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Assessment of the Antifibrotic Activity of Polysaccharides Extracted from Oyster Mushroom (*Pleurotus ostreatus*) Mycelium in the Rats Liver

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تقييم النشاط المضاد للتليف لعديدى التسكر المستخلص من مايسيليوم عيش الغراب المحارى (*Pleurotus ostreatus*) فى كبد الجرذان

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Assessment of the Antifibrotic Activity of Polysaccharides Extracted from Oyster Mushroom (*Pleurotus ostreatus*) Mycelium in the Rats Liver

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Abstract

The present study aims at evaluating the hepato-therapeutic activity of polysaccharopeptides (PSP) extracted from *Pleurotus ostreatus* mycelia on thioacetamide (TAA) - induced liver fibrosis in rats. Experimental hepatic fibrosis was induced in rats by intraperitoneal administration of 200 mg TAA/ Kg b.w./ twice weekly for 8 weeks. Two treatment modalities were implemented in this study; Colchicine (reference group) and PSP (therapeutic group). The results of this study revealed that PSP treatment (25 mg/ Kg b.w./ 3 times weekly for 5 weeks) of fibrotic rats restores hepatic matrix metalloproteinase (pro-MMP-2& -9) activities, the concentrations of MDA and GSH, as well as the relative protein expression of Fas receptor back to normal levels. However, more pronounced increases in hepatic TNF- α and NO concentrations were recorded, compared to untreated fibrotic rats. In addition, PSP treatment increased hepatic relative BCL-2 protein expression and produced lower elevations in the hepatic concentrations of TGF- β 1, TIMP-1 and hydroxyproline, as well as hepatic caspase-3 activity, compared to TAA group. The histological examination of the liver tissue had demonstrated that PSP treatment reverses TAA-induced alterations, especially fibrosis (F0), apoptosis (G0) and necrosis (G0), compared to the normal control. In conclusion, experimental liver fibrosis can be treated by PSP, due to its immuno-stimulatory, antioxidant, anti-fibrotic and anti-necrotic activities.

Key words: *Pleurotus ostreatus* mycelium – Polysaccharopeptides – Thioacetamide – Colchicine – TGF- β 1 – Relative caspase-3 activity – Relative Fas receptor protein expression – Relative BCL-2 protein expression – Histological studies - Rats.

List of Abbreviations

A1R	Adenosine 1 receptor
AKt	serine/ threonine-specific protein kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransaminase
Apaf1	Apoptosis-activating factor1
APO-1	Apoptosis receptor
ASGP	Asialoglycoprotein
A-SMase	Acidic sphingomyelinase
AST	Aspartate aminotransaminase
ATP	Adenosine triphosphate
Bak	BCl-2-antagonist/killer
Bax	BCl-2-associated X protein
BCIP	Bromo-4-chloro-3-indolylphosphate
BCI-2	B-cell lymphoma-2
BH3	Bcl-2 homology region
Bid	BH3-interacting domain agonist
Bim	BCl-2-interacting mediator
BMP	Bone morphogenic proteins
BSA	Bovine serum albumin
cAMP	Cyclic adenosine monophosphate
CARD9	Caspase-recruitment domain 9
Caspases	CysteinyI aspartate specific proteases
CAT	Catalase
CBP	cAMP-response element-binding protein
CCl₄	Carbon tetrachloride
CCN2	Cysteine-rich 61/connective tissue growth factor
cGMP	Cyclic guanosine mono phosphate
CINC	Cytokine-induced neutrophil chemo attractant
Col 1A1	Collagen 1A1 gene
CR3	Complement receptor 3
CRD	Cysteune-rich domain
CSF	Colony stimulating factor
CTGF	Connective tissue growth factor

Cyt. C	Cytochrome C
DC	Dendritic cell
DD	Death domains
DDR	Discoidin domain receptor
DED	Death effector domains
DEVD-pNA	Asp-Glu-Val-Asp-p-nitroaniline
DISC	Death inducing signaling complexes
DTNB	5, 5'-dithiobis-2-nitrobenzoic acid
DTT	Dithiothreitol
EC	Endothelial cell
ECE	Endothelin converting enzyme
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ET-1	Endothelin-1
FADD	Fas associated protein with death domain
Fas	F ragment aoptosis stimulating
FasL	Fas ligand
FGF	Fibroblast growth factor
GCS	Gamma-glutamylcysteine synthetase
GPI	Glycosyl phosphatidyl inositol
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Reduced glutathione
H&E	Hematoxylin and Eosin
H₂O₂	Hydrogen peroxide
HBV	Hepatitis C virus
HCV	Hepatitis B virus
HGF	Hepatocyte growth factor
HRP	Horseradish peroxidase
HSC	Hepatic stellate cell
HSP 70	Heat shock protein 70
iC3b	Inactivated complement 3b

ICAM	Intracellular adhesion molecules
IFN-α	Interferon alpha
IGF	Insulin-like growth factor
IKK	Inhibitor of kappa B kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
kDa	Kilo Dalton
LacCer	Lactosylceramide
LAP	Latency-associated peptide
L-TGFβ	Latent-transforming growth factor beta
MAPK	Mitogen-activated protein kinase
MCM	Mushroom complete medium
MCP-1	Monocyte chemotactic peptide-1
MDA	Malondialdehyde
MIP2	Macrophage inflammatory protein 2
MMP	Matrix metalloproteinase
MPT	Mitochondrial Permeability Transition
MT1-MMP	Membrane type 1- Matrix metalloproteinase
MyD88	Myeloid differentiation factor 88
NADP⁺	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NAPQI	N-acetyl- <i>p</i> -benzoquinone imine
NASH	Hepatitis and nonalcoholic steatohepatitis
NBT	Niroblue tetrazolium chloride
NEDD	N-1-naphthylethylenediamine
NEMO/IKKγ	NF- κ B Essential Modulator/
NFAT	Nuclear factor of activated T cell
NF-κB	Nuclear factor kappa B
NK	Natural killer cells
NKT	Natural killer T cells
NO	Nitric oxide
N-SMase	Neural sphingomyelinase
PAF	Platelet activating factor
PAGE	Polyacrylamide gel electrophoresis

PBS	Phosphate-buffered saline
PBST	Phosphate-buffered saline-Tween 20
PDGF	Platelet derived growth factor
PI3K	Pro-survival kinases phosphoinositol 3 kinase
PKC	Protein kinase C
PMSF	Phenylmethanesulfonyl fluoride
pNA	p-nitroaniline
PSP	Polysaccharopeptides
PTP	Permeability transition pore
PUMA	p53-up-regulated modulator of apoptosis
PVDH	Polyvinylidene difluoride
RIP	Receptor-interacting protein
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
R-SMAD	Receptor-associated SMAD
RTK	Receptor tyrosine kinase
SARA	SMAD anchor for receptor activation
SDS	Sodium dodecyl sulphate
SIGNR1	specific ICAM-3-grabbing non-integrin homolog-related1
SMAD	Sma and mothers against decapentaplegic (Mad) homologues
Smurf	SMAD ubiquitin regulatory factors
SOD	Super oxide dismutase
SP	Streptavidin-peroxidase
STAT	Signal transducer activator of transcription 3
SYK	Tyrosine kinase
TAA	Thioacetamide
TBA	Thiobarbituric acid
t-Bid	Truncated Bid
TCA	Trichloro acetic acid
TEMED	N, N, N, N Tetramethyl Ethylene Diamine
TGF-α	Transforming growth factor- alpha
Th	T helper cells

TIMP	Tissue inhibitor matrix metalloproteinase
TLRs	Toll like receptors
TMB	Tetramethyl-benzidine
TNF-R1	Tumor necrosis factor-receptor1
TNFRSF6	Tumor necrosis factor receptor superfamily 6
TNF-α	Tumor necrosis factor-alpha
TRADD	TNF-R1 associated death domain protein
TRAF	TNF-associated factor
TRAIL	TNF- α -related apoptosis-inducing ligand
TRAP2	Type 1 receptor-associated protein 2
TβR	Transforming growth factor receptor
UTP	Uridine triphosphate
VCl₃	Vanadium chloride
VDAC	Voltage-dependent anion channel
VEGF	Vascular endothelial cell growth factor
α-SMA	Alpha-smooth muscle actin