

**ASSESSMENT OF SELECTED PLASMA PROTEIN LEVELS IN
NIGERIAN PROSTATE CANCER PATIENTS AND *IN-SILICO*
THERAPEUTIC TARGETING OF AR SIGNALING**

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AUGUST, 2024

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BY

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**A DISSERTATION SUBMITTED TO THE SCHOOL OF POSTGRADUATE
STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR
THE AWARD OF THE DEGREE OF MASTER OF SCIENCE (M.Sc.) IN
BIOCHEMISTRY IN THE DEPARTMENT OF BIOCHEMISTRY,
COLLEGE OF SCIENCE AND TECHNOLOGY, COVENANT
UNIVERSITY, OTA, OGUN STATE, NIGERIA**

AUGUST, 2024

ACCEPTANCE

This is to attest that this dissertation is accepted in partial fulfilment of the requirements for the award of a Master of Science (M.Sc.) in Biochemistry in the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Nigeria.

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DECLARATION

I, **ZAKARI, SULEIMAN (22PCP02390)**, hereby declare that this research work was carried out by me under the supervision of Prof. Olubanke O. Ogunlana in the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State. I attest that the dissertation has not been presented wholly or partially for the award of any degree elsewhere. All sources of data and scholarly information used in this dissertation were duly acknowledged.

ZAKARI, SULEIMAN

Signature and Date

CERTIFICATION

We certify that the dissertation titled “**ASSESSMENT OF SELECTED PLASMA PROTEIN LEVELS IN NIGERIAN PROSTATE CANCER PATIENTS AND *IN-SILICO* THERAPEUTIC TARGETING OF AR SIGNALING**” is an original work carried out **ZAKARI SULEIMAN (22PCP02390)** in the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State, Nigeria under the supervision of Prof. Olubanke O. Ogunlana. We have examined and found this work acceptable as part of the requirement for the award of a Master of Science (M. Sc.) degree in Biochemistry.

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DEDICATION

I would like to dedicate my project to God for his direction and protection over my life. Also, my family members that have constantly supported and encouraged me throughout my academic journey.

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TABLE OF CONTENTS

CONTENTS	PAGES
OVER PAGE	
TITLE	
PAGE	ii
ACCEPTANCE	iii
DECLARATION	iv
CERTIFICATION	v
DEDICATION	vi
ACKNOWLEDGEMENTS	vii
TABLE OF CONTENTS	viii
LIST OF FIGURES	xi
LIST OF TABLES	xii
LIST OF ABBREVIATIONS	xiii
ABSTRACT	xiv
CHAPTER ONE: INTRODUCTION	1
1.1 Background to the Study	1
1.2 Statement of Problem	3
1.3 Research Questions	3
1.4 Aim and Objective of Study	3
1.5 Justification for the Study	4
1.6 Scope of the Study	4
CHAPTER TWO: LITERATURE REVIEW	6
2.1 The Prostate Gland	6
2.2 Prostate Cancer	8
2.3 Incidence and Risk Factors of Prostate Cancer	8
2.4 Diagnosis of Prostate Cancer	9
2.5 Treatment of Prostate Cancer	12
2.5.1 Androgen Deprivation Therapy (ADTs)	12
2.5.2 Androgen Receptor Signaling Inhibitors (ARSIs)	13

2.5.3	Combination Therapies	14
2.6	Molecular Aspects of Prostate Cancer	15
2.6.1	The Androgen Receptor (AR) Signaling Pathway	16
2.6.2	Steroid Receptor Coactivator-3 (SRC-3)	17
2.6.3	Speckle-type POZ protein (SPOP)	18
CHAPTER THREE: MATERIALS AND METHODS		23
3.1	Materials	23
3.1.1	Equipment's	23
3.1.2	Reagents	23
3.2	Methodology	23
3.2.1	Study Population	23
3.2.2	Study Area	23
3.2.3	Inclusion and exclusion criteria	23
3.2.4	Sampling Technique	24
3.2.5	Blood Collection	24
3.2.6	Ethical Clearance	24
3.2.7	Enzyme-linked Immunosorbent Assay (ELISA)	24
3.3	Computational Analysis	25
3.3.1	Ligand selection and preparation	26
3.3.2	Protein Preparation	26
3.3.3	Virtual screening and molecular docking	26
3.3.4	Absorption Distribution Metabolism Excretion and Toxicity (ADMET)	27
3.4	Methods of Statistical Analysis	27
CHAPTER FOUR: RESULTS		28
4.1	Levels of Human SPOP, AR, and SRC-3	28
4.2	Computational Analysis	31

4.2.1 Ligands	31
4.2.2 Physicochemical Properties	32
4.2.3 Drug-likeness results	33
4.2.4 Virtual screening and molecular docking analyses	33
4.2.5 Predicted ADMET profiles of the isolated compounds	41
CHAPTER FIVE: DISCUSSION	44
5.1 Human SPOP, AR, SRC-3 Protein Levels	44
5.2 Computational Analysis	45
CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS	50
6.1 Summary	50
6.2 Conclusion	51
6.3 Contributions to knowledge	51
6.4 Recommendations	52
REFERENCES	53

LIST OF FIGURES

FIGURES	LIST OF FIGURES	PAGES
Figure 1	The prostate gland	6
Figure 2	Androgen signaling pathway	21
Figure 3	Dysregulated AR signalling in PCa	22
Figure 4	Structure of SPOP protein	27
Figure 5	The ubiquitin-proteasome system	29
Figure 6	Bar graph of the levels (Mean \pm SEM) of SPOP, AR, and SRC-3 in disease and control samples	37
Figure 7	Estimation plot of Welch's t test of SPOP protein in disease and control samples	38
Figure 8	Estimation plot of Welch's t test of AR protein in disease and control samples	38
Figure 9	Estimation plot of Welch's t-test of SRC-3 protein in disease and control samples	39
Figure 10	Scatter matrix plot of the correlation of SPOP, AR and SRC-3 levels of the correlation of SPOP, AR and SRC-3 levels	40
Figure 11	Chemical structures of selected pure compounds from <i>Caesalpinia bonduc</i>	41
Figure 12	The 2D and 3D views of the COMP1, 2, 3, 4 and Enzalutamide interactions with mutant SPOP	45
Figure 13	The 2D and 3D views of COMP1, 2, 3, 4 and Apalutamide interactions with AR-V7	49

LIST OF TABLES

TABLES	LIST OF TABLES	PAGES
Table 1	Combination therapies targeting AR and PI3K/AKT/mTOR pathways	17
Table 2	Coding exons of SPOP gene	26
Table 3	Physicochemical Properties of the Selected Pure Compounds Isolated from <i>Caesalpinia bonduc</i> and the standard compounds, Enzalutamide and Apalutamide	42
Table 4	Adherence of isolated and reference compounds to the known drug-likeness guidelines	42
Table 5	Molecular docking analysis of pure compounds showing estimated binding free energy and interacting residues in the binding site of mut SPOP	53
Table 6	Molecular docking analysis of pure compounds showing estimated binding free energy and interacting residues in the binding site of AR-V7	57
Table 7	Predicted molecular adsorption profile of selected pure compounds of <i>Caesalpinia bonduc</i>	51
Table 8	Predicted molecular metabolism profile of selected pure compounds from <i>Caesalpinia bonduc</i>	51
Table 9	Predicted molecular toxicity profile of isolated compounds of selected pure compounds from <i>Caesalpinia bonduc</i>	52
Table 1	Combination therapies targeting AR and PI3K/AKT/mTOR pathways	17
Table 2	Coding exons of SPOP gene	26
Table 3	Physicochemical Properties of the Selected Pure Compounds Isolated from <i>Caesalpinia bonduc</i> and the standard compounds, Enzalutamide and Apalutamide	42
Table 4	Adherence of isolated and reference compounds to the known drug-likeness guidelines	42

LIST OF ABBREVIATIONS

Abbr	Full meaning
ADT	Androgen deprivation therapy
ADMET	Absorption Distribution Metabolism Excretion and Toxicity
AR	Androgen Receptor
AR-V7	Androgen Receptor Variant 7
ARSI	Androgen Receptor Signaling Inhibitors
ctDNA	circulating tumor DNA
COMP1	4,4'-dihydroxy-2'-methoxy-chalcone (2'-methoxyisoliquiritigenin)
COMP2	7,4'-dihydroxy-3,11-dehydrohomoisoflavanone
COMP3	5,7,3',4'-tetrahydroxy-flavone (Luteolin)
COMP4	7,3',4'-tetrahydroxy-3-methoxyflavone (quercetin-3-methyl ether)
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
ELISA	Enzyme-linked immunosorbent assay
Pca	Prostate cancer
PSA	Prostate-Specific Antigen
SPOP	Speckle Type POZ Protein
SRC-3	Steroid Receptor Coactivator 3

ABSTRACT

Prostate cancer (PCa) is one of the most common male cancers and one of the main cancer-related causes of mortality in men. In 2020, there were more than 1.4 million fresh instances of PCa worldwide. Therefore, more new and efficient therapeutic targets and biomarkers are needed urgently for better PCa management. This study aimed to quantify SPOP, AR, and SRC-3 proteins in PCa patients and non-cancer controls, and screen the potential inhibitors toward mutated SPOP and Androgen Receptor Variant 7 (AR-V7) computationally. A case-control study design was used, selecting 40 PCa patients with histologically confirmed cases and 40 healthy controls. Plasma levels of SPOP, AR, and SRC-3 were estimated by ELISA. Moreover, computational analysis, with the use of simulations, was conducted to predict the physicochemical properties of some selected compounds from *Caesalpinia bonduc*, drug-likeness, and binding affinity toward mutant SPOP and AR-V7. The mean SPOP, AR, and SRC-3 levels did not differ significantly between PCa and controls ($p > 0.05$). Pearson correlation analysis revealed a very strong positive correlation between AR and SRC-3 levels ($r = 0.9$, $p < 0.0001$), SPOP and AR levels was moderately high ($r = 0.7$, $p < 0.0001$), while the correlation between SPOP and SRC-3 was more moderate ($r = 0.6$, $p < 0.0001$). Computational analyses identified 4 *C. bonduc* compounds; 4,4'-dihydroxy-2'-methoxy-chalcone (2'-methoxyisoliquiritigenin), 7,4'-dihydroxy-3,11-dehydrohomoisoflavanone, 5,7,3',4'-tetrahydroxy-flavone (Luteolin), 7,3',4'-tetrahydroxy-3-methoxyflavone (quercetin-3-methyl ether) designated as COMP1, COMP2, COMP3 and COMP4 respectively, with favorable physicochemical properties and drug-likeness. Molecular docking showed that COMP2 and COMP3 exhibited stronger binding affinities to mutant SPOP than Enzalutamide. COMP2, COMP3, and COMP4 also showed stronger binding to AR-V7 than Apalutamide. While SPOP, AR, and SRC-3 levels did not differ between PCa and controls, correlation results suggest a meaningful interplay between SPOP, AR, and SRC-3 in the context of prostate cancer. Larger cohort proteomic profiling studies should be conducted to validate this study's findings and establish the clinical relevance of protein profiling in prostate cancer management. Computational analyses identified *C. bonduc* compounds: COMP2, COMP3, and COMP4 with promising therapeutic potential targeting mutant SPOP and AR-V7. For their clinical utility to be established, more validation is necessary.

Keywords: Androgen receptor, SPOP gene, SRC-3, Prostate Cancer, In-Silico, Therapeutic Targeting