



3rd International Electronic Conference on Medicinal Chemistry

1-30 November 2017

chaired by Dr. Jean Jacques Vanden Eynde

sponsored by



pharmaceuticals

Hepatoprotective Effect of Oligoribonucleotides-D-mannitol Complexes under Thioacetamide-induced Hepatotoxicity

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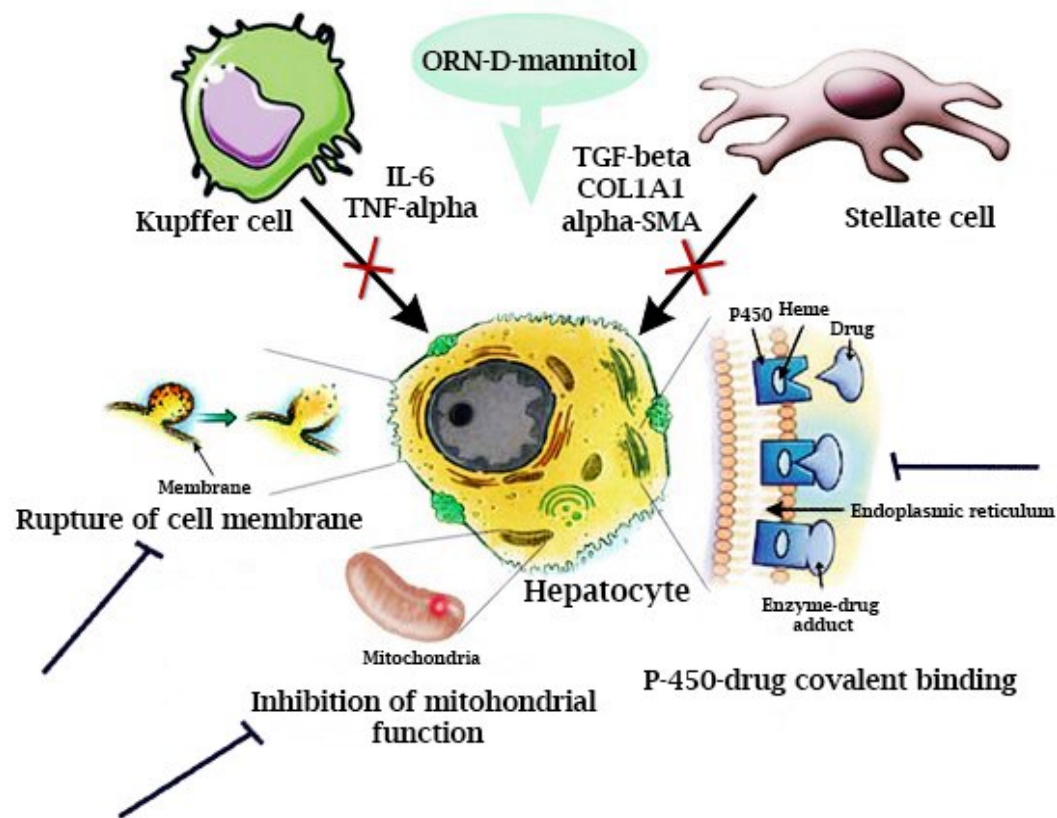
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Hepatoprotective Effect of Oligoribonucleotides-D-mannitol Complexes under Thioacetamide-induced Hepatotoxicity

The results of this research demonstrate that the oligoribonucleotides-D-mannitol have the hepatoprotective effect during acute liver injury. These complexes attenuate thioacetamide-induced free-radical damage of liver biopolymers and modulate the expression of some genes which are involved in the development of liver damage at the thioacetamide toxicity.



* Adapted to – W. M. Lee / The New England Journal of Medicine (2003)



Abstract: The liver plays a crucial role in the metabolic elimination of the most drugs and other foreign compounds, thus making it is an important target for toxicity. So hepatoprotective action against liver toxic injury remains one of the major challenges for clinical therapy. Oligoribonucleotides-D-mannitol complexes(ORNs-D-M) display a vast spectrum of biological effects including cellular metabolism stimulation with activation of endogenous synthesis of regulatory proteins. ORNs-D-M have been demonstrated to be efficient therapeutics for correction of such liver pathologies as chronic viral hepatitis and nonalcoholic steatohepatitis. However, the mechanism of ORNs-D-mannitol hepatoprotective activity is still not clear. The objective of this research was to study effects of the ORNs-D-M under thioacetamide liver toxicity in mice.

It was demonstrated, that the ORNs-D-M attenuated thioacetamide-induced free radical damage of hepatic biopolymers that is expressed in reduction of TBA-reactive products, carbonyl derivatives and in recovery of protein thiol groups, reduced glutathione. The complexes also demonstrate a significant decrease of the IL-6, TNF- α , COL1A1, α SMA, TGF- β 1 gene expression. Thus, the results of this study show that the ORNs-D-M complexes produce the hepatoprotective effect during acute thioacetamide-induced hepatotoxicity.

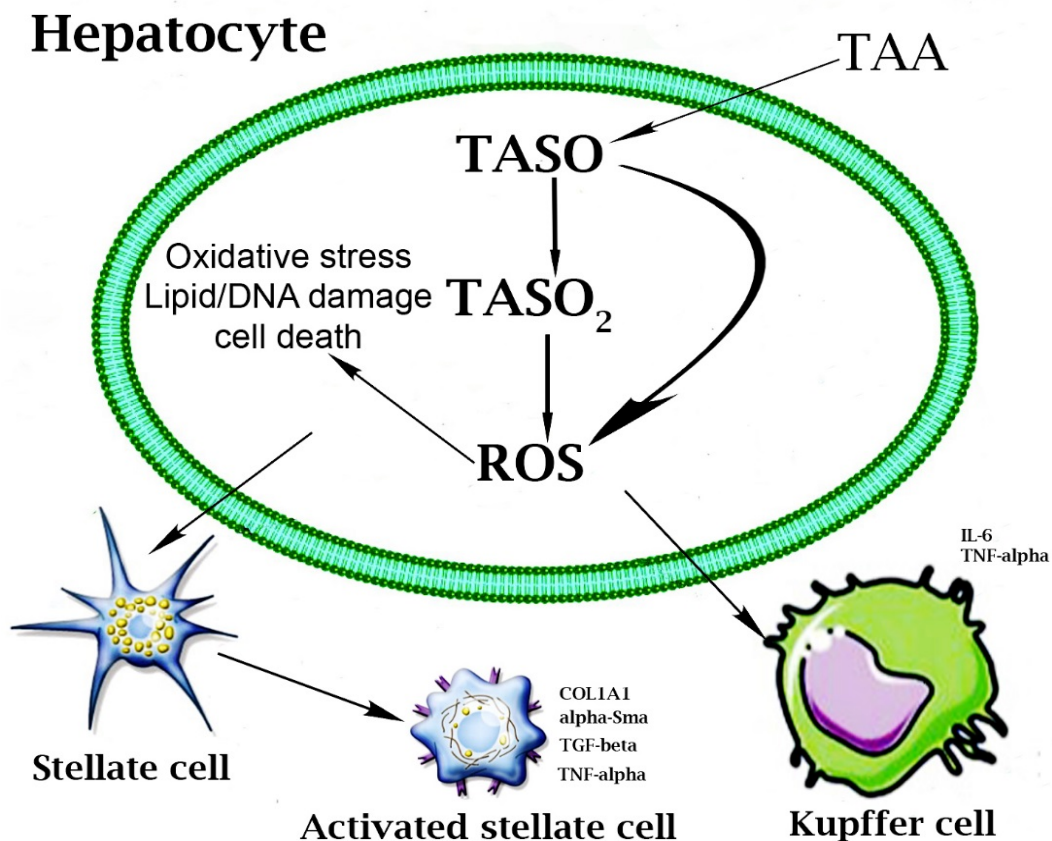
Keywords: thioacetamide; hepatotoxicity; oligoribonucleotides-D mannitol; hepatoprotective effect.



Introduction

The main pathogenic mechanisms, which responsible for functional and organic damage caused by toxins, are an inflammation, dysfunction of cytochrome P450, mitochondrial dysfunction and oxidative stress.

The hepatic nonparenchymal cells, Kupffer, sinusoidal endothelial, stellate cells, newly recruited cells of the immune system also contribute to the pathogenesis of hepatic toxicity. Kupffer cells and neutrophils are a source of the proinflammatory cytokines, chemokines, reactive oxygen and nitrogen species. The hepatic stellate cells play a key role in the liver fibrosis.



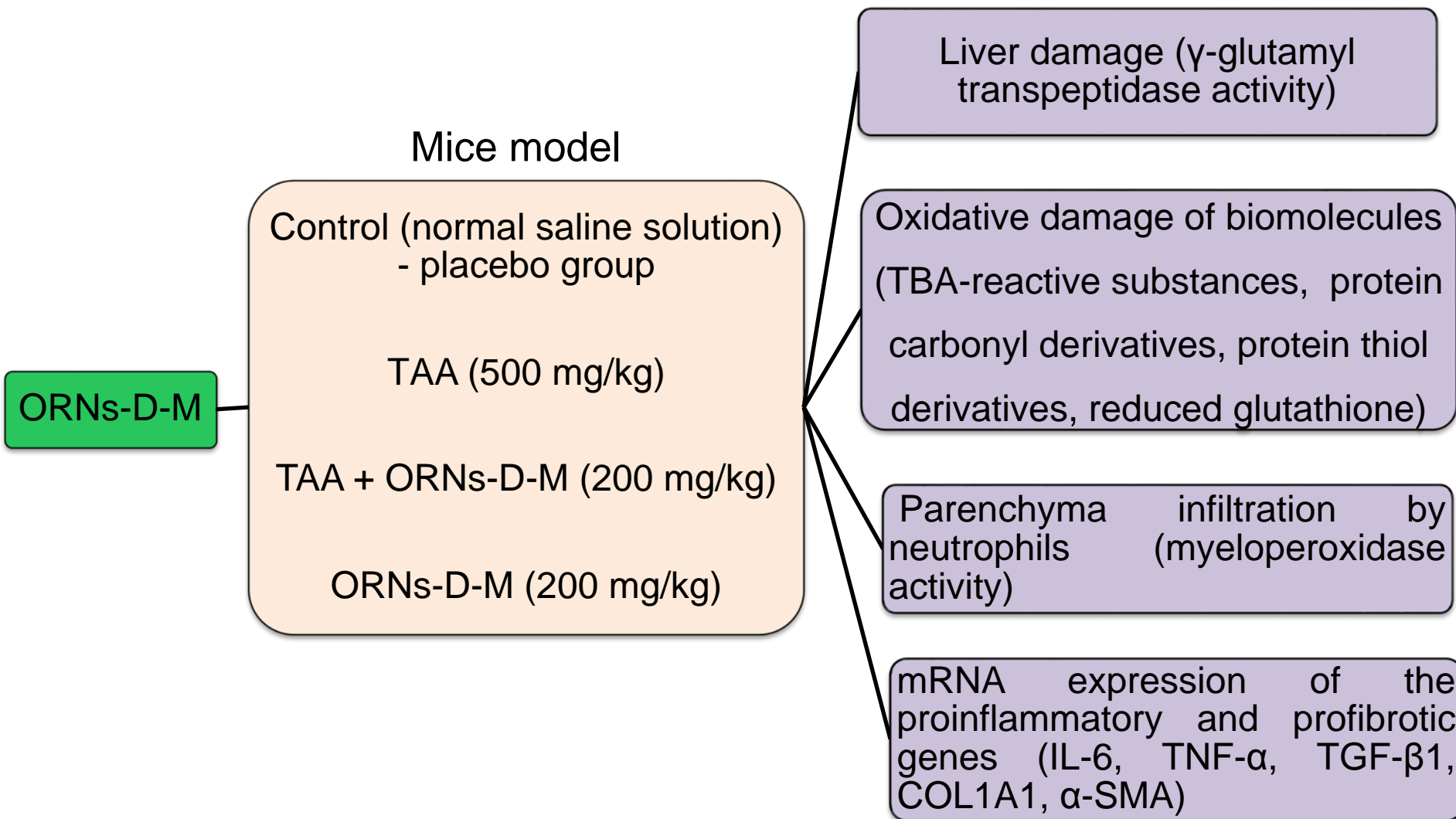
Introduction (Cont.)

Natural and synthetic oligoribonucleotides (ORN) display a vast spectrum of biological effects, including:

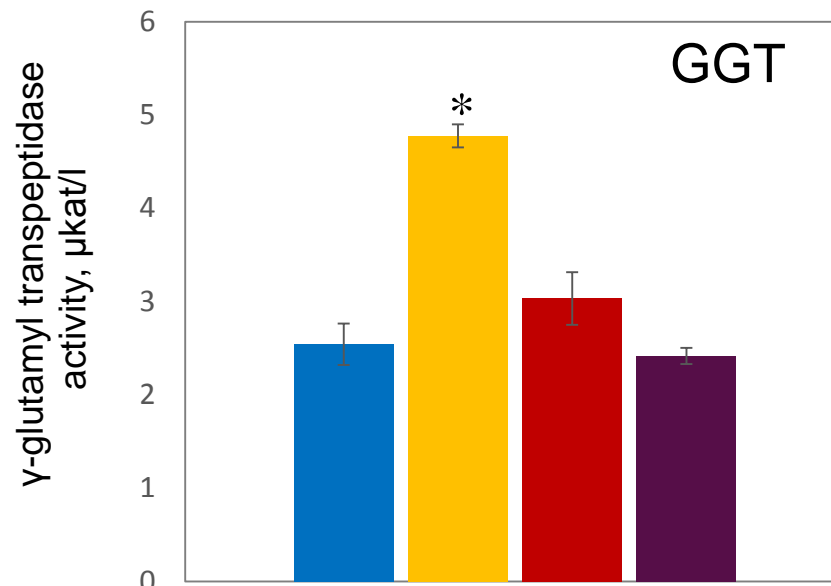
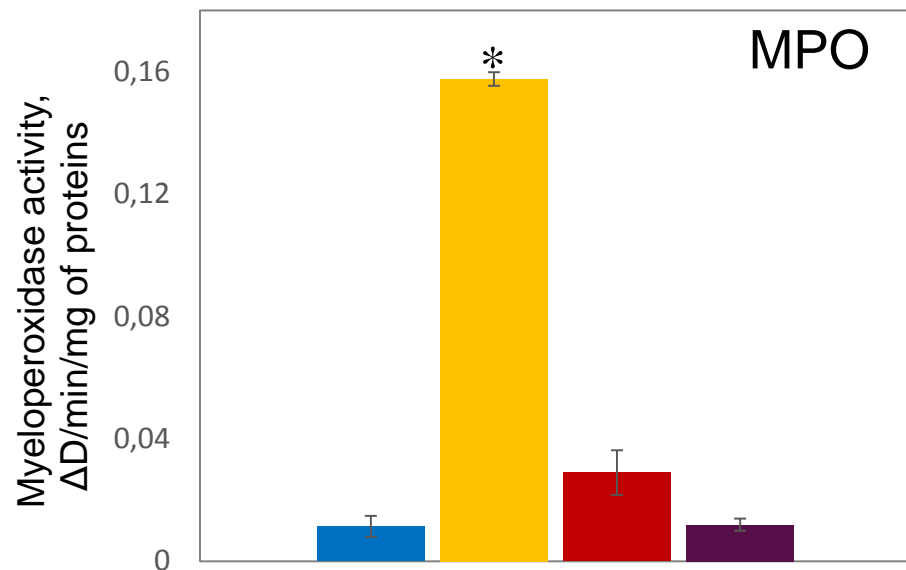
- cellular metabolism stimulation with activation of endogenous synthesis of nucleic acids, regulatory proteins and enzymes;
- increase in cellular mitotic activity;
- stimulation of reparation processes;
- stimulation of ATP synthesis;
- membrane stabilizing effect;
- anti-inflammatory effect.



Introduction (Cont.)



Results and discussion



- Control
- TAA
- TAA+ORNs-D-M
- ORNs-D-M

This results demonstrate that the ORNs-D-M attenuate the hepatotoxicity caused by the single dose of thioacetamide. The hepatoprotective effect is manifested as 40 % decreased blood serum γ -glutamyl transpeptidase activity in comparison to group with TAA, in which this parameter was nearly double that of the control group.

On the other hand, myeloperoxidase activity (which is an indicator of inflammatory infiltration of liver parenchyma by neutrophils) did not differ significantly under co-administration of the ORNs-D-M with TAA and in control conditions.



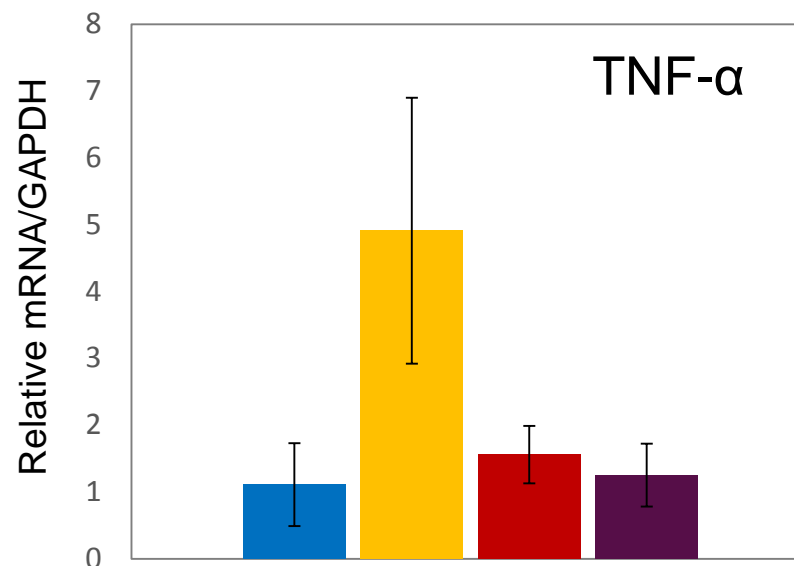
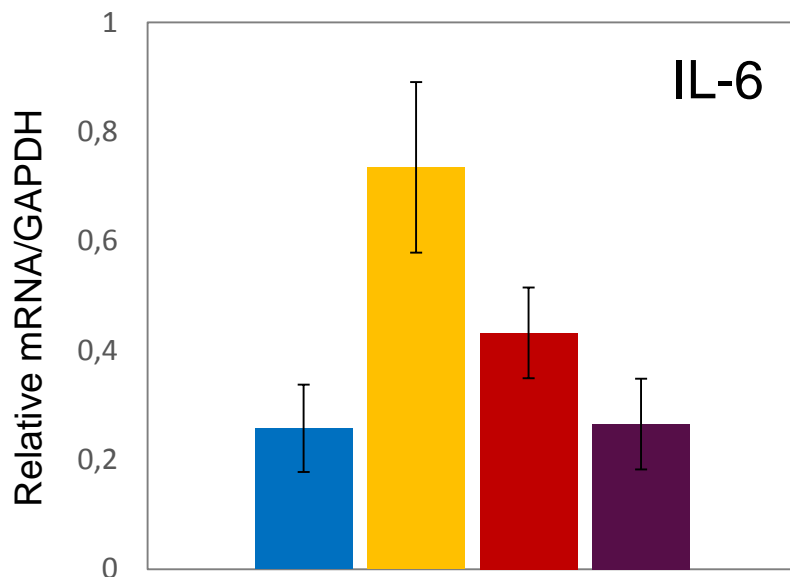
Results and discussion

	Liver TBARS (nmol/mg of protein)	Protein carbonyl derivatives in liver (nmol/mg of protein)	Protein thiol groups in liver (nmol/mg of protein)	Reduced glutathione in liver (mg/mg of protein)
Control	9,271±0,88	182,66±15,08	9367,726±529,60	1,223±0,06
TAA	50,591±2,60	579,91±30,95	2927,469±242,02	0,317±0,02
TAA+ORNs-D-M	19,165±1,65	272,34±20,02	5738,456±280,15	0,955±0,08
ORNs-D-M	11,375±0,99	189,32±17,18	10102,52±316,19	1,438±0,06

ORNs-D-M application attenuates thioacetamide-induced free radical damage of hepatic biopolymers. Complexes decrease levels of protein carbonyls and secondary products of lipid peroxidation, and increase levels of protein, non-protein thiol groups.



Results and discussion



- Control
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The IL-6 and TNF- α are a commonly used markers of inflammation. Their expression has been demonstrated to increase during acute hepatotoxicity.

Our data show the upexpression of IL-6 and TNF- α induced by the TAA in comparison to control.

Normalized expression of these genes was observed at co-administration of the ORNs-D-M with TAA.

The obtained results indicate an anti-inflammatory effects of the complexes.



Results and discussion

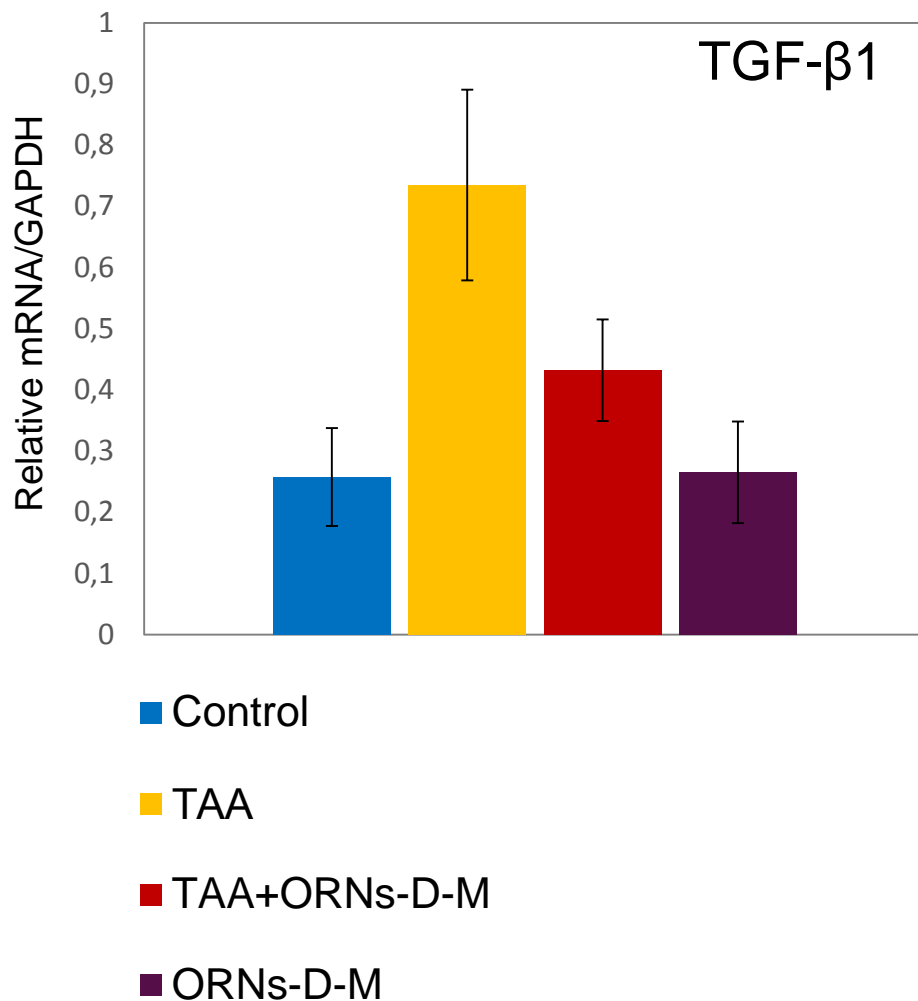
Transforming growth factor $\beta 1$ (TGF- $\beta 1$) is one of the most potent pro-fibrogenic cytokine in liver disease. TGF- $\beta 1$ is expressed by activated hepatic stellate cells (HSC).

TGF- $\beta 1$ leads to an autocrine induction of fibrogenic genes expression in HSC.

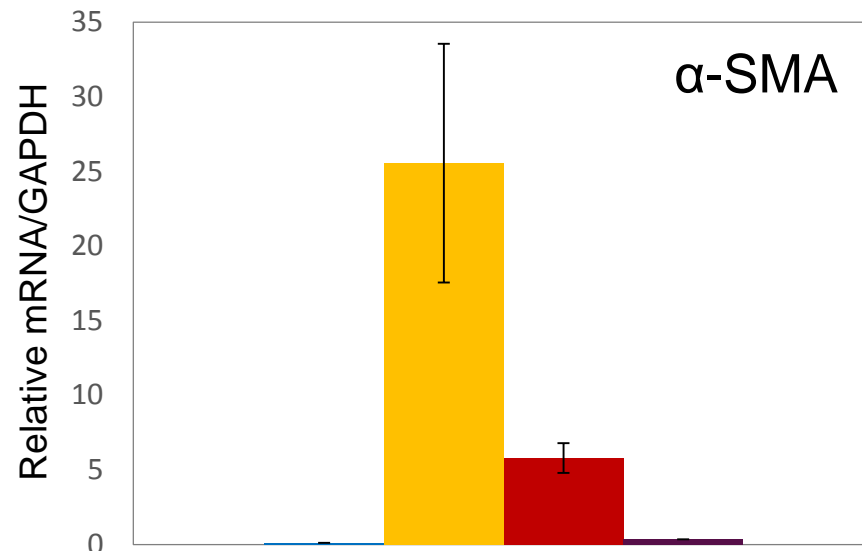
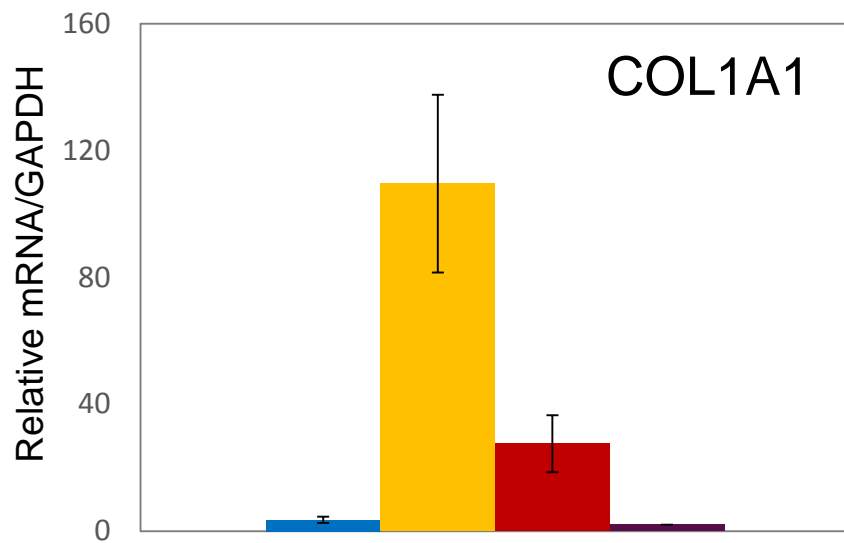
Treatment with TAA induced the upregulation of TGF- $\beta 1$ mRNA expression in parenchyma liver.

ORNs-D-M complexes reduced the TAA-induced expression of TGF- $\beta 1$ in liver.

Thus, the ORNs-D-M have protective effects on the formation of fibrosis after acute liver injury induced by the TAA.



Results and discussion



- Control
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HSC activation is a central event in the development of hepatic fibrosis and occurs early in response to liver injury.

That's why, we studied the mRNA level of COL1A1 and α -SMA (an indicator of hepatic stellate cell activation) which are expressed by hepatic activated stellate cell.

ORNs-D-M treatment reduces the TAA-induced expression of COL1A1 and α -SMA.



Conclusions

1. The oligoribonucleotides-D-mannitol complexes have a hepatoprotective effect, that is associated with decrease parenchyma lesions and inflammatory infiltration.
2. The ORNs-D-mannitol attenuated thioacetamide-induced free radical damage of hepatic biopolymers that is expressed in reduction of TBA-reactive products, carbonyl derivatives and in recovery of protein thiol groups, reduced glutathione.
3. Complexes modulate the expression of proinflammatory and profibrotic genes that are involved in the development of liver damage at the thioacetamide toxicity.
4. The inhibitory effects on fibrogenic factors of the ORNs-D-M indicate the potential prevention and treatment of hepatic fibrosis in patients with (chronic) liver disease when using these complexes.

