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AKILLI İLAÇ VE KANSER TEDAVİSİ

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ÖZET. Kanser, vücuttaki hücrelerin kontrol edilemeyen bir şekilde büyümesi ve gelişmesidir ve küresel ölçekte ölümlerin en büyük nedenlerinden biridir. Kanser mekanizmalarının anlaşılmasında kaydedilen ilerlemeye rağmen, araştırmaya dayalı stratejiler hala başlangıç aşamasındadır ve başta kemoterapi olmak üzere geleneksel tedaviler kanser tedavisinin en yaygın şekli olmaya devam etmektedir. Bununla birlikte, bu geleneksel tedavilerin hedef dışı etkiler, ilaç direnci, toksisite, ilaçların tümör dokusuna biyoyararlanımının zayıf olması gibi çeşitli dezavantajları vardır. Kanser tedavisinin bu tür sınırlamalarını çözmek için tıp ve teknolojideki gelişmeler nedeniyle akıllı ilaçlar ve nanoyapılı ilaç dağıtım araçları genellikle kanser tedavisi için uygulanmaktadır. Bu nedenle, akıllı ilaçlar geleneksel tedavilere kıyasla kanser için daha etkili ve daha az yan etkili bir tedavi sunmaktadır. Bu derlemede, son yıllarda kanser tedavisinde kullanımı giderek artan akıllı ilaçları incelemeyi amaçladık.

Anahtar Kelimeler: Akıllı ilaç, kanser, nanoteknoloji.

SMART DRUGS AND CANCER TREATMENT

ABSTRACT. Cancer is an uncontrollable growth and development of cells in the body and one of the biggest reasons for death on a global scale. Despite the progress made in the understanding of cancer mechanisms, the strategies based on research are still at an incipient stage and the conventional treatments, mainly chemotherapy, remain the most widespread form of cancer treatment. However, these conventional therapies have several drawbacks, such as off-target effects, drug resistance, toxicity, and poor bio-availability of drugs to tumor tissue. Smart drugs and nanostructured drug delivery vehicles have been generally applied for cancer therapy due to improvements in medicine and technology to solve these such limitations of cancer treatment. Therefore, smart drugs offer more effective and less side-effect treatment for cancer compared to conventional therapies. In this review, we aimed to examine smart drugs, which have been increasingly used in cancer treatment in recent years.

Keywords: Cancer, nanotechnology, smart drug.

INTRODUCTION

Cancer is a health crisis globally and stands as the second leading cause of death worldwide (Navya et al., 2019; Mahfuz et al., 2023). Technological and medical advancements have created diversified treatment alternatives for cancer patients (Kumar, 2018). Chemotherapy, radiation therapy and surgery are the primary treatment modalities for cancers (Shawer et al., 2002; Sudradhar and Amin, 2014; Karacivi, 2019). Yet these treatments come with many side effects and complications. For example, chemotherapy, which is one of the most commonly used methods among traditional cancer treatment methods, affects healthy cells because it cannot separate cancerous cells from normal cells, and this often leads to off-target side effects (Misra et al., 2010; Jin et al., 2020; Mahfuz et al., 2023). Furthermore, the metabolism of some chemotherapy drugs can be impeded because of their low solubility leading to multimodal drug resistance in many cases (Tran et al., 2019; Amjad et al., 2021). All those drawbacks in conventional cancer treatment methods drove researchers to find new ways of treating cancer. In this regard, the development of nanotechnology-based smart drugs in recent years is a greater step forward than conventional treatment strategies that have major drawbacks. These nanoparticles are designed to "zero-in" on cancer cells while avoiding healthy ones (Navya et al., 2019, Senepati et al., 2019). Hence, research in nanostructured smart drugs for precision drug delivery has now attracted significant attention as a solution for this barrier to cancer care. Additional advancements in this area offer significant potential for decreasing the toxicity of therapy on normal tissues and increasing its potency in cancer therapy.

Cancer and Traditional Treatment Methods

Cancer is a heterogeneous and multifactorial disease that causes an abnormal and uncontrolled increase in cells in the body due to genetic or carcinogenic factors (De Smet et al., 2013; Senapati et al., 2018). Cancer cells grow by utilizing the body's oxygen and other resources, depriving other cells of regular supplies and growth factors (Yipel et al., 2016; Riu-Viladoms et al., 2019). The concept of cancer as a disease was first proposed by Hippocrates around 400 BC. This term was later replaced with the Latin word "cancer" by Celsus. Many medical works have described various types of malignancies in humans, and multiple treatment approaches have been used in different parts of the world (Arruebo et al., 2011; Yıldızhan et al., 2019). However, the development of strategies for treating the disease remained stagnant until the early twentieth century. Until the last quarter of the century, cancer was traditionally treated using surgery, radiation therapy, and chemotherapy. Although these treatments aim to eliminate cancerous cells in various ways, they often come with high levels of side effects on the patient's overall health due to the application challenges (Yipel et al., 2016; Nagini, 2017). Surgery involves the physical removal of tumors and surrounding tissues, but it may not always be feasible, especially in cases where cancer has spread to multiple sites or vital organs (Arruebo et al., 2011). Radiation therapy utilizes high-energy radiation to kill cancer cells or prevent their growth, but it can also damage healthy tissues in the process (Rajamanickam et al., 2012; Abbas and Rehman, 2018; Karaçivi et al., 2019). Chemotherapy, the most commonly used treatment modality, involves administering drugs that target rapidly dividing cells, including cancer cells (MacDonald, 2009; Wang et al., 2022). While chemotherapy serves as a cornerstone of cancer treatment, it lacks specificity and is the treatment modality most associated with serious side effects due to the nonspecific uptake of drugs by normal cells (Baskar et al., 1999).

Smart Drug

Smart drug is a drug delivery system that has been developed by using nanotechnology and other recent techniques to deliver the therapeutic effect of traditional cancer treatments, like chemotherapeutics and radiotherapeutics (Li et al., 2010; Wicki et al., 2015; Mahfuz et al., 2023). These smart drugs utilize nanotechnology to allow the specific release of the active agent to the targeted site, thereby acting on specific sites or tissues and protecting healthy tissues (Cuenca et al., 2006; Park, 2007; Saini et al., 2010). Furthermore, by increasing the solubility and circulating retention time of active ingredients in cancer therapy, minimizing drug clearance and facilitating their accumulation in tumor tissues, they improve the pharmacokinetics of these drugs and reduce the side effects of conventional chemotherapy (Senepati et al., 2018; Hossen et al., 2019; Tran et al., 2019; Wang et al., 2022). These features of smart drugs make them superior to other cancer therapy drugs. By using these systems in cancer therapy, medical practitioners greatly increase the efficacy of treatment and reduce potential side effects (Shi et al., 2011; Navya et al., 2019). At the same time, the critical functions of smart drugs, such as improving drug targeting and reducing systemic toxicity, have greatly contributed to improving the therapeutic efficacy of conventional cancer treatments (chemotherapy, radiotherapy, etc.) (Qin et al., 2017; Kalaydina et al., 2018; Hossen et al., 2019). Therefore, in recent years, smart drug delivery systems have taken a very important place in cancer therapy and researchers are increasingly interested in developing these systems for anticancer control.

Smart Drugs: Mechanism of Action

Smart drugs use nanomaterial-structured systems that can enhance the selectivity of therapeutic drugs to deliver the active ingredient of the agent specifically to the tumor site and thus reduce their systemic toxicity. They achieve this target-specific drug delivery function using different carrier systems, such as aerosol, liposome, polymer, or micelle-based systems (Wilczewska et al., 2012; Dawidczyk et al., 2014; Prasad and Shrivastav, 2014; Liu et al., 2016). Nanoparticles have some special properties and mode of action for targeted/controlled drug delivery. These nanostructures are designed to precisely sense, select and bind to patient cells to deliver drugs to the target site of malignancy. These properties make nano-based smart drugs superior to other cancer treatment methods. This is because they bypass healthy cells and specifically destroy cancer cells, thereby minimizing off-target side effects (Jain and Stylianopoulos, 2010; Singh et al., 2018; Acar and Altuntaş, 2019; Wang et al., 2022).

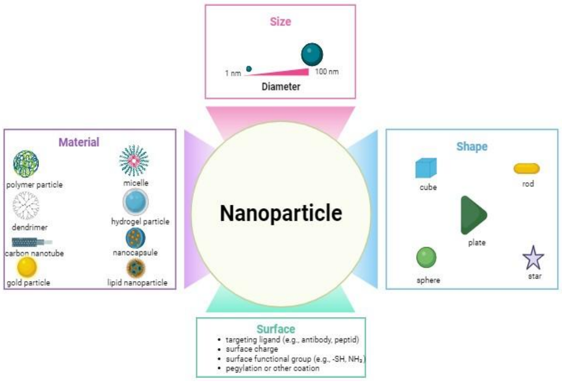

Figure 1. A summary of nanoparticles, their types and biophysicochemical properties (Figure adapted from Sun et al., 2021).

Nanoparticles minimize the exposure of healthy tissues through different strategies for drug delivery to tumor sites, including stimuli-responsive materials, targeting ligands, and nanocarriers. Besides this targeted delivery to the site of action, i.e., the tumor, nanoparticles modulate the stability, solubility, and release profiles of anticancer drugs for controlled and sustained release of such agents (Bharali et al., 2009; Liu et al., 2010; Gao et al., 2014; Mahfuz et al., 2023). Smart drug systems overcome the disadvantages of conventional chemotherapy by taking advantage of the powerful properties brought by nanomaterials, such as poor aqueous solubility and drug resistance issues (Malam et al., 2009; Din et al., 2017; Senapati et al., 2018; Hossen et al., 2019). These systems can be endowed with additional functionalities triggered by external stimuli such as pH, temperature, and light to enhance their therapeutic efficacy against cancer (Lohcharoenkal et al., 2014; Yan et al., 2020). Smart drugs can therefore provide critical information on response to treatment and disease progression by allowing simultaneous visualization of tumor volume and drug distribution maps. At the same time, multifunctional smart drug systems allow real-time monitoring of the distribution pattern and efficacy of anticancer drugs, enabling physicians to select an appropriate treatment plan and administer effective therapy (Park et al., 2009; Feng et al., 2013; Xin et al., 2017; Negut and Bita, 2023).

Cancer Treatment Using Smart Drugs

Nanomedicine has revolutionized the field of oncology, enabling the design and engineering of nanoparticles with unique properties specifically designed for cancer treatment (Conde et al., 2012, Sun et al., 2014). The small size of nanoparticles provides the advantage of preventing uptake by normal cells and increasing permeability and the retention effect in tumor tissue, thus increasing intratumoral exposure and improving therapeutic indices by reducing systemic exposure and toxicity of anticancer drugs compared to conventional therapies. At the same time, the nanostructures of smart cancer drugs can be functionalized with targeting ligands to recognize specific receptors overexpressed on cancer cells and allow for selective binding (Mok and Zhang, 2012; Onoue et al., 2014).

Smart drugs, with their potential to enhance drug delivery to the brain, have been particularly advantageous in the treatment of brain cancer. The treatment of brain cancer is highly limited, due to the impenetrability of the blood-brain barrier, which prevents most agents from reaching the brain (Hossen et al., 2019). Smart drugs, and in particular liposomal formulations, have made significant progress in delivering drugs to the brain. These liposomal formulations improve the efficacy and reduce the side effects of anticancer therapy by regulating drug release, pharmacokinetics, and biodistribution profiles (Alotaibi et al., 2021). They are also tumor-specific to kill off the cancerous cells in the brain while leaving the rest of the healthy brain cells intact and avoiding the toxicity of chemotherapy. Moreover, smart drugs can be used to overcome drug resistance, which is one of the major challenges in cancer treatment (Kalaydina et al., 2018; Negut and Bita, 2023). Designing smart drugs to achieve higher permeability of the blood-brain barrier enables higher dose infusion of therapeutic agents into brain tissue. These advancements in drug delivery systems present a significant opportunity to improve treatment outcomes in difficult-to-treat cases such as brain cancer (Khaitan et al., 2018; Karaçivi et al., 2019). In summary, smart drugs significantly improve cancer treatment outcomes by enhancing drug delivery and overcoming barriers such as poor solubility and drug resistance. Physicians have achieved significant results in cancer prognosis using nanostructured smart drug delivery systems (Navya et al., 2019).

Smart drug delivery systems have shown significant interest as they can reduce the off-target effects in cancer treatment (Liu et al., 2016). Biocompatible nanoparticles with desirable properties have shown promising results in drug delivery systems. Different varieties of nanoparticles are applied in smart drug delivery for cancer treatment, including liposomes, micelles, polymeric nanoparticles, gold nanoparticles, and bio-nanocapsules (Wang, 2008; Wicki et al., 2015; Navya et al., 2019; Cheng et al., 2021). These nanoparticles are designed to carry drugs to the tumor site so that the drug agents affect the tumor more than healthy tissues (Dawidczyk et al., 2014; Mahfuz et al., 2023).

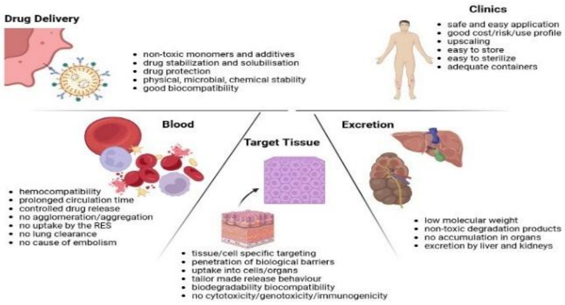

Figure 2. Characteristics of smart nanostructured drug-delivery systems at drug delivery stages (Figure adapted from Grund et al., 2011).

Advantages

The use of smart drugs in cancer treatment offers many advantages over other treatment methods. These include:

- Enhanced drug delivery: Enhances drug efficacy and reduces toxicity in healthy tissues by increasing the specific delivery of drugs to tumor sites (Yingchoncharoen et al., 2016; Mahfuz et al., 2023).

- Reduced side effects: Significantly reduces side effects on healthy cells as it acts specifically on the target tumor focus (Bharali et al., 2009).

- Improved drug solubility: Some chemotherapy drugs have low aqueous solubility, which reduces their efficacy. Liposomal formulations and nanoparticle-based platforms used in smart drugs help improve the solubility and therapeutic efficacy of these drugs (Senepati et al., 2018; Mahfuz et al., 2023).

- Overcoming drug resistance: Smart drug systems encapsulate therapeutic agents in nanoparticles, bypassing mechanisms of drug resistance and providing an improved treatment option. This helps to overcome drug resistance, a major challenge in cancer treatment (Qin et al., 2017; Yi et al., 2023).

- Targeted therapy: The main point of smart drug delivery systems is to increase the amount of therapeutic agent reaching its target while reducing side effects. This target-specific therapeutic action increases therapeutic efficacy at the cancer cell level while reducing the likelihood of systemic toxicity (Jeswani and Paul, 2017; Senepati et al., 2015).

- Long-term and controlled drug release: Systems such as lipid-based nanoparticles offer the opportunity to deliver drugs better and in a more controlled manner through sustained release of therapeutic agents. The sustained therapeutic effect of this controlled release reduces the need for frequent drug administration (Liu et al., 2016; Wang et al., 2022).

Smart drug delivery systems have demonstrated their bright future in cancer treatment by guiding cancer therapy more effectively and showing superiority over conventional chemotherapy in achieving better treatment outcomes. Advances in the nanomedicine-enabled pharmaceutical industry have greatly contributed to cancer treatment with the invention of targeted drug delivery systems that overcome disadvantages in cancer therapies (Liu et al., 2016; Mahfuz et al., 2023; Neguț and Bita, 2023).

Disadvantages

Although there have been significant progress in the field of smart drug delivery systems, they are still not the answer to all the problems for an improved cancer treatment (Jong, 2008). Development and manufacturing are complex, which makes them quite costly. Another drawback is that some smart drug delivery systems may cause an immune system response or their components could be toxic (Dawidczyk et al., 2014; Neguț and Bița, 2023). Another disadvantage is that the efficacy of smart drug delivery systems can be altered depending on certain characteristics of the tumor and patient-related factors (Rana et al., 2023; Yi et al., 2023). These all point to the fact that further research and scrutiny are needed regarding the long-term effects and safety profiles of smart drug delivery systems in clinical practice, particularly in cancer therapy.

Clinical Applications and Ongoing Research

Clinical applications for smart drug delivery systems in cancer therapy are rapidly increasing (Li et al., 2019). In this context, new strategies and techniques are constantly being explored to further enhance the clinical utility of smart drug delivery systems. Research focuses on the further development of a wide range of nanostructured systems, including lipid-based, polymer-based, and inorganic nanoparticles (Navya et al., 2019). Furthermore, research authorities aim to improve the synthesis and functionality of such nanostructured systems at the biochemical and biological levels. In fact, the most significant success story of the smart pharma field is the development of nanoparticle-based drug delivery systems (Gao et al., 2014; Liu et al., 2016; Patra et al., 2018). Such novel systems not only enable drug targeting but also facilitate early diagnosis and enable personalized cancer treatment. For example, nanoparticle-based drug delivery systems overcome some of the drawbacks of conventional cancer therapy by increasing the solubility of drugs, overcoming chemoresistance, reducing systemic toxicity, expanding therapeutic indices, or increasing bioavailability upon oral administration. Another notable development is the integration of smart drug delivery with extended release systems. This has improved the efficiency of nanoparticles and thus drug delivery, bioavailability and safety profiles (Xin et al., 2017; Tran et al., 2017; Fan et al., 2023; Mahfuz et al., 2023). Many new ideas and continuous improvements in the field of clinical applications of smart drugs are promising for the therapeutic elimination of cancer.

Future Directions and Challenges

Considered one of the most powerful cancer therapies today, smart drug therapy still has several limitations and areas for improvement for the future (Qin et al., 2017). The first aspect involves further refinement in design and functionality of nanostructured systems to better enhance their capability for selective targeting of cancer cells and reduce off-target effects (Dawidczyk et al., 2014; Rana et al., 2023). Another area is that much better undestanding of nanoparticles' complicated interactions with the tumor microenvironment is required. This would be useful in effectively overcoming of tumor barriers to enhance therapeutic efficacy based on alterations to the drug delivery systems (Li et al., 2010; Sudradhar and Amin, 2014; Shi et al., 2016; Kalaydina et al., 2018). Other research areas in the future pertain to the development of increasingly individualized and personalized smart drug delivery systems. Further personalization of the drug delivery process by individual patient parameters, such as type of cancer or genetic predisposition, can allow this approach to realize better outcomes. For this reason, further studies are needed in the optimization of these systems, addressing remaining challenges, and proving their safety and efficacy in clinical settings (Wicki et al., 2015). Notwithstanding, smart drug delivery systems together with nanostructured systems have high potential to help overcome different challenges already existing in this domain and improv treatment outcomes.

CONCLUSION

In conclusion, the ability of smart and extended-release drug delivery systems to overcome the limitations associated with conventional cancer treatment methods by enabling precise delivery of anticancer drugs to the tumor site without harming healthy cells has made the cancer treatment process more effective and safer. Moreover, personalized treatment approaches that can be tailored to individual patient profiles further emphasize their importance in optimizing treatment outcomes. In summary, impressive strides have been made in the field of smart medicine in the recent past, and these systems have proven to be the safest methods, especially in cancer treatment. As long as research and development in the field of smart medicine continue, it will be inevitable that future cancer treatments will be more effective, have fewer side effects, and be equipped with more advanced technologies.

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