LOADING OF PRAZIQUANTEL IN NANOCARRIER AS A NEW THERAPEUTIC APPROACH TOWARDS SCHISTOSOMIASIS MANSONI: AN EXPERIMENTAL STUDY

Thesis submitted to Faculty of Medicine, Ain Shams University for Partial Fulfillment of M.D. Degree in Basic Medical Sciences (Parasitology)

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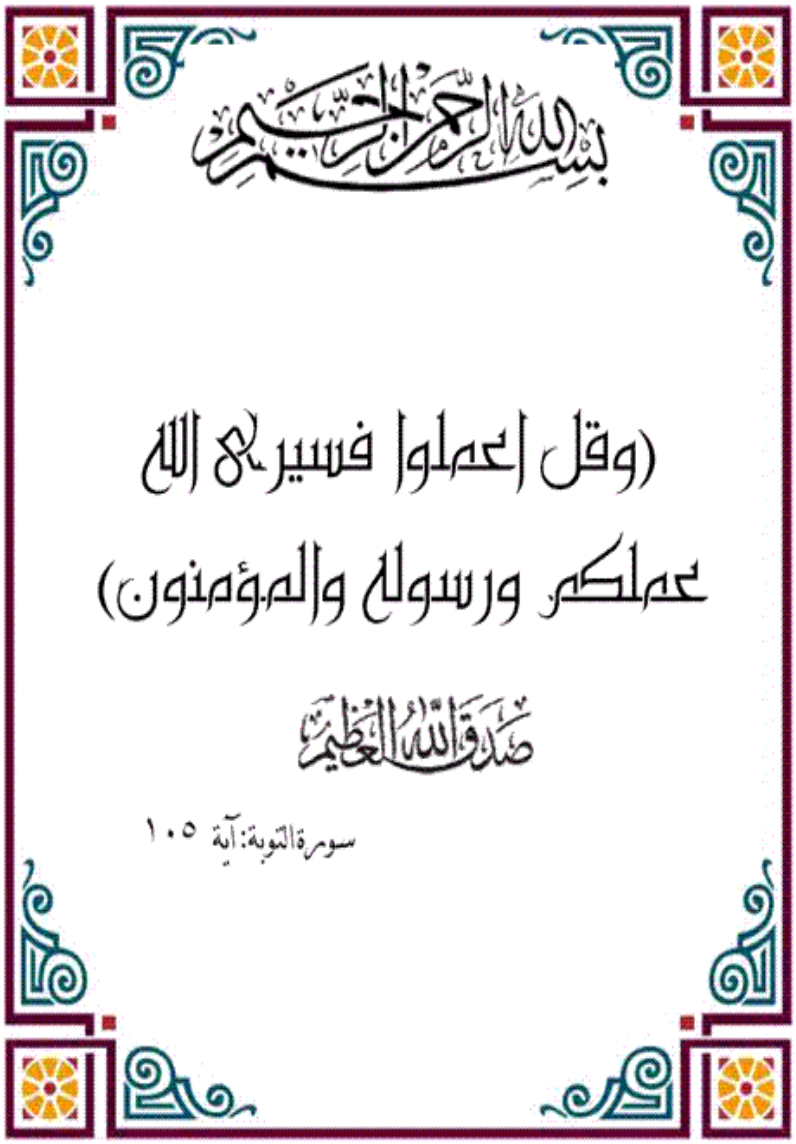
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Marmar Ahmed Hanafy

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Objective:

The use of nanoparticles (NPs) as a drug carrier can improve todays' therapies. The main objective of this work focuses on the preparation of chitosan and mesoporous silica nanoparticles loaded with praziquantel (PZQ-Cs and PZQ-Si, respectively) in order to enhance the therapeutic efficacy and overcome the drawbacks of conventional praziquantel (PZQ) therapy.

Methodology:

After preparation of PZQ-Cs and PZQ-Si, detailed physicochemical characterization was carried out. Mice were experimentally infected with *S. mansoni* and treated 6 weeks post-infection with PZQ in different doses either via oral or intraperitoneal (IP) routes. PZQ in the same doses orally administered to *S.mansoni* infected mice was used as a drug control and infected and non-infected non-treated mice served as positive and negative controls, respectively.

Results:

PZQ-Si exhibited the best physicochemical attributes in terms of small uniform size (105 nm), spherical shape

and PZQ entrapment efficiency (83%). A maximum antischistosomal effect was achieved using orally administered PZQ-Si as reflected by total worm burden, tissue egg count, oogram pattern and hepatic granuloma count and diameter. The biomarkers related to liver oxidative stress status and immunomodulatory effect (serum TNF-α and IL-10) were significantly improved. Data obtained implied that IP route was less efficacious for the delivery of PZQ-Si. Encapsulation of PZQ permits the reduction of the used therapeutic dose of PZQ. Only improvement of infection induced inflammatory and hepatic oxidative stress reactions were achieved with PZQ-Cs. Hepatic DNA fragmentation, measured by comet assay, was significantly improved in infected mice treated with a maximum dose of PZQ loaded in prepared nanoparticles as compared to positive or PZQ control groups.

Conclusion:

The results indicate that mesoporous silica NPs are promising safe nanocarriers for PZQ potentiating its antischistosomal effect, with antioxidant, immunomodulatory and anti-inflammatory action in animal model infected with *S. mansoni*. From a practical standpoint, PZQ-Si using a lower dose of PZQ could be suggested for effective PZQ antischistosomal mass chemotherapy.

Keywords: Chitosan nanoparticles, Mesoporous silica nanoparticles, *Schistosoma mansoni*, liver, histopathology, oxidative stress, genotoxicity.

List of Abbreviations

Abbreviation		Full name
A_{blank}	**:**	Absorbance of blank
A_{sample}	**:**	Absorbance of the sample
$A_{standard}$	**:**	Absorbance of the standard
AgNPs	**:**	Silver NPs
ANOVA	**:**	Analysis of variance
A.U.	**:**	Arbitary unit
CCA	**:**	Circulating anodic antigen
CD4	**:**	Cluster of differentiation
C_{free}	**:**	Free drug concentration
C_i	**:**	Initial concentration
CsNPs	**:**	Chitosan nanoparticles
Cs-TPP	**:**	Chitosan- sodium tri-poly-phosphate
DLS	**:**	Dynamic Light Scattering
DMSO	**:**	Dimethyl sulfoxide
DNA	**:**	Deoxy ribonucleic acid
DTNB	**:**	5, 5` di-thio bis- 2-nitrobenzoic acid
EDTA	**:**	Disodium ethylene-diamine-tetra-acetic acid
EE	**:**	Encapsulation efficiency
ELISA	**:**	Enzyme linked immunosorbent assay
EPR	**:**	Enhanced permeability and retention
FDA	**:**	Food and Drug Administration
gm	**:**	Gram

GTPase	**:**	Guanosine triphosphatase
GSH	**:**	Reduced glutathione
HBV	**:**	Hepatitis B virus
HCV	**:**	Hepatitis C virus
HRP	**:**	Horseradish Peroxidase
Hx and E	**:**	Hematoxylin and Eosin
IFN- γ	**:**	Interferon-gamma
IgE	**:**	Immunoglobulin E
IgM	**:**	Immunoglobulin M
IgG	**:**	Immunoglobulin G
IHA	**:**	Indirect haemagglutination
IL-	**:**	Interleukin
ILARC	**:**	International Labor Rights Case Law
IP	**:**	Intraperitoneal
Kg	**:**	Kilogram
LSD	**:**	Least significant difference
M	**:**	Mole
MDA	**:**	Malondialdehyde
MSNPs	**:**	Mesoporous silica nanoparticles
min	**:**	Minute
mg	**:**	Milligram
ml	**:**	Milliliter
mV	**:**	Millivolt
mM	**:**	Millimole
MSP_{10}	**:**	Merozoite surface protein 10

NaCl	**:**	Sodium Chloride
NaOH	**:**	Sodium Hydroxide
NEDA	**:**	1-naphthyl Ethylene-diamine
nm	**:**	Nanometer
nmol	**:**	Nanomole
NO	**:**	Nitric oxide
NODCAR	**:**	National Organization for Drug Control and Research
NPs	**:**	Nanoparticles
NSCP	**:**	National Schistosomiasis Control Program
PBS	**:**	Phosphate buffered saline
PCR	**:**	Polymerase chain reaction
PEG	**:**	Polyethylene glycol
pg	**:**	Picogram
PLGA	**:**	Poly d, l-lactic-coglycolic acid
PMMA	**:**	Poly-methyl-methacrylate
P-value	**:**	Probability
PZQ	**:**	Praziquantel
PZQ-Cs	**:**	Praziquantel-loaded chitosan nanoparticles
PZQ-NPs	**:**	Praziquantel-loaded nanoparticles
PZQ-Si	**:**	Praziquantel-loaded mesoporous silica nanoparticles
RBCs	**:**	Red blood cells
RNS	**:**	Reactive nitrogen species

ROS	**:**	Reactive oxygen species
rpm	**:**	Round per minute
S.	**:**	*Schistosoma*
SCGE	**:**	Single cell gel electrophoresis
SD	**:**	Standard deviation
SEA	**:**	Soluble egg antigen
SH	**:**	Thiol group
SLN	**:**	Solid Lipid Nanoparticles
spp.	**:**	Species
SWA	**:**	Soluble worm antigen
SWAP	**:**	Soluble worm antigenic preparation
TBRI	**:**	Theodor Bilharz Research Institute
TEM	**:**	Transmission electron microscopy
Th1	**:**	T-helper lymphocyte type 1
Th2	**:**	T-helper lymphocyte type 2
US EPA	**:**	United States Environmental Protection Agency
V: V	**:**	Volume: volume
WBCs	**:**	White blood cells
WHO	**:**	World Health Organization
ZP	**:**	Zeta Potential
18s rRNA	**:**	18s ribosomal ribonucleic acid
µm	**:**	Micrometer
µmol	**:**	Micromole

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