Protective Effects of Certain Natural Product(s) on Experimentally-induced Benign Prostatic Hyperplasia

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Oxidative stress and suppression of apoptosis play a central role in initiation and progression of benign prostatic hyperplasia (BPH). Chrysin, a natural flavone, possesses diverse biological activities, such as antioxidant, anti-inflammatory and anti-cancer activities. The aim of current study was to explore the protective effect of chrysin against testosterone-induced BPH in rats as well as underlying mechanisms. An initial dose-response study showed that when chrysin was administered at doses of (25, 50 and 100 mg/kg p.o.), 50 mg/kg of the drug was the most effective dose in preventing the increase in prostate weight, prostate weight/body weight ratio and total prostate-specific antigen level. Moreover, this dose of chrysin prevented testosterone-induced histopathological changes. Testosterone at dose of 3mg/kg subcutaneously significantly reduced glutathione level, superoxide dismutase and catalase activities and significantly increased lipid peroxidation. Caspase-3 enzyme level, Bax/Bcl-2 ratio and mRNA expression of the genes encoding for proapoptotic p53 protein & cell cycle regulator p21 protein were significantly decreased by testosterone while protein expression of proliferating cell nuclear antigen (PCNA) was increased. On the other hand, chrysin alleviated testosterone-induced oxidative stress and restored caspase-3 level, Bax/Bcl-2 ratio and mRNA expression of p53 & p21 to normal. Furthermore, chrysin protected against testosterone-mediated elevation of both nuclear factor kappa B (NF-kB) protein expression and mRNA expression of (IGF-1) & insulin-like growth factor 1 receptor (IGF-1R). The present study suggests the protective role of chrysin against testosterone-induced BPH. This could

be explained - at least partly - by virtue of its proapoptotic, antiproliferative and antioxidant effects.

Keywords: Chrysin; Benign prostatic hyperplasia; Oxidative stress; Apoptosis

5-ARIs	5-Alpha-reductase Inhibitors
AAP	4-aminophenazone
Apaf-1	Apoptotic protease-activating factor-1
AR	Androgen Receptor
Bcl-2	B-cell lymphoma/leukemia-2
BLSA	Krimpen and Baltimore Longitudinal Study of Aging
BMI	Body Mass Index
BOO	Bladder Outlet Obstruction
BPE	Benign Prostate Enlargement
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostate Obstruction
BSA	Bovine Serum Albumin
cAMP	Cyclic Adenosine Monophosphates
CASP3	Caspase-3
CAT	Catalase
CCl_4	Carbon tetrachloride
c-FLIP	Cellular FLICE (FADD-like IL-1β-converting enzyme)-Inhibitory Protein
cGMP	Cyclic Guanosine Monophosphate
COX-2	Cyclo-oxygenase -2
Ct	Cycle Threshold
CZ	Central Zone
DHBS	3,5-Dichloro-2-hydroxybenzene sulfonic acid
DHT	Dihydrotestosterone
DMSO	Dimethyl Sulfoxide
DNTB	5,5’ dithiobis (2-nitrobenzoic acid)
dNTP	Deoxynucleoside Triphosphate
DRE	Digital Rectal Examination
DSS	Dextrane Sodium Sulfate
E2	Estradiol
EGF	Epidermal Growth Factor
ERs	Estrogen Receptors
FGF	Fibroblast Growth Factor
f-PSA	Free PSA
GAGs	Glycosaminoglycans
GR	Glutathione Reductase

GSH	Reduced Glutathione
GSH-P_X	Glutathione Peroxidase
H_2O_2	Hydrogen peroxide
HMBA	2-hydroxy-4-methoxy benzoic acid
IAP	Inhibitors of Apoptosis Protein
IFN γ	Interferon gamma
IGFs	Insulin-like Growth Factors
IGFBPs	IGF-Binding Proteins
IGF-Rs	IGF tyrosine kinase Receptors
IκB	Inhibitor of kappa B
IL	Interleukin
iNOS	Inducible NO Synthase
IPSS	International Prostate Symptom Score
K_2HPO_4	Dipotassium hydrogen phosphate
KGF	Keratinocyte Growth Factor
KH_2PO_4	Anhydrous potassium dihydrogen phosphate
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
LPS	Lipopolysaccharide
LUTS	Lower Urinary Tract Symptoms
MDA	Malondialdeyde
MMP	Matrix Metalloproteinases
NF-κB	Nuclear Factor kappa B
NO	Nitric Oxide
OD	Optical Density
P.O.	*Per Os*
PCNA	Proliferating Cell Nuclear Antigen
PDE	Phosphodiesterase
PGE	Prostaglandin E
PMS	Phenazine Methosulphate
PSA	Prostate Specific Antigen
PVR	Postvoid Residual
PXR	Pregnane x Receptor
PZ	Peripheral Zone
ROS	Reactive Oxygen Species

RT-PCR	Real Time–Polymerase Chain Reaction
S.C.	Subcutaneously
SERM	Selective Estrogen Receptor Modulators
SOD	Superoxide Dismutase
SULT	Sulfotransferase
TBA	Thiobarbituric acid
TBARS	Thiobarbituric Acid Reactive Substances
TBS	Tris Buffered Saline
TCA	Trichloroacetic Acid
TGF	Transforming Growth Factor
TNF	Tumor Necrosis Factor
TRAIL	TNF-Related Apoptosis Inducing Ligand
TUMT	Transurethral Microwave Thermotherapy
TUNA	Transurethral Needle Ablation
TURP	Transurethral Resection of the Prostate
TZ	Transition Zone
UTI	Urinary Tract Infection
VEGF	Vascular Endothelial Growth Factor
α1-AR	Alpha-1-Adrenergic Receptor
β-ME	Beta-Mercaptoethanol

INTRODUCTION