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The implication and advantages of small-molecule drug

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Abstract. Small-molecule drugs are a widely used and theoretically mature therapeutic approach. Due to their small size and stable chemical structure, they can better penetrate the cell membrane and directly reach the intercellular target side, and their pharmacokinetics are more predictable. Many small-molecule drugs have contributed to medical advances and improved the lives of patients. At present, they have shown relatively high efficiency in the targeted treatment of a variety of diseases. In this review, we highlight their mechanisms and possibilities in the treatment of individual human diseases such as Alzheimer's disease, cancer, and Covid-19 by comparing them with traditional macromolecular drugs, as well as the percentage of small molecule drugs used in current drugs, specific improvements in patient efficacy, or new insights into the mechanisms of action of small molecule drugs. For the prospects of small molecule drugs, new drugs will also emerge along with new challenges.

Keywords: Small Molecule Drug, Alzheimer's Disease, Cancer, Covid, Tacrine

1. Introduction

Small molecule medications, often known as chemically synthesized drugs, typically possess a molecular weight under 1000 for organic compounds. These drugs offer benefits such as broad applicability and well-established theories. Statistically, small-molecule medications make up approximately 98% of all commonly used drugs [1]. Small molecule drugs constitute 98% of all drugs. Their structural attributes exhibit strong spatial dispersion, and their chemical nature ensures favorable medicinal and pharmacokinetic traits. Such features provide these drugs with significant benefits in drug development and potential applications.

Compared with large molecule drugs, small molecule drugs have the advantages of wide application, stable structures in use, and lower cost in production and transportation. The effects of macromolecular drugs are strongly dependent on their stereoscopic configurations, which can be easily changed under changing external conditions. Therefore, the control of formulation is very strict, and even slight differences during production can lead to very serious consequences. Some macromolecular drugs, such as proteins and antibodies, require refrigeration for storage and transportation, which increases costs. Unlike large molecule drugs. Small molecule drugs exhibit strong spatial distribution, and their chemical attributes lead to favorable medicinal and pharmacokinetic qualities. These traits give them a notable edge in drug research and related pharmaceutical areas.

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In terms of mechanism of action, macromolecular targeted drugs generally act on targets on the cell surface, inhibit protein interaction, and have strong specificity, which makes it difficult to enter the cell. As traditional drugs, small-molecule targeted drugs can be taken orally, can enter cells and act on intracellular targets, and can usually bind and act directly on target proteins.

Now, novel approaches have emerged that ensure precise interactions between small molecules and macromolecules, leading to more confident conclusions. A technique commonly employed in protein phosphatases and kinases is the bump/hole strategy. Scientists typically modify an amino acid side chain's size or adaptability that associates with the small molecule regulator, producing a "hole." They then incorporate a complementary "bump" side into the small molecule that dominates the drug-sensitive allele. This approach prevents binding to the original drug target.

This review paper examines and accesses some emerging small-molecule drugs for therapeutic use in Alzheimer's disease, cancer, covid. Specifically, we discuss Tacrine and Tacrine Homodiplets regarding drug targeting efficiency for Alzheimer's Disease, the signaling pathway of Sorafenib with a clinical trial report for liver cancer, and lastly, Azvudine stability as an adjunct treatment in covid.

2. Small Molecule Drug Therapy in Disease

2.1. AD

AD is a common degenerative disease of the nervous system and is dementia. At present, the symptomatic treatment of AChE inhibitors (AChEIs) is the main treatment for AD. The AChEIs currently in clinical use are tacrine, Donepezil, rivastigmine, and galantamine. AChE is an important active enzyme in the process of nerve conduction; the active enzyme participates in the formation of nerve cells and can participate in the regeneration and development of nerve cells. The destruction of the cholinergic system can cause the production of AD. Therefore, increasing the concentration of Ach in the human body is one of the effective means to improve the cholinergic activity in the human body and to improve learning and memory ability. Studies have shown that inhibiting AChE production and increasing Ach content can improve AD symptoms [2].

Tacrine is a typical acetylcholinesterase inhibitor, which has high lipid solubility [3], easily penetrates the blood-brain barrier, inhibits AChE in plasma and tissues, directly acts on cholinergic alkyne M receptors and nicotinic N receptors, promotes ACh release through M1 receptors, and blocks potassium ion channels. Inhibit monoamine oxidase activity and prevent the uptake of monoamine neurotransmitters.

The newly developed tacrine homodiplet are formed by the tacrine unit connecting to other units through a length of methylene chain, and if the tacrine unit is connected to itself, the advantage of the tacrine droplets is that they can act simultaneously with the catalytic site and peripheral site of AChE, making the activity and selectivity significantly higher than that of tacrine. In addition, it also has the most obvious effect on other AD targets, such as inhibition of Aβ aggregation. In this study [4], bis(7) -tacrine was 149 times more efficient than tacrine and 250 times more selective (IC50=1.5nmol/L) in a series of tacrine homodiplet designed with computer aid. The structure is formed by seven methylene groups joining two tacrine units. In vivo and in vitro studies, bis(7) -tacrine was found to have good pharmacological activity. In vivo studies found that rats were given bis(7) -tacrine to inhibit AChE in a meal-dependent manner, and the efficacy was ten times that of tacrine. These data prove that the bis(7)-tacrine has a more significant effect and higher efficiency than Tacrine in the process of combating AD.

2.2. Cancer

Liver cancer is a tumor with high mortality and malignancy. Sorafenib is a typical drug for liver cancer. By inhibiting a variety of targeted molecules, it can inhibit the proliferation of tumor cells and promote apoptosis. Being a multi-target kinase inhibitor, Sorafenib can directly inhibit the proliferation of tumor cells by inhibiting RAS/RAF/MEK/ERK signaling pathway. By inhibiting the activity of these molecules, sorafenib can interfere with multiple signaling pathways in cancer cells to achieve inhibition

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of cancer cells. RAS/RAF/MEK/ERK signaling pathway plays an important role in cell cycle regulation, gene expression, cell proliferation, and differentiation [5]. Most of the factors that stimulate cell growth, including EGF, PDGF, vascular endothelial growth factor (VEGF), and c-KIT, bind to the receptors on the cell surface. RAS can be first activated by autophosphorylation of receptor tyrosine kinase, and RAS further activates RAF/MEK/ERK signal transduction pathway, bringing growth factor signals into the nucleus, thus playing a role in regulating gene transcription and promoting cell proliferation. Increased activity of growth factor receptor tyrosine kinase, mutation and overexpression of RAS gene, and mutation of RAF gene can lead to overactivation of signal transduction pathways, resulting in excessive cell proliferation [6]. On the other hand, sorafenib blocks tumor neovasculangiogenesis by inhibiting the activity of several tyrosine kinase receptors associated with angiogenesis and tumor development, including vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor-B (PDGFR-p) and c-KIT proto-oncogenes. Indirectly inhibit the growth of tumor cells, thus playing an anti-tumor role. Especially for liver cancer, it is a highly vascularized tumor with high expression of VEGF, so sorafenib may have a more significant effect on tumor angiogenesis.

Sorafenib has also shown promising results in clinical trials. In a randomized multicenter placebo-controlled trial conducted in the United States and Europe, patients were randomized to receive sorafenib or placebo [7]. The findings revealed that the sorafenib group had a median survival (OS) of 10.7 months, compared to 7.9 months in the placebo group, indicating a notably longer duration. The time until disease advancement (TTP) was 5.5 months for those on sorafenib and 2.8 months for those on placebo. Another Phase III clinical trial conducted in Asia to explore the safety and efficacy of sorafenib in patients with liver cancer in the Asia-Pacific region showed that sorafenib prolonged OS (6.5 months vs.4.2 months) and doubled TTP [8]. These results confirm that sorafenib is effective in the treatment of HCC patients in different regions. According to the latest clinical trial report [9], sorafenib can be tolerated in Child-pugh grade B HCC patients with satisfactory safety. All these results demonstrate the efficacy of sorafenib in the treatment of cancer and it is a relatively reliable and effective antitumor drug [10].

2.3. Treatment via Azvudine in Coronavirus Diseases

Coronavirus disease (COVID-19), identified as a severe acute respiratory syndrome, has emerged and spread across the globe since Dec. 2019. It is an enveloped, single-stranded positive RNA virus. In vivo, alterations due to COVID-19 encompass swift viral multiplication, intense inflammatory reactions, and harm to the lymphatic system.[11]. More importantly, covid has been noted to have a fast mutation. Thus, the efficiency of drugs and their associated clinical development plays a crucial role in properly resolving and controlling the spreading of such diseases. As a result, small molecule drug with broad-spectrum antivirus, Azvudine(FNC) as an example, can be a more prudent approach other than vaccines since it specifically targets conserved proteins required for the viral replication of all coronaviruses in the thymus with controlled inflammatory responses, along with the potential to boost the lymphatic system. On the other hand, Azvudine utilizes nucleoside derivatives with low toxicity but also resolves the problem of resistant variants to prevent drug resistance.

Azvudine, a small molecule drug with a broad-spectrum anti-virus, is an oral tablet treatment showing antiviral activity against coronavirus with more controlled inflammatory responses in vivo. It is a nucleoside derivative antiviral drug that is synthetic and chemically modified nucleoside analogs. After entering a human body, the nucleoside analogs convert to nucleoside triphosphate, which then embeds in viral DNA or RNA during viral DNA or RNA synthesis, resulting in viral DNA or RNA chain synthesis to terminate and thus inhibit viral replication. Specifically, it targets the relevant non-structural proteins (nsp) such as RdRp, nsp14, and nsp16 in covid virus as inhibitors [10].

FNC demonstrates excellent targeting capabilities with controlled and stable signaling pathways in vivo to best minimize side effects. The 2’-fluoro group of FNC increases its acid stability and has a major impact on the electronic properties and conformational shape of nucleosides, while modifications at the 4’-position, such as the introduction of an azido group, cause the nucleosides to have an unnatural 3’-C-endo conformation [12]. The results showed that Azvudine and the active phosphorylated

triphosphate were mainly concentrated in the thymus gland and peripheral blood mononuclear cells and showed an immune-targeting function [11]. FNC triphosphate (FNC-TP) was only detected in the thymus. Studies using ultra-high performance liquid chromatography coupled with a tandem mass spectrometer (UHPLCMS/MS) confirm that FNC is highest in the thymus and spleen, suggesting an FNC accumulation effect in thymic tissue [11]. Other organs show low to undetectable levels of FNC-TP, indicating an inherent and steady transfer of FNC to its monophosphate, diphosphate, and triphosphate analogs in the thymus.

Modified nucleosides, 4'-modified nucleosides in this case, are generally challenging for intracellular enzymes to recognize, thus crucial in therapeutic use with low toxicity in vivo. Recent research has confirmed the low toxicity of FNC with a reduced dosage of 5 mg per day compared to remdesivir, which requires 100 mg per day to present positive results [13]. FNC has demonstrated excellent targeting ability in the thymus, thereby promoting host immunity to cure SARS-CoV-2. Notably, in a monkey experiment, FNC exhibited a controlled protective effect on lymphocytes [11]. By evaluating the chemical structure of FNC, researchers expect that the 3'-OH group with modifications in FNC can lead to significantly decreased inhibitory activity and reduces the risk of the emergence of cross-resistance/drug resistance [14].

The termination of nascent RNA synthesis effectively halts the replication of the virus. Research data from a clinical trial suggest that the use of azvudine may lead to a reduction in the time for mild covid-19 patients till nucleic acid negative results. Azvudine exhibits its antiviral effects primarily in the thymus, where it acts to shield the host immune system from the assault of SARS-CoV-2 and enhance the functioning of T-cell immunity, thereby contributing to the potential cure for COVID-19.

3. Conclusion

The small-molecule drugs have contributed to medical progress and social change in the history of medicine. Small-molecule drugs have now grown more rapidly to become the best way to optimize drug potency and selectivity for chemists and biologists, considering their capability to upgrade drug properties with controlled pathways. However, limitations have emerged in new applications, including addressing the target space of previously inaccessible drugs.

Research on small molecule drugs is ongoing, and new medications continue to emerge, bringing hope to some patients with refractory AD. It has also become an important research direction for anti-cancer diseases and anti-tumor drug therapy while showing its role in COVID-19. Delving deeper into drugs with minimal resistance, high efficiency, and few side effects, combined with exploring novel drug regimens, there's optimism that significant advances will soon be made in treating numerous challenging diseases. The pharmaceutical industry aims to address human diseases with a broad mix of approaches, including small molecules, antibodies, nucleic acids, glycans, cells, and gene therapies. In future small molecule drug research, we need to develop better and more efficient small molecule drugs to treat more kinds of diseases better so that they can adapt to more different scenarios.

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Tianyu Lu and Jiayi Yang contributed equally to this work and should be considered co-first authors.

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