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# Protective effect of low molecular fraction of MGN-3, a modified arabinoxylan from rice bran, on acute liver injury by inhibition of NF-κB and JNK/MAPK expression

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ABSTRACT

D-Galactosamine (GalN) induces acute hepatitis in experimental animals; this hepatitis has been shown to be suppressed by oral or intraperitoneal administration of modified arabinoxylan from rice bran (MGN-3), and active low molecular fraction isolated from MGN-3 (LMW). We previously reported that this protective mechanism is mediated in part by downregulation of interleukin-18 (IL-18). The present study shows for the first time that nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK) and CD14 are involved in the suppressive action of LMW on GalN-induced hepatitis. Wistar rats (aged 4 weeks, SLC) were intraperitoneally treated with either MGN-3 or LMW. Then, rats were given GalN at 400 mg/kg at 1 h after the initial treatment. The serum activity of transaminases (ALT and AST) was significantly higher after GalN treatment; these changes were attenuated by MGN-3 and LMW. Furthermore, LMW abrogated inhibitor of κB kinase (IκB) degradation induced by GalN, and this was associated with the inhibition of NF-κB activation. Moreover, phosphorylated stress-activated protein kinase/c-Jun N-terminal kinase (JNK) protein expression in the liver after GalN treatment was significantly higher, and LMW reduced this increase. We also found that GalN treatment induced *TLR4* and *CD14* mRNA expression, and LMW significantly inhibited *CD14* mRNA expression. These results suggest that the suppressive effects of LMW on GalN-induced hepatitis are possibly related to inhibition of NF-κB, JNK phosphorylation and *CD14* expression.



## 1. Introduction

Hepatitis is a serious health problem worldwide associated with significant morbidity and mortality. A better knowledge of the basic mechanisms governing immune response in the pathogenesis of liver disease has allowed the development of targeted therapies for the management and treatment of hepatitis [1–3]. D-Galactosamine (GalN)-induced hepatitis has been used as an animal model for acute liver injury, since its morphological and pathophysiological characteristics are similar to those of human hepatitis B [4,5]. Hepatitis induced by GalN in rats is considered to be mediated by inhibited macromolecular glycoprotein and RNA biosynthesis through depletion in cellular UTP concentration [6] and elevation of blood levels of tumor necrosis factor-α (TNF-α) caused by increasing absorption of lipopolysaccharide (LPS) endotoxin, from the intestine to the bloodstream [7,8]. However, the precise mechanism for GalN-induced hepatitis has not yet been elucidated.

MGN-3, a modified water-soluble hemicellulose from rice bran has a variety of immune functions. It has been reported that NK cell, T cell, and B cell functions are augmented by MGN-3 both in vitro and in vivo [9–11]. In addition, when MGN-3 is administered in conjunction with conventional chemotherapeutic agents, it has been highly effective in inducing cancer remission in animal models [4]. In our previous study, we showed that GalN-induced hepatitis was suppressed in part by IL-18 reduction following ingestion of BioBran (MGN-3), a modified arabinoxylan from rice bran, or its active fraction (LMW). MGN-3 was hydrolyzed with HCl at 100 °C, and then the hydrolysate treated with cation or anion exchange resin was fractionated by molecular weight (high molecular weight fraction (≥2,000,000 Da), medium molecular weight fraction (2,000,000–400 Da), and low molecular weight fraction (LMW; ≤400 Da)). We concluded that LMW has a stronger hepato-protective effect than MGN-3 [12]. The molecular weight of LMW was measured by ESIMS, and an intense peak at m/z 409 was observed [12]. LMW is a mixture of monosaccharide and oligosaccharides, constituted by glucose as the main component (glucose, 22.8%; mannose, 1.5%; galactose, 0.5%; arabinose, 0.3%; protein, 2.85%) [12]. In our previous study, the results indicate that neutral oligosaccharides and monosaccharides in the LMW seem to be candidates for the effective ingredients for treating GalN-induced liver injury.

IL-18 is a unique activating cytokine belonging to a novel family of inflammatory cytokines that function in the immune response [13–16]. In an animal experimental model, IL-18 is released from murine macrophages or Kupffer cells through Toll-like receptor 4 (TLR4)/CD14-dependent signaling pathways [17].

*Abbreviations:* NF-κB, nuclear factor-κB; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase.

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