Pharmacology & Therapeutics 170 (2017) 80–97

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: I. Kimura

Chitosan oligosaccharide: Biological activities and potential therapeutic applications

Chatchai Muanprasat *, Varanuj Chatsudthipong

Excellent Center for Drug Discovery and Department of Physiology, Faculty of Science, Mahidol University, Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

ARTICLE INFO

Available online 20 October 2016

Keywords:
Chitosan
Chitosan oligosaccharide
Chitin
Polymers
Drug discovery

ABSTRACT

Chitosan oligosaccharide (COS) is an oligomer of β-(1 → 4)-linked D-glucosamine. COS can be prepared from the deacetylation and hydrolysis of chitin, which is commonly found in the exoskeletons of arthropods and insects and the cell walls of fungi. COS is water soluble, non-cytotoxic, readily absorbed through the intestine and mainly excreted in the urine. Of particular importance, COS and its derivatives have been demonstrated to possess several biological activities including anti-inflammation, immunostimulation, anti-tumor, anti-obesity, anti-hypertension, anti-Alzheimer's disease, tissue regeneration promotion, drug and DNA delivery enhancement, anti-microbial, anti-oxidation and calcium-absorption enhancement. The mechanisms of actions of COS have been found to involve the modulation of several important pathways including the suppression of nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPK) and the activation of AMP-activated protein kinase (AMPK). This review summarizes the current knowledge of the preparation methods, pharmacokinetic profiles, biological activities, potential therapeutic applications and safety profiles of COS and its derivatives. In addition, future research directions are discussed.

Contents

Abbreviations: ACE, angiotensin-converting enzyme; AChE, acetylcholine esterase; AD, Alzheimer's disease; AMPK, AMP-activated protein kinase; AP-1, activator protein 1; Aβ, amyloid beta; CaSR, calcium-sensing receptor; COS, chitosan oligosaccharide; COX-2, cyclooxygenase-2; DD, degree of deacetylation; DM, diabetes mellitus; DP, degree of polymerization; EGFR, epidermal growth factor receptor; ERK 1/2, extracellular signal-regulated kinase; FITC, fluorescein isothiocyanate; GlcN, D-glucosamine; GlcNAc, *N*-acetyl-D-glucosamine; GLUT4, glucose transporter 4; HUVEC, human umbilical vein endothelial cells; IBD, inflammatory bowel disease; IEC, intestinal epithelial cells; IFN-γ, interferon gamma; IκB, inhibitory kappa B; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK 1/2, C-Jun-N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MIC, minimum inhibitory concentration; MAPKK, mitogen-activated protein kinase kinase; MMP, matrix metallopeptidase; MW, molecular weight; NIDDM, non-insulin-dependent diabetes mellitus; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOAEL, no observed adverse effect level; P_A, pattern of *N*-acetylation; PGE_2, prostaglandin E_2; PK, pharmacokinetics; PPAR, peroxisome proliferator-activated receptor; PVA, poly(vinyl alcohol); STZ, streptozotocin; TNF-α, tumor necrosis factor-α.

* Corresponding author at: Department of Physiology, Faculty of Science, Mahidol University, Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.
E-mail address: chatchai.mua@mahidol.ac.th (C. Muanprasat).

http://dx.doi.org/10.1016/j.pharmthera.2016.10.013
0163-7258/

1. Introduction

1.1. Chemical structure and physicochemical properties of chitosan oligosaccharides (COS)

Chitin and chitosan are linear polymers composed of β-(1 ➔ 4)-linked *N*-acetyl-D-glucosamine (GlcNAc, acetylated unit A) and D-glucosamine (GlcN, deacetylated unit D) (Fig. 1). Chitin contains a high proportion of GlcNAc, while chitosan is mainly composed of GlcN, which can be protonated to form a positively charged moiety (NH_3^+) at neutral/physiological pH, making chitosan a positively charged polymer at neutral/physiological pH. Chitosan oligosaccharide (COS) is an oligomer of chitosan, which usually has a degree of polymerization (DP) < 50–55 and an average molecular weight (MW) <10,000 Da (Fig. 1). The chemical characteristics of COS can also be described by the degree of deacetylation (DD), which corresponds to the molar fraction of GlcN in the COS molecule, molecular weight distribution (polydispersity or PD) and the sequence or pattern of *N*-acetylation (P_A). These chemical characteristics have great impacts on the physicochemical and biological properties of COS.

Compared with chitosan, COS has a higher water solubility and lower viscosity, making it a more favorable candidate for therapeutic applications. COS is completely soluble in water and partially soluble in methanol and dimethyl sulfoxide but insoluble in acetone and ethanol. COS with a DP of 2–4 is soluble in methanol, but COS with a DP > 5 is less soluble (Aam et al., 2010). Low-MW COS (MW < 1500 Da) is soluble in water over a wide range of pH due to the low intermolecular interactions, including van der Waals forces (Aam et al., 2010).

1.2. Preparation of COS from natural sources

COS is a degradation product of chitosan, which can be prepared from the deacetylation of chitin, which is the second most abundant polymer in nature after cellulose and found in the exoskeletons of

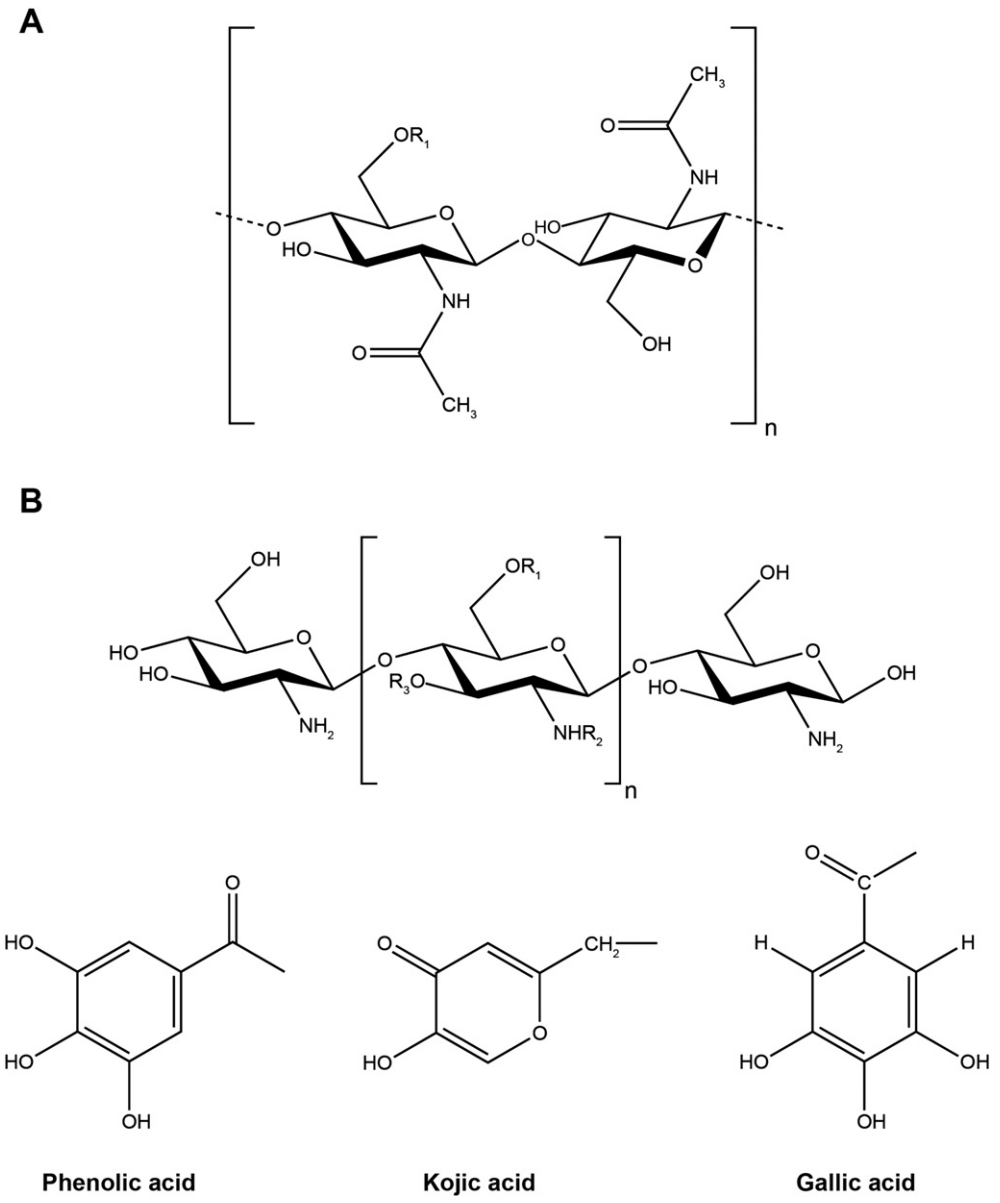

Fig. 1. Chemical structures of chitin, chitosan, chitosan oligosaccharide (COS) and their derivatives. (A) Chemical structure of chitin and its derivatives. R_1=H for chitin. R_1=$(CH_2)_2NH_2$ for aminoethyl-chitin. n > 27 (MW > 10,000 Da; DP > 55). (B) Chemical structures of chitosan, COS and their derivatives. Chitosan: n > 53 (MW > 10,000 Da; DP > 55). COS: n ≤ 53 (MW ≤ 10,000 Da; DP ≤ 55); R_1=H, R_2=H, R_3=H. Aminoethyl-COS: R_1=$(CH_2)_2NH_2$, R_2=H, R_3=H. Carboxylated COS: R_1=H, R_2=$CO(CH_2)_2COO^-$, R_3=H. Sulfated COS: R_1, R_2, R_3=H or SO_3^-. Phenolic acid-conjugated COS: R_1=H, R_2=phenolic acid, R_3=H. Kojic acid-conjugated COS: R_1=kojic acid, R_2=H, R_3=kojic acid. Gallic acid-conjugated COS: R_1=H, R_2=gallic acid, R_3=H.