Chapter

Role of Drug Repurposing in Cancer Treatment and Liposomal Approach of Drug Targeting

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Abstract

Cancer is the leading cause of death, and incidences are increasing significantly and patients suffering from it desperately need a complete cure from it. The science of using an already-invented drug that has been approved by the FDA for a new application is known as "drug repurposing." Currently, scientists are drawn to drug repositioning science in order to investigate existing drugs for newer therapeutic uses and cancer treatment. Because of their unique ability to target cancer cells, recently repurposed drugs and the liposomal approach are effective in the treatment of cancer. Liposomes are nanovesicles that are drastically flexible, rapidly penetrate deeper layers of cells, and enhance intracellular uptake. More importantly, liposomes are biocompatible, biodegradable; entrap both hydrophobic and hydrophilic drugs. This chapter summarizes various approaches to drug repurposing, as well as drug repurposing methods, advantages and limitations of drug repurposing, and a liposomal approach to using repurposed drugs in cancer targeting. This chapter also summarizes liposomal structure, drug loading, and the mechanism of liposomes in targeted cancer treatment. The lipid-based liposomal approach is emerging as a powerful technique for improving drug solubility, bioavailability, reducing side effects, and improving the therapeutic efficacy of repurposed drugs for cancer treatment.

Keywords: cancer, drug repurposing, liposomes, drug targeting, enhanced permeability effect, Etc.

1. Introduction

During the treatment of cancer in a patient, it is necessary to follow certain principles, such as diagnosing the disease at an early stage, making efforts for its prevention, and completing the eradication of malignant cells. Whereas three modes of treatment are available to treat cancer, including surgery, chemotherapy (also called pharmacotherapy), and radiation therapy [1], Radiation therapy is nothing but the eradication of malignant cells by means of radiation. This technique helps to destroy localized cancer cells (**Figure 1**). In pharmacotherapy, various chemical entities are used to kill and disorganize an uncontrolled cell growth programme in a body [2]. Cancer does not only affect humans; it can also harm wildlife and other life forms. Tumour cells might break out from the initial bulk and begin the unregulated growth cycle all over again. The phenomenon of tumour cells leaving one location and developing cells that travel and proliferate over other body parts is known as metastasis. It was estimated by the WHO that cancer is the foremost cause of death in the world, and in the year 2018, it is expected that 9.6 million people died as a result of it. It is categorized by the development of osteocytes, bone lesions, anaemia, skeletal destruction, renal failure, and hypocalcaemia. It is a bone marrow cancer that affects both the marrow and the bones. It also affects different body locations; hence it is called multiple myeloma. Bone marrow-originating myeloid cells such as myeloid resultant suppressor cells, macrophages, myeloid dendritic cells, monocytes, osteoclasts, and lymphocytes are drafted to tumours, which can either increase anti-tumour immune function or encourage tumour growth [3]. Recent research indicates that anti-resorptive targeted therapies can have an impact on tumour-associated myeloid cells through direct or indirect pathways, indicating that anti-resorptives have an osteoclastin-dependent mechanism of action. As the cancer progresses, the signs and symptoms change dramatically. Symptoms can be entirely dissimilar from

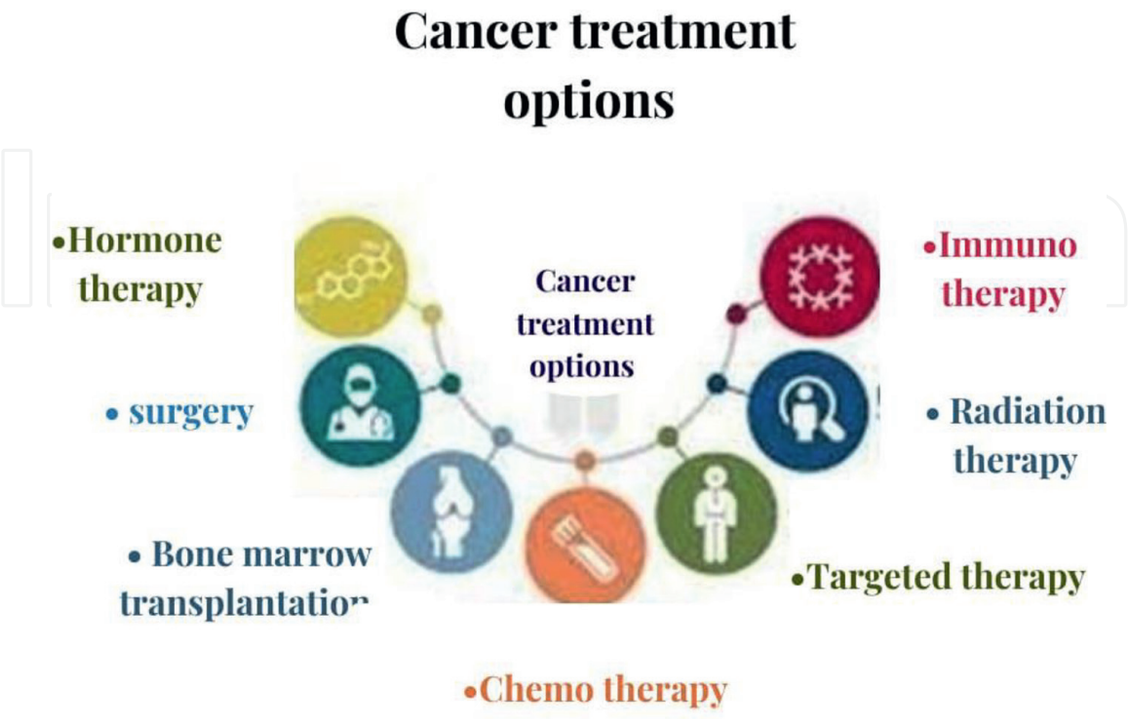

Figure 1.
Schematic representation of cancer treatments.

patient to patient. A few symptoms are most common, like fatigue, bone problems, kidney problems, and low blood counts. Some symptoms become severe; these are: osteoporosis, osteocytes, bone lesions, and skeletal destruction [4].

Targeted cancer treatment, in which the selected cancer cells are eliminated and healthy cells are left alone, is becoming extremely prevalent [5]. The arrival of nanostructures has resulted in the development of advanced materials and channels for cancer treatment targeting [6, 7]. Nanotechnology has opened up new possibilities for biological and biomedical applications, such as improving the targeted administration of anticancer drugs. Nanotechnology has a lot of benefits for treating cancer. In reality, tumour blood vessels are severely disordered, with an ineffective lymph capillary network and loose endothelial cells in comparison with normal tissue. Because of their improved permeability and high body retention, nanoparticles such as liposomes can be transported preferentially to the tumour location [8].

2. Drug repurposing in cancer treatment

This technique helps to destroy localized cancer cells. In pharmacotherapy, various chemical entities are used to kill and disorganize an uncontrolled cell growth programme in a body [8]. Chemotherapeutic agents pose the greatest risk to cancer patients because of the drugs' lethal effects and the possibility of cell damage to their bone marrow, which makes them more susceptible to other diseases. If we have not targeted the malignant cell only, then these chemotherapeutic agents also kill the normal cells in the same host, which creates more damage to the patient's body and its biological structure [9]. Different strategies of drug repurposing are denoted in **Figure 2**.

Extensive research is carried out to investigate and develop new therapeutic entities in the oncology field and drug research to achieve the maximum therapeutic effect with greater patient comfort and a lower toxicity profile. On the other hand it raises the cost of treatment for a patient, making it necessary to exert maximum effort to achieve desired treatment goals at the lowest possible cost of treatment. Drug repurposing is the most effective way to reduce the effort required to develop new drug molecules while also lowering treatment costs. The science of using an already-invented drug that has been approved by the FDA for a newer application is known as drug purposing. Now a day drug repositioning science attracts the more researchers to investigate existing drugs for its newer therapeutic use. The drug being repositioned is already being used to treat diseases in humans, giving the manufacturer access to knowledge regarding its safety, effectiveness, therapeutic, and toxicity profiles. To reposition medications that are already approved for human use efficiently, rigorous selection is required, followed by a detailed demonstration of the treatment's usefulness in new biological contexts. The following methods are used to select drug candidates for drug repositioning [10].

2.1 Repositioning based on therapeutic activity

This method involves testing the therapeutic effectiveness of a drug by performing an in vitro or in vivo study. For the finding of therapeutic entities, comprehensive public library data is used. The therapeutic agent is examined for its protein targets and cellular targets while searching for a suitable drug candidate through activity-based repurposing of the drug (**Figure 3**) [11, 12].

Figure 2.
Strategies to repurpose the drug candidates.

2.2 Drug repositioning through literature evidence

This drug repurposing method involves the selection of a drug based on its published therapeutic evidence. The literature study of such drug databases available on PubMed, ClinicalTrail.gov, Drug Quest, MEDLINE, and other available databases is screened, and the required potential molecules are identified by applying such data in a dynamic way (**Figure 4**) [13].

2.3 In silico method: In this method

Various bioinformatics tools and a public database are used to understand drug protein interactions. For this method, extensive genomic studies and structural evaluations of various proteins are carried out. Most pharmaceutical drug manufacturers adopt the in silico method for drug repurposing. To identify the protein interaction and possible drug candidate, researchers use the science of

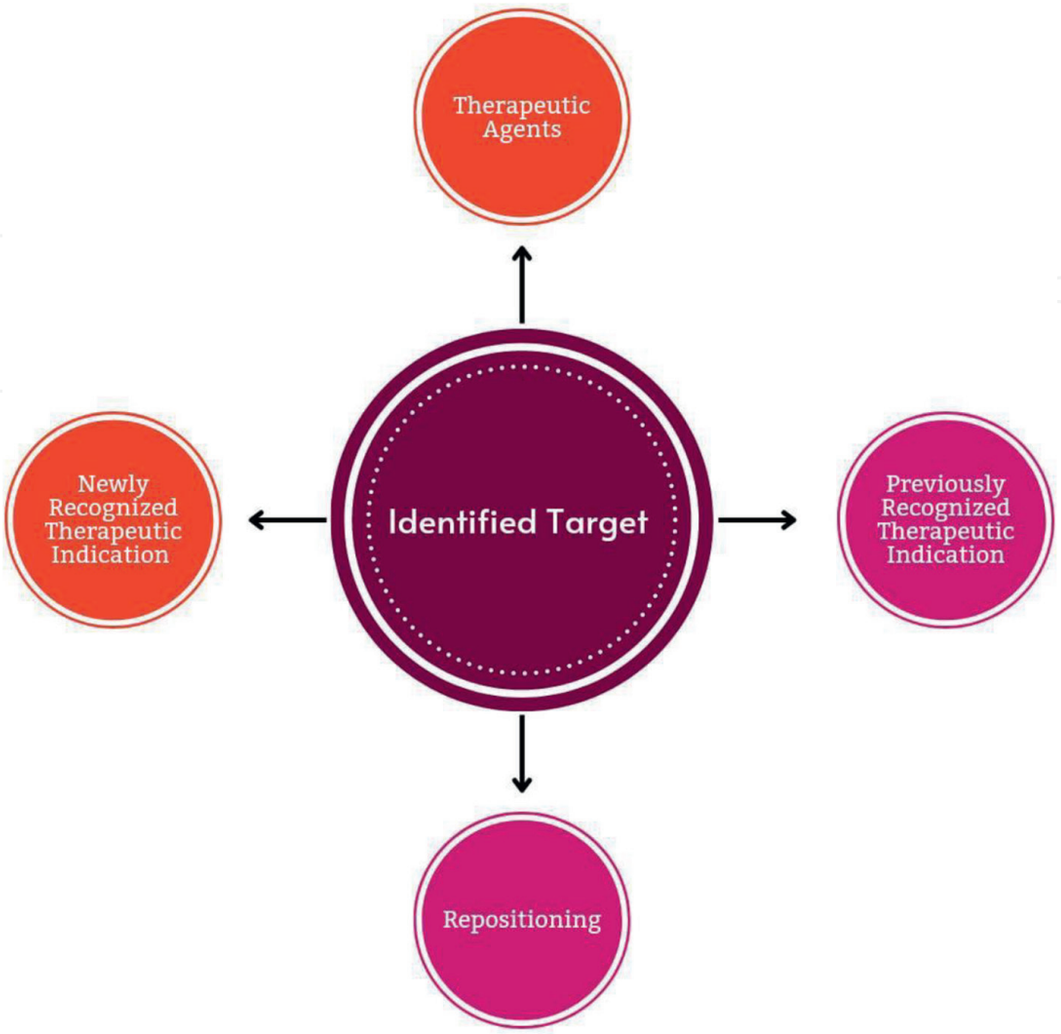

Figure 3.
Diagrammatic representation of Drug Repositioning (Case A).

artificial intelligence, neural network techniques, and other bioinformation tools (**Figure 5**) [11, 14].

2.4 Advantages of drug repositioning

1. Drug repositioning helps to curtail the drug development cost, which leads to an improvement in the economy of the treatment [15].

2. It helps to cut down the risk associated with the task of drug development.

3. Minimize the time requirement in drug investigation as compared to the traditional method of drug development.

4. The availability of extensive data related to drug kinetic and dynamic properties reduces the efforts required to select a suitable dosage form, and assess the safety and toxicity of a drug.

5. Researchers can skip performing preclinical experiments by relocating drugs, which helps reduce the drug development cost.

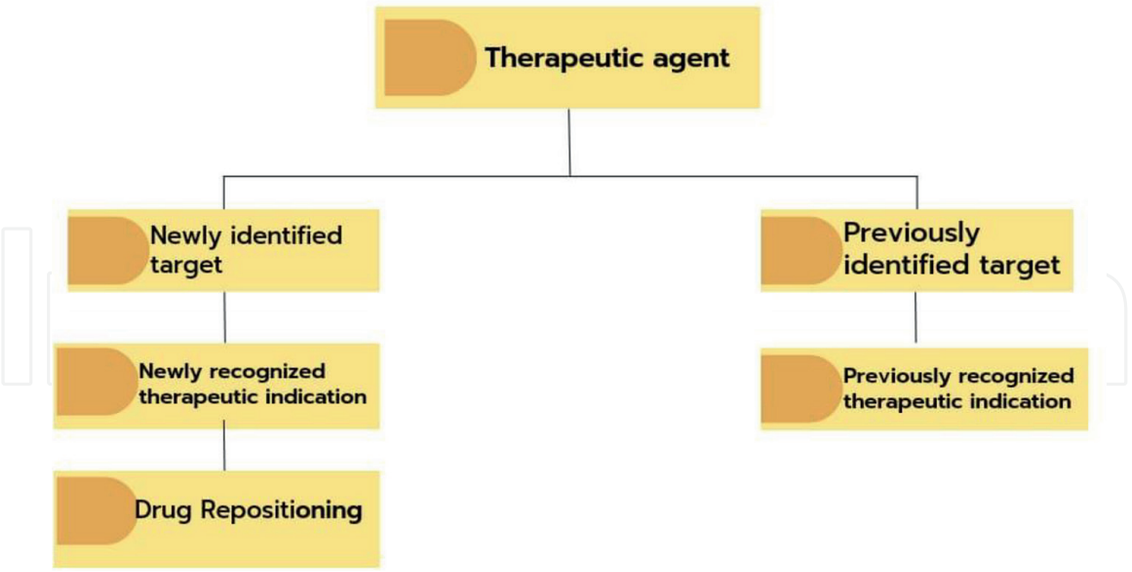

Figure 4.
Diagrammatic representation of Drug Repositioning (Case B).

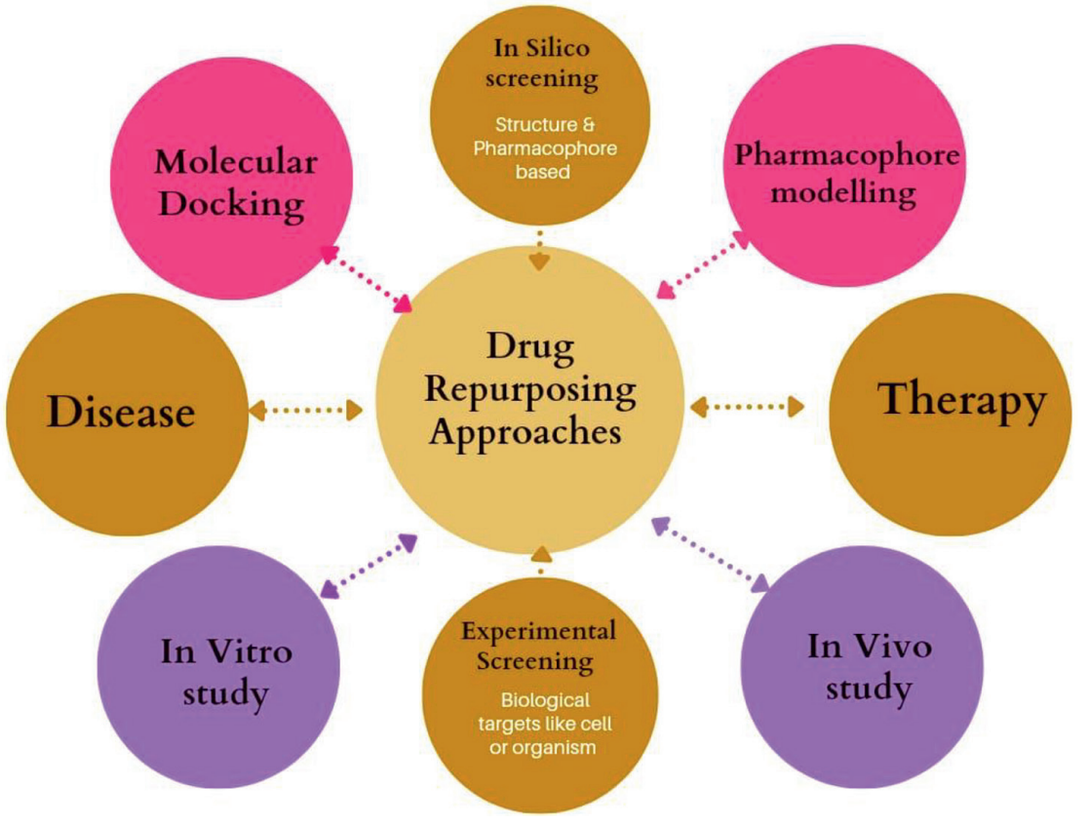

Figure 5.
Diagrammatic representation of drug repurposing approaches.

2.5 Limitations of drug repositioning

1. More money is spent on licensing requirements for drug repositioning to investigate new therapeutic applications of already approved drugs [16].

2. The drug repositioning process includes intellectual property protection for repurposed medications, which is especially important for off-patent drugs.

3. Pharmaceutical industries have shown little interest in repurposing medications because such rights are difficult to grant.

4. Anticancer activity of repurposed medications is more commonly reported when used in conjunction with established cytotoxic drugs rather than as single agents.

3. Repurposed drug targeting

Nanoparticulate drugs (including liposomal drugs) are generally developed for therapeutics developed against cancer to avoid non-specific distribution to healthy cells and tissues that generally causes lethal side effects. Due of the permeable tumour vasculature and decreased lymphatic outflow, the nanomedicines (including liposomes) with prolonged circulation durations preferentially penetrate tumour tissue. This phenomenon is referred to as the "increased permeability and retention (EPR) effect Drug repurposing is a technique for finding new applications for medicines that go beyond their original medicinal indications. On the other hand, drug repurposing is the most effective way to reduce the coast, time and effort required to develop new drug molecules while also lowering treatment costs. The development of nanomedicines (including liposomes) for these repurposed drugs could provide many benefits; increased kinetic, dynamic and biopharmaceutical characteristics, and avoids their primary indications via targeting them to tumour through EPR effect. Furthermore, these nanomedicines could be easily surface modified to passively and actively target tumour cells and cellular components. Therefore, nanomedicines composed of repurposed drug could be preferred over plain drugs or their conventional generic dosage forms currently available in the market.

4. Liposomes (LPs)

An LPs is a spherical vesicle made up of one or more lipid vesicles that is increasingly being used to deliver therapeutic entities. Liposomes are one of several promising drug delivery systems that represent an efficient approach for delivering active compounds to the target site, and various formulations are currently in clinical use. LPs technology has been developed from typical vesicles to second generation liposomes, which are created by changing the lipid composition, length, and charge of vesicle liposomes and can be employed on a regular basis as what the body does to drugs and what drugs do to the body can be controlled. The LPs provide selective passive targeting to tumour tissues, and the encapsulation method contributes to increased effectiveness, therapeutic index, and stability. Reduced polymer toxicity, site evading effect, helping to enhance the pharmacokinetics of the therapeutic moiety, and suppleness to bind ligands at specific sites to achieve active targeting, to name a few advantages [6]. Liposomes were studied for the first time at the Babraham Institute in Cambridge by two scientists who used an electron microscope to examine phospholipids in dry form with negative staining. These two scientists are Dr. Alec Bengham and R. W. Horne, who identified the liposome assembly in 1961 and

published their study in 1964. Liposome is the name given to a compound made up of lipids (lipo) and body (soma). So that liposome is nothing but a lipid body in which medicine is to be delivered [17]. Many anticancer medications have been designed to terminate tumour cells that are developing uncontrollably because they divide more quickly than normal cells. However, in this instance, ordinary cells grow fast, and a chemotherapeutic agent might harm such cells, resulting in chemotherapy side effects. Blood cells that create bone marrow, cells in the digestive tract (cells in the mouth, stomach, gut, and oesophagus), and sexual organs and hair follicles are among the fast-growing normal cells that are impacted. Some anticancer medications have the capacity to harm cells in key organs, including the heart, kidney, bladder, lungs, and neurological system. Medication diffusion in solid tumours is hampered by a variety of vascular supply and cellular gravity within tumour cells, particularly in tumour regions. Drug delivery design develops in such a way to ensure that macromolecular medicines are released slowly via the tumour. Advanced technologies are designed to improve tumour tissue permeability. These are triggered by the maladaptive nature of tumorigenesis, which is characterized by structural and physiological abnormalities that lead to hyperpermiability. The medicinal compounds have a larger molecular structure, which leads to the build-up of high-molecular-weight molecules with limited distribution volumes and the ability to circulate for lengthy periods of time through aberrant arteries and concentrate in tumours [18–20].

4.1 Structural features of liposome

LPs are small cell membrane sacs. Because these LPs can be packed with medications, they are a viable option for treating illnesses and cancer. Liposome membranes are composed of phospholipids with a head and a tail group. Because of the length of the hydrocarbon chain, the head part is hydrophilic and the tail part is hydrophobic. Phospholipids are naturally occurring two-layer stable membranes. Because head groups are hydrophilic, they are fascinated by water and arrange in such a way to form a surface-like assembly away from it when there is water present. In a cell with outside water, while the other is fascinated by water within the cell. They resemble tiny spheres that are smaller than a normal cell's size, whether as bilayers or monolayers. Liposomes are created as bilayers, while micelles are formed as monolayers. Phospholipids form the mainstream of the lipids in the plasma membrane; these phospholipids are phosphatidyl ethanolamine and phosphatidylcholine [19–21]. Liposomes have the capability to penetrate cancer in its natural state. Endothelium cells are contained by tight junctions in the endothelial walls of all healthy human blood vessels. These tight connections prevent large blood particles from spilling out of the vessel. In the event of a tumour vessel, this type of arrangement does not exist, making it symptomatically porous. This capacity is known as the enhanced permeability and retention effect (EPR) (**Figure 6**). Liposomes with a diameter of less than 400 nm can enter tumours quickly from the bloodstream, but they are maintained in the bloodstream by the endothelium wall in healthy tissue [23–25].

4.2 Drug loading mechanism into liposome

The drug features and the lipids determine how pharmaceuticals are loaded into liposomes. Hydrophilic medications are confined in the inner watery compartment,

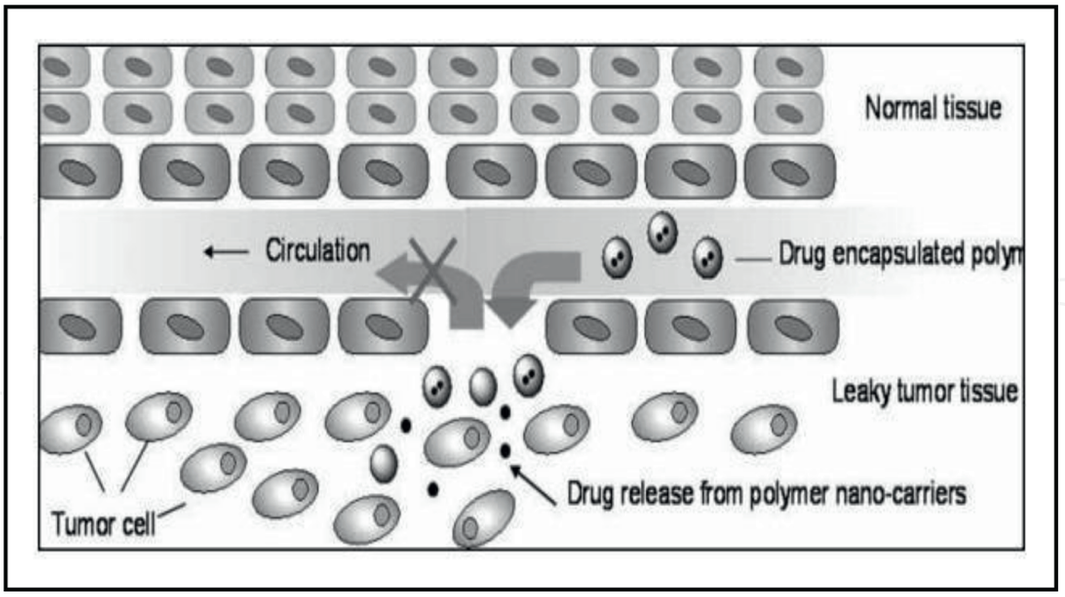

Figure 6.
Diagrammatic representation of EPR effect [22].

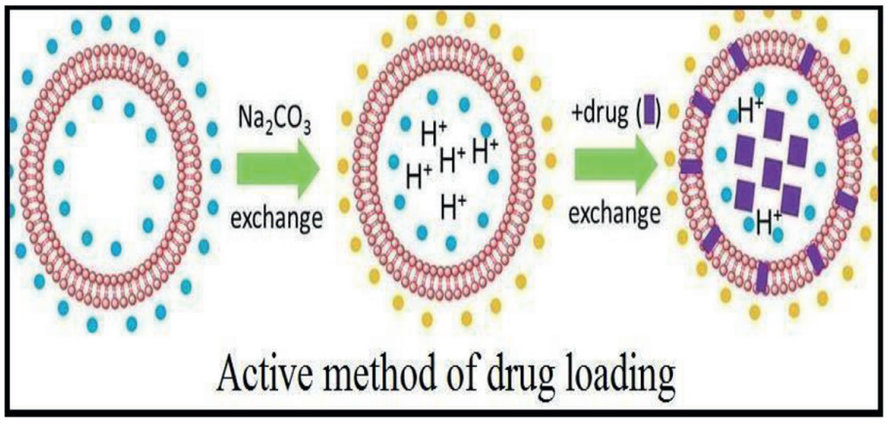

Figure 7.
Active loading of drug into liposome [26].

while hydrophobic pharmaceuticals can screen within the lipid hydrocarbon area. In practice, few medicines may segregate into hydrocarbon or aqueous compartments; for example, Amphotericin-B (Amph-B) binds to hydrophobic lipid membranes. The resulting lipid configuration influences Amph-B parcelling and its rate of exchange outside of the liposome envelope (**Figure 7**). Incorporating a negatively charged lipid improves the stability of the membrane's connection [27, 28].

According to the trans-membrane pH gradient, weak bases can concentrate in liposomes. Liposome formation is dependent on two critical steps: the formation of a pH gradient with a lower intra-liposomal pH and the subsequent loading of the drug. Gradient generation of a trans-membrane proton can be done in a variety of ways. Liposomes are made in citrate buffer, and then transferred to a pH 7.5 buffer by an exogenous buffer exchange. Ionophores, on the other hand, can be employed with action gradients. Ultimately, liposomes developed in the presence of significant amounts of ammonium sulphate (**Figure 8**). The withdrawal of salt solution causes the creation of a pH gradient, which is also accountable for the drug entrapment mechanism [22, 30, 31].

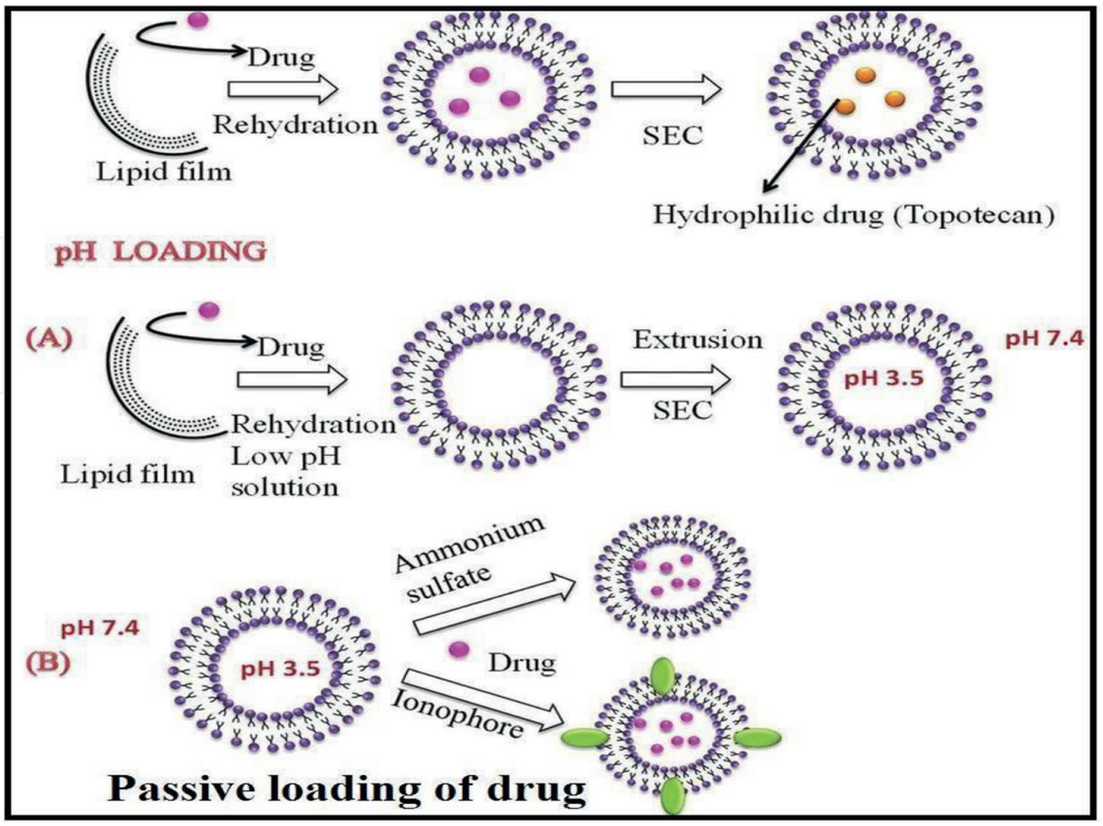

Figure 8.
Passive loading of drug into liposome [29].

5. Drug targeting

Much of the effort in liposome research has been focused on tumour targeting. Liposomes in circulation extravagate through the 'leaky' tumour vasculature; alternatively, attachment of specific antibodies or other proteins to the liposome surface may cause specific targeting. However, the increased clinical efficacy of such targeting in human patients has not been easy to prove. Most of a liposomal drug given intravenously is taken up by phagocytosis into the reticulo-endothelial system, which is extremely efficient at trapping particulate matter circulating intravenously (**Figure 9**). The reticulo-endothelial system may be circumvented by several different methods, such as saturation with large doses of liposome particles or selective macrophage inactivation by pharmacological means However, such a strategy could theoretically further compromise the immune system of cancer patients [33, 34].

Liposomes as a Drug Depot Many drugs are most effective when they are delivered over extended periods of time. For example, agents specific for the division phase of the cell cycle kill cancer cells only when they are dividing. However, even for the most rapidly growing tumours, only a small fraction of the cells are dividing during the drug's residence time. Therefore, depot formulations are needed to maintain therapeutic concentrations for prolonged periods. In contrast to biodegradable polymers or chemical modifications of the standard drug, liposomes and other lipid-based formulations have the advantage of not creating a new chemical entity, and the need for extensive toxicological studies is largely avoided. This is especially the case for the more efficient lipid-based drug delivery systems, where the amount of lipid used is small relative to the amount of drug delivered (**Figure 9**). Even if

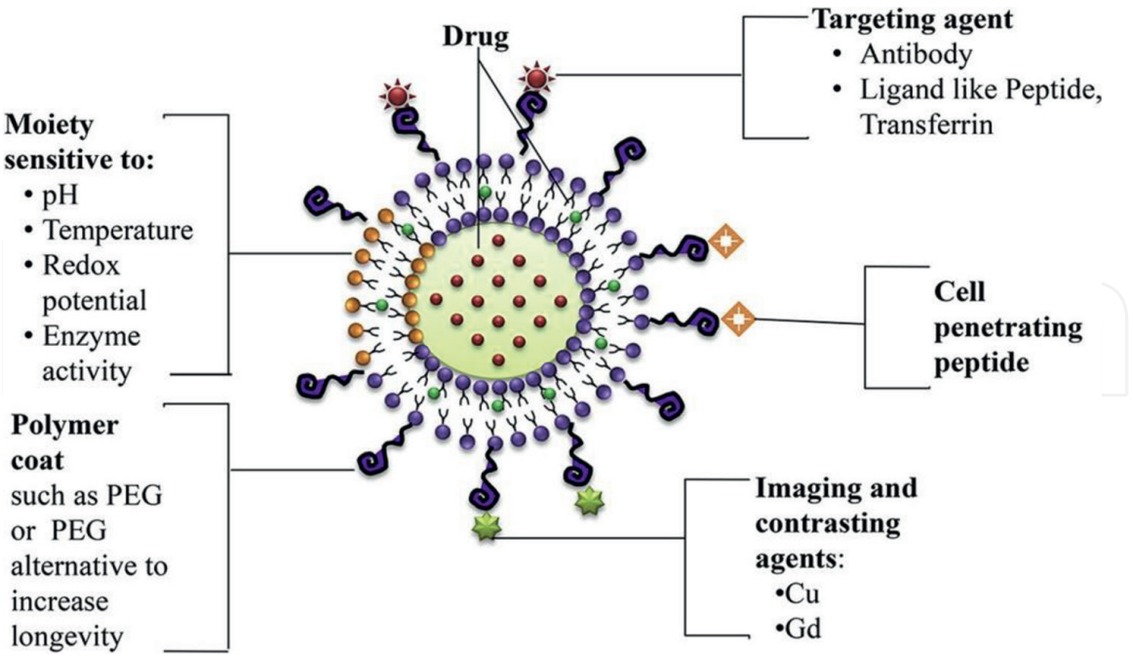

Figure 9.
Liposomal drug delivery to treat cancer [32].

efficacy and toxicity remain unchanged, the convenience and improved patient compliance of fewer painful injections may be sufficient for those drugs that require frequent multiple injections or continuous infusions [35–37].

6. Conclusions

Nowadays drug repurposing and drug targeting through nanoparticulate drug delivery gain significant attention for delivering various APIs in treatment of cancer through oral and topical route successfully. Loading the repurposing drug in to liposomes escalate therapeutic efficacy and residences toxic effects along with patients compliance. Nanomedicines could be easily surface modified to passively and actively target tumour cells and cellular components. Therefore, nanomedicines composed of repurposed drug could be preferred over plain drugs or their conventional generic dosage forms currently available in the market. The advantages of various methodologies and strategies for drug targeting are outlined in the current chapter, along with information on liposomal drug targeting, liposomal structure, mechanism of liposomal drug loading, and liposomal drug targeting. Drug repurposing and liposomal drug targeting are potent methods for enhancing solubility and bioavailability, minimizing side effects, and developing innovative drug delivery systems to increase the therapeutic effectiveness of drug repurposing to treat cancer.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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Abbreviations

API	active pharmaceutical ingredient
HA	hyaluronic acid
LP	liposomes
PCB	poly carboxybetaine
PEG	poly ethylene glycol
NDDS	nanoparticulate drug delivery
WHO	World Health Organization
EPR	enhanced permeability and retention effect

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