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COMPREHENSIVE REVIEW

Therapeutic applications of carbohydrate-based compounds: a sweet solution for medical advancement

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Abstract

Carbohydrates, one of the most abundant biomolecules found in nature, have been seen traditionally as a dietary component of foods. Recent findings, however, have unveiled their medicinal potential in the form of carbohydrates-derived drugs. Their remarkable structural diversity, high optical purity, bioavailability, low toxicity and the presence of multiple functional groups have positioned them as a valuable scaffold and an exciting frontier in contemporary therapeutics. At present, more than 170 carbohydrates-based therapeutics have been granted approval by varying regulatory agencies such as United States Food and Drug Administration (FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA), Chinese National Medical Products Administration (NMPA), and the European Medicines Agency (EMA). This article explores an overview of the fascinating potential and impact of carbohydrate-derived compounds as pharmacological agents and drug delivery vehicles.

Keywords Carbohydrates-derived drug · Drug delivery system · Antibiotic · Anticancer · Antiparasitic · Antidiabetic drug

Introduction

Carbohydrates are one of the most fundamental classes of biological compounds, accounting for 75% of all biomolecules on earth, primarily in the form of cellulose and chitin [1, 2]. They are polyhydroxy of carbonyl compounds (aldehydes and ketone), having carbon, hydrogen and oxygen atoms in the ratio 1:2:1, with the ability to form an intramolecular hemiacetal or hemiketal.[3, 4] Nowadays, the definition has been greatly expanded to consist of molecules in their oxidized and reduced states as well as those with heteroatoms like halogens, nitrogen, and sulfur [5]. Based on their degree of polymerization, carbohydrates can be classified into four main groups namely, monosaccharides, disaccharides, oligosaccharides and polysaccharides (Fig. 1) [6].

Normally, carbohydrates are found in all living organisms, either as free molecules or as glycans [7, 8]. In humans, a disaccharide sugar known as lactose acts as the major source of energy during infancy, which is provided through breast milk [9]. After weaning, it continues to be the central powerhouse, providing 40–80% of the total energy required [9, 10]. Aside from being an essential dietary component in many biological systems, carbohydrates are incomparable assets that play a major role in various life-important operations. They are the intrinsic components for the construction of important genetic materials and cell walls in different organisms and are an integral part of the exoskeleton in the phylum Arthropoda. Moreover, they often act as the major source of metabolic fuels and energy storage as well as the chief architect of numerous intercellular and extracellular recognition processes [11–13].

Given their ubiquitous existence in nature as essential components in numerous living organisms, it is understandable that saccharide-derived compounds have generated a robust foundation for the advancement of pharmaceutical research and development [14–16]. Currently, more than 170 carbohydrate-containing compounds have received clinical approval across the globe.[17] However, when considering the widespread occurrence and myriad biological functions of carbohydrates, their application as therapeutics remains quite restricted. Recent studies have shown that carbohydrate-derived compounds possess great therapeutic potential, rendering this a rapidly expanding field of research and

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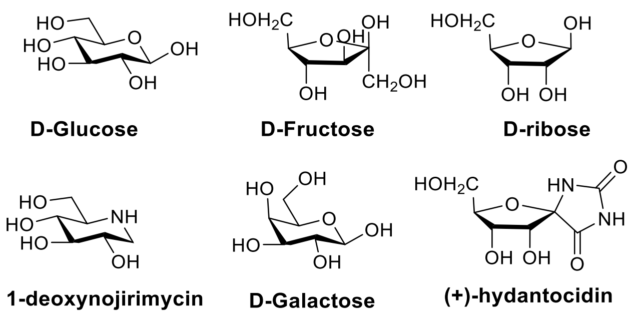

Fig. 1 Few examples of biological important monosaccharides

redefining a drug discovery strategy due to the advent of new analytical tools and improved synthetic processes. [14, 18–21] They have been studied in a wide range of therapeutic fields, including cancer, infectious illnesses, autoimmune disorders, and neurological diseases. One of their unique characteristics is their versatility, which allows them to be adaptable for a wide range of medical applications. In this article, we will provide a brief overview of the chemical structures and various applications of carbohydrate-derived compounds as pharmacological agents (antibacterial, anticancer, antiparasitic, and antidiabetic) and delivery systems.

Carbohydrate-derived antibiotic agents

Previously, antibiotics were defined as substances obtained from bacteria or fungi that have the ability to inhibit the growth of other microorganisms [22]. Nowadays, the definitions include all molecules having bactericidal action, including those that are naturally occurring, semi-synthetic and fully synthetic substances [23]. To date, the majority of carbohydrate-based antibiotics that have been reported so far are primarily from natural sources, with a few being semi-synthetic [14, 24]. These antibiotics containing carbohydrate components can be divided into four main classes: aminoglycosides, macrolides, glycopeptides and nucleosides.

Aminoglycoside antibiotics (AGAs), which include a 6-membered aminocyclitol ring that has been glycosylated to a variety of amino sugars, are mostly obtained from the species streptomyces and strains of actinomycetes bacteria [24]. Aminoglycosides (AGs) interacts with the bacterial RNA on the 30S subunit of the ribosome, resulting in the disruption of protein translation [25]. The first AGAs, streptomycin (Fig. 2A), was isolated in 1943 and has been used effectively to treat tuberculosis since the middle of the 1940s. Following this initial success of streptomycin, several other AGAs such as neomycin (Fig. 2B), gentamycin (Fig. 2C), tobramycin (Fig. 2D) and sisomicin (Fig. 2K) were then introduced [25]. All of them showed good to excellent bactericidal activity against gram-negative bacteria and specific gram-positive bacterial infection. The continuous application of these antibiotics in medical practice has led to the prevalence of resistance and adverse effects, such as ototoxicity, neuromuscular block and nephrotoxicity, were becoming more obvious [26–29]. As a result, there were attempts to enhance the pharmacological characteristics of AGAs, which ultimately led to the identification and subsequent introduction of semi-synthetic second-generation AGs [20, 25]. These include dibekacin (Fig. 2E), arbekacin (Fig. 2F), amikacin (Fig. 2G), isepamicin (Fig. 2H) and netilmicin (Fig. 2I). However, the introduction of broad-spectrum antibiotics such as fluoroquinolones, carbapenems and cephalosporins, with fewer side effects resulted in a decrease in enthusiasm for the pursuit of novel AGAs. As of 2010, AGAs accounted for a mere 2.7% of the overall antibiotic market share [25].

Nevertheless, the increasing resistance to routinely used antibiotics, particularly in hospital-acquired infections, has once again directed clinical interest towards AGAs. Of note, after the regulatory approval of isepamycin in 1988 and arbekacin in 1990, two AGs, namely paromomycin and plazomicin, were clinically approved in the years 2006 and 2018. Paromomycin (Fig. 2J) is a classical AG medication that was extracted from the filtrates of *Streptomyces krestomuceticus* in the 1950s [30]. It has a broad-spectrum of antibacterial activity, targeting both Gram-negative bacteria and several Gram-positive bacteria [31]. The FDA has approved paromomycin for the treatment of amoebiasis since it has a potent oral medication for treating complications that result from intestinal protozoa, including *Entamoeba histolytica, Giardia lamblia and Dientamoeba fragilis*.[32] Further application of paromomycin for the treatment of leishmaniasis will be discussed in "Carbohydrate-derived antiparasitic agents" Sect., carbohydrate-based antiparasitic agents. In 2010, Aggen and co-workers reported the synthesis of plazomicin (Fig. 2J) by modifying the structure of sisomicin, which was isolated from *Micromonospora sinositola* bacteria. Plazomicin was obtained by attaching hydroxy-aminobutyric acid and hydroxyethyl substituents to the sisomicin structure at positions C-1 and C-6′ [33, 34]. The results obtained from a phase II, randomized, double study in patients with urinary tract infections (UTIs) showed that levofloxacin at 750 mg had a microbiological eradication rate of 58.6%, while plazomicin at 10 and 15 mg/kg had a rate of 50 and 60.8%. No cases of nephrotoxicity or ototoxicity were observed during the trail [35]. Moreover, plazomicin has completed another phase III clinical trials for treating complicated UTIs successfully and was shown to be non-inferior to the drug meropenem [36]. Based on these observations, the FDA granted the approval of plazomicin in 2018.

Macrolides, consisting of one or more deoxy or amino sugars that are bonded to large macrocyclic lactones,