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Review

Anti-HBV agents derived from botanical origin

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ABSTRACT

There are 350,000 hepatitis B virus (HBV) carriers all over the world. Chronic HBV infection is at a high risk of developing liver cirrhosis and hepatocelluar carcinoma (HCC), and heavily threatened people's health. Two kinds of drugs approved by FDA for anti-HBV therapy are immunomodulators (interferon α, pegylated-interferon α) and nucleos(t)ide analogues (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate). These drugs have been proved to be far from being satisfactory due to their low specificity, side effects, and high rate of drug resistance. There is an urgent need to discover and develop novel effective anti-HBV drugs. With vast resources, various structures, diverse biological activities and action mechanisms, as well as abundant clinical experiences, botanical agents become a promising source of finding new anti-HBV drugs. This review summarizes the recent research and development of anti-HBV agents derived from botanical origin on their sources and active components, inhibitory effects and possible toxicities, as well as action targets and mechanisms, and also addresses the advantages and the existing shortcomings in the development of botanical inhibitors. This information may not only broaden the knowledge of anti-HBV therapy, and offer possible alternative or substitutive drugs for CHB patients, but also provides considerable information for developing new safe and effective anti-HBV drugs.

Contents

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1. Introduction

Chronic hepatitis B virus (HBV) infection is correlated with a significant increased risk of liver failure, liver fibrosis and cirrhosis which predisposes individuals to hepatocellular carcinoma (HCC) worldwide [1,2]. It is estimated that approximately 350 million people worldwide and 93 million in China alone are HBV carriers, causing approximately 500 thousand deaths every year. Although safe and effective vaccines for HBV are available, approximately 5–10% of individuals treated are nonresponders to the hepatitis B vaccine [3,4]. Moreover, there is still no effective treatment for the millions of chronically infected individuals. Two kinds of antiviral drugs have been approved by the FDA for the treatment of hepatitis B currently, one kind is immunomodulators, such as interferon α (IFN-α) and pegylated-interferon α (peg-IFN-α); and the other kind is nucleos(t)ide analogues, including lamivudine(LAM, 3TC), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF). These drugs improve circulating HBV DNA levels and postpone disease progression to some extent, but they cannot eradicate HBV closed circular DNA (cccDNA) in the infected hepatocytes.They are effective in only part of the patients, and may lead to numerous side effects as well as the generation of drug-resistant mutants over prolonged antiviral administration [5–7]. So there exists a significant unmet medical need for new safe and effective anti-HBV drugs.

2. HBV life cycle

HBV belongs to the Hepadnaviridae family of animal viruses, and packages a small (3.2 kb), circular, partially double-stranded DNA genome. After entering the hepatocyte, the relaxed circle DNA (rcDNA) of HBV is released from the viral nucleocapsid, and then transported into the nucleus. Inside the nucleus, the plus strand is elongated and the rcDNA is converted to a cccDNA. The HBV replication starts from the reverse transcription of pgRNA and other functional subgenomic mRNAs with the cccDNA as the template. In the cytoplasm, HBV polymerase recognizes the RNA packaging signal/origin of replication ε of pgRNA and binds to it. This complex is further packaged into the viral capsid consisting of HBcAg. Subsequently, the process involving the reverse transcription of pgRNA to minus DNA, the incomplete plus DNA synthesis and RNase degradation, is carried out in the nucleocapsid. The nucleocapsid containing minus-and plus-DNA may reenter the nucleus or bud into the endoplasmic reticulum, and then enveloped and eventually secreted outside the cells.

Four length mRNAs are transcripted with the cccDNA as the template, including the 3.5 kb, 2.4 kb, 2.1 kb, and 0.7 kb mRNA. The 3.5 kb mRNA serves not only as the reverse transcription substrate (pregenomic mRNA, pgRNA), but also the template for the HBV core antigen (HBcAg), E antigen (HBeAg) polymerase proteins; the 2.4 kb and 2.1 kb mRNAs encode three surface proteins, including the large (LHBs), middle (MHBs) and small (SHBs or HBsAg) surface proteins; and the 0.7 kb mRNA encodes the X antigen (HBxAg). Among these viral proteins, HBcAg is the main structure protein in