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Targeted drug delivery in cancer therapy: A promising approach for effective treatment

Mohd Anas Mohd Mateen *, Pooja R. Hatwar, Tejas V. Solanki, Ravindra L. Bakal and Vaishnavi G Karule

Shri Swami Samarth Institute of Pharmacy, At. Dhamangaon Rly, Dist. Amravati (444709) Maharashtra, India.

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Abstract

Cancer remains one of the leading causes of mortality worldwide, necessitating innovative approaches to treatment. Targeted drug delivery systems have emerged as a promising strategy to enhance the efficacy of cancer therapy while minimizing side effects. By delivering therapeutic agents directly to the site of action, these systems can increase the concentration of drugs in tumor tissues while reducing exposure to healthy cells. This review highlights the principles, advantages, and challenges of targeted drug delivery in cancer therapy, with a focus on nanotechnology-based approaches. Various types of nanocarriers, including nanoparticles, dendrimers, liposomes, and micelles, have shown potential in delivering drugs to cancer cells in a targeted manner. Active and passive targeting strategies have been explored, with active targeting utilizing ligands to bind to overexpressed receptors on cancer cells. Despite the promise of targeted drug delivery, further research is needed to overcome challenges such as rapid removal of nanocarriers from the body and potential toxicity. Nevertheless, targeted drug delivery holds great potential for improving cancer treatment outcomes and reducing side effects.

Keywords: Targeted Drug Delivery; Cancer Therapy; Nanotechnology; Nanocarriers; Active Targeting; Passive Targeting

1. Introduction

In most regions of the world, cancer continues to rank among the top causes of mortality. Numerous novel avenues for treatment have been made possible by the early prognosis of the disease brought about by routine screening and a deeper comprehension of the mechanism of tumor progression. After the majority of solid tumors are surgically removed, the cancer cells that remain are treated using a range of techniques, such as immunotherapy, chemotherapy, radiotherapy and more [1]. Second only to heart disease, cancer is one of the main causes of mortality and a significant global health issue. It was estimated that there would be more than 1.6 million new cases and more than 500,000 cancer-related deaths in the US alone in 2016. Death rates from cancers of the liver, pancreatic and uterus are continuously rising despite advancements in treatment techniques, even while improved diagnostic, preventive and therapeutic measures have undoubtedly helped to lower incidence rates for some cancers, such as those of the prostate and colon [2]. The process of giving a patient medicine in a way that raises the concentration of the drug in specific areas of the body compared to others is known as targeted drug delivery. The goal of targeted drug delivery is to lower the relative concentration of the drug in the other tissues while increasing the concentration of the drug in the targeted tissues. This lessens adverse effects while increasing the product's effectiveness. This lessens adverse effects while increasing the product's effectiveness [3]. It is becoming more widely acknowledged that cancer is a diverse illness that necessitates individualized treatment plans based on the genetic composition, tumor features and clinical profiles of each patient. The necessity of personalized medical techniques is highlighted by the possibility that standardized treatment protocols may not effectively address each patient's individual demands [4]. Drug design and development leverages a variety of

* Corresponding author: Mohd Anas Mohd Mateen

nanotechnologies to address the fundamental flaws in cancer treatments, resulting in safer and more effective medications [5]. One of the most difficult diseases to treat is cancer and even with the most advanced modern medical treatments, the majority of cancer patients still pass away. Surgery can eliminate cancer focuses, but it cannot eradicate micro-focuses or free cancer cells, which are frequently the cause of relapses. Anticancer medicine chemotherapy is the primary supplementary treatment, but it frequently fails due to its terrible side effects, which patients cannot tolerate. The study of cancer biology has advanced remarkably over the last few decades. Nevertheless, despite remarkable progress in the basic biology of cancer, these findings have not been translated into equivalent advancements in clinical settings [6]. One of the most difficult diseases to treat is cancer and even with the most advanced modern medical treatments, the majority of cancer patients still pass away. Surgery can eliminate cancer focuses, but it cannot eradicate micro-focuses or free cancer cells, which are frequently the cause of relapses. Anticancer medicine chemotherapy is the primary supplementary treatment, but it frequently fails due to its terrible side effects, which patients cannot tolerate. The study of cancer biology has advanced astronomically over the last few decades [7]. By making it possible to encapsulate huge quantities of medicinal pharmaceuticals into nanoparticles, nanotechnology holds great potential for overcoming these obstacles. This simultaneously improves the pharmacokinetic profile and therapeutic efficacy of medications by lengthening their half-life and decreasing harmful side effects [8]. Researchers in recent decades have drawn attention to nanotechnology, an amazing technological trend that includes the explosive expansion of electronics for use in environmental monitoring, communication and health care (known as nanomedicine). The scientific bottlenecks that affect the longevity of living things particularly humans, are the subject of a lot of contemporary research. The majority of these bottlenecks are caused by illnesses that have little or no other options for treatment and recovery [9].

In the majority of malignancies, symptoms show only after a significant number of healthy body cells have already been transformed into malignant cells by these unseen forces. These "rebellion cells" continue to spread throughout the lymphatic system, causing additional tumors to develop in the tissues and organs nearby [10]. According to the presumed origin of the tumor cells, cancers are classified into several types, including carcinoma, sarcoma, lymphoma, leukemia, germ cell tumor and blastoma. Of these, carcinoma denotes cancer that originates from the epithelial cells and includes almost all cancers in the breast, prostate, lung, pancreas and colon. Cancer is a class of diseases caused by unregulated cell growth and these abnormal cells have the ability to spread or invade other parts of the body [11]. Tumors that grow in the lips, hard palate, buccal mucosa, anterior two-thirds of the tongue, sublingual region, upper and lower alveolar ridges, retromolar trigons and floor of the mouth are referred to as oral cancer [12]. Despite present obstacles, TMAs are justifiedly being developed further and attracting more commercial attention, which is evidence of the hard work and aptitude of numerous scientists and engineers working in labs across the world [13]. Additionally, it is predicted that the number of cancer-related deaths will rise, with an estimated 12 million deaths expected in 2030. Therefore, it is crucial but still difficult to develop efficient cancer monitoring, diagnosis and treatment. Currently available cancer therapies include chemotherapy, radiation therapy and surgery, among others [14]. However, in order to address the drawbacks of the oral route, the parenteral route of administration is the most popular natural substitute. Traditionally, a syringe and a hypodermic needle are used to give medications parenterally. Despite being the natural (and costly) alternative, the parenteral method did present a number of risks to patients, including excruciating pain, thrombus formation at the administration site and hypersensitivity [15]. A targeted medication delivery system works by delivering a specific quantity of a therapeutic agent to a specific sick location of the body over an extended period of time. This keeps the body's necessary plasma and tissue drug levels stable, preventing the drug from harming healthy tissue [16]. Novel nanomaterials with physico-chemical properties (a greater surface-to-volume ratio) that make them a great prospect for use in biomedical science have been developed as a result of advancements in nanotechnology. "Nanomedicine" is a new field of science and engineering that has the potential to significantly alter both individual and population-based health care through its applications in illness screening, diagnosis, and treatment [17]. Designing nanoparticles with adjustable sizes is the most straightforward and manageable method out of all of them. Numerous investigations have revealed a strong relationship between the size of nanodrugs and their anticancer activity [18]. Since they showed a lot of promise in the field of drug delivery, nanocarriers have been the subject of much research in recent decades. Because of their high surface area to volume ratio, nanocarriers can change the fundamental characteristics and bioactivity of medications. Among the characteristics that nanocarriers can provide to drug delivery systems are enhanced pharmacokinetics and biodistribution, reduced toxicities, enhanced solubility and stability, controlled release and site-specific delivery of therapeutic agents [19].

2. Need for targeted drug delivery

To overcome these limitations and inherent drawbacks of traditional DDSs, targeting is required. Topical lotions and ointments can only have local effects, oral administration is not an option for medications produced from proteins or peptides, and parenteral delivery is extremely intrusive. Furthermore, unless the medicine is administered at a dosage and rate that maximizes therapeutic effects while minimizing side effects, the efficacy of drug–target interactions is

jeopardised. In addition, simpler drug-administration procedures, decreased drug quantity, which reduces therapeutic costs, and the potential to sharply increase drug concentration in target compartments without adverse effects on nontarget compartments are promising benefits of TDD. Generally, drug targeting results in increased efficacy, modulated pharmacokinetics, controlled biodistribution, increased specificity of localization, decreased toxicity, reduced dose, and improved patient compliance [20].

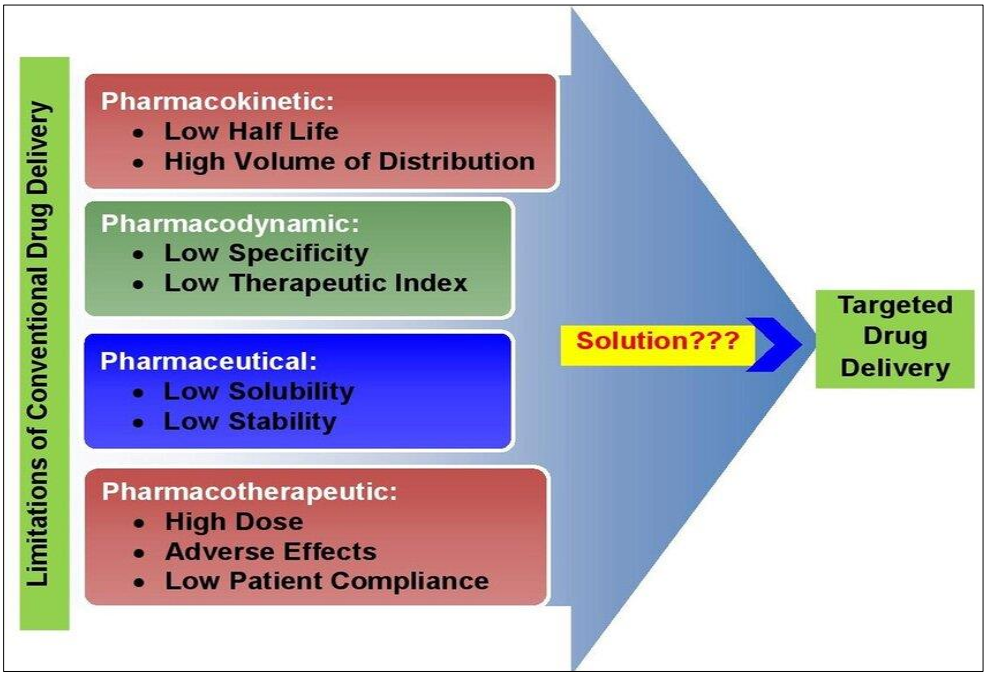

Figure 1 The need for targeted drug delivery [19]

3. Principles of targeted drug delivery

The goal of targeted drug delivery is to minimize exposure to healthy tissues while delivering therapeutic medicines precisely to the site of action, such as sick tissues or cells. Targeted drug delivery systems use a variety of mechanisms to improve the specificity, accuracy and efficacy of drug delivery, in contrast to systemic administration, which distributes medications throughout the body through the bloodstream. Targeted drug delivery is based on several fundamental ideas [4].

4. Advantages of drug targeting [19]

- The drug administration procedure becomes more straightforward.
- Targeting a particular spot reduces the drug's toxicity.
- A tiny dose can produce the desired pharmacological reaction.
- Steer clear of the first-pass effect.

5. Disadvantages of drug targeting [21]

- A high dose frequency due to the drug's quick removal from the body.
- Redistributing and disseminating medications that have been released.
- The delivery to the location of use must be managed and controlled by professionals.
- First-pass metabolism, dietary interactions, deterioration of the flora in the digestive tract, etc.
- Poor bioavailability.

6. Targeted delivery for cancer therapy

One of the main challenges with nanocrystal medication delivery is getting to the target location without increasing nonspecific toxicity. Given that the body is composed of successive barriers, it is easy to understand how medication

accumulation that is not optimal at the target site can result in undesirable bio-distribution to healthy tissues [22]. These days, there are many different types of targeted medicines that are utilized to treat cancer. By examining examples, one can gain a better understanding of how these medications work. There are several types of medications used in targeted therapy [23].

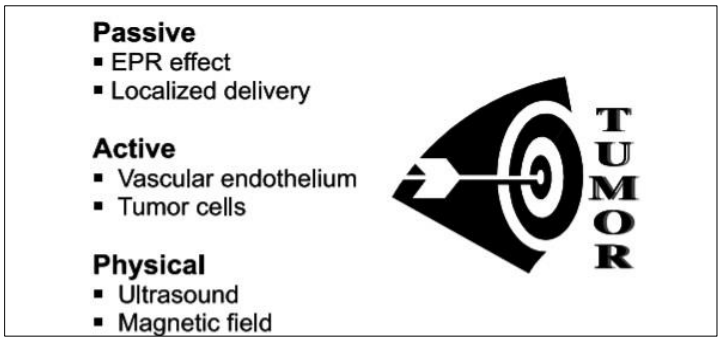

Figure 2 Schematic representing different drug targeting approaches to tumor [1].

6.1. Passive delivery

Non-functionalized nanoparticles have been demonstrated to be rapidly removed from the bloodstream due to their absorption by the liver, lungs, spleen and kidneys. The vascular endothelium's intercellular connections are closely packed, making it impossible for nanoparticles to reach healthy tissues. However, as tumor tissues develop, an inflammatory response occurs, which is characterized by an increase in vascular permeability. This endothelial dilation allows nanoparticles to permeate and penetrate malignant tissues [22].

6.2. Active delivery

They were unable to replace traditional chemotherapy medications due to a decline in both systemic toxicity and therapeutic efficacy. This restriction can be addressed by using an active targeting technique, which will raise the concentration and bioavailability of nanocarriers at tumor locations. To facilitate the targeted transport of the nanoparticle to certain cells or tissues, a variety of targeting ligands, including antibodies and non-antibodies, are used. These include proteins like transferrin, peptides like RGD, vitamins like folic acid, and aptamers [24].

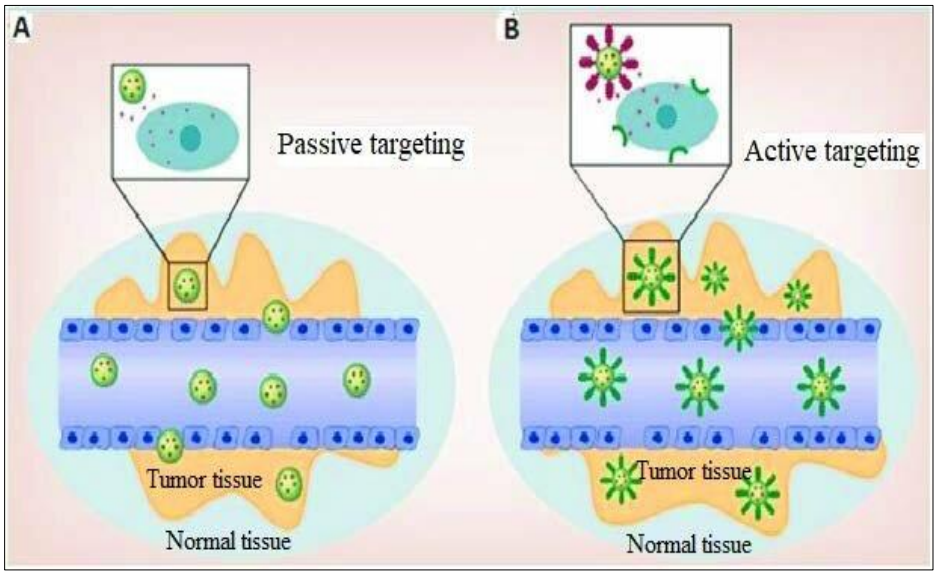

Figure 3 Mechanism of passive targeting and active targeting [20]

7. Drug targeting strategies in cancer therapy

The primary problem in combination chemotherapy is the distribution of co-delivered anticancer medicines to healthy cells. Typically, the co-delivered medication disrupts metabolic processes has adverse effects and harms both malignant

and healthy cells. The transport of anticancer medications to healthy tissues decreased their concentration and effectiveness at the intended site. Targeted strategies need to be enhanced in order to get around this restriction. When used in conjunction with chemotherapy, nanocarriers have been shown to be effective in delivering drugs to cancer cells in a targeted manner with less cytotoxicity and longer blood circulation times. Active and passive targeted medication delivery are the two targeting strategies that are typically used. While passive targeting takes advantage of aberrant fenestrations on the surface of tumor cells, active targeting relies on ligands conjugated to nanocarriers that can connect with the overexpressed receptors on the targeted cells' surface [25].

8. Fundamental features of targeted drug delivery systems [26]

A medicine must be in physical contact with its target and stay in contact with the targeted area for a sufficient amount of time in order to have the expected effect. Not all pharmaceuticals are appropriate for drug delivery systems.

9. Magnetic drug delivery

A drug carrier with a magnetic property is driven to a specific location in the body by applying an external magnetic field. This is the idea behind magnetic drug delivery. Particularly in biomedical applications, magnetite and maghemite are the most widely employed magnetic minerals among the many classes of MNPs.

Potential of magnetic hyperthermia of magnetic drug delivery systems. An approach to cancer treatment called hyperthermia uses extreme heat to destroy tumor cells. Greek etymology is the source of the name "hyperthermia," which is composed of the words "hyper," which literally means "rise," and "thermia," which physically means "heat." The process of hyperthermia involves locally producing and raising the temperature of tumor cells to a specific range, often between 41°C and 46°C, for a duration of 20 to 60 minutes to kill the tumor cells.

10. Nanotechnology-based drug delivery systems

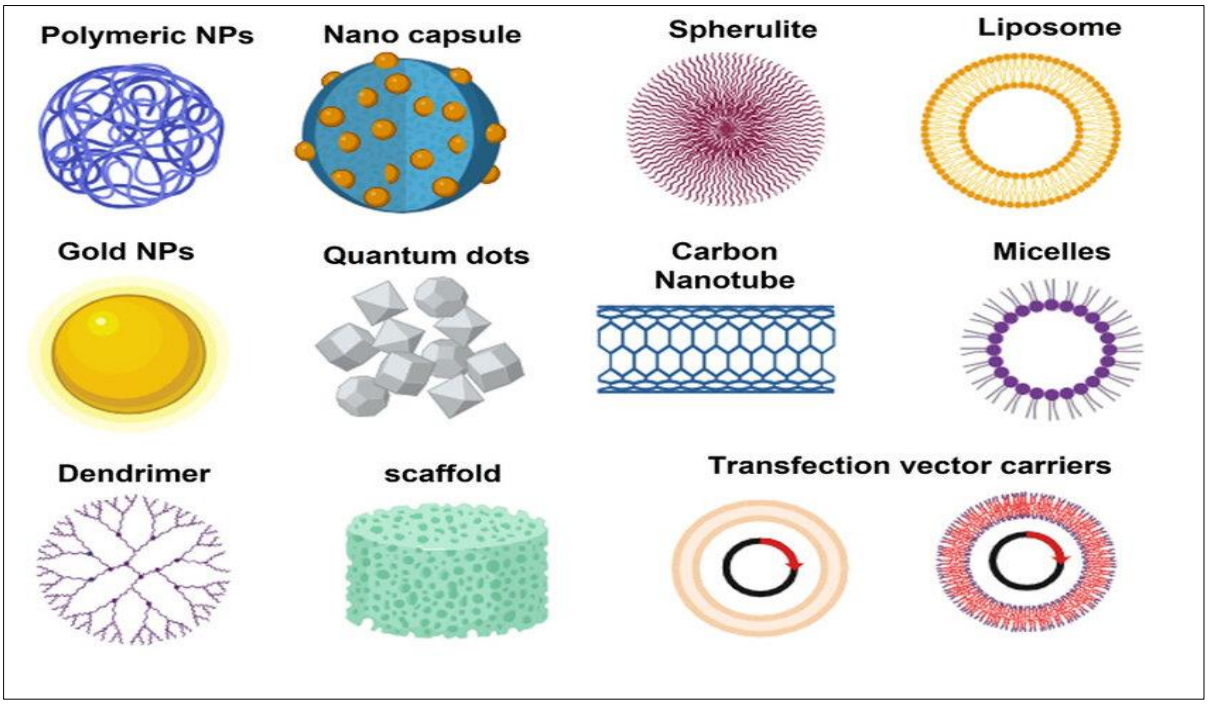

Figure 4 Nanostructured NPs with their average preparatory-method-dependent diameter [10].

10.1. Nanoparticles

Nanoparticles are solid supramolecular structures that are ultradispersed and range in size from 10 to 1,000 μm. 95–97 Drugs can be dissolved, trapped, encapsulated or bonded to a matrix of nanoparticles, which serves as a reservoir for particulate systems and is crucial for therapeutic drug administration, especially in oncology [27].

10.2. Dendrimers

Dendrimers are described as distinct nanostructures with dimensions between 1 and 10 nm. Dendrimers are made up of surface functional groups on the outside and a network of branching chains surrounding the center core. The medications or chemicals can be transported to the target site by the space between the branched chains in the central core. Different forms of dendrimers can be made depending on the basic structure; the most commonly used type of dendrimers are those made up of clusters of poly (amidoamine) (PAMAM) units [28].

10.3. Liposomes

In 1968, liposomes were first described. These are tiny synthetic spherical vesicles composed of cholesterol and naturally occurring, non-toxic phospholipids. Liposomes are attractive drug delivery vehicles because of their size, hydrophobicity, biocompatibility and ease of manufacture. Developments in liposomal vesicles have produced tailored drug delivery (disease-specific localization) as well as controlled drug release. Since chemotherapy, radiation therapy, and surgical resection are the first-line treatments for cancer, this feature is basically beneficial for cancer treatment [26]. Liposomes are artificially produced vesicular forms of lipid bilayers. While lipid-soluble and amphiphilic medications insert themselves into the phospholipid bilayer, water-soluble medications are found in aqueous compartments. Liposomes have gained popularity for a variety of uses including medicine administration in nutrition and nutritional supplements, DNA delivery in gene therapy and genetic engineering and cosmetics [29].

10.4. Micelles

Micelles are collections of amphiphilic particles scattered across a liquid. The micelle core area can be used to solubilize a lipophilic emulsion that is insufficiently water-answerable for convenient administration. Pluronic block co-polymer-based miceelles are the most researched micellar nanocarriers. Their impact on improved drug transport across the blood-brain barrier was shown in both in vitro and in vivo investigations. The amphiphilic particles in micelles and the bulk product are constantly exchanging places. Conversely, polymeric micelles also referred to as polymersomes are tone-assembled polymer shells made of block copolymer amphiphiles that resemble polyethylene glycol-polylactic acid (cut-PLA) and cut-polycaprolactone (cut-PCL) [30].

10.5. Cyclodextrins

A type of cyclic oligosaccharides known as cyclodextrins (CD) is produced when starch is broken down by enzymes. Through host-gust inclusion interactions, CD can aggregate hydrophobic guest molecules including as the anticancer medications docetaxel, cisplatin, methotrexate and paclitaxel [31].

10.6. Hydrogel

For more than 50 years, hydrogels have been utilized in many biological domains such as ophthalmology (for contact lenses) and numerous therapeutic settings to treat diseases like diabetes mellitus, osteoporosis, asthma, heart disease, and neoplasms [32].

10.7. Liquid crystals

Materials in a differential state that exhibit characteristics of both solids and liquids are known as LCs. Because the prefix "meso-" signifies "intermediate," this stage is known as mesophase. The two types of LCs are lyotropics, which arise from their relationship with amphipathic chemicals and solvents and thermotropics, which are structured by temperature. Most mesophase lyotropics are cubic, hexagonal or lamellar [27].

11. Nanotechnology in cancer treatment [33]

Finding cancer at the earliest stage of carcinogenesis is a crucial step in the treatment of cancer. The scientific community is being motivated by the findings of nanotechnology research to develop novel, non-invasive instruments for these uses at the nanoscale level.

11.1. Magnetic nanoparticles

Iron oxide particles with sugar molecules wrapped around them are known as magnetic nanoparticles. Thus, the immune system is unable to recognize these. When exposed to an external magnetic field, these particles have the ability to heat up and kill tumor cells while leaving healthy tissues unaffected. Biodegradable magnetic nanoparticles have been created by a team of researchers utilizing nanosized magnetites and organic polymers.

11.2. Colloid gold nanoparticles

The development of colloid gold nanoparticles as a possible medication delivery method for cancer treatment is presently underway. There are many different treatment theories and in-depth studies are being conducted to examine the effects of these approaches.

11.3. Polymeric micelles

The regulated release of hydrophobic anticancer medicines and their target selectivity make polymeric micelles an innovative drug delivery technology. Poly (ethylene glycol)-poly (α,β-aspartic acid) block copolymer conjugation of doxorubicin has shown to be an effective way to deliver cytotoxic medicines to cancer cells utilizing polymeric micelles.

12. Environmental risk factors for cancer [34]

12.1. Physical factors

12.1.1. Ionising radiation

One of the most commonly mentioned carcinogens, ionising radiation can result in tumours in any organ where the cancer develops on its own. Due to the observations of children who had received prenatal RTG and children who had survived the bombings of Hiroshima and Nagasaki, the first research on the risks of ionising radiation was conducted in the middle of the 20th century. Leukaemia and thyroid cancer are now more common.

12.1.2. Ultraviolet radiation

UV light is the most common environmental factor that affects the skin and has the most detrimental impact on it. In addition to late-stage indicators of accelerated skin ageing and even post-solar carcinogenesis, prolonged and severe sun exposure frequently results in early-onset issues like erythema or sunburn.

12.2. Chemical factors

12.2.1. Smoking tobacco

Tobacco use is the leading preventable risk factor for cancer death, killing about 6 million people year worldwide. According to the WHO FCTC, all tobacco products whether made fully or in part from tobacco leaves used for chewing, sniffing, or smoking are sources of many carcinogens and other dangerous compounds.

12.2.2. Alcohol

Epidemiological studies indicate that alcohol consumption is linked to an increased risk of cancer. Alcohol consumption increases the risk of cancer of the mouth, throat, larynx, oesophagus, liver, and breast. biological elements

12.3. Biological Factors

12.3.1. Diet

Poor eating habits are one of the main causes of malignant tumour development. Because of the development of civilisation, there are a number of dangerous substances that have a carcinogenic effect in the environment, the food, and the surrounding places.

12.3.2. Mutagenic and carcinogenic compounds in food

Mutagenic and carcinogenic substances, depending on environmental factors, are present in various food products. These can be natural substances or formed as a result of food storage and processing. Most of them are classified as genotoxins, i.e. active forms of mutagen, which covalently bind to the DNA molecule, modifying the nitrogen basis, which leads to the synthesis of a protein with the substituted sequence.

12.3.3. Infections

Infectious agents that are important in the etiology of various diseases are receiving more and more attention in the development of cancer.

13. Conclusion

Targeted drug delivery systems offer a promising approach for effective cancer treatment by delivering therapeutic agents directly to the site of action, thereby increasing efficacy and reducing side effects. Nanotechnology-based approaches, including nanoparticles, dendrimers, liposomes, and micelles, have shown great potential in delivering drugs to cancer cells in a targeted manner. Active and passive targeting strategies have been explored, with active targeting utilizing ligands to bind to overexpressed receptors on cancer cells. While challenges such as rapid removal of nanocarriers from the body and potential toxicity need to be addressed, targeted drug delivery holds great promise for improving cancer treatment outcomes and reducing side effects. Further research is needed to optimize targeted drug delivery systems and translate them into clinical practice. With continued advancements in nanotechnology and targeted drug delivery, it is likely that these systems will play an increasingly important role in the treatment of cancer and other diseases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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