

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

***Thesis presented by***

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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- $\kappa$ B) 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

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



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

## *List of Abbreviations*

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

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# *INTRODUCTION*