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Review Article

Nanoparticles and drug delivery for chemoprevention in cancers

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Abstract
Cancer is a major global issue that is responsible for morbidity and mortality all over the world. Radiation therapy, surgery, and chemotherapy are categorized into traditional cancer treatment methods that cause systemic toxicity and limited efficacy because of non-specific drug delivery. As a result, various side effects compromise a patient's quality of life. Thus, innovative approaches are required that can enhance therapeutic outcomes and result in fewer adverse effects. Nanotechnology addresses such challenges and provides a promising avenue for treating cancer. Engineered nanoparticles offer a platform for targeted drug delivery, that enhances therapeutic efficacy and shows minimum adverse effects. In this context, researchers have now developed strategies to improve cancer chemoprevention. This review demonstrates the application of various nanoparticles in cancer chemoprevention and focuses on their mechanisms of action, advantages, and novel research advancements. In cancer chemoprevention, the mechanisms of action of nanoparticles are diverse and are dependent on targeted cancer and particular nanoparticle types. Nanoparticles can inhibit tumor cell proliferation, induce apoptosis, and cause tumor cell destruction. They can promote an immune response against tumor cells, causing effective anti-tumor effects. Researchers are developing various novel nanoparticles platforms that have improved targeting efficiency, biocompatibility, and drug release kinetics. Furthermore, researchers are also trying to combine nanoparticles with other therapeutic applications such as immunotherapy, to get synergistic anti-tumor effects.
Key Words: Nanoparticles, Chemoprevention, Drug Delivery Systems, Enhanced Permeability and Retention (EPR) Effect, Biocompatibility, Tumor Targeting, Controlled Release

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INTRODUCTION

Cancer remains one of the major causes of death worldwide despite ongoing advancements in the medical field and technology because of its dynamic nature [1]. Many cancer therapies including radiation, surgery, and chemotherapy, are in use today but these are facing major challenges. Chemotherapy may result in systemic toxicity by presenting its action on non-cancerous cells along with normal cells [2]. The potential of chemotherapy can further be increased by combinational strategies. Nano-oncology is now emerging as a multidisciplinary field that is expected to outperform various traditional cancer treatment methods [3]. Nanotechnology can be utilized in diagnosis and managing various types of cancers [4]. In comparison to conventional drugs, nanoparticle-based drug delivery possesses advantages, such as biocompatibility and enhanced stability, increased permeability and retention effect, as well as precise targeting [5]. The targeting mechanisms are passive and active targeting in which one relies on the EPR effect where nanoparticles accumulate in tumor tissues due to poor lymphatic drainage and their leaky vasculature [6]. The other relies on modifying nanoparticles with ligands that further specifically bind to receptors that are overexpressed on tumor cells and finally increase targeting efficiency [7]. The use of nanotechnology to achieve chemoprevention is considered an effective strategy that enhances the bioavailability of phytochemicals and ultimately their therapeutic efficacy [8].

Mechanisms of Chemoprevention

Cancer chemoprevention aims to delay, suppress, or prevent tumor occurrence by using natural or synthetic bioactive agents as shown in Table 1. Mechanistically, these chemo-preventive agents are also helpful in mitigating cancer development, either by blocking the division of premalignant cells or by impeding DNA damage [9]. The agents for chemoprevention are categorized into two principal categories: (a) "blocking" agents and (b) "suppressing" agents [10, 11]. Blocking agents are those that block the initiation stage, and the ones that affect the promotion stage are

known as suppressing agents [12]. The first group of compounds tends to neutralize RNS/ROS as well as reactive metabolites, change the metabolism of carcinogen, and cause an increase in detoxification and repair. In conditions where the initiation phase has taken place already, suppressive agents are responsible for promoting apoptosis, eliminating reactive oxygen species, reducing cell proliferation, altering gene expression and inhibiting inflammation [13].

Chemoprevention approaches are classified into three categories: primary, secondary, and tertiary chemoprevention. Primary chemoprevention implies a healthy population that is highly susceptible to develop cancer. Secondary chemoprevention applies to those who are already exposed to carcinogenic agents or have developed premalignant lesions, and tertiary chemoprevention is specific for those individuals who have already developed the disease before and then recovered from the treatment. In this way, this tertiary chemo-preventive approach targets the development of new as well as second primary cancers [14, 15]. Different pharmacological characteristics or various mechanisms are vital for a potential candidate to be an effective chemo-preventive agent such as anti-inflammatory properties, anti-proliferative properties, cell cycle arrest, an inhibition of growth factor pathways, and angiogenesis [16]. Hence, various compounds show chemo-preventive characteristics at all stages of carcinogenesis such as curcumin, quercetin, and resveratrol [17-19].

Tamoxifen

It was the first FDA-approved chemo-preventive agent, that helps reduce the risk of estrogen receptor (ER)-positive breast cancer as shown in Figure 1 [26]. The mechanism of action is carried out by its binding to estrogen receptors and then blocks proliferative actions of estrogen on the mammary epithelium. For this antiproliferative action, the suggested mechanism is the synthesis of the cytokine transforming growth factor-β (TGF-β) by tamoxifen, which serves as the negative autocrine molecule [27].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are known as anti-inflammatory agents that have been classified as cancer chemoprevention agents [28]. Their mechanism of action is that they inhibit cyclo prostaglandin E2 and oxygenase (COX) pathways, as well as via COX-independent pathways [29].

Piperine

Piperine is an active alkaloid having various therapeutic properties such as anti-inflammatory, antioxidant, and immunomodulatory effects and has garnered attention for treating cancer [30].

Mechanisms of Nanoparticles-Based Drug Delivery

Nanotechnology has been widely studied for cancer treatment, and nanoparticles of various types are in use today, playing a significant role in a drug delivery system as shown in Table 2 and 3 [5]. In comparison to conventional drugs, nanoparticle-based drug delivery possesses advantages such as biocompatibility and improved stability, increased permeability and retention effect, and finally, precise targeting as shown in Figure 2 and Figure 3 [31, 32]. Nanoparticles possess the EPR effect to assemble in tumor sites because of their leaky vasculature that allows for targeted drug delivery [33]. The surface of nanoparticles can easily be modified with antibodies or ligands to improve their targeting capabilities. This functionalization increases binding to specific receptors on various target cells, which facilitates uptake as well as controlled release [34]. Nanoparticles can further be engineered to release therapeutic payloads. This can be established through several mechanisms such as degradation of nanoparticle matrix, diffusion, or changes in environment (temperature or pH) that enhance drug release [35]. Nanoparticles can penetrate their biological barriers and further taken up by cells in an efficient manner than the larger particles [36].

Table 1: Agents for Cancer Chemoprevention

Active Compound	Type	Mechanism of Action	Cancer targeted	References
Resveratrol	Natural	Inhibits cell proliferation and induces apoptosis	Colon, Breast	[20, 21]
Sulforaphane	Natural	Induces phase II detoxification enzymes	Colon, Lung	[22, 23]
Tamoxifen	Synthetic	Selective estrogen receptor modulator	Breast	[24]
Eflornithine	Synthetic	Irreversibly inhibits activity of ornithine decarboxylase	Colorectal cancer	[25]

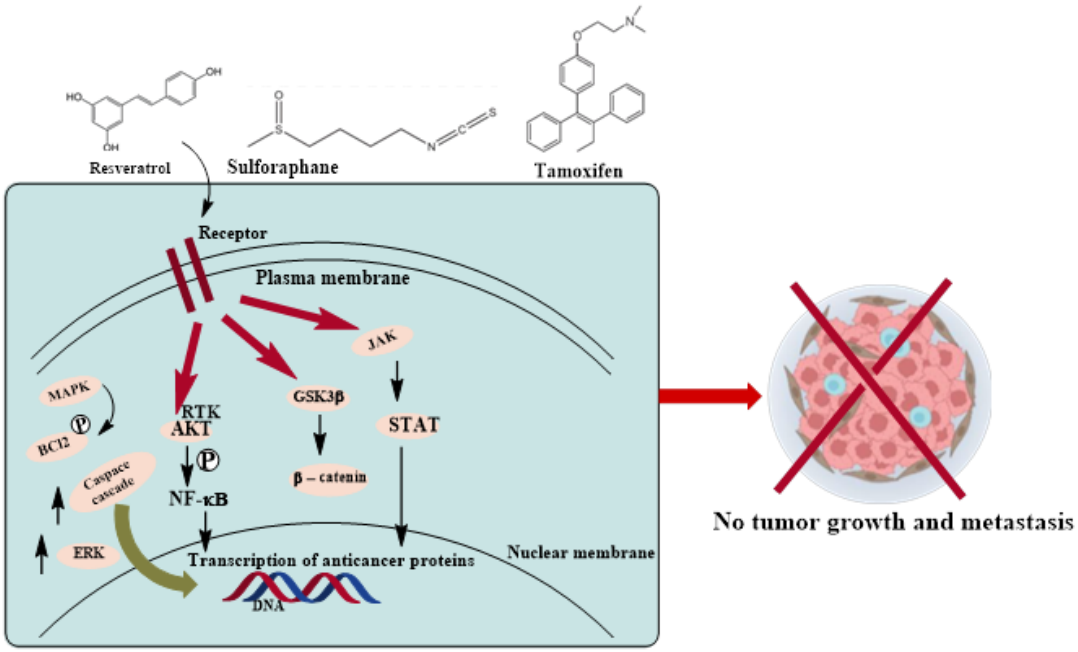

Figure 1: Chemoprevention at different stages of cancer

Table 2: Nanoparticles-based FDA-approved drugs being used in cancer treatment.

Product	Drug Nanoparticle system	Drug	Company/ Year	Mechanism of action	Indication	Nanoformulation Advantages	Reference
Doxil® (Caelyx)	Liposome-PEG (Lipid-based nanodrugs)	Doxorubicin	Janssen/ 1995	DNA double strand breaks. Replication arrest. Topoisomerase II activity inhibition.	Metastatic Ovarian cancer, Metastatic breast cancer	↑blood circulation time ↑tumor uptake (EPR) ↓cardiotoxicity	(37-39)
Onivyde®	Liposome (Lipid-based nanodrugs)	Irinotecan	Merrimack/ 2015	Serves as apoptotic death inductor. Results in inhibition of topoisomerase I activity.	Pancreatic cancer	↑blood circulation time ↑tumor uptake (EPR) ↓toxicity	(37, 39)
Ameluz®	Lipid-based nanodrug	5-aminolevulinic acid	Biofrontera AG/ 2016	Cytotoxic activity by production of oxygen-free radicals.	Actinic keratosis, Squamous cell carcinoma	sustained release ↓toxicity	(37, 40)
Ontak®	Protein-drug conjugate nanoparticles	Denileukin diftitox	Eisai Co., Ltd./ 1999	Inhibits protein synthesis. Binds to IL2R and shows cytotoxic activity.	Human CD25+ cutaneous T-cell lymphoma (CTCL)	↑blood circulation time ↑tumor uptake (EPR) ↑selectivity ↓severe toxicity	(37, 41-43)
Eligard®	Protein-drug conjugate nanoparticles	Leuprolide acetate	Tolmar, Inc./ 2002	Anti-tumor activity by serving as: GhRHR agonist Decreases gonadotrope secretion of FSH/ LH. Stops gonadal production of sex steroid.	Prostate cancer	↑blood circulation time ↑tumor uptake (EPR)	(37, 39, 44)

Table 3: Nanoparticles in Cancer Therapy

Type of Nanoparticle	Description	Mechanism of Action	Clinical Applications	References
Polymeric Nanoparticles	Made from biodegradable polymers. Allows controlled drug release.	It can be engineered for active and passive targeting by modification of surface properties.	Targeted delivery in ovarian and breast cancers.	[40, 41]
Liposomes	Spherical vesicles that can encapsulate drugs. Enhance stability and solubility.	Passive targeting through increased Permeability and Retention (EPR) effect.	Can be used for delivering chemotherapeutic agents.	[42]
Iron Oxide Nanoparticles	Magnetic nanoparticles can be utilized for imaging as well as for drug delivery.	Magnetic targeting permits precise localization at various tumor sites.	Employed in MRI imaging as well as drug carriers for many targeted therapies.	[43]
Nano-emulsions	Colloidal systems that increase bioavailability of poorly soluble drugs.	Improve drug stability and solubility Increased absorption at the tumor site.	Used in formulations such as fisetin for treating cancer.	[44, 45]
Dendrimers	Highly branched macromolecules have a well-defined structure for carrying out drug delivery.	Helps in targeted delivery through receptor-mediated endocytosis.	Effective in delivering small molecule drugs and nucleic acids.	[46, 47]

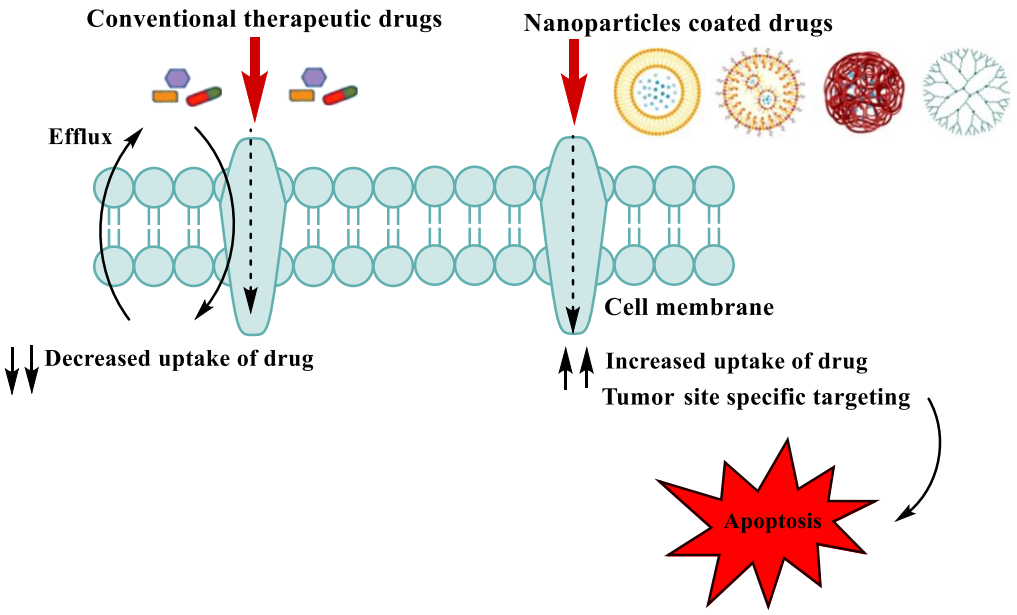

Figure 2: Nanoparticles and drug delivery for chemoprevention in cancers

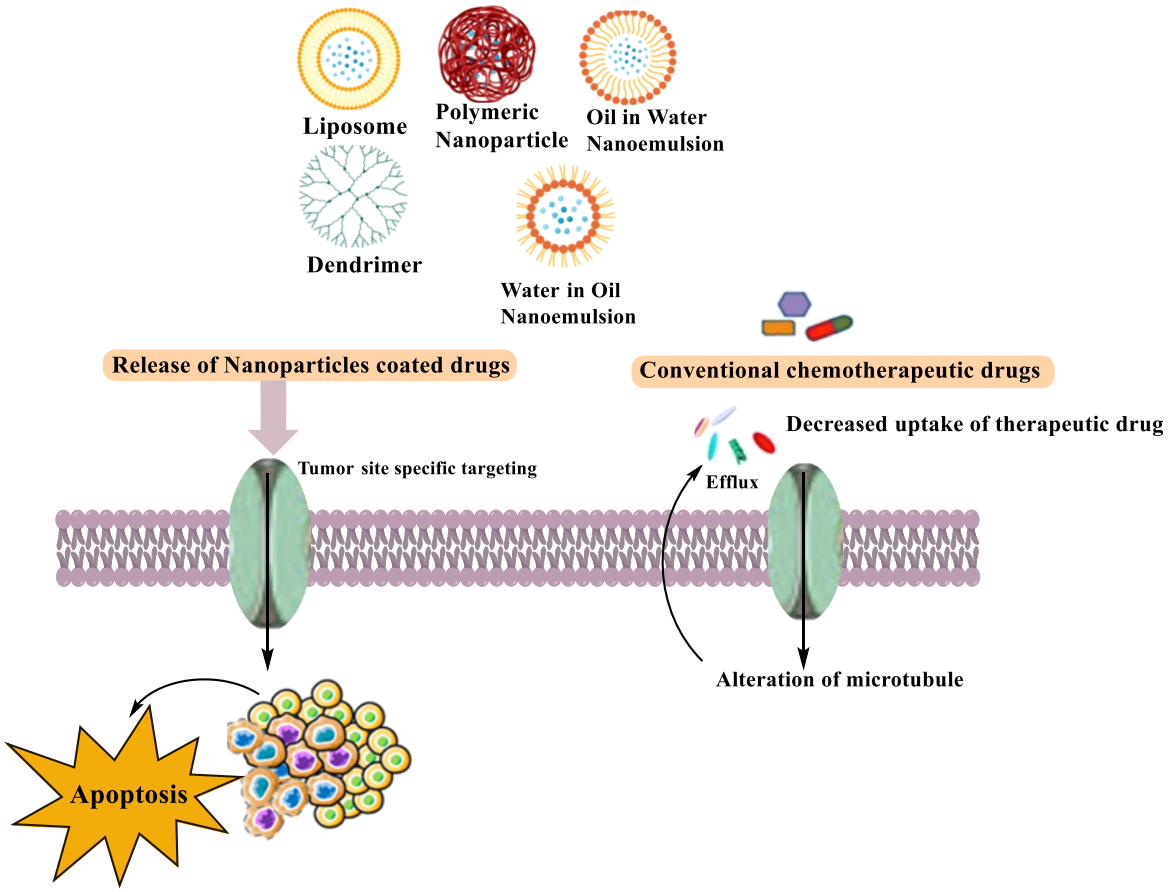

Figure 3: Mechanism of Nanoparticle-based Drug Delivery

Conclusion and Future Perspectives

Nanoparticles harbor a comparatively more effective approach to deliver the drugs for targeted cancer therapeutic purposes. Unlike conventional/traditional procedures for cancer treatment, nanoparticles provide advanced treatment options to overcome various limitations like toxicity and unrelated damage to healthy cells. Due to certain diagnostic features, such as improved cell permeability and retention effect. Nanoparticles can selectively target cancerous cells, thereby reducing toxicity. Different tailoring strategies like surface and charge modifications may assist in precise tumor treatments with better outcomes. There is a dire need to investigate innovative technologies that may enhance the nanoparticles' efficacy for targeted cancer therapy. Tailoring strategies must be developed with the assistance of artificial intelligence to boost the potential of nanoparticles and make them more biocompatible without any hint of toxicity. More mechanistic research is inevitable to locate the gaps, optimization of the procedures and establishing multidisciplinary research collaborations for a better future of nanoparticles-based strategies. Finally, industrial collaboration is necessary for long-term solutions based on the global impacts of nanoparticles for cancer-related issues.

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