66.
56. Barik S, Behera L, Badamali SK. Assessment of thermal and antimicrobial properties of PAN/Zn-Al layered double hydroxide nanocomposites. Composite Interfaces. 2017;24(6):579-591.
57. Dewhirst MW, Secomb TW. Transport of drugs from blood vessels to tumour tissue. Nature Reviews Cancer. 2017;17(12):738-750.
58. Eblan MJ, Wang AZ. Improving chemoradiotherapy with nanoparticle therapeutics. Translational cancer research. 2013;2(4):320.
59. Steinskog ESS, Sagstad SJ, Wagner M, Karlsen TV, Yang N, Markhus CE, et al. Impaired lymphatic function accelerates cancer growth. Oncotarget. 2016;7(29):45789.
60. Rathbone MJ. Advances in Delivery Science and Technology. 2013.
61. Ediriwickrema A, Saltzman WM. Nanotherapy for cancer:

targeting and multifunctionality in the future of cancer therapies. ACS biomaterials science & engineering. 2015;1(2):64-78.
62. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson AB, et al. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. JNCI: J Natl Cancer Inst. 2017;109(9):djx030.
63. Facts C. Cancer facts and figures (2017). Atlanta: American Cancer Society. 2013.
64. Mukherjee A, Waters AK, Kalyan P, Achrol AS, Kesari S, Yenugonda VM. Lipid–polymer hybrid nanoparticles as a next-generation drug delivery platform: state of the art, emerging technologies, and perspectives. Int J Nanomedicine. 2019;14:1937.
65. Jain A, Jain SK. In vitro release kinetics model fitting of liposomes: an insight. Chemistry and physics of lipids. 2016;201:28-40.
66. Jeon I-Y, Baek J-B. Nanocomposites derived from polymers and inorganic nanoparticles. Materials. 2010;3(6):3654-3674.
67. Longmire M, Choyke PL, Kobayashi H. Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats. 2008.
68. Zeineldin R, Syoufjy J. Cancer nanotechnology: opportunities for prevention, diagnosis, and therapy. Cancer Nanotechnology. 2017:3-12.
69. McGuire A, Brown JA, Malone C, McLaughlin R, Kerin MJ. Effects of age on the detection and management of breast cancer. Cancers. 2015;7(2):908-929.
70. Balasubramanian R, Rolph R, Morgan C, Hamed H. Genetics of breast cancer: management strategies and risk-reducing surgery. Br J Hosp Med. 2019;80(12):720-725.
71. McDonald JA, Goyal A, Terry MB. Alcohol intake and breast cancer risk: weighing the overall evidence. Current breast cancer reports. 2013;5(3):208-221.
72. Reeder J, Vogel V. Breast cancer prevention." In Advances in Breast Cancer Management, (pp. 149-164). Boston, MA: Springer; 2008.
73. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006;354(3):270-282.
74. Santoro E, DeSoto M, Hong Lee J. Hormone therapy and menopause. National Research Center for Women & Families. 2009.
75. Gage M, Wattendorf D, Henry L. Translational advances regarding hereditary breast cancer syndromes. J Surg Oncol. 2012;105(5):444-451.
76. Bao T, Rudek MA. The clinical pharmacology of anastrozole. Eur Oncol Haematol. 2011;7(2):106-108.
77. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol. 2014;32(21):2255.
78. Massarut S, Baldassarre G, Belletti B, Colombatti A, D'Andrea S, Candiani E, et al. Intraoperative radiotherapy impairs breast cancer cell motility induced by surgical wound fluid. Journal of Clinical Oncology. 2006;24(18_suppl):10611.
79. Belletti B, Vaidya JS, D'Andrea S, Entschladen F, Roncadin M, Lovat F, et al. Targeted intraoperative radiotherapy impairs the stimulation of breast cancer cell proliferation and invasion caused by surgical wounding. Clinical Cancer Research. 2008;14(5):1325-1332.
80. Leite AdM, Macedo AVS, Jorge AJL, Martins WdA. Antiplatelet Therapy in Breast Cancer Patients Using Hormonal Therapy: Myths, Evidence and Potentialities–Systematic Review. Arquivos brasileiros de cardiologia. 2018;111:205-212.
81. Komarala EP, Tyagi H, Thiyagarajan S, Pradhan L, Aslam M, Bahadur D. NIR absorbing Au nanoparticle decorated layered double hydroxide nanohybrids for photothermal therapy and fluorescence imaging of cancer cells. Journal of Materials Chemistry B. 2017;5(21):3852-3861.
82. Khorsandi K, Hosseinzadeh R, Shahidi FK. Photodynamic treatment with anionic nanoclays containing curcumin on human triple-negative breast cancer cells: Cellular and biochemical studies. J Cell Biochem. 2019;120(4):4998-5009.
83. Anirudhan T, Sekhar VC. Fabrication of functionalized layered double hydroxide/chitosan nanocomposite with dual responsive drug release for the targeted therapy of breast cancer. European Polymer Journal. 2020;139:109993.
84. Liu J, Liu K, Zhang L, Zhong M, Hong T, Zhang R, et al. Heat/pH-boosted release of 5-fluorouracil and albumin-bound paclitaxel from Cu-doped layered double hydroxide nanomedicine for synergistical chemo-photo-therapy of breast cancer. Journal of Controlled Release. 2021;335:49-58.
85. Guo Z, Xie W, Lu J, Guo X, Chi Y, Wang D, et al. Ferrous ions doped layered double hydroxide: Smart 2D nanotheranostic platform with imaging-guided synergistic chemo/photothermal therapy for breast cancer. Biomaterials Science. 2021;9(17):5928-5938.
86. Ananikov VP. Organic–Inorganic Hybrid Nanomaterials. Multidisciplinary Digital Publishing Institute; 2019.
87. Narain A, Asawa S, Chhabria V, Patil-Sen Y. Cell membrane coated nanoparticles: next-generation therapeutics. Nanomedicine. 2017;12(21):2677-2692.
88. Ickenstein LM, Garidel P. Lipid-based nanoparticle formulations for small molecules and RNA drugs. Expert opinion on drug delivery. 2019;16(11):1205-26.
89. DeFrates K, Markiewicz T, Gallo P, Rack A, Weyhmiller A, Jarmusik B, et al. Protein polymer-based nanoparticles: fabrication and medical applications. International journal of molecular sciences. 2018;19(6):1717.
90. da Silva Santos S, Igne Ferreira E, Giarolla J. Dendrimer prodrugs. Molecules. 2016;21(6):686.
91. Rode A, Sharma S, Mishra DK. Carbon nanotubes: classification, method of preparation and pharmaceutical application. Current drug delivery. 2018;15(5):620-629.
92. Singh P, Pandit S, Mokkapati V, Garg A, Ravikumar V, Mijakovic I. Gold nanoparticles in diagnostics and therapeutics for human cancer. Int J Mol Sci. 2018;19(7):1979.
93. Wang Y, Zhao Q, Han N, Bai L, Li J, Liu J, et al. Mesoporous silica nanoparticles in drug delivery and biomedical applications. Nanomedicine: Nanotechnology, Biology and Medicine. 2015;11(2):313-327.
94. Lu AH, Salabas EeL, Schüth F. Magnetic nanoparticles: synthesis, protection, functionalization, and application. Angewandte Chemie International Edition. 2007;46(8):1222-1244.
95. Chaturvedi VK, Singh A, Singh VK, Singh MP. Cancer nanotechnology: a new revolution for cancer diagnosis and therapy. Current drug metabolism. 2019;20(6):416-429.
96. Choi S-J, Oh J-M, Park T, Choy J-H. Cellular toxicity of inorganic hydroxide nanoparticles. J Nanosci Nanotechnol 2007;7(11):4017-4020.
97. Oh J-M, Park M, Kim S-T, Jung J-Y, Kang Y-G, Choy J-H. Efficient delivery of anticancer drug MTX through MTX-LDH nanohybrid system. Journal of Physics and Chemistry

of Solids. 2006;67(5-6):1024-1027.
98. Pooresmaeil M, Nia SB, Namazi H. Green encapsulation of LDH (Zn/Al)-5-Fu with carboxymethyl cellulose biopolymer; new nanovehicle for oral colorectal cancer treatment. International journal of biological macromolecules. 2019;139:994-1001.
99. Senapati S, Mahanta AK, Kumar S, Maiti P. Controlled drug delivery vehicles for cancer treatment and their performance. Signal transduction and targeted therapy. 2018;3(1):1-19.
100. Kim T-H, Lee GJ, Kang J-H, Kim H-J, Kim T-i, Oh J-M. Anticancer drug-incorporated layered double hydroxide nanohybrids and their enhanced anticancer therapeutic efficacy in combination cancer treatment. BioMed research international. 2014;2014.
101. Zhao H, Zhang X. Enhanced apoptosis and inhibition of gastric cancer cell invasion following treatment with LDH@ Au loaded Doxorubicin. Electronic Journal of Biotechnology. 2018;32:13-8.
102. Zhao X-F, Wang W-Y, Li X-D, Li S-P, Song F-G. Core-shell structure of Fe3O4@ MTX-LDH/Au NPs for cancer therapy. Materials Science and Engineering: C. 2018;89:422-428.
103. Li D, Zhang Y-T, Yu M, Guo J, Chaudhary D, Wang C-C. Cancer therapy and fluorescence imaging using the active release of doxorubicin from MSPs/Ni-LDH folate targeting nanoparticles. Biomaterials. 2013;34(32):7913-7922.
104. Li L, Qian Y, Sun L, Han FY, Zhang R, Wang P-Y, et al. Albumin-stabilized layered double hydroxide nanoparticles synergized combination chemotherapy for colorectal cancer treatment. Nanomedicine: Nanotechnology, Biology and Medicine. 2021;34:102369.
105. Saha S, Bhattacharjee A, Rahaman SH, Basu A, Chakraborty J. Synergistic anti-cancer activity of etoposide drug loaded calcium aluminium layered double hydroxide nanoconjugate for possible application in non small cell lung carcinoma. Applied Clay Science. 2020;188:105496.
106. Shahabadi N, Razlansari M. Biological application of Layered double hydroxides in drug delivery systems. Journal of Nanoanalysis. 2018;5(4):210-226.
107. Li L, Gu W, Chen J, Chen W, Xu ZP. Co-delivery of siRNAs and anti-cancer drugs using layered double hydroxide nanoparticles. Biomaterials. 2014;35(10):3331-3339.
108. Kim H-J, Jeung D-G, Oh J-M. Boosting the anticancer activity of doxorubicin with a layered double hydroxide nanocarrier. Applied Clay Science. 2021;203:106000.
109. Mokhtari S, Solati-Hashjin M, Khosrowpour Z, Gholipourmalekabadi M. Layered double hydroxide-galactose as an excellent nanocarrier for targeted delivery of curcumin to hepatocellular carcinoma cells. Applied Clay Science. 2021;200:105891.
110. Andrade KN, Knauth P, López Z, Hirata GA, Martinez SJG, Arízaga GGC. Assembly of folate-carbon dots in GdDy-doped layered double hydroxides for targeted delivery of doxorubicin. Applied Clay Science. 2020;192:105661.
111. Kim H-J, Lee JY, Kim T-H, Gwak G-H, Park JH, Oh J-M. Radioisotope and anticancer agent incorporated layered double hydroxide for tumor targeting theranostic nanomedicine. Applied Clay Science. 2020;186:105454.
112. Mei X, Liang R, Peng L, Hu T, Wei M. Layered double hydroxide bio-composites toward excellent systematic anticancer therapy. Journal of Materials Chemistry B. 2017;5(17):3212-3216.
113. Kim H-J, Lee GJ, Choi A-J, Kim T-H, Kim T-i, Oh J-M. Layered double hydroxide nanomaterials encapsulating Angelica gigas Nakai extract for potential anticancer nanomedicine. Frontiers in pharmacology. 2018;9:723.
114. Shafiei SS, Solati-Hashjin M, Samadikuchaksaraei A, Kalantarinejad R, Asadi-Eydivand M, Osman NAA. Epigallocatechin gallate/layered double hydroxide nanohybrids: Preparation, characterization, and in vitro anti-tumor study. PLoS One. 2015;10(8):e0136530.
115. Zhang L-x, Sun X-m, Xu ZP, Liu R-t. Development of multifunctional clay-based nanomedicine for elimination of primary invasive breast cancer and prevention of its lung metastasis and distant inoculation. ACS applied materials & interfaces. 2019;11(39):35566-76.
116. Choi G, Kwon O-J, Oh Y, Yun C-O, Choy J-H. Inorganic nanovehicle targets tumor in an orthotopic breast cancer model. Scientific reports. 2014;4(1):1-7.
117. Zheng W, Yin T, Chen Q, Qin X, Huang X, Zhao S, et al. Co-delivery of Se nanoparticles and pooled SiRNAs for overcoming drug resistance mediated by P-glycoprotein and class III β-tubulin in drug-resistant breast cancers. Acta biomaterialia. 2016;31:197-210.
118. Kim JY, Choi S-J, Oh J-M, Park T, Choy J-H. Anticancer drug-inorganic nanohybrid and its cellular interaction. Journal of Nanoscience and Nanotechnology. 2007;7(11):3700-3705.
119. Zhang C, Li L, Han FY, Yu X, Tan X, Fu C, et al. Integrating Fluorinated Polymer and Manganese-Layered Double Hydroxide Nanoparticles as pH-activated 19F MRI Agents for Specific and Sensitive Detection of Breast Cancer. Small. 2019;15(36):1902309.
120. Xie W, Guo Z, Cao Z, Gao Q, Wang D, Boyer C, et al. Manganese-based magnetic layered double hydroxide nanoparticle: A PH-sensitive and concurrently enhanced T 1/T 2-weighted dual-mode magnetic resonance imaging contrast agent. ACS Biomaterials Science & Engineering. 2019;5(5):2555-2562.
121. Barahuie F, Hussein MZ, Hussein-Al-Ali SH, Arulselvan P, Fakurazi S, Zainal Z. Preparation and controlled-release studies of a protocatechuic acid-magnesium/aluminum-layered double hydroxide nanocomposite. Int J Nanomedicine. 2013;8:1975.
122 Ahmadi-Kashani M, Dehghani H, Zarrabi A. A biocompatible nanoplatform formed by MgAl-layered double hydroxide modified Mn3O4/N-graphene quantum dot conjugated-polyaniline for pH-triggered release of doxorubicin. Materials Science and Engineering: C. 2020;114:111055.
123. Cao W, Muhammad F, Cheng Y, Zhou M, Wang Q, Lou Z, et al. Acid susceptible ultrathin mesoporous silica coated on layered double hydroxide nanoplates for pH responsive cancer therapy. ACS Applied Bio Materials. 2018;1(3):928-935.
124. Vajedi FS, Dehghani H, Zarrabi A. Design and characterization of a novel pH-sensitive biocompatible and multifunctional nanocarrier for in vitro paclitaxel release. Materials Science and Engineering: C. 2021;119:111627.
125. Yoo SS, Razzak R, Bédard E, Guo L, Shaw AR, Moore RB, et al. Layered gadolinium-based nanoparticle as a novel delivery platform for microRNA therapeutics. Nanotechnology. 2014;25(42):425102.