

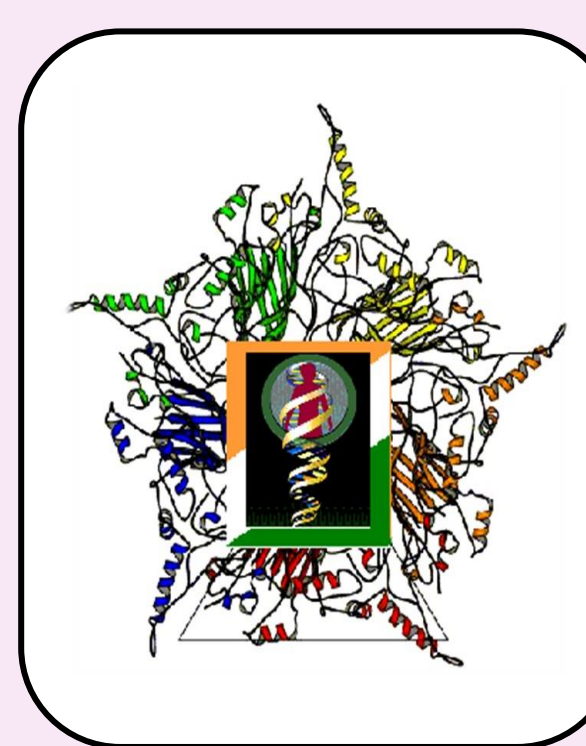
A STUDY ON THE CHEMO PREVENTIVE AND ANTICANCER POTENTIAL OF DIHYDROXY GYMNEMIC TRIACETATE ISOLATED FROM *GYMNEMA SYLVESTRE* WITH RESPECT TO PROSTATE CANCER

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INTRODUCTION

Prostate cancer is one of commonly diagnosed malignancy among men. Chemotherapy is used in hormone-refractory and metastatic prostate cancer, but survival benefits have been modest. Drugs from plant source have gained a much interest in the cancer due to their multi-functional, therapeutic properties and for overall safety. DGT is a novel triterpenoid saponin isolated from *G. sylvestre* and proved for its anti-diabetic activity.

HYPOTHESIS

DGT has an anticancer effect and chemopreventive activity against prostate cancer. DGT may exerts its action by the activation of apoptosis in prostate cancer cells.

OBJECTIVES

- To evaluate the **antagonist effect** and drug like properties of DGT, against Bcl-2 and Bcl-XL protein through molecular docking and molecular dynamic studies.
- To evaluate the **cytotoxic potential** and mode of action of DGT in PC-3 cells through cell proliferation assay, staining studies and flow cytometric along with **protein expression studies** of Bcl-2, Bcl-XL, Mcl-1, Bad, Bax, Caspase 9 and Caspase 3.
- To assess **chemopreventive effect** of DGT in N-Methyl-N-nitrosourea (MNU) + Testosterone (T)-induced Sprague-Dawley male rats.

MATERIALS & METHODS

in-silico

- Docking- Glide scrodinger software
- Molecular simulation- Desmond of scrodinger software
- Electronic scetural properties- Jaguar of scrodinger software
- Biological activity prediction of DGT- pass server
- ADME properties of DGT- Qik prop of scrodinger software

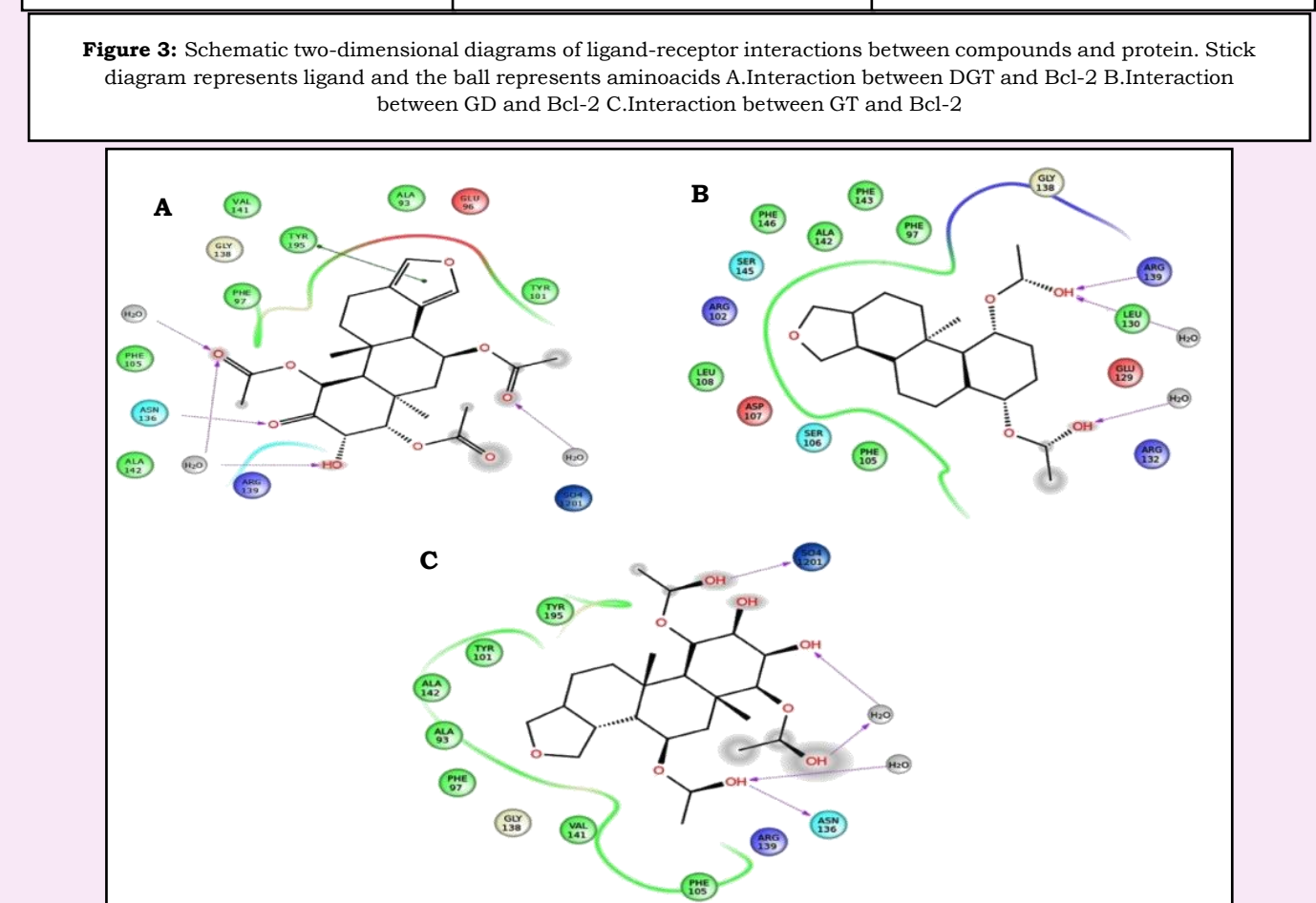
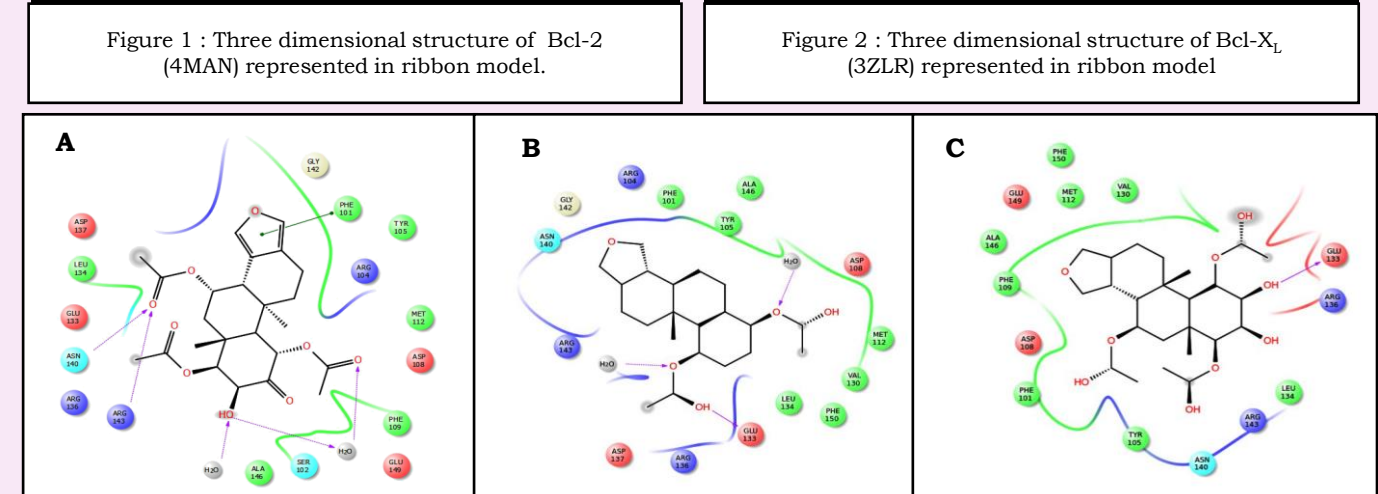
in-vitro

- MTT assay
- Flow cytometry analysis
- Western blotting- Bcl-2, Bcl-XL, Bax, Bad, Caspase 9, Caspase 3- PC-3 cell lines.

in-vivo

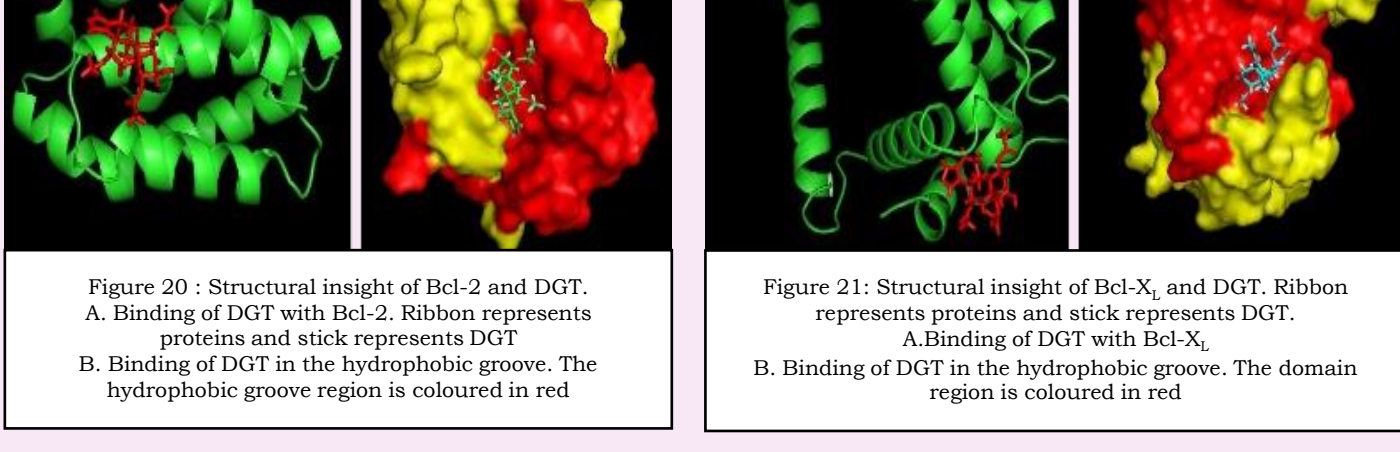
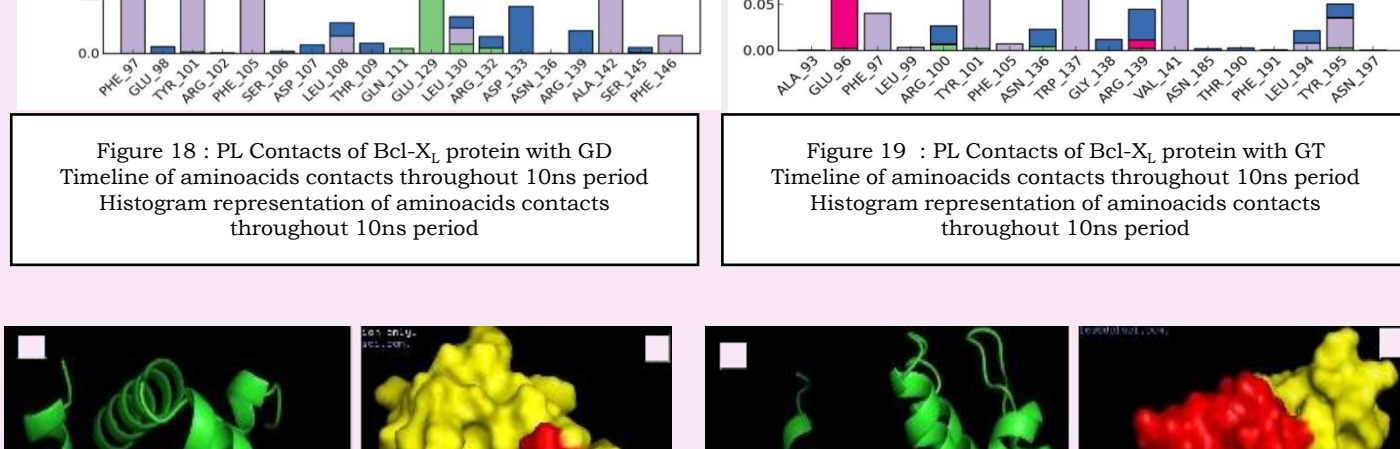
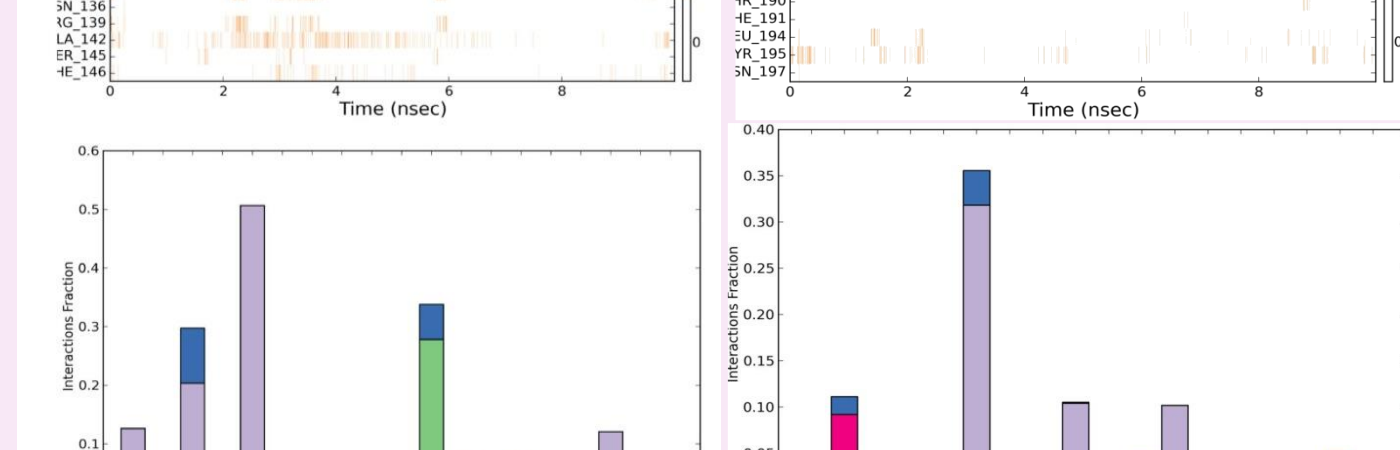
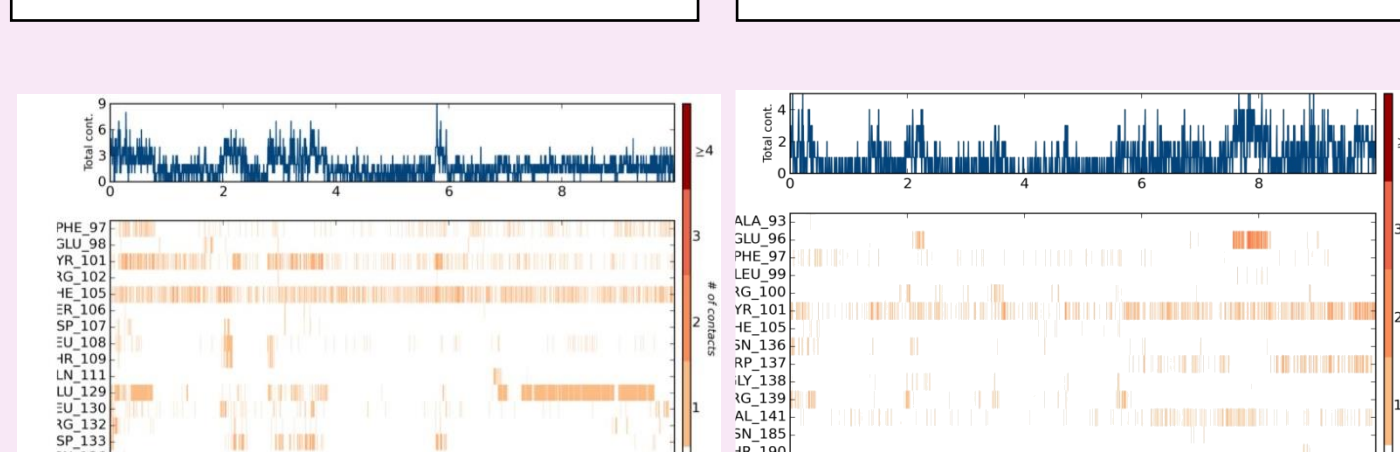
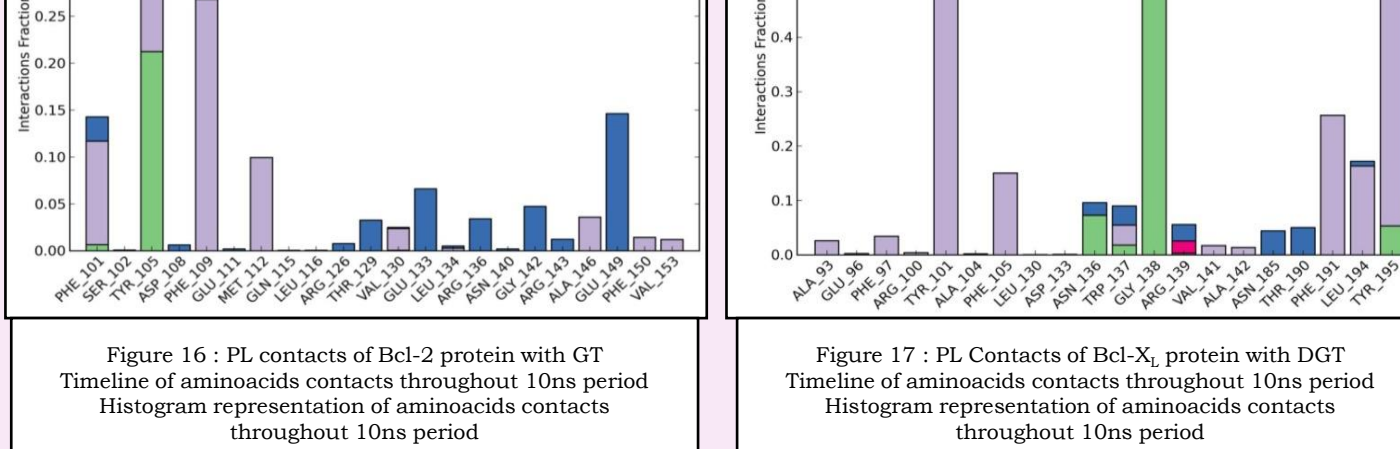
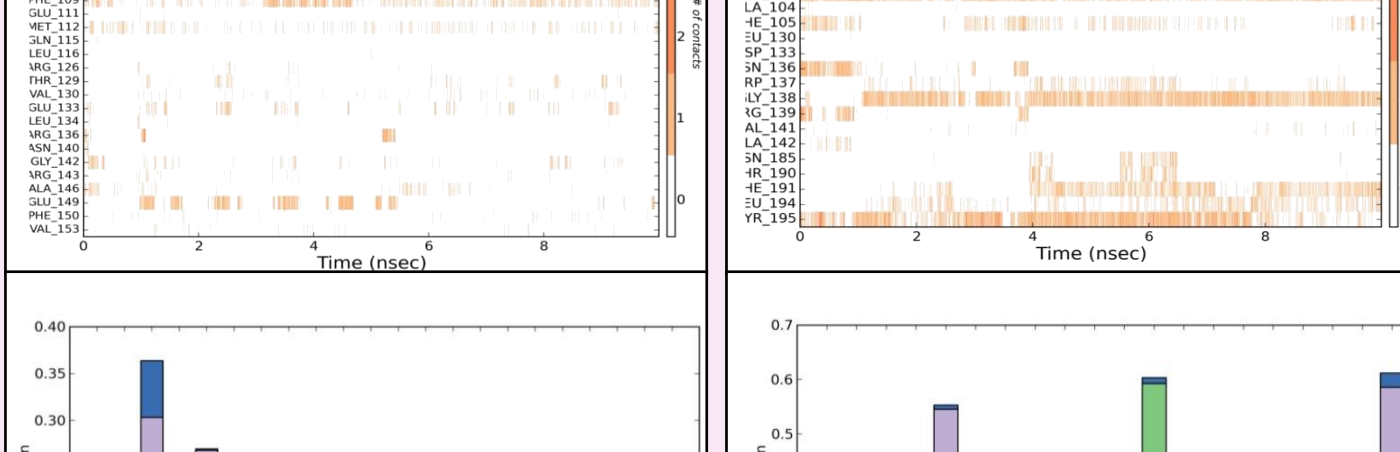
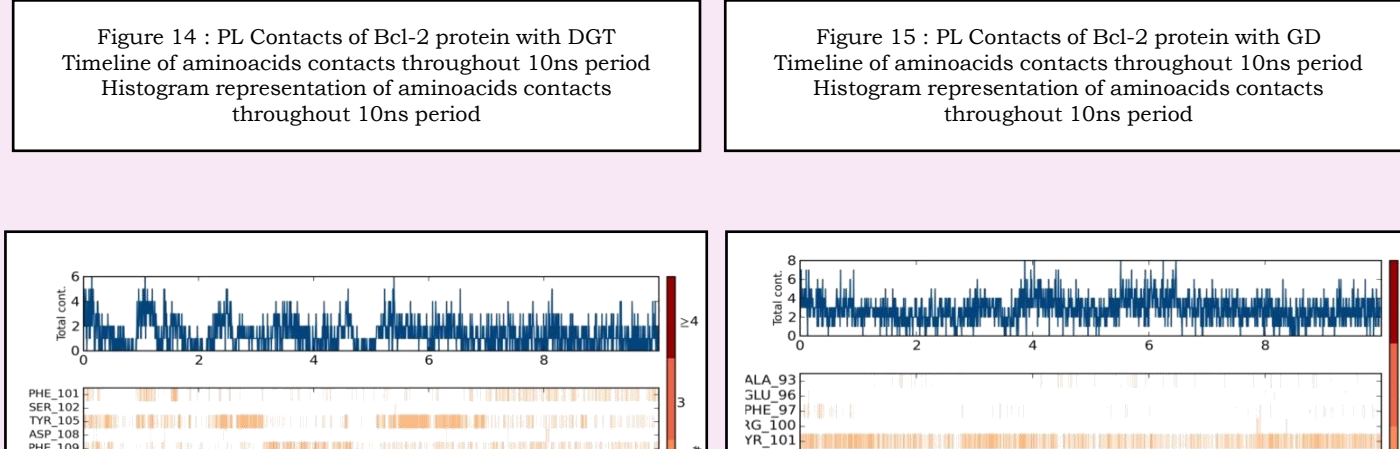
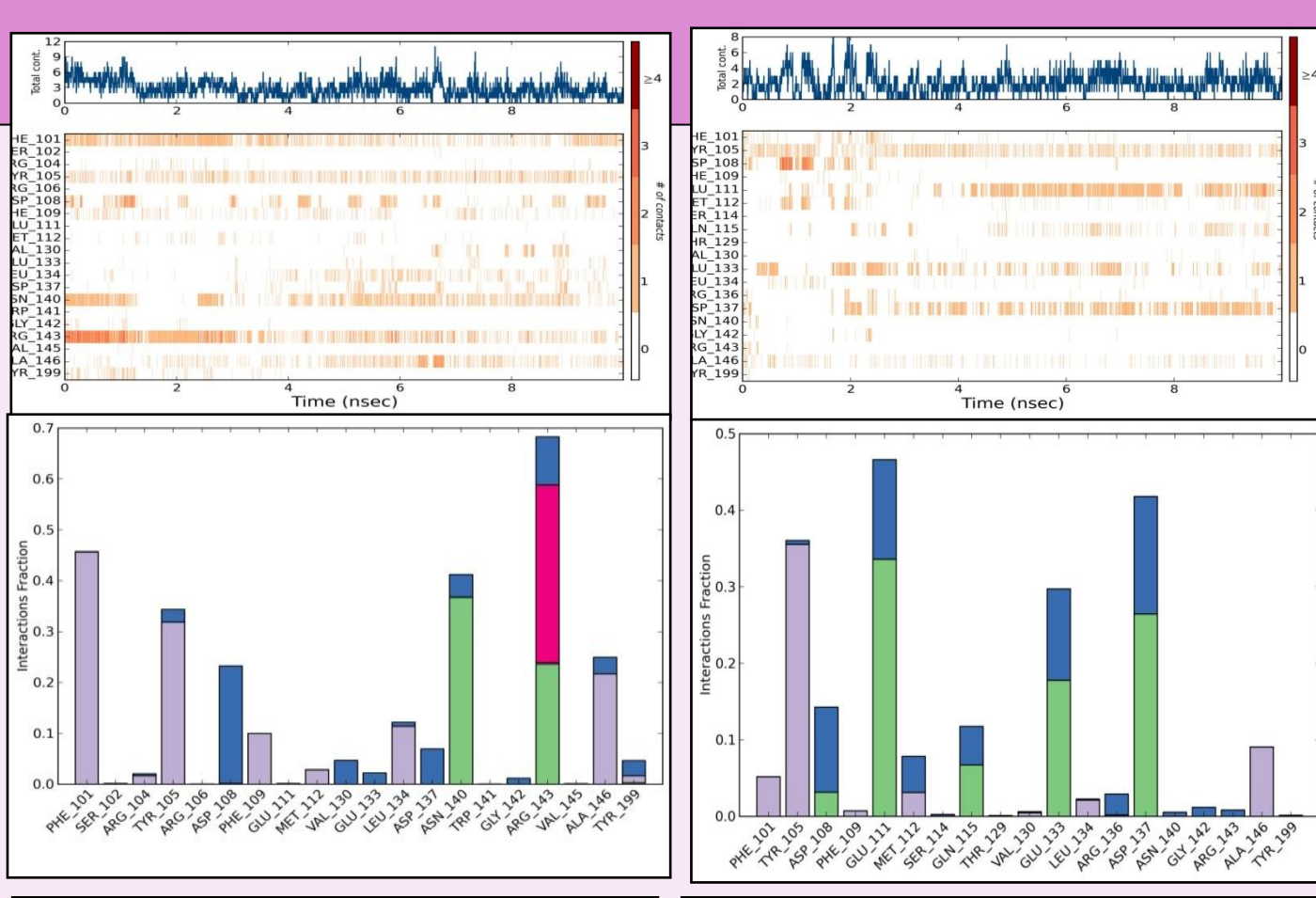
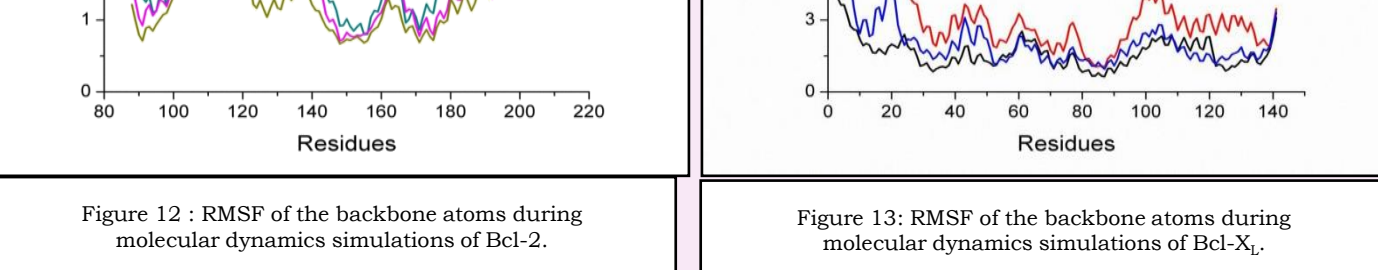
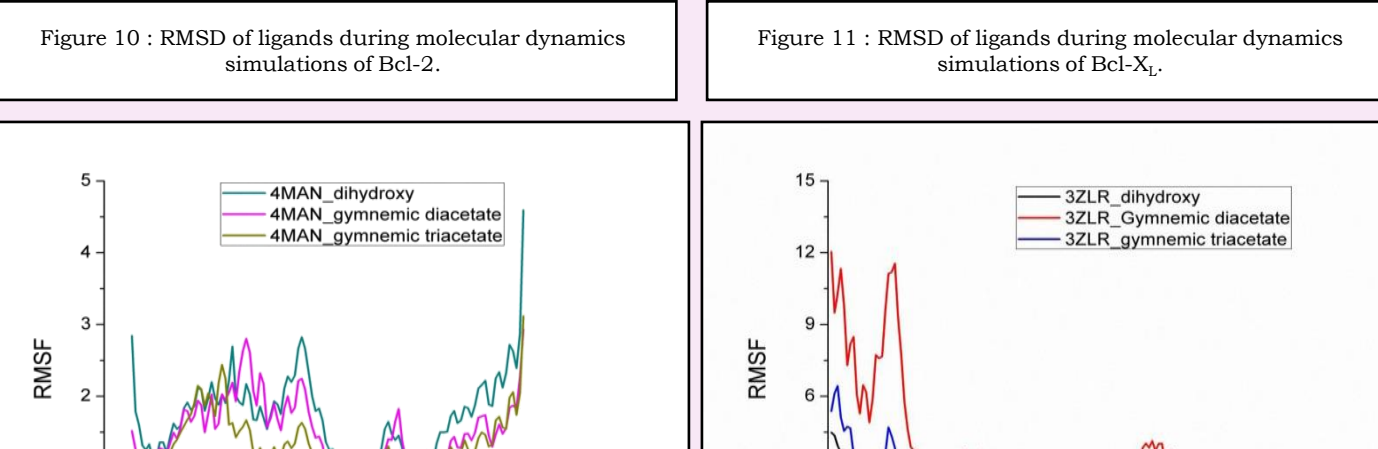
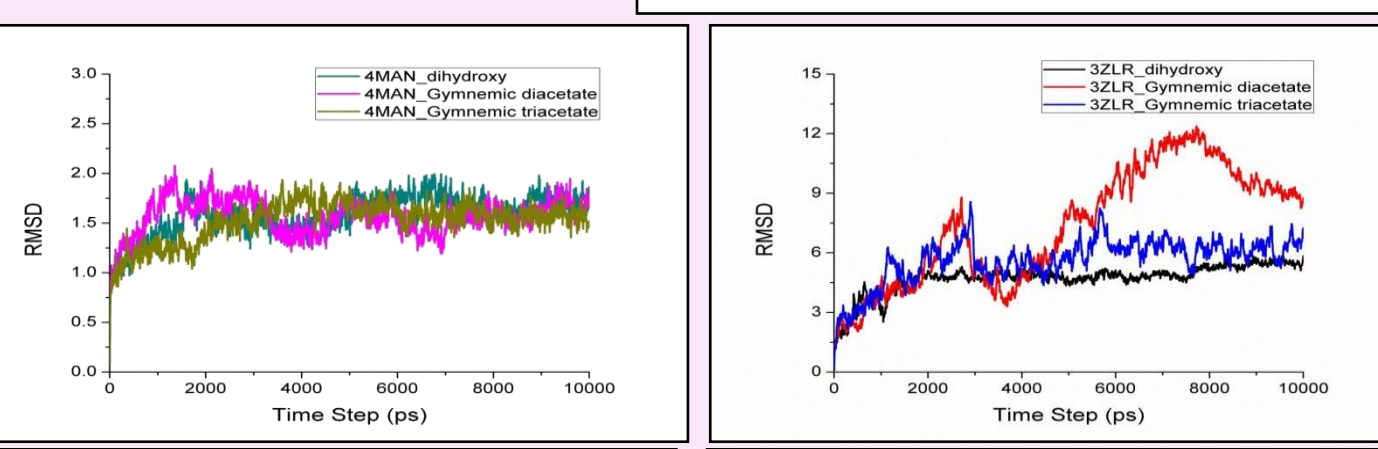
- Body and prostate weight measurement of both normal and compound treated animals
- Morphological analysis of prostate with light microscopy studies
- Western blotting analysis- Bcl-2, Bcl-XL, Bax, Bad, Caspase 9, Caspase 3
- Antioxidant studies of prostate gland.

RESULTS

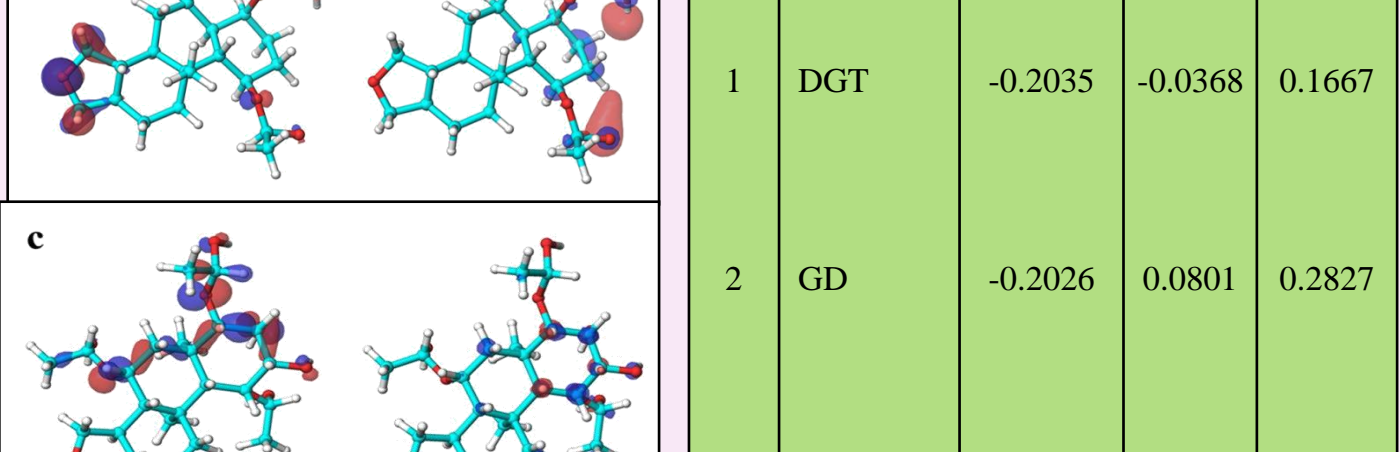


Protein	Ligand	Docking score	Glide score	Glide energy	IPD score
1 Bcl-XL	DGT	-6.808	-6.188	-39.187	
	GD	-5.934	-5.934	-38.399	
	GT	-5.967	-5.967	-32.749	
2 Bcl-2	DGT	-5.964	-5.964	-35.892	
	GD	-5.052	-5.052	-33.365	
	GT	-4.933	-4.933	-37.270	

Compound	Pa	Pi	Activity
DGT	0.635	0.011	Prostate cancer treatment



S.No	Compound	HOMO (eV)	LUMO (eV)	HLG (eV)
1	DGT	-0.2035	-0.0368	0.1667
2	GD	-0.2026	0.0801	0.2827
3	GT	-0.2085	0.0790	0.2875



S. No	Compound	QLogS	Human Oral absorption	QLogK _{oa}	QLogP	QPPCaco	Metab	Rule of five
1	DGT	-1.606	3	-1.22	0.145	397.763		0

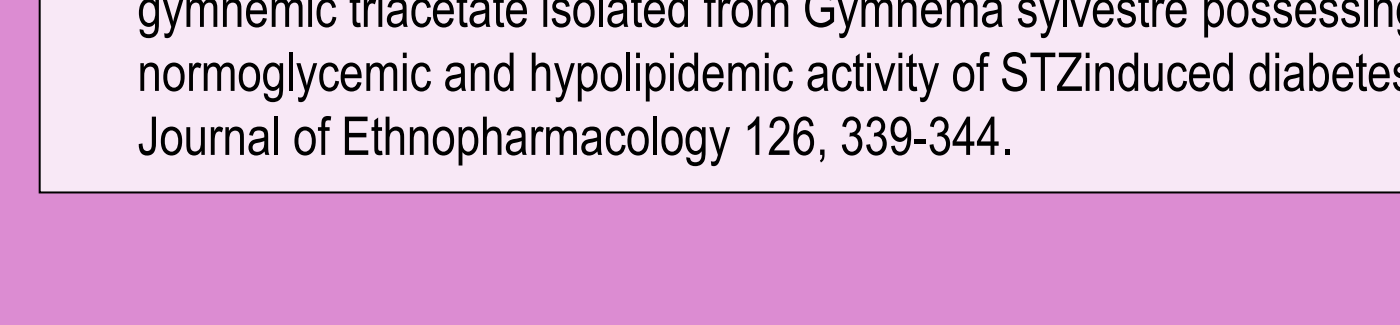
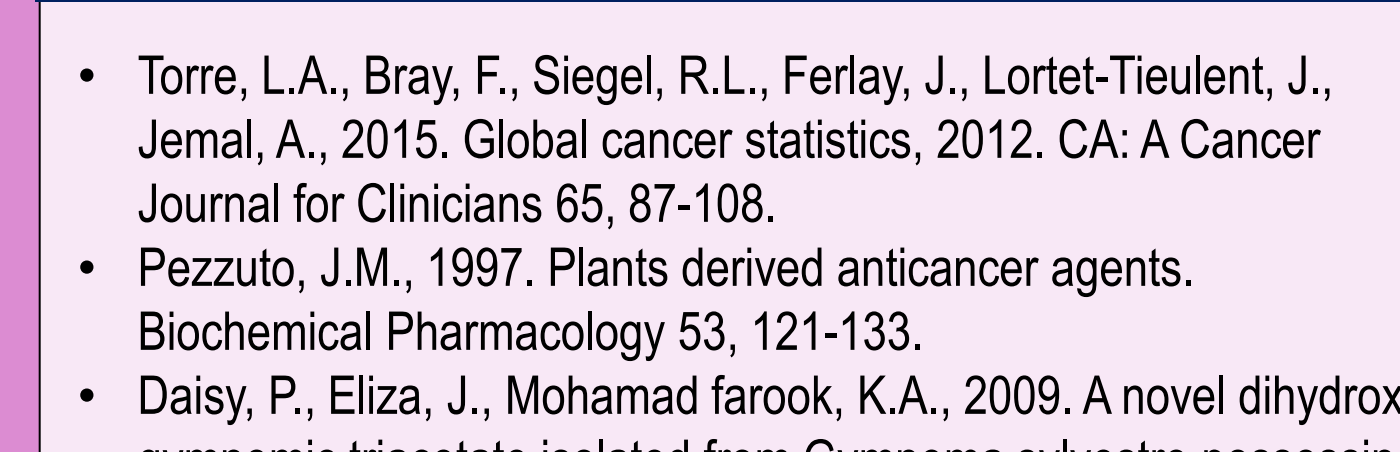
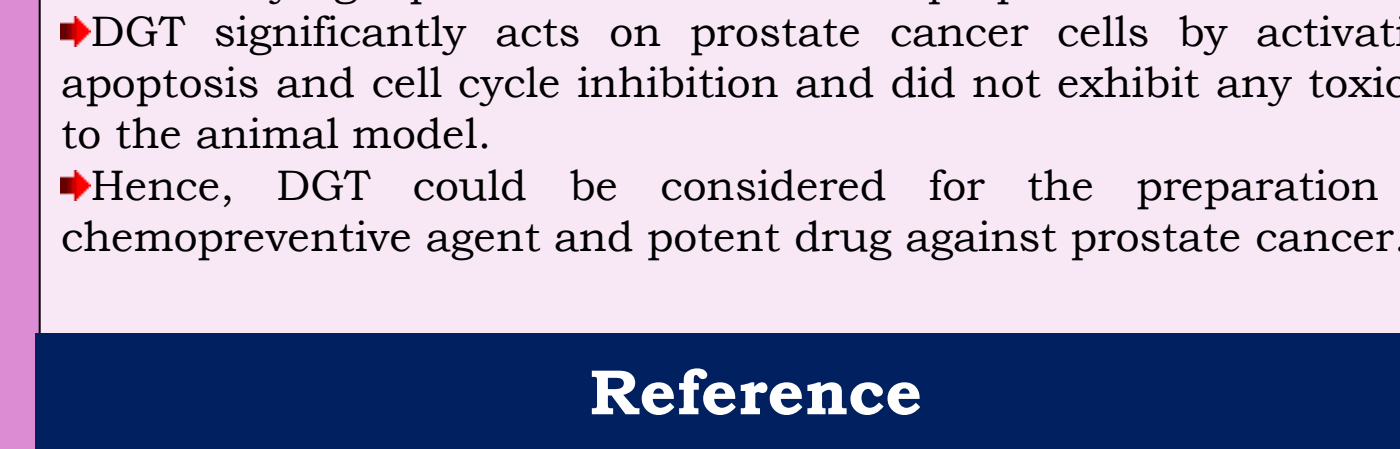
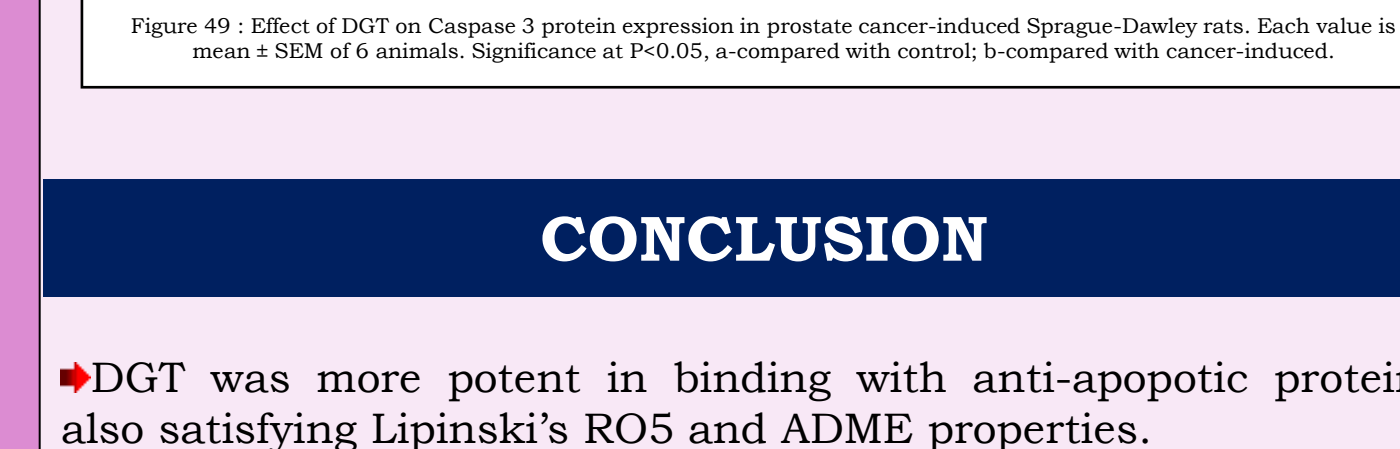
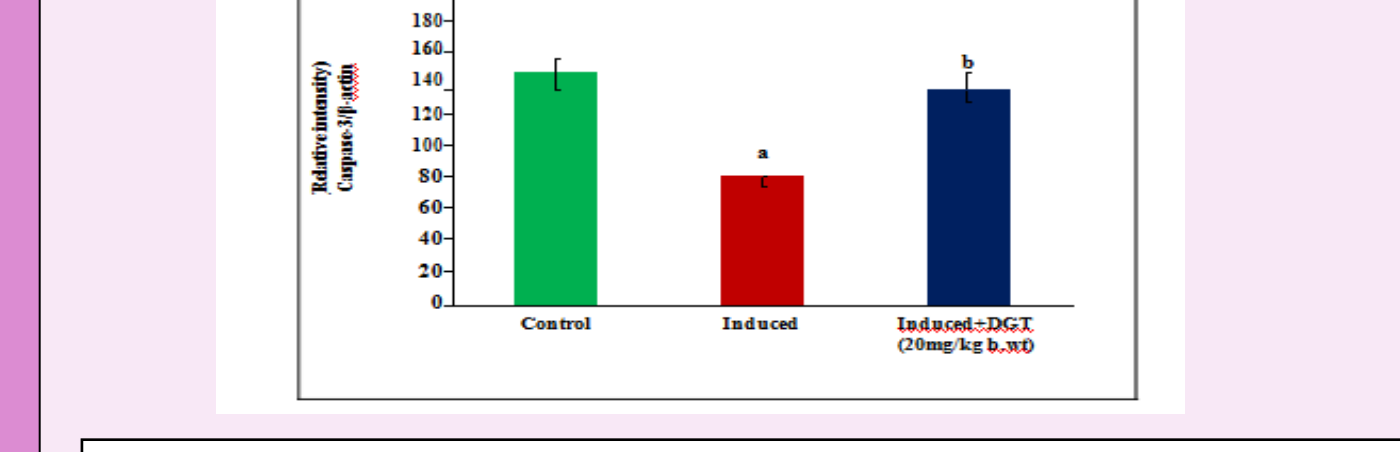
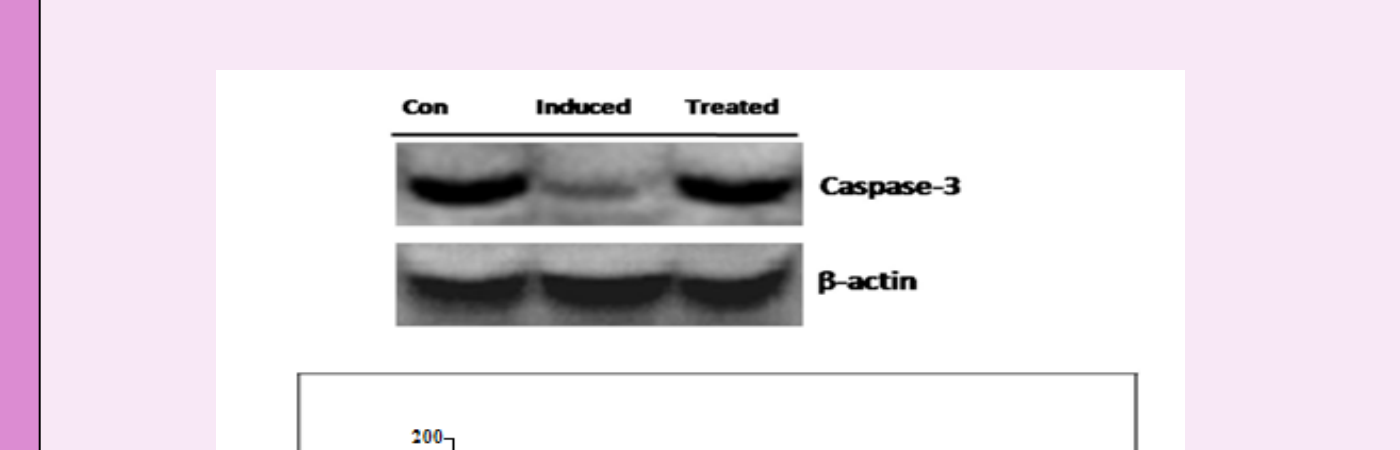
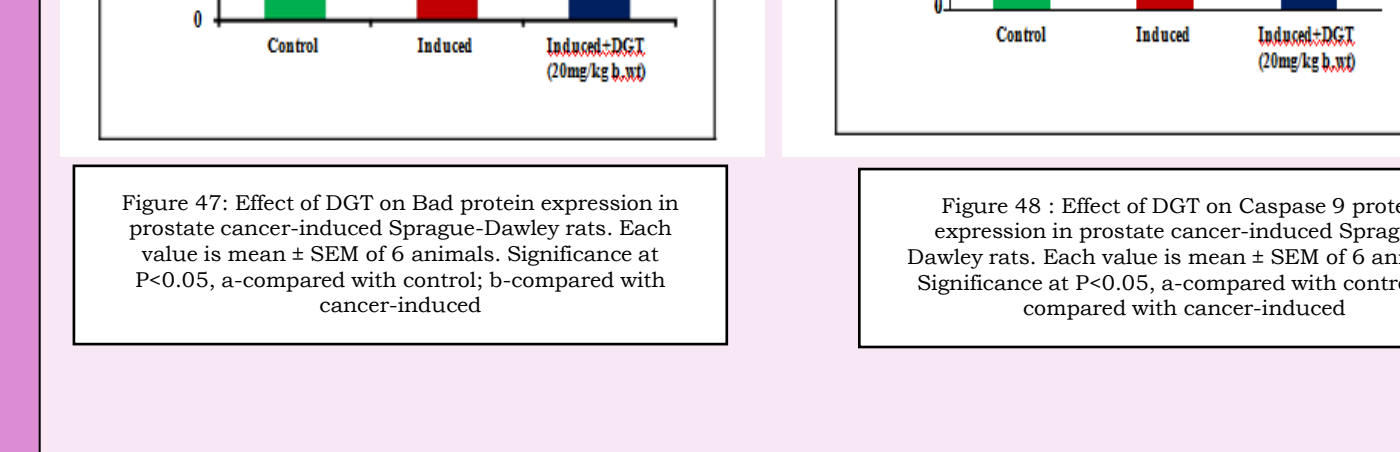
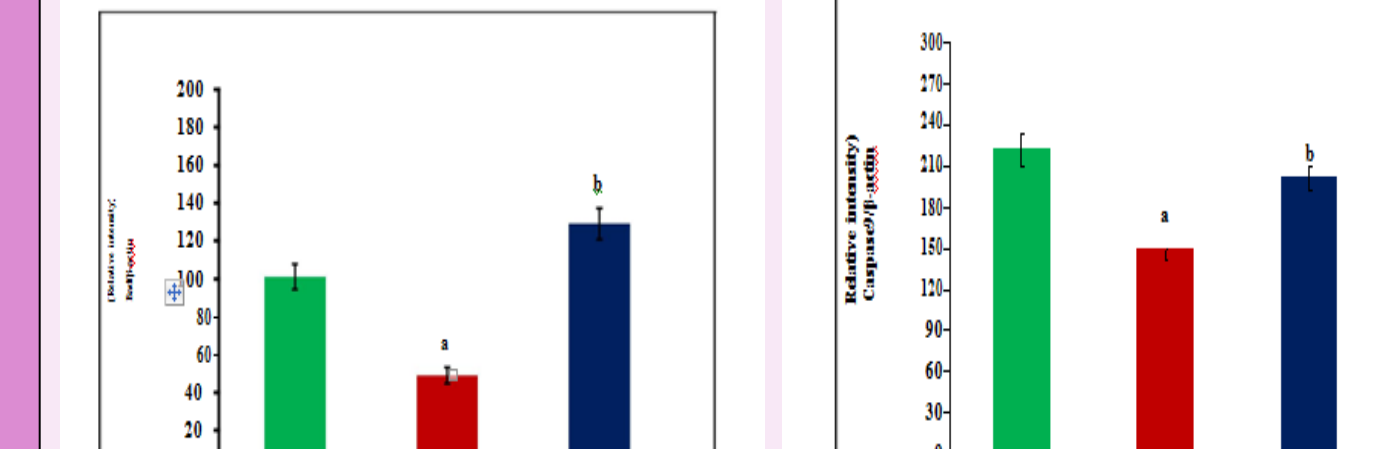
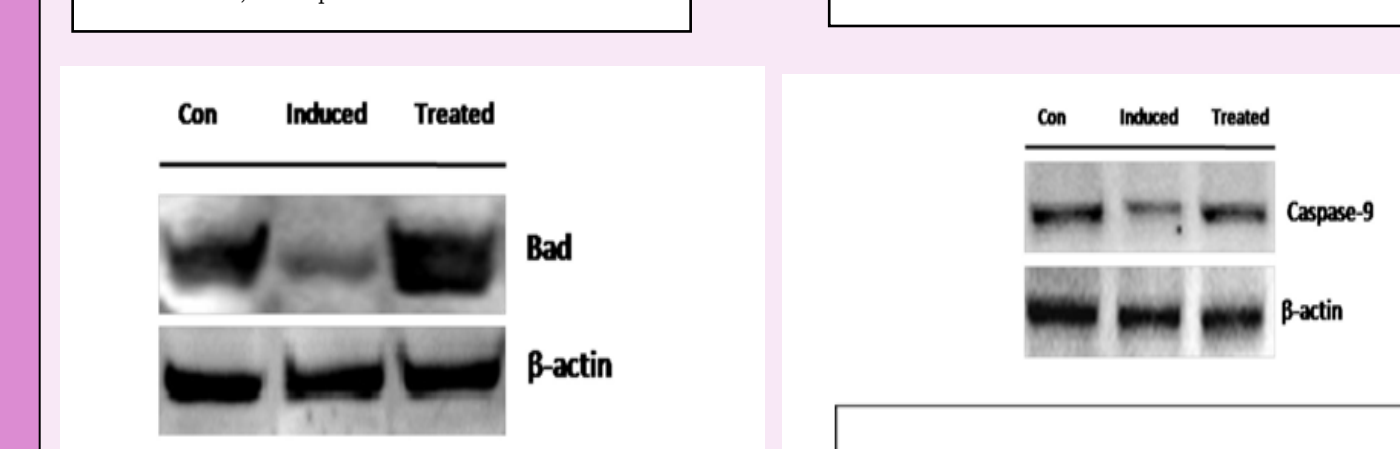
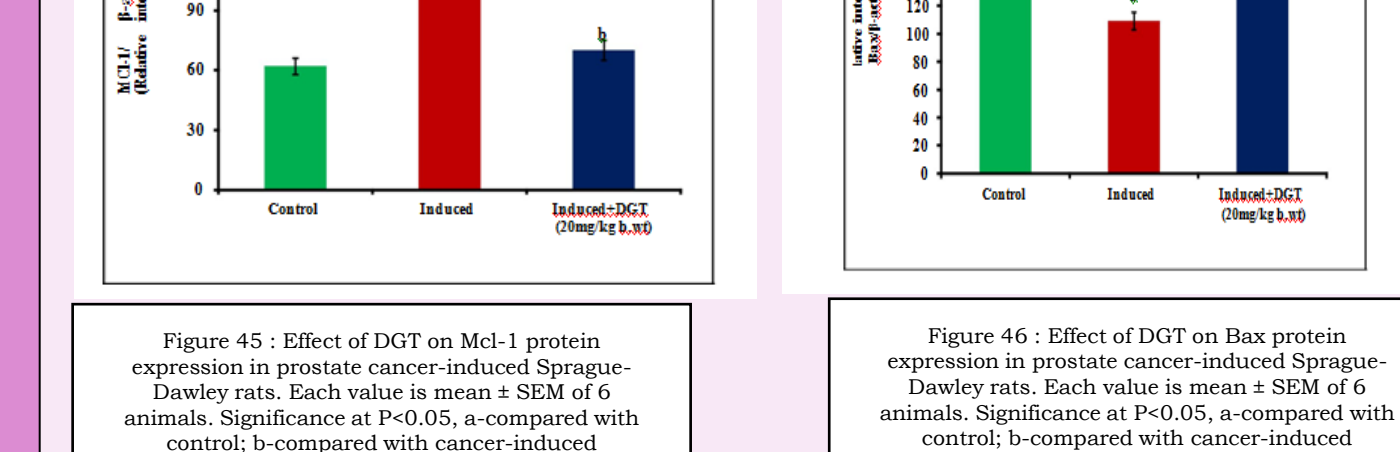
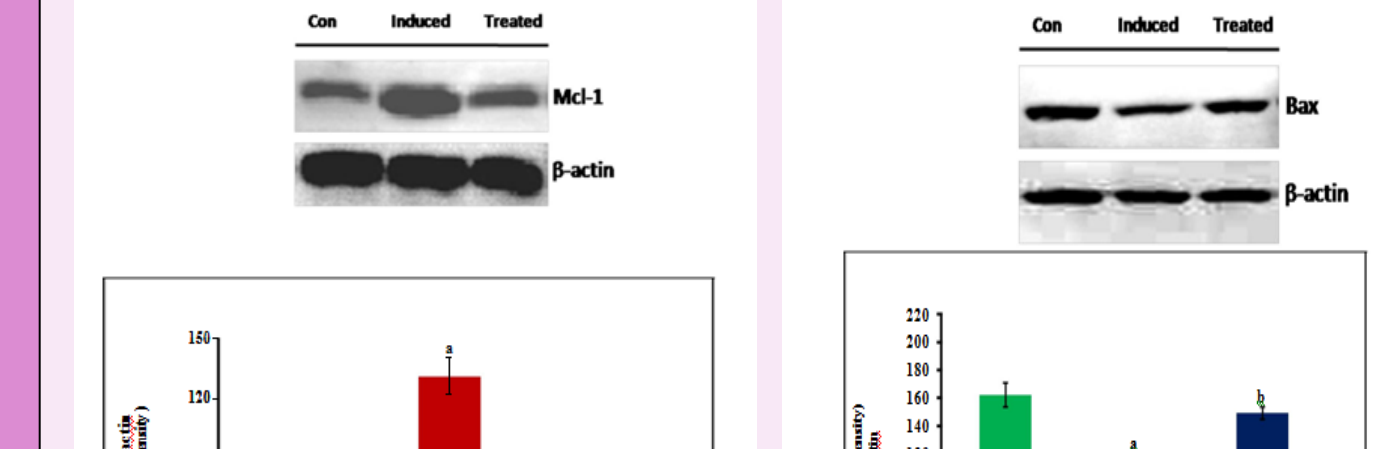
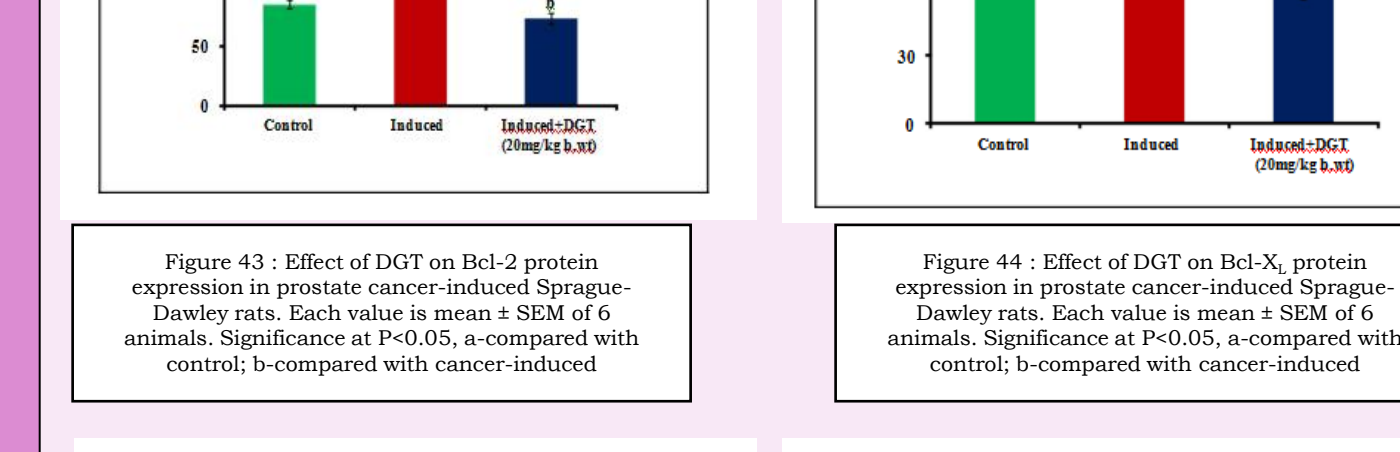
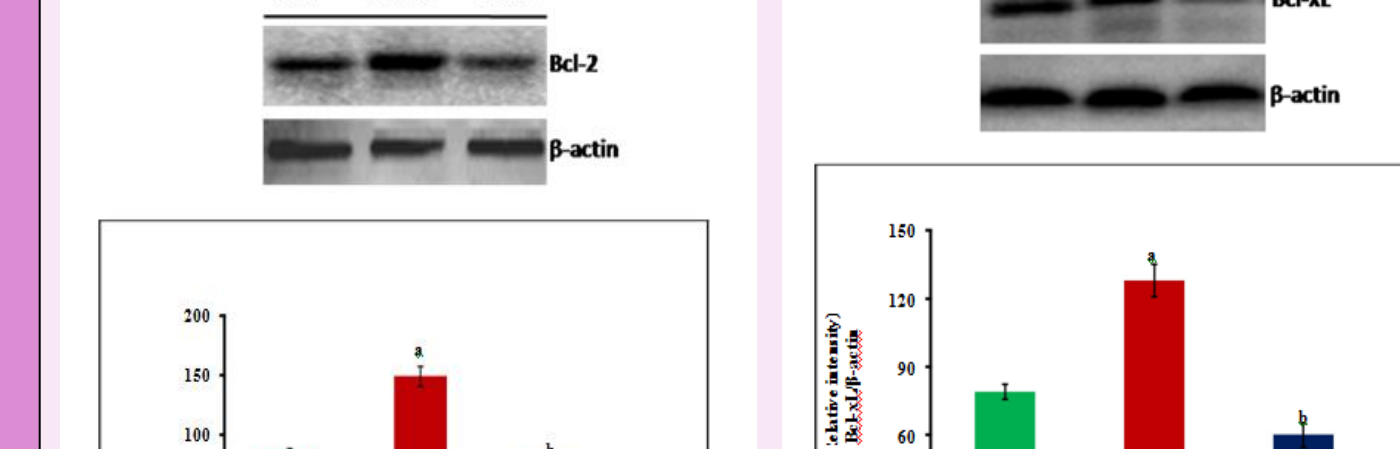
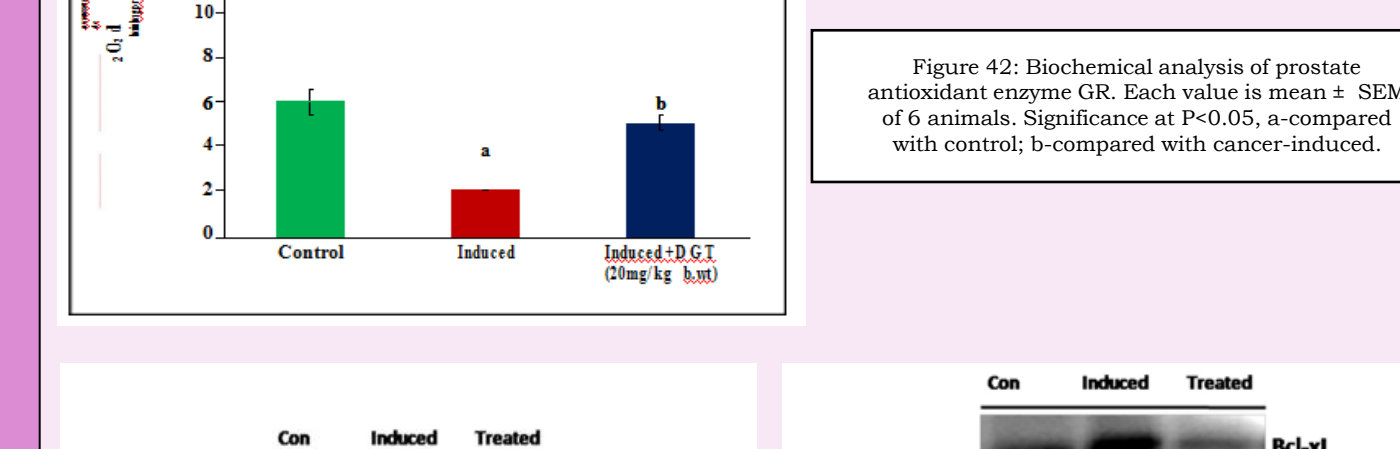
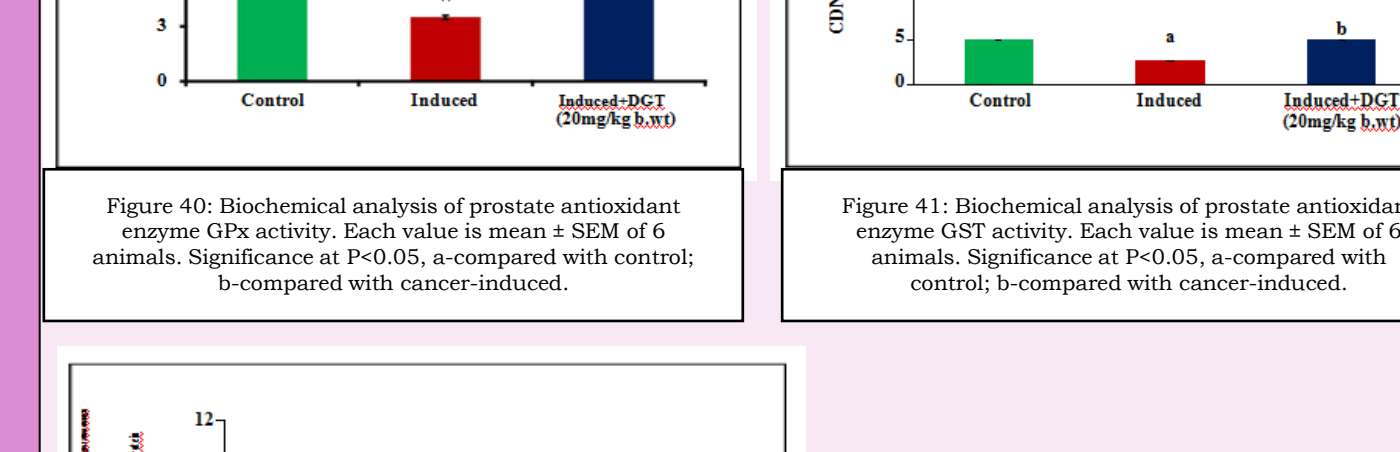
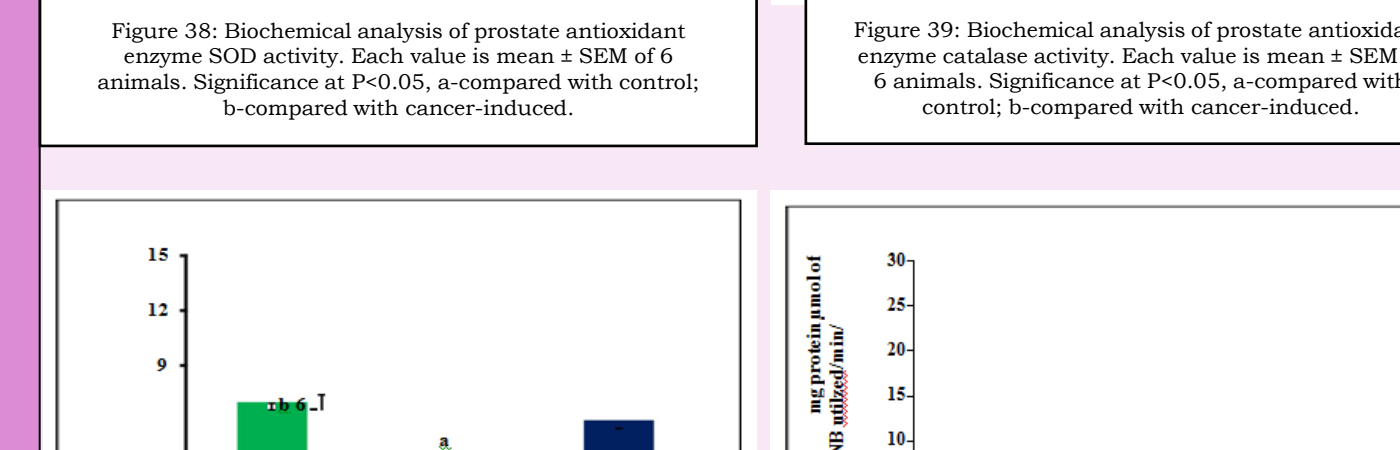
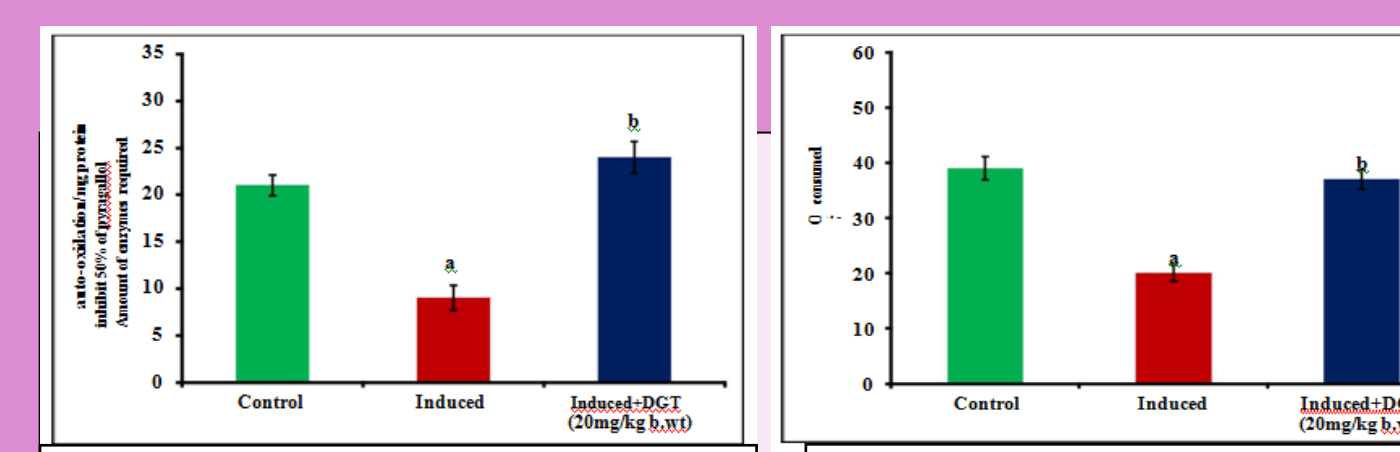
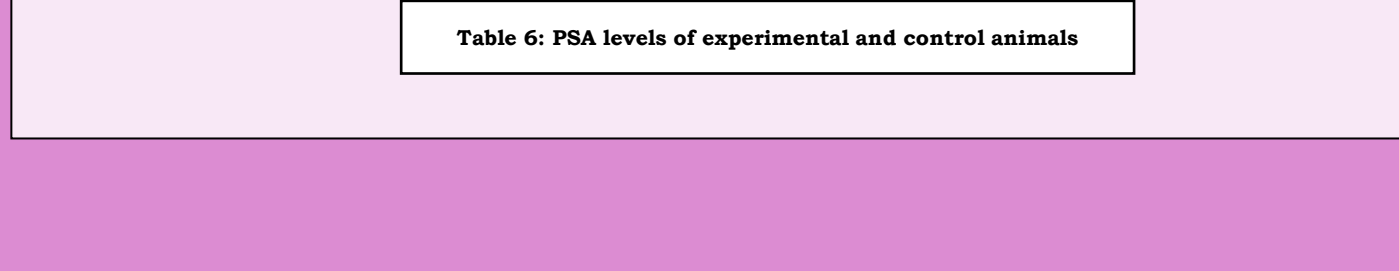
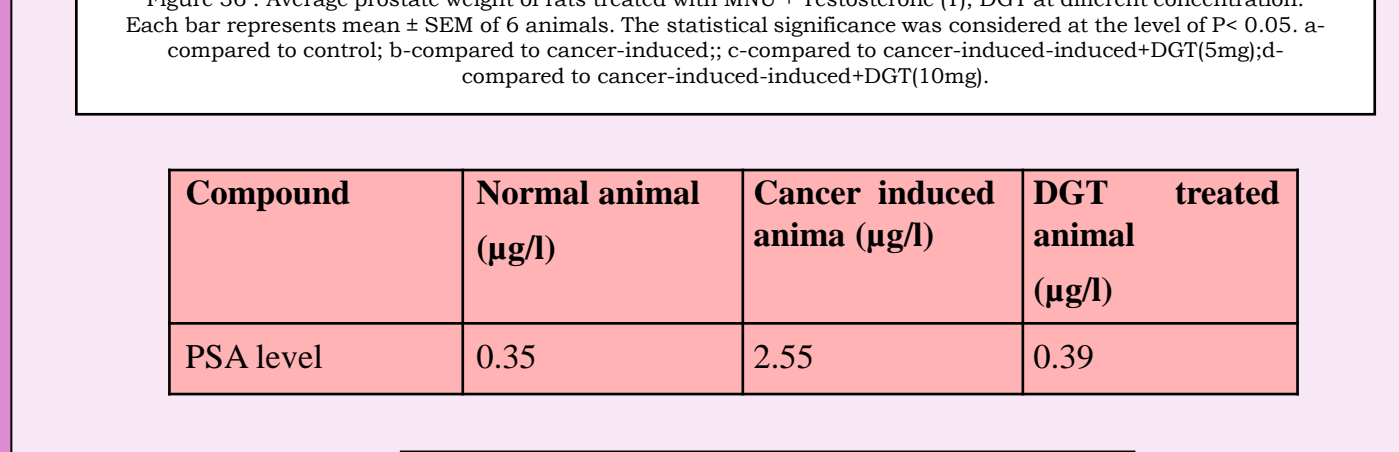
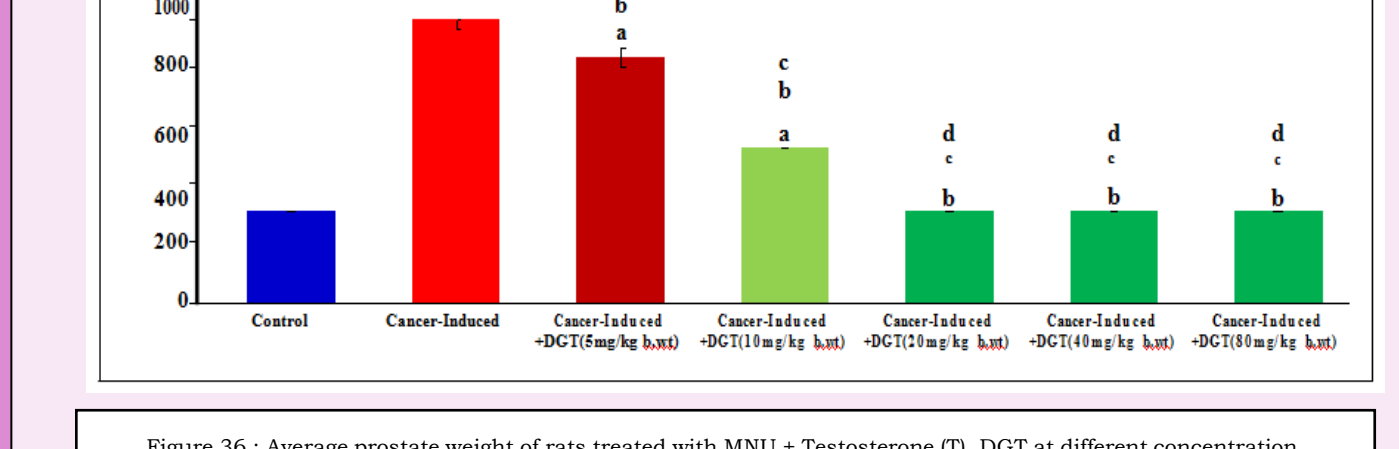
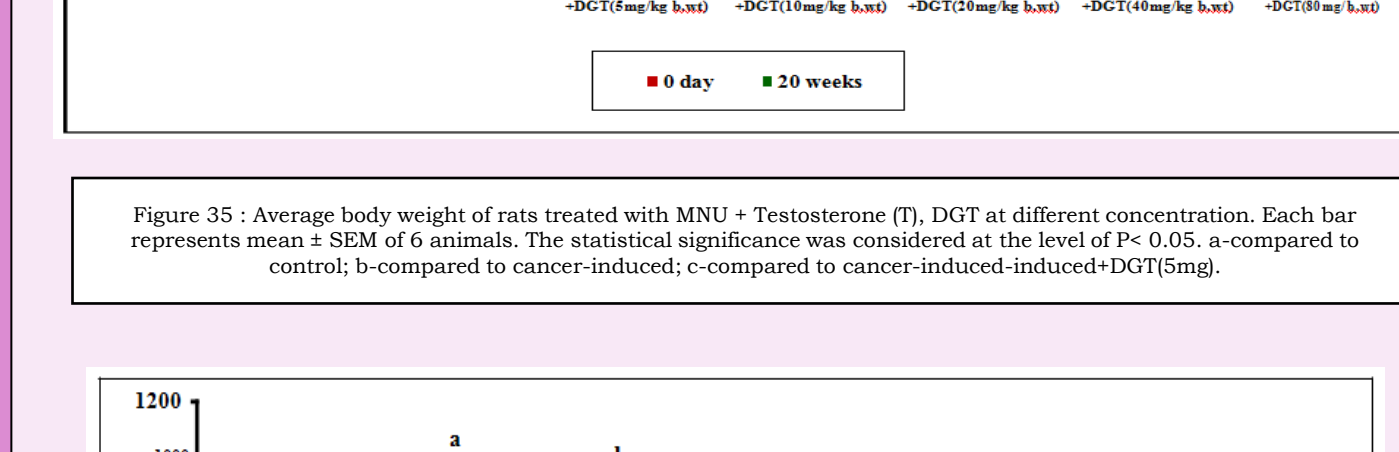
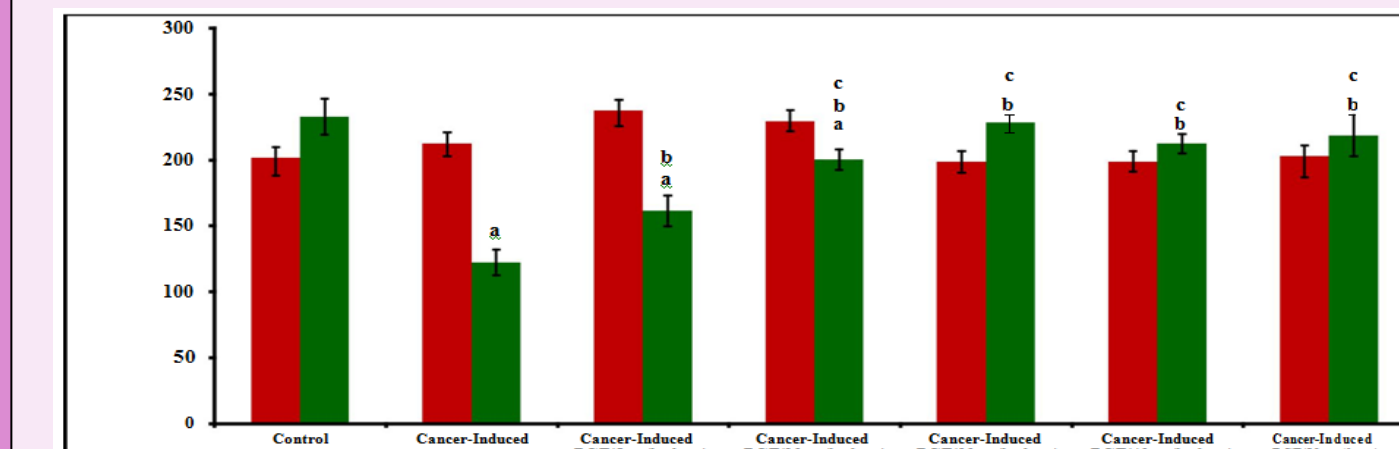
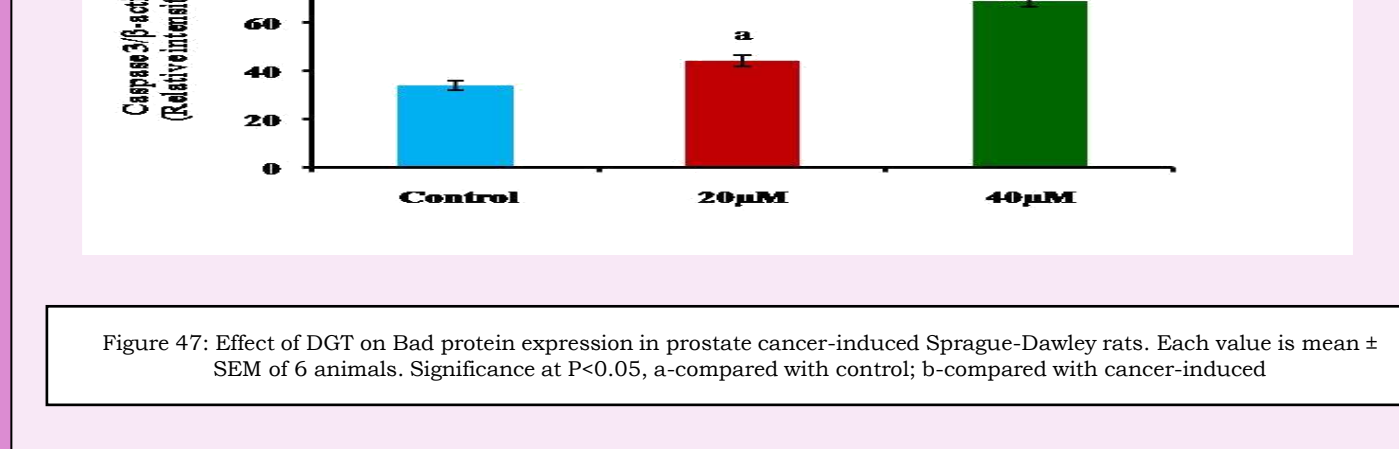
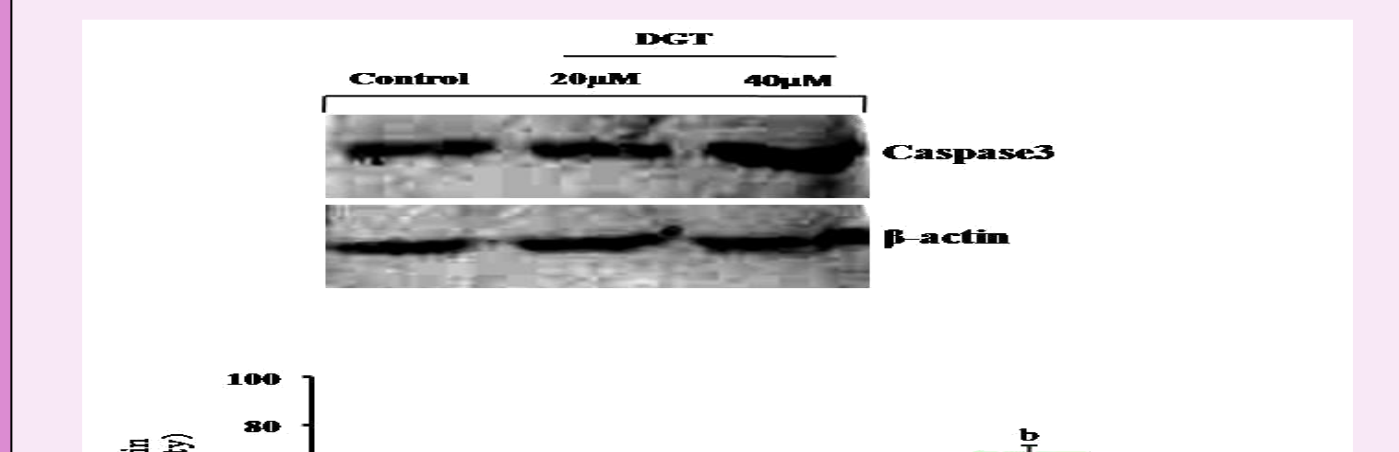
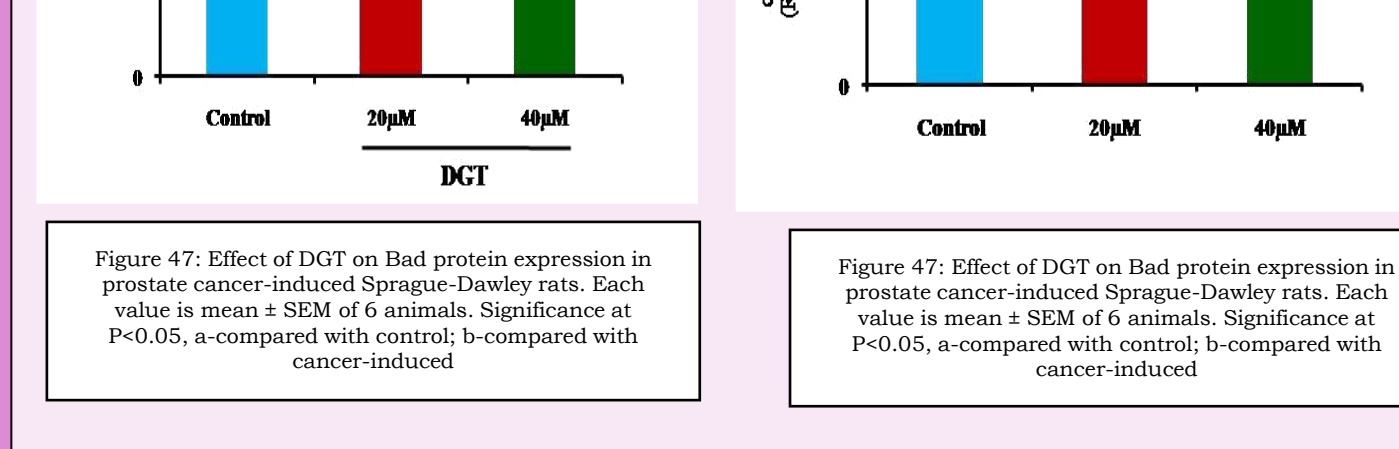
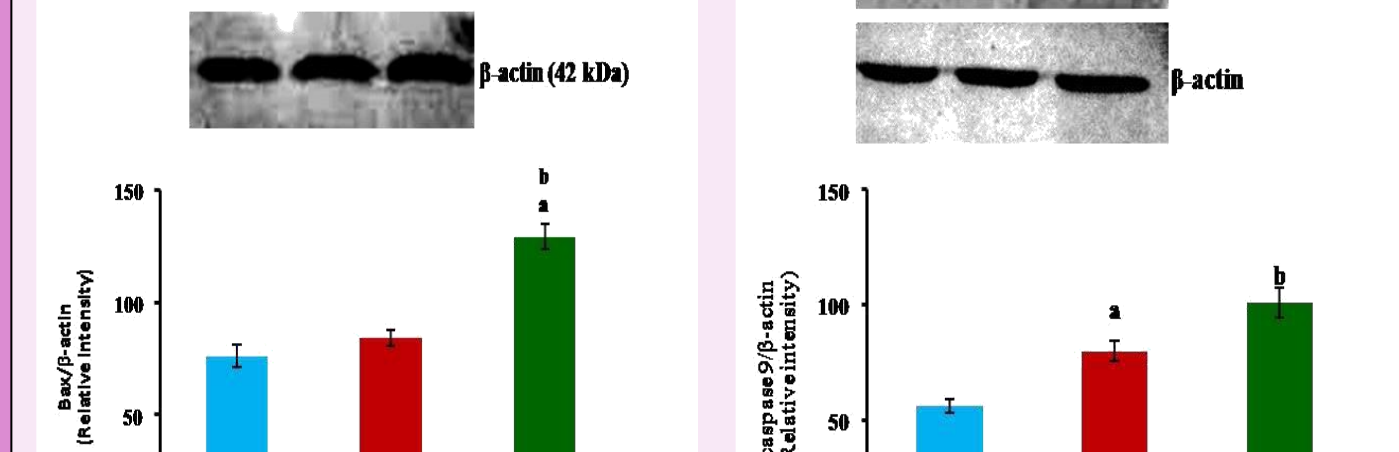
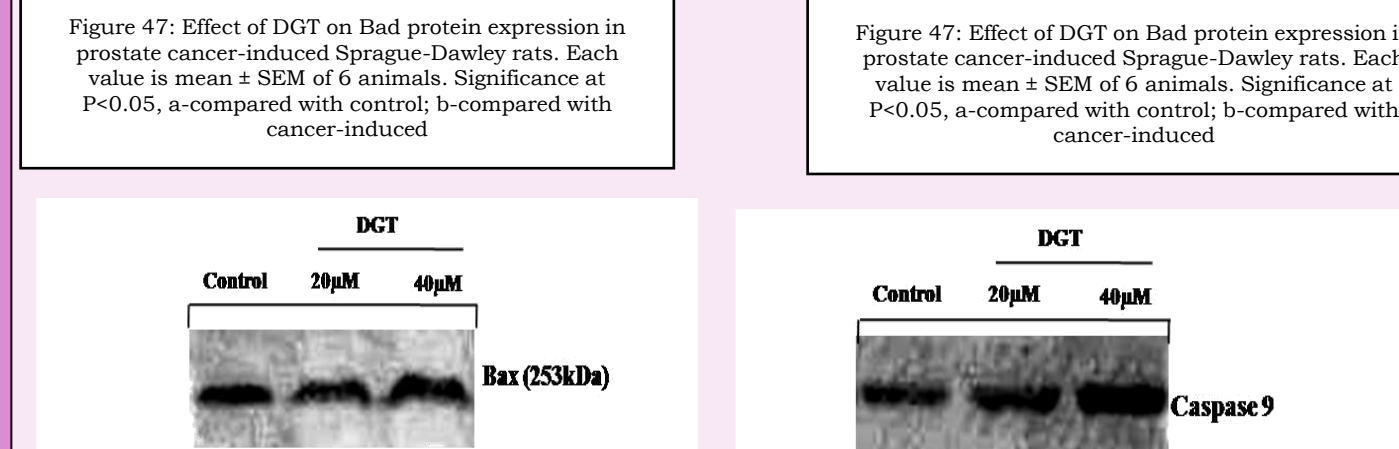
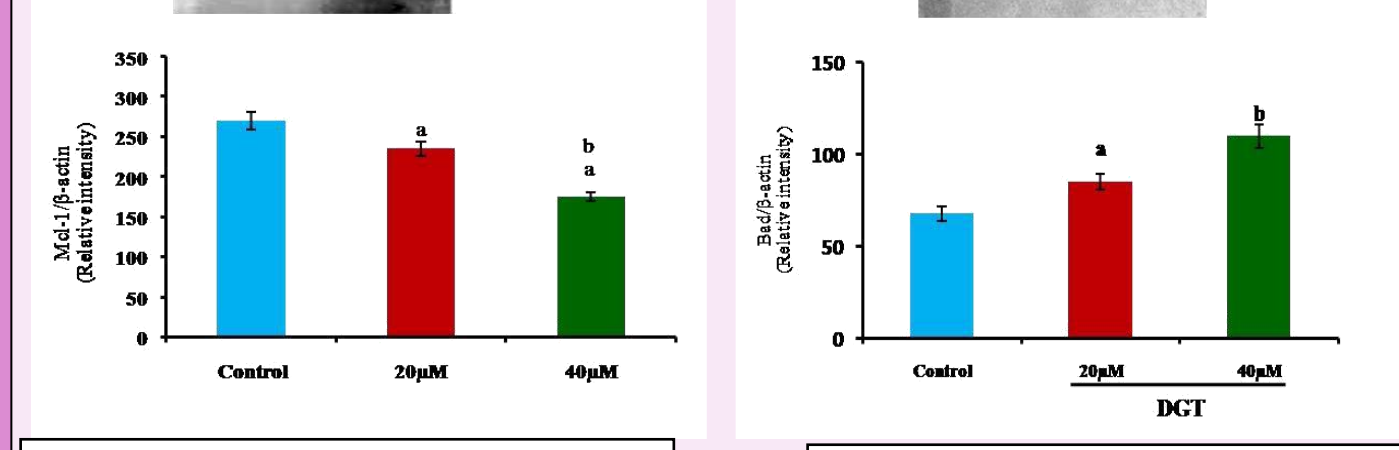
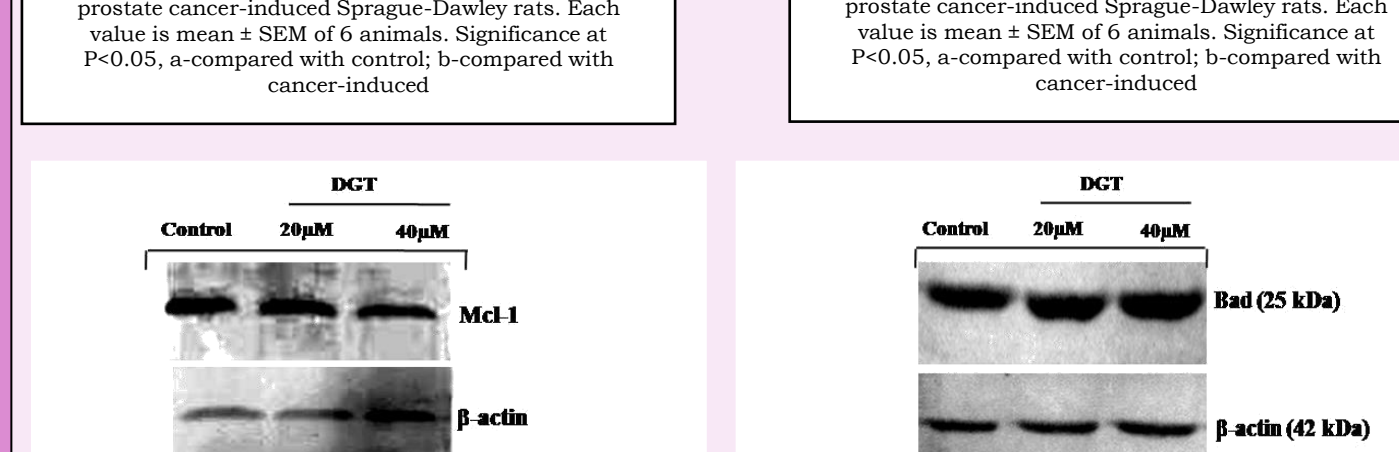
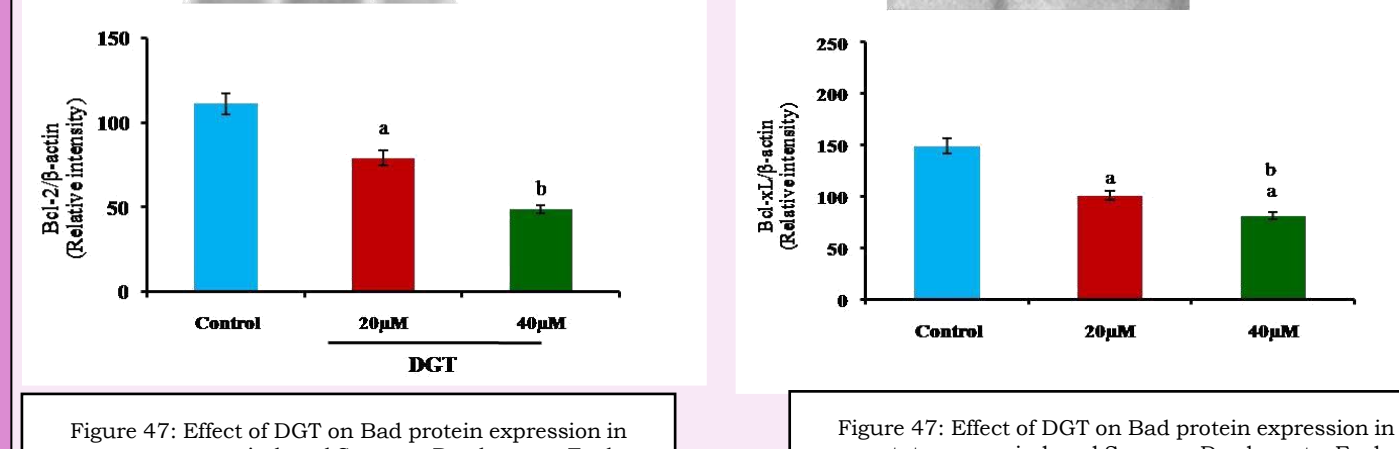
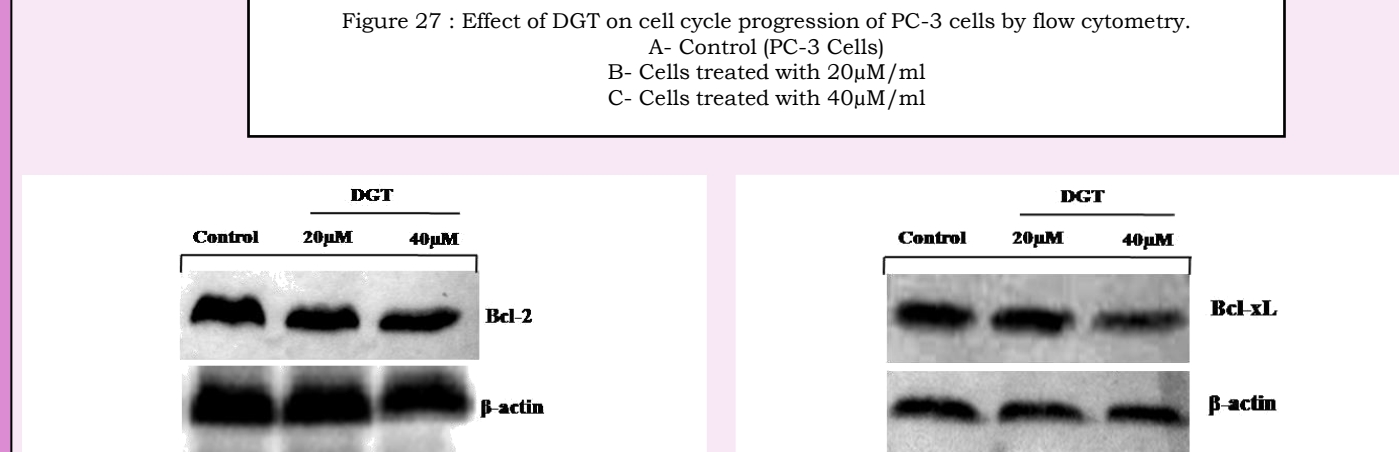
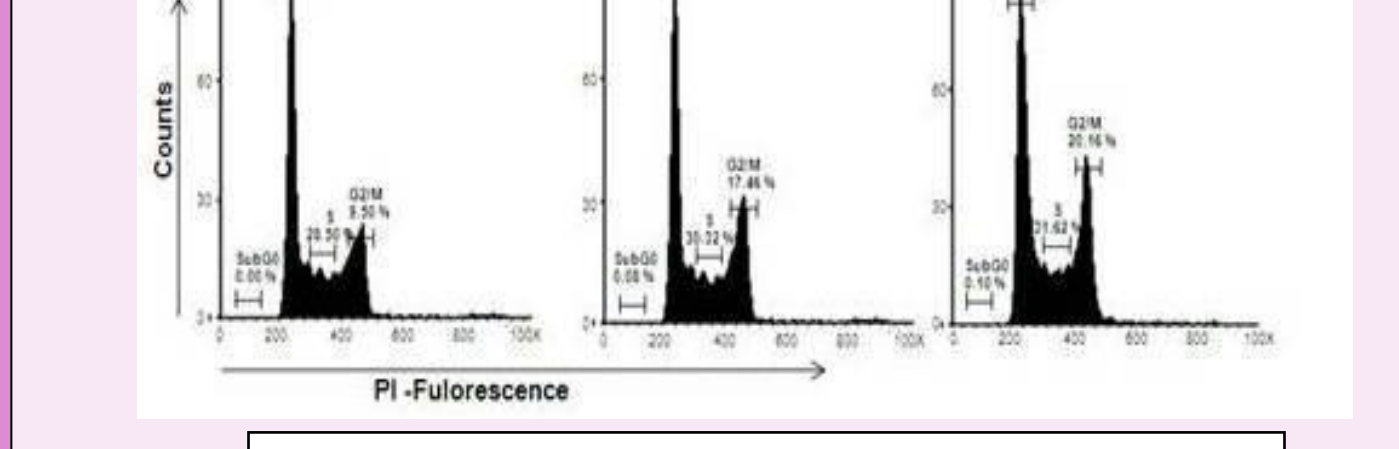
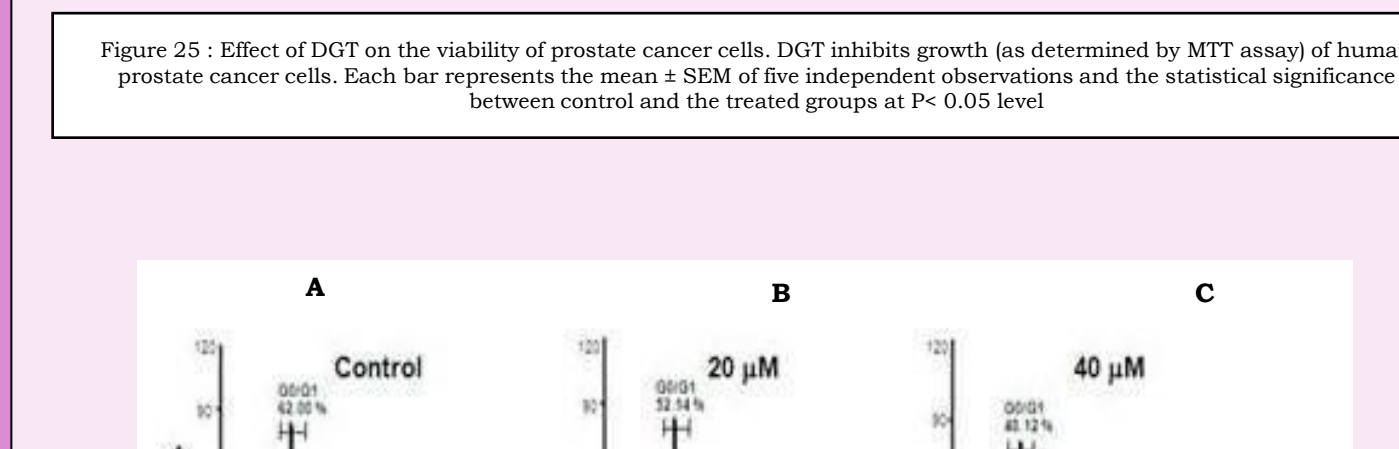
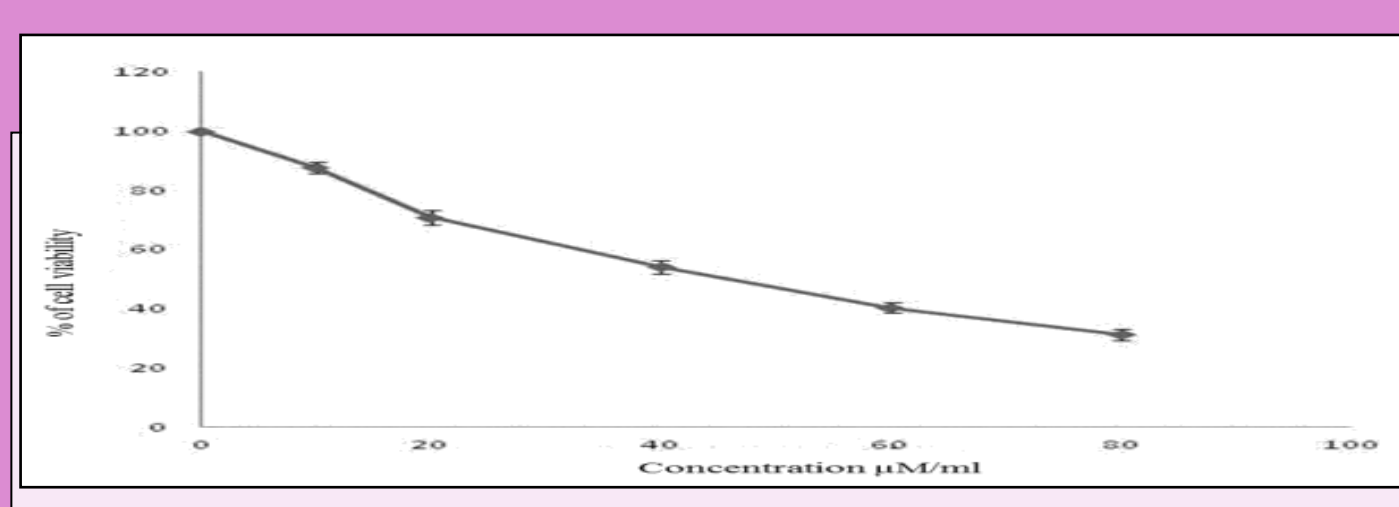
Compound	Normal animal (µg/l)	Cancer induced animal (µg/l)	DGT treated animal (µg/l)
PSA level	0.35	2.55	0.39

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CONCLUSION

- DGT was more potent in binding with anti-apoptotic proteins, also satisfying Lipinski's RO5 and ADME properties.
- DGT significantly acts on prostate cancer cells by activating apoptosis and cell cycle inhibition and did not exhibit any toxicity to the animal model.
- Hence, DGT could be considered for the preparation of chemopreventive agent and potent drug against prostate cancer.

Reference

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