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

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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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Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

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 "**ASSESSEMENT 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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Prof. Joseph O. Adebayo
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Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

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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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
ARSIs	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 physiochemical 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