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Antitumor TCM combined with nano drug delivery system

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Abstract. Up to now, cancer still is a main reason causing people death in global. Traditional Chinese medicine therapy, an emerging therapy, can treat tumor by using herbs which have less side effects and multiple targeting, and has exhibited promising antitumor potential. But tumors are led by many factors that need to treat by combined drugs and the bioavailability of TCM is low, hence a new treatment approach that the drugs combined TCM with TCM or Western medicine, are delivered by nano drug delivery system. This article reviews the TCM combined treatments and the nano drug delivery systems are analyzed and summarized.

Keywords: Antitumor, Traditional Chinese Medicine, Nano Drug Delivery System, TCM Combined Therapy.

1. Introduction

Now, cancer is one of the most major global problems. In 2021, WHO published a global-cancer statistics, the data showed that about 19.3million new cancer and nearly 10million people died due to cancer in 2020. Besides, global cancer burden probably will reach 28.4million in less than 20 years [1]. Nowadays, Conventional cancer treatments incorporate surgical treatment, chemotherapy and radiotherapy. Although these treatments can eradicate tumor cells, they have extremely serious side effects, toxicity and postoperative complications, and the recurrence and metastasis of malignant tumors are frequent. Therefore, cancer therapy urgently requires updating the therapeutic approaches and technology constantly to overcome these shortages.

Traditional Chinese Medicine (TCM), is part of what makes up modern medicine. Herbs and animals have been used as medicines to treat various diseases over thousands of years in eastern Asia [2]. With raising people ‘s acknowledgement of TCM in the treatment of tumors, and having a growing understanding of tumor, the active ingredients of TCM are more and more prominent in antitumor aspect at present. It has the benefits of enhancing body immune activity, inducing tumor cells apoptosis, inhibiting the growth of tumor cells and tumor angiogenesis, and blocking tumor cell metastasis. The TCM’s characteristics of multitarget, less side effect and difficulty making tolerant to the drug lead to be hot treatment in antitumor at present.

However, malignant diseases are caused by many complex factors and single drug treatment is not enough. Parts of antitumor TCM are high hydrophobicity, low bioavailability and poor vivo stability. Based on classical TCM theory, the combined therapy of TCM owns huge potential and reaches an effect that cannot be achieved by single chemotherapy drug. Moreover, the combination generating

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complementation, which is the major development direction of anti-tumor clinical treatment and experimental study.

The novel nano-targeted drug delivery system, compared with free drugs, it can effectively improve TCM's bioavailability, enhance the stability in vivo, and have more targeting and slower release. The integration of TCM and nano-drug delivery system plays a vital role in addressing the limitations of conventional tumor treatments.

By referring to the relevant literature both in domestic and abroad, this article reviews some TCM have been discovered to own antitumor effects, the combination of western medicine and TCM, and the nano-targeted drug delivery system of effective components of TCM, and puts forward prospects to promote the development of TCM combined with nano-drug delivery system in the treatment of tumors,

2. TCM therapy

TCM has played a significant role in cancer therapy, a number of herbal monomers and their structure analogues have been shown to have made a great contribution to pharmacotherapy. Certain TCM herbs may play a therapeutic role by acting directly on cancer cells or mitigating the side effects of anti-tumor drugs, while others control tumor growth and metastasis by boosting anti-tumor immunity. TCM has been shown to enhance the immune system, prolong the survival in advanced cancer patients, and reduce toxicities and side effects. Recently, more and more TCM extracted from medicinal plant are reported to treat tumor. There are two kinds of common tumor treatments of TCM: TCM monomer therapy and TCM-combination therapy in antitumor.

2.1. TCM monomer therapy

A number of herbal monomers and their structure analogues have been shown to have made a great contribution to pharmacotherapy. Hedyotis diffusa Willd (EEHDW) has been used to clinically treat colorectal cancer. Cai et al. have found that the ethanol extract of EEHDW, can promote colorectal cancer cell apoptosis and inhibit the proliferation by restraining STAT3 phosphorylation in tumor tissues. Liujunzi (LJZD), a TCM, having been widely used in clinic, Han et al. [3]'s research verified that LJZD has the ability to hinder the growth of cancer cells by disturbing the activation of the miR-34a/STAT3/IL=6R feedback loop, which suggested that LJZD could be a promising therapeutic option for tumors.

2.2. TCM-combination therapy

TCM-combination therapy in antitumor, is a new type of strategy for cancer. Combination therapy involves two or more therapeutic ingredients and it enables medicines complement each other. That is, TCM-combination therapy is a treatment combines the active ingredient of antitumor TCM with other antitumor drugs. The combination has made a more effective treatment effect. Xia C et al. 's research has shown that Cryptotanshinone(CTS) extracted from Salvia miltiorrhiza Bunge combined with cisplatin can reverse cisplatin resistance, and induce apoptosis; Li CJ et al. have clarified that the co-administration of Triptolide and Cisplatin results in complete inhibition of tumor growth. Furthermore, low concentrations of Triptolide and Cisplatin may work better together to enhance efficacy.

3. Nano drug delivery systems

Nano drug delivery system, generated by nanoscience, generally refers to sizes ranging from 1-1000nm drug carriers such as liposome and nano micelle. Its fundamental purpose is delivering drug to a specific target-organ by a particular guidance mechanism. Now, with the development of science and nanotechnology, nano drug delivery system is expected to enhance the effectiveness of oncotherapy. It can improve the efficiency of drug delivery by reinforcing permeability and retention (EPR)effect in order to enhance the therapeutic effect.

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3.1. Liposome

One or more than one lipid bilayers compose a type of globular micro-vesicles which is called Liposomes. It is one of the most studied nano carriers, can simultaneously encapsulate lipophilic drugs and hydrophilic drugs [4]. Steffes et al. [5] have investigated on paclitaxel (PTX), a cancer drug, was contained in a cationic liposome (CL)NP system and modified by PEG. Their research indicated that CLPTXNPs have a greater effect on vivo delivery. Also the numerical of IC50 has declined, demonstrating that CLPTXNPs has a better inhibition of tumor cell proliferation compared to solute PTX; Jia-Wen Song et al. [6] appended DP to the liposomes, measuring the Curcumin contents in liposomes and observing the effect of DP ratio on drugs. The research showed that the combination of Cur, DP and liposome not only ameliorates the bioavailability of Cur increases antitumor effect Cur's, but also increases antitumor effect Cur.

3.2. Nano micelles

Nano micelles [7], a kind of nanoparticles which are formed by self-assembled of amphiphilic molecules at Critical Micelle Concentration (CMC). The unique structure of nano micelles allows them to be drug delivery carriers, and dissolve hydrophobic drugs to improve their slightly solubility. Polymeric micelles (Self-assembled block copolymers), have been widely studied in preclinical.

Liu et al. [8] synthesized the amphiphilic polymer micelles by self-assembling, putting the Cur into the micelle. The study demonstrated that the carrier exhibits a more potent inhibitory on tumor cells and the viabilities of HepG2 cells were still above 85% after AA/ASP-AZO-Fc (AAAF) treated. That is, the Cur carried by AAAF has a great bioavailability and antitumor effect.

3.3. Passive targeted drug-delivery systems

Drugs, which are encapsulated and using nanoparticles (NPS) as carriers, for instance, liposome, gold nanoparticles (GNPS) and protein and molecular complex, are delivered to specific organ through normal physiological function. The combination of two antitumor ingredients can foster mutually, forming a preferable therapeutic effect. Conventional approaches cannot effectively deliver drugs due to their poor bioavailability. Raghavendra et al. [9] developed a NPs, named CelePlum777, that contains both Celecoxib and Plumbagin. The study has revealed that the NPs have the potential to inhibit melanoma tumor growth. It inhibited cell proliferation by declining levels of key cyclins which are vital for tumor cell survival and proliferation, and can synergistically kill melanoma cells and thus achieve the optimal effect.

3.4. Active targeted drug-delivery systems

Active targeted preparation, a kind of nano carriers which surface is modified, enables drugs accumulate at the targeted tumor site. This nano drug-delivery system can escape from the recognition and phagocytosis [10]. Numerous studies have demonstrated that Transferrin (TF) can bind to the TF receptor, allowing it to reach the intended tumor site. Song et al. [11] designed a novel formulation of liposomes containing vincristine and tetrandrine which have been modified with TF. The experiment manifested that higher release rate of TF modified vincristine plus tetrandrine liposomes was observed in vitro compared those liposomes which have not been modified by TF. In vivo observation of mice with glioma, this special liposome clustered more obviously in tumor sites, compared to the liposomes that have not been modified. Therefore, vincristine plus tetrandrine liposomes modified by TF exhibit significant antitumor efficacy both in vitro and in vivo.

3.5. Physicochemical targeted drug-delivery systems

As nano drug delivery systems rely on the EPR effect which have caused some uncontrol problems [12] in clinic, such as endosomal escape and heterogeneity. What's more, it is difficult to control the drugs release. Therefore, according to the tumor microenvironment, the surface of NPs is adopted physicochemical means, namely temperature, pH and magnetic field, and then the drugs have been stimulated and are led to particular site to release. Such delivery systems are called Physicochemical

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targeted drug-delivery systems. Bai et al. converted graphene oxide (GO) to reduced graphene oxide (RGO), and utilized ultrasonic cavitation to acquire stable RGO nano-dispersion which was used as carrier for PTX. By MTT assay, the vitro analysis showed that RGO-PTX nano-dispersion was biocompatible towards normal cells and toxic only towards cancer cells, revealing a great potential of antitumor effect.

4. Conclusion

In recent years, owing to the escalating prevalence and fatality of cancer, the existing therapeutic means cannot satisfy the clinical needs, and it is urgent to apply new therapeutic treatment ways to the clinic. In today's anti-tumor field, the trend turns to use some pure natural drugs to reduce the adverse effects on normal cells, TCM is a matchable choice which is one of the most precious treasures in Chinese traditional culture. Previous research has demonstrated that the components of traditional Chinese medicine have presented vital therapeutic effects in anticancer, such a broad development prospect has attracted the attention of experts and scholars. Benefiting from the continuous development of polymer chemistry and the uninterrupted cross-integration of pharmacy, pharmacology, biochemistry, physical chemistry and other disciplines, nano targeted drug delivery systems have germinated rapidly for the past few years. A growing body of research is evidence that nano targeted drug delivery systems possess remarkable advantages in antitumor-treatment, as their distinctive nano size and EPR effect. However, the progress of nano preparation technology of antitumor TCM is lagging behind. Since most of the nano technology is TCM monomer, it is not as effective as Western medicine nano preparation in antitumor, nor can it highlight the antitumor characteristics of TCM, therefore, the technique is still in its infancy and need to develop persistently. Some TCM has been used in the treatment of cancer in recent decades, showing great potential, but at the same time, there are still many latent problems that need to be figured out. Consequently, Loading the combination of TCM active ingredients and other antitumor ingredients into nanocarriers, is a crucial direction for the future development of TCM. The combination of nanotechnology with TCM prompts TCM international. Besides, it broadens the application of TCM and turns TCM to modernization.

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