THE HEPATOPROTECTIVE EFFECT OF CASEIN GLYCOMACROPEPTIDE AS COMPARED TO PTEROSTILBENE AND CURCUMIN

By

MOSTAFA AHMED MOHAMED AMEEN LOTFY
B.Sc. Agric. Sci. (Food Science), Fac. Agric., Cairo Univ., 2013

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APPROVAL SHEET

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Title of Thesis: The hepatoprotective effect of casein glycomacropeptide as compared to pterostilbene and curcumin
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ABSTRACT

This study was conducted to study the effect of feeding of casein glycomacropeptide (CGMP) on alleviating different stages of liver fibrosis developed in male adult Wistar albino rats by their injection with CCl_4. Moreover, it was to compare the improvement effect of CGMP with the effect of pterostilbene and curcumin as a proposed effective polyphenols for treating liver fibrosis. Liver functions, liver histopathology and fibrotic parameters were examined. Also, the effect on kidney functions and histology were determined.

Two experiments were carried out to study the following:

a- The comparison between the beneficial effect of feeding CGMP (50 and 100 mg/kg), curcumin (100 mg/kg) and pterostilbene (15 and 40 mg/kg) on liver of rats injected with CCl_4 for 5 weeks.

b- Determination of the beneficial effect of feeding CGMP (150 mg/kg) on rats already developed liver fibrosis by their injection with CCl_4 for 5 weeks before starting feeding. This was also compared with feeding rats with CGMP (150 mg/kg) coincided with CCl_4 injection.

CGMP (100 mg) and pterostilbene (40 mg) significantly improved liver functions with no significant differences between both items. Both significantly reduced liver enzymes ALT, AST and ALP, reduced MDA, LDH and bilirubin and increased the antioxidants CAT, SOD and GPx. Lower concentrations of both additives showed less improvement. Curcumin improved the above functions but with a lower percentage than pterostilbene (40 mg) and CGMP (100 mg). CGMP (150 mg/kg) significantly improved the functions of fibrotic liver and in particular ALT and greatly increased the antioxidants CAT, SOD and GPx than all other ingredients. This means a good reduction of oxidative stress in liver and might be proof that the effect of CGMP would last longer than the polyphenols.

Key words: Liver fibrosis, casein glycomacropeptide, curcumin, pterostilbene, milk protein, antioxidant activity.

DEDICATION

I dedicate this work to whom my heartfelt thanks; to my father, my mother, my dear brother Karim, my sisters as well as my life partner Ayat Ibrahim for all the support they lovely offered me throughout my life, work and post-graduation.

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LIST OF ABBERVIATIONS

°C	Celsius temperature scale
$^1O_2$	Singlet oxygen
ACF	Aberrant crypt foci
AGEs	Advanced glycation end products
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP-1	Activator protein -1
AST	Aspartate aminotransferase
BCE	Bisabolocurcumin ether
BDL	Bile duct ligation
bw	Body weight
Ca^{++}	Calcium
CAT	Catalase
$CCl_3^{\cdot}$	Trichloromethyl
CCl_4	Carbon tetrachloride
CGMP	Casein glycomacropeptide
CMP	Caseinomacropeptide
COX-2	Cyclooxygenase-2
CPT1a	Carnitine palmitoyl transferase
CYP450	Cytochrome P450
DMH	Dimethylhydrazine
DMN	Dimethylnitrosamine
ECM	Extracellular matrix
ERS	Endoplasmic reticulum stress
Gal	Galactose
GalNAc	*N*-acetylgalactosamine
GGT	Gamma-glutamyl transferase
GHP	GMP hydrolysates obtained with papain
GMP	Glycomacropeptide
GOT	Glutamic oxaloacetic transaminase
GP	Glutathione peroxidases
GPT	Glutamic pyruvic transaminase
GPx	Glutathione peroxidase
GRAS	Generally recognized as safe
GSH	Hepatic reduced glutathione
h	Hours

H&E	Hematoxylin and eosin stain
H_2O_2	Hydrogen peroxide
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HFD	High-fat diet
HGF	Hepatocyte growth factor
HMGB1	High mobility group protein B1
HMGCR	3-Hydroxy-3-methylglutaryl-coA reductase
HO-1	Hemeoxygenase-1
HPLC	High performance liquid chromatography
HSC_s	Hepatic stellate cells
HSI	Hepatosomatic index
IFNγ	Interferon gamma
IL-1	Interleukin 1
IL_s	Interleukins
iNOS	Inducible nitric oxide synthase
IRS-1	Insulin receptor substrate 1
KC_s	Kupffer cells
Kg	Kilogram
L.S.D.	Least significant difference
µL	Microlitre
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
$LSEC_s$	Liver sinusoidal endothelial cells
µm	Micrometer
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein 1
MDA	Malondialdehyde
mg	Milligram
mg/dL	Milligrams per decilitre
min	Minutes
mM	Millimole
MMP	Matrix metalloproteinase
mol	Mole; unit of amount of substance
mRNA	Messenger RNA
MUC2	Mucin 2
MUFA	Monounsaturated fatty acids