ANDROGEN LEVELS IN NIGERIAN PROSTATE CANCER PATIENTS AND *IN SILICO* SCREENING OF POTENTIAL INHIBITORS OF SRD5A2 ENZYME

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AUGUST, 2024

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A DISSERTATION SUBMITTED TO THE SCHOOL OF POST GRADUATE 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, **AYENI, TIMOTHY OLUWATIMILEYIN (22PCP02379)** hereby declare that this research work was carried out by me under the supervision of Prof. Shalom N. Chinedu of the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State. I attest that the dissertation has not been presented either wholly or partially for the award of any degree elsewhere. All sources of data and scholarly information used in this dissertation were duly acknowledged**.**

AYENI, TIMOTHY OLUWATIMILEYIN

Signature and Date

CERTIFICATION

We certify that the dissertation titled "**ANDROGEN LEVELS IN NIGERIAN PROSTATE CANCER PATIENTS AND *IN SILICO* SCREENING OF POTENTIAL INHIBITORS OF SRD5A2 ENZYME"** is an original work carried out by **AYENI, TIMOTHY OLUWATIMILEYIN (22PCP02379)** in the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State, Nigeria under the supervision of Prof. Shalom N. Chinedu. 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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(Dean, School of Postgraduate Studies) **Signature and Date**

DEDICATION

I dedicate this dissertation to the Almighty God, who equipped me with the intellectual, physical and emotional strengths to complete this research.

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LIST OF ABBREVIATIONS

ADT -Androgen deprivation therapy

DHT- Dihydrotestosterone

AR – Androgen receptor

SRD5A2 – Steroid 5-alpha reductase type 2

ADME – Absorption, digestion, metabolism, and excretion

PC – Prostate cancer

aPC - aggressive PC

mPCa – metastatic prostate cancer

mCRPC - castration-resistant prostate cancer

PDB – Protein data bank

K-3-O-BDG - Kaempferol-3-O-beta-D-glucopyranosyl-7-O-alpha-L-rhamnopyranoside

24-M - 24-Methylcholesta-7,22-dien-3β-ol

GIA - gastrointestinal absorption

ABSTRACT

Globally, cancer has been recognized as the second most common disease occurring in various organs of the body. Prostate cancer (PC) is among the most prevalent cancer types. It is reportedly the most common form of male cancer in men of African descent, having the highest susceptibility rate. Androgens, such as testosterone and dihydrotestosterone (DHT), are among several risk factors associated with PC risk and progression. They have been well-established to have an essential role in PC development, even at advanced stages. Dihydrotestosterone (DHT), a more active androgen, has been linked to PC development and progression due to its ability to bind the androgen receptor (AR) and initiate its signalling. The steroid 5-alpha-reductase type-2 (SRD5A2) enzyme, which transforms testosterone into DHT, has been targeted in hormonal therapy for PC using finasteride. However, side effects, including sexual dysfunction, osteoporosis, and cardiovascular diseases, have been associated with the treatment, thereby indicating a need for novel and safer SRD5A2 inhibitors. This study was aimed at determining the levels of circulating androgens (Testosterone and DHT) among Nigerian prostate cancer patients and identify potential drug targets against these androgens. Testosterone and DHT levels were determined using an ELISA assay. A systematic review was performed to identify previously reported plants as SRD5A2 inhibitors, including their phytoconstituents. Thirty-four phytoconstituents from nine medicinal plants were selected and evaluated alongside the standard SRD5A2 inhibitor (finasteride) by employing in silico techniques, including molecular docking, pharmacokinetic prediction, and toxicity profiling. Among the bioactive compounds evaluated, gamma-oryzanol showed the highest binding affinity with SRD5A2 with a binding energy of -11.6 Kcal/mol comparable to the finasteride. Its pharmacokinetics and toxicity profiles were also predicted to be better than finasteride, suggesting its therapeutic potential in drug development for PC treatment. However, further studies should be conducted on gamma-oryzanol to ascertain its toxicity compared to finasteride. We also recommend that additional studies be carried out to evaluate the expression of the SRD5A2 gene in Nigerian PC patients, as this would help establish a personalized treatment for this population.