Professorial
Inaugural Lecture

by

Professor Benedicta Nkeh-Chungag

LECTURE TITLE:
ARE CARDIOVASCULAR DISEASES A CAUSE FOR CONCERN IN PEOPLE OF AFRICAN ANCESTRY?

Date: Wednesday, 9 November 2022
Time: 15h00
Venue: Health Resource Centre,
Nelson Mandela Academic Hospital, Mthatha

WSU
Walter Sisulu University
In pursuit of excellence

Programme

Programme Director:	Professor Elphina Bandla Cishe
Welcome:	Vice-Chancellor, Professor Rushiella Nolundi Songca
Introduction of Inaugural Professor:	Deputy Vice-Chancellor Academic Affairs, Professor Mashudu Davhana-Maselesele
Keynote Address:	Professor Benedicta Nkeh Chungag
Academic Respondent:	Professor Francis Hyera
Congratulatory Message:	Professor Jabu Mbokazi
Vote of Thanks:	Deputy Vice-Chancellor Institutional Support, Dr Prince Jaca

Professor Benedicta Nkeh-Chungag

Professor Benedicta Ngwenchi Nkeh-Chungag's BIO

Professor Benedicta Ngwenchi Nkeh-Chungag is a Full Professor of Physiology and Dean of the Faculty of Natural Sciences, Walter Sisulu University. Professor Nkeh-Chungag is an NRF rated researcher, a scholar of the Organization for Women in Science for the Developing World (OWSD), a Fellow of the International Hypertension Society, Deputy President and co-founder of the newly established Childhood Hypertension Consortium of South Africa, Deputy Chairperson of the South African National Committee for International Union for Physiological Sciences (ICSU-IUPS), Chairperson of the Cardiometabolic Research Niche Area – WSU and Chairperson of the Animal Research Ethic Committee. She oversees the Carrier Orientation and International Mentoring Program run by Harness Ideas Association (HIDAS).

Professor Nkeh-Chungag has published extensively in the of cardiovascular research covering epidemiology and African medicinal plants. She has served as an Associate Editor for the journal Frontiers in Public Health and is on the editorial board of two journals, Bioinformatics and Clinical Interventions in Aging. She is a member of several knowledge bodies including the International Hypertension Society.

As an accomplished and passionate scholar, Professor Nkeh-Chungag enjoys both national and international recognition in her field of research. Her focus on the risk for cardiovascular diseases in children of African ancestry has attracted interest and funding from both national and international organizations. Her research findings have been showcased at many scientific fora including as keynote addresses.

Professor Nkeh-Chungag is married to Dr Anye Chungag and they are blessed with four boys.

Curriculum Vitae

PERSONAL DATA

Name:	Benedicta Ngwenchi Nkeh-Chungag
Rank:	Full Professor
Official designation:	Professor of Physiology and Dean: Faculty of Natural Sciences
Status:	Married
Official address:	Faculty Office
	Faculty of Natural Sciences
	1 Nelson Mandela Drive
	Mthatha Campus, Walter Sisulu University.

EDUCATION, QUALIFICATIONS, LEADERSHIP TRAINING

Institution attended:	Walter Sisulu University
Period:	2010 – 2014
Qualification:	MPH
Institution attended:	University of the Witwatersrand
Period:	2000 – 2005
Qualification:	PhD
Institution attended:	University of Yaoundé, Cameroon
Period:	1990-1995
Qualification:	Doctorat de Troisieme Cycle
Institution attended:	University of Yaoundé, Cameroon
Period:	1989-1990
Qualification:	BSc (Honours)
Institution attended:	University of Yaoundé, Cameroon
Period:	1985 - 1988
Qualification:	BSc
Institution attended:	Rhodes University
Period:	2017
Qualification:	Diploma: Strengthening Postgraduate Supervision

EMPLOYMENT

1. Dean: Faculty of Natural Sciences, Walter Sisulu University (since 2018).
2. Professor of Physiology, Walter Sisulu University (since 2013).
3. Associate Professor, Department of Biological and Environmental Sciences (2010 – 2013).
4. Senior Lecturer, Department of Physiology (2006-2010)
5. Lecturer, Department of Biology and Physiology, University of Yaoundé (1995-1999)

INTERNATIONAL AND NATIONAL PROFESSIONAL RECOGNITIONS

Fellow of the International Hypertension Society

Reviewer for several peer-reviewed journals including Frontiers in Pediatrics.

ROLES PLAYED IN THE NATIONAL RESEARCH FOUNDATION (NRF) RESEARCH REVIEW SYSTEM

1. Member of the ICSU-IUPS
2. Deputy Chairperson - ICSU-IUPS (since 2022)
3. Reviewer, NRF IKS Initiative
4. Reviewer, NRF Rating Applications
5. Reviewer, NRF Competitive program for rated researchers (CPRR)
6. Reviewer, NRF Thuthuka Initiative
7. NRF panel member: for NRF rating, CPRR, Thuthuka and IKS.

ACCREDITED RESEARCH PUBLICATIONS

Google citations

	All	Since 2017
Citations	1731	1094
h-index	22	17
i10-index	40	32

PUBLICATIONS IN PEER REVIEWED JOURNALS

1. Engwa GA, Anye C, Nkeh-Chungag BN. Association between obesity and lung function in South African adolescents of African Ancestry. BMC pediatrics. 2022 Dec;22(1):1-7.

2. Edna Ngoakoana Matjuda, Godwill Azeh Engwa, Muhau Muhulo Mungamba, Constance Rufaro Sewani-Rusike, Benedicta Ngwenchi Nkeh-Chungag. Oxidative stress is associated with markers of renal dysfunction in children aged 6-9 years old in a South African population. Pan-African Medical Journal. 2022; 42:35. https://doi.org/10.11604/pamj.2022.42.35.26443. (Index in Scopus, DHET).

3. Engwa GA, Nweke FN, Nkeh-Chungag BN. Free Radicals, Oxidative Stress-Related Diseases and Antioxidant Supplementation. Alternative Therapies. 2022; 28:(1)114-129.

4. Tata C, Sewani-Rusike C, Aremu O, Nkeh-Chungag B. Journal of Medicinal Herbs. Journal of Medicinal Herbs. 2022; 13(1): 19-25.

5. Nkeh-Chungag BN, Engwa GA, Businge C, Mdondolo M, Medina MP, Goswami N. Assessment of the impact of HIV infection and anti-retroviral treatment on the cardiometabolic health of pregnant mothers and their offspring (ARTMOMSBABES). BMC Cardiovascular Disorders. 2021 Dec;21(1):1-0.

6. Nkeh-Chungag BN, Engwa GA, Businge C, Kutllovci-Hasani K, Kengne AP, Goswami N. Assessment of the cardiovascular risk profile of infants exposed to pre-eclampsia in-utero: A prospective parallel arms cohort study among South African Children of African Ancestry. Frontiers in Cardiovascular Medicine. 2021 Nov 23:1701.

7. Mokwena MA, Engwa GA, Nkeh-Chungag BN, Sewani-Rusike CR. Athrixia phylicoides tea infusion (bushman tea) improves adipokine balance, glucose homeostasis and lipid parameters in a diet induced metabolic syndrome rat model. BMC Complementary Medicine and Therapies (2021) 21:292.

8. Sewani-Rusike CR, Ntongazana O, Engwa GA, Musarurwa HT, Nkeh-Chungag BN. Sclerocarya birrea fruit peel ameliorates diet-induced obesity and selected parameters of metabolic syndrome in female wistar rats. Pharmacognosy Magazine. 2021 Jul 1;17(75):482.

9. Engwa GA, Schmid-Zalaudek K, Anye C, Letswalo BP, Anye PC, Mungamba MM, Sewani-Rusike CR, Goswami N, Nkeh-Chungag BN. Assessment of Anthropometric Indices for Optimal Cut-Offs for Obesity Screening in a South African Adolescent Population. Biology. 2021 Nov;10(11):1118.

10. Ntlahla EE, Mfengu MM, Engwa GA, Nkeh-Chungag BN, Sewani-Rusike CR. Gut permeability is associated with hypertension and measures of obesity but not with Endothelial Dysfunction in South African youth. African Health Sciences. 2021 Sep 27;21(3):1172-84.

11. Sekokotla AM, Iputo JE, Sewani-Rusike CR, Malema IM, Adeniyi OV, Goon DT, Nkeh-Chungag BN. Serum Magnesium and High-sensitive C-reactive Proteins in Hypertensive, Obese Female School Learners. West Indian Medical Journal. 2021 Jan 1;69(1).

12. Engwa GA, Nwalo FN, Ozokonkwo CO, Agbafor KN, Nkeh-Chungag BN, Ubi BE. Association of TCF7L2 rs12255372–G/T polymorphism with type 2 diabetes in a Nigerian population. 2021. DOI http://dx.doi.org/10.4238/gmr18662

13. Sewani-Rusike CR, Buso A, Engwa GA, Nkeh-Chungag BN. In utero exposure to Hypoxis hemerocallidea Fisch., CA Mey. & Avé-Lall. improves metabolic syndrome parameters in pregnant rats and offspring. Journal of Pharmacy & Pharmacognosy Research. 2021;9(2):113-25.

14. Woodiwiss AJ, Gafane-Matemane LF, Norton GR, Uys L, Myburgh C, Nkeh-Chungag BN, Kruger L, Orchard A, Peterson VR, Kolkenbeck-Ruh A, Ahiante BO. May Measurement Month 2019: an analysis of blood pressure screening results from South Africa. European Heart Journal Supplements. 2021 May;23(Supplement_B):B134-7.

15. Tata CM, Sewani-Rusike CR, Aremu O, Oyedeji OO, Nkeh-Chungag BN. Antihypertensive Effects of Osteospermum Imbricatum in Two Hypertensive Rat Models. Pharmacognosy Journal. 2021;13(3).

16. Nkeh-Chungag BN, Goswami N, Engwa GA, Sewani-Rusike CR, Mbombela V, Webster I, De Boever P, Kessler HH, Stelzl E, Strijdom H. Relationship between Endothelial Function, Antiretroviral Treatment and Cardiovascular Risk Factors in HIV Patients of African Descent in South Africa: A Cross-Sectional Study. Journal of Clinical Medicine. 2021 Jan;10(3):392.

17. Chungag A, Engwa GA, Sewani-Rusike CR, Nkeh-Chungag BN. Effect of Seasonal Variation on the Relationship of Indoor Air Particulate Matter with Measures of Obesity and Blood Pressure in Children. Journal of Health Pollution. 2021 Jun;11(30):210610.

18. Schmid-Zalaudek K, Brix B, Sengeis M, Jantscher A, Fürhapter-Rieger A, Müller W, Matjuda EN, Mungamba MM, Nkeh-Chungag B, Fredriksen PM, Goswami N. Subcutaneous Adipose Tissue Measured by B-Mode Ultrasound to Assess and Monitor Obesity and Cardio–Metabolic Risk in Children and Adolescents. Biology. 2021 May;10(5):449.

19. Matjuda EN, Engwa GA, Anye SN, Nkeh-Chungag BN, Goswami N. Cardiovascular Risk Factors and Their Relationship with Vascular Dysfunction in South African Children of African Ancestry. Journal of Clinical Medicine. 2021 Jan;10(2):354.

20. Letswalo BP, Schmid-Zalaudek K, Brix B, Matjuda EN, Klosz F, Obernhumer N, Gaisl M, Engwa GA, Sewani-Rusike C, Fredriksen PM, Nkeh-Chungag B. Cardiometabolic risk factors and early indicators of vascular dysfunction: a cross-sectional cohort study in South African adolescents. BMJ open. 2021 Mar 1;11(3):e042955.

21. Lederer AM, Fredriksen PM, Nkeh-Chungag BN, Everson F, Strijdom H, De Boever P, Goswami N. Cardiovascular effects of air pollution: current evidence from animal and human studies. American Journal of Physiology-Heart and Circulatory Physiology. 2021 Apr 1;320(4):H1417-39.

22. Goswami N, Fredriksen PM, Lundin KE, Agu C, Elias SO, Motaung KS, Brix B, Cvirn G, Sourij H, Stelzl E, Kessler HH. COVID-19 and its effects on endothelium in HIV-positive patients in sub-Saharan Africa: Cardiometabolic risk, thrombosis and vascular function (ENDOCOVID STUDY). BMC Infectious Diseases. 2021 Dec;21(1):1-1.

23. Reisinger C, Nkeh-Chungag BN, Fredriksen PM, Goswami N. The prevalence of pediatric metabolic syndrome—A critical look on the discrepancies between definitions and its clinical importance. International Journal of Obesity. 2021 Jan;45(1):12-24.

24. Chungag A, Engwa GA, Nkeh-Chungag BN. Distribution of indoor air pollutants relative to meteorological parameters in selected schools in the Eastern Cape Province of South Africa: A preliminary study. Indian

Journal of Environmental Protection. 2021; 41(7) 745-753.

25. Matjuda EN, Engwa GA, Sewani-Rusike CR and Nkeh-Chungag BN. An overview of vascular dysfunction and determinants: the case of children of African ancestry. Frontiers in Pediatrics. 2021; 9.

26. Matjuda EN, Sewani-Rusike CR, Chungag-Anye SN, Engwa GA and Nkeh-Chungag BN. Relationship between high blood pressure and microalbuminuria in children aged 6-9 years in a South African Population. Children 2020, 7, 131; doi:10.3390/children7090131

27. Woodiwiss AJ, Kruger R, Norton GR, Schutte AE, Myburgh C, Nkeh-Chungag B, Sewani-Rusike CR, Vally M, Jones E, Peterson V, Marsh J. May Measurement Month 2018: an analysis of blood pressure screening results in South Africa. European Heart Journal Supplements. 2020 Aug 1;22 (Supplement_H):H115-8.

28. Tata CM, Sewani-Rusike CR, Oyedeji OO, Gwebu ET, Nkeh-Chungag BN. Renoprotective effects of the hydroethanolic extract of Senecio serratuloides against Nw-nitro L-arginine methyl ester-induced oxidative stress in wistar rats. Pharmacognosy Magazine. 2020 Apr 1;16(70): 418.

29. Matjuda EN, Engwa GA, Letswalo PB, Mungamba MM, Sewani-Rusike CR, Nkeh-Chungag BN. Association of Hypertension and Obesity with Risk Factors of Cardiovascular Diseases in Children Aged 6–9 Years Old in the Eastern Cape Province of South Africa. Children. 2020 Apr;7(4):25.

30. Tata CM, Sewani-Rusike CR, Oyedeji OO, Mahlakata F, Shauli M, Nkeh-Chungag BN. Senecio serratuloides extract prevents the development of hypertension, oxidative stress and dyslipidemia in nitric oxide-deficient rats. Journal of Complementary and Integrative Medicine. 2020 Feb 8.

31. Tata CM, Ndinteh D, Nkeh-Chungag BN, Oyedeji OO, Sewani-Rusike CR. Fractionation and bioassay-guided isolation of antihypertensive components of senecio serratuloides. Cogent Medicine. 2020 Jan 1(just-accepted):1716447. doi.org/10.1080/2331205X.2020.1716447

32. Aremu OO, Tata CM, Sewani-Rusike CR, Oyedeji AO, Oyedeji OO, Gwebu ET & Nkeh-Chungag BN. Acute and sub-chronic antihypertensive properties of Taraxacum officinale leaf (TOL) and root (TOR), Transactions of the Royal Society of South Africa. 2019; 74(2), 132-138, DOI: 10.1080/0035919X.2019.1592031

33. Tata CM, Sewani-Rusike CR, Oyedeji OO, Gwebu ET, Mahlakata F, Nkeh-Chungag BN. Antihypertensive effects of the hydro-ethanol extract of Senecio serratuloides DC in rats. BMC complementary and alternative medicine. 2019; 19(1):52. 10.1186/s12906-019-2463-2

34. Aremu OO, Oyedeji AO, Oyedeji OO, Nkeh-Chungag BN, Rusike CR. In Vitro and In Vivo Antioxidant Properties of Taraxacum officinale in Nω-Nitro-l-Arginine Methyl Ester (L-NAME)-Induced Hypertensive Rats. Antioxidants. 2019; (8):309. doi.org/10.3390/antiox8080309

35. Chungag A, Tata CM, Sewani-Rusike CR, Nel W, Nkeh-Chungag BN. Ellisras Longitudinal Study 2017: association of hypertension with increasing levels of adiposity in 10-to 14-year-old boys and girls in the Eastern Cape (ELS 31). Cardiovascular journal of Africa. 2019 Sep;30(5):258-61.

36. Musarurwa HT, Sewani-Rusike CR, Nkeh-Chungag BN, Goswami N. Antiretroviral Drugs and the Human Gut Microbiome: Implications for the development of cardiovascular diseases in people living with HIV-An Austrian/South African Project. InACTA PHYSIOLOGICA 2019 Sep 1 (Vol. 227, pp. 42-42). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY.

37. Tata CM, Sewani-Rusike CR, Oyedeji OO, Gwebu ET, Mahlakata F, Nkeh-Chungag BN. Antihypertensive effects of the hydro-ethanol extract of Senecio serratuloides DC in Aremu OO, Tata CM, Sewani-Rusike CR, Oyedeji AO, Oyedeji OO, Nkeh-Chungag BN. Phytochemical composition, and analgesic and antiinflammatory properties of essential oil of Chamaemelum nobile (Asteraceae L All) in rodents. Tropical Journal of Pharmaceutical Research. 2018; 17: 1939-45.

38. Aremu OO, Tata CM, Sewani-Rusike CR, Oyedeji AO, Oyedeji OO, Nkeh-Chungag BN. Phytochemical composition, and analgesic and antiinflammatory properties of essential oil of Chamaemelum nobile (Asteraceae L All) in rodents. Tropical Journal of Pharmaceutical Research. 2018; 17: 1939-45. DOI: 10.4314/tjpr.v17i10.7

39. Tata CM, Gwebu ET, Aremu OO, Nkeh-Chungag BN, Oyedeji AO, Oyedeji OO, Rusike CR. Acute toxicity study and prevention of Nω-nitro-L-arginine methyl ester-induced hypertension by Osteopermum imbricatum. Tropical Journal of Pharmaceutical Research. 2018; 17:1111-8. DOI: 10.4314/tjpr.v17i6.18

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41. Sekotla MA, Goswami N, Sewani-Rusike CR, Eputo JE, Nkeh-Chungag BN. Prevalence

of metabolic syndrome in adolescents living in Mthatha, South Africa. Ther Clin Risk Manag. 2017; 13: 131–137. DOI:10.2147/TCRM.S124291

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45. Taylor A, Oyedeji OO, Aremu O, Oyemitan I, Gwebu ET, AO Oyedeji, Nkeh-Chungag BN. Assessment of the analgesic, anti-inflammatory and sedative effects of dichloromethanol extract of Schinus molle. European Review for Medical and Pharmacological Sciences. 2016; 20; 372-380.

46. Rali S, Oyedeji O, Aremu K, Oyedeji O, Nkeh-Chungag B. Semi-synthesis of derivatives of oleanolic acid from Syzygium aromaticum and their antinociceptive and anti-inflammatory properties. Mediators of Inflammation. 2016; https://doi.org/10.1155/2016/8401843

47. Sekokotla AM, Nkeh-Chungag BN, Iputo JE, Sewani-Rusike CR, Malema IM, Adeniyi OV, Goon DT. Serum magnesium and high sensitive c-reactive protein in hypertensive obese female school learners. 2016. DOI: 10.7727/wimj.2015.292. http://www.mona.uwi.edu/fms/wimj/article/2879 (epub)

48. Rungqu P, Oyedeji O, Nkeh-Chungag B, Songca S, Oluwafemi O, Oyedeji A. Anti-inflammatory activity of the essential oils of Cymbopogon validus (Stapf) Stapf ex Burtt Davy from Eastern Cape, South Africa. Asian Pacific Journal of Tropical Medicine 2016; ▪(▪): 1–6. doi:10.1016/j.apjtm.2016.03.031

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50. Siviwe Stolom, Idris A. Oyemitan, Reuben Matewu, Opeoluwa O. Oyedeji, Samuel O. Oluwafemi, Benedicta N. Nkeh-Chungag, Sandile P. Songca, Adebola O. Oyedeji Chemical and biological studies of Lobelia flaccida (C. Presl) A.DC leaf: a medicinal plant used by traditional healers in Eastern Cape, South Africa. Trop J Pharmaceut Res. 2016; 15: 1715-1721. DOI: 10.4314/tjpr.v15i8.17

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55. Nkeh-Chungag BN, Sekokotla AM, Sewani-Rusike C, Namugowa A, Iputo JE. Prevalence of Hypertension and Pre-Hypertension in 13–17 Year Old Adolescents Living in Mthatha – South Africa: a Cross Sectional Study. Central European Journal of Public Health. 2015; 23: 211-214. DOI: 10.21101/cejph.a3922

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57. Sekokotla AM, Nkeh-Chungag BN, Iputo JE, Sewani-Rusike CR, Malema IM, Adeniyi OV, Goon DT. Serum Magnesium and High Sensitive C-Reactive Proteins in Hypertensive, Obese Female School Learners. West Indian Med J DOI: 10.7727/wimj.2015.292.

58. Nkeh-Chungag BN, Oyedeji OO, Oyedeji AO, Ndebia EJ. Anti-Inflammatory and

Membrane-Stabilizing Properties of Two Semisynthetic Derivatives of Oleanolic Acid. Inflammation. 2015; 38: 61-69. (2014 Aug 31. [Epub ahead of print]DOI: 10.1007/s10753-014-0007-y)

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65. Ralebona N, Sewani-Rusike CR, Nkeh-Chungag BN. Effects of ethanolic extract of Garcinia kola on sexual behaviour and sperm parameters in male Wistar rats. African Journal of Pharmacy and Pharmacology. 2012; 6: 1077 – 1082. doi: 10.1111/and.12447

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RESEARCH GRANTS

Funding Agency	Funding Period	Sum in Rand
NRF Competitive Program for Rated Researchers	2021 – 2023	
European and Developing Countries Clinical Trials Partnership (**EDCTP**)/ DSI COVID research fund Co-PI)	2021 – 2022	
South African Medical Research Council (SHIP)	2021 – 2022	
MRC Self-Initiated Research Grant (PI)	2018 – 2020	
TIA Seed funds for product development (PI)	2017	
NRF Competitive Program for Rated Researchers	2017– 2019	
Austria-South Africa Collaborative research projects (Co-PI)	2017 – 2018	
ERAfrica/DST EndoAfrica (WSU – PI):	2016 – 2018	
NRF IKS funds (PI):	2015 – 2017	
TIA Research Funds (PI):	2015	
NRF IKS seed fund (PI):	2014	
NRF IKS (co-investigator)	2013 – 2015	
Walter Sisulu University Research Grant (PI):	2013	
MRC SIR Grant (PI):	2011	
NRF rated scientist incentive fund (PI)	2012 – 2017	
Walter Sisulu Institutional Research Grant (PI):	2010	
Walter Sisulu Institutional Research Grant (PI):	2009	
Walter Sisulu Institutional Research Grant (PI):	2008	

CONFERENCE ATTENDANCE

1. Engwa G, Letswalo P, Nkeh-Chungag B. Obesity, hypertriglyceridaemia and endothelial dysfunction are risk factors of hypertension in South African adolescents. ESH-ISH Joint Conference (11-14 April 2021). Journal of Hypertension. 39:e187, April 2021. (Abstract)

2. Nkeh-Chungag BN, Matjuda E. A study of determinant of blood pressure in 6–9 year old children in the eastern cape of South Africa. . ESH-ISH Joint Conference (11-14 April 2021). Journal of Hypertension. 39:e332, April 2021. (Abstract)

3. Letwalo PB, Matjuda EN, Sewani-Rusike CR, Nkeh-Chungag BN. An exploration of the relationship between endothelial function, blood pressure and anthropometric measurements in 6-8 year old rural versus urban children in the Eastern Cape Province of South Africa. Hypertension. 2018; 72 (Suppl 1): AP105 (Abstract)

4. Nkeh-Chungag BN, Chungag A, Sewani-Rusike CR. Urban and rural differences in exposure and effects of micro air particles on blood pressure parameters. Hypertension. 2018;72. AP106 (abstract) doi.org/10.1161/hyp

5. Matjuda EN, Letswalo PB, Sewani-Rusike, Nkeh-Chungag BN. Association of pulse wave velocity with hypertension and anthropometric measurements in 6-8 years old children in Mthatha, South Africa. Hypertension. 2018; 72. (abstract) doi. org/10.1161/hyp.

6. Nkeh-Chungag B, Matjuda EN, Sewani-Rusike C. Relationship between endothelial function and blood pressure in 6–8 year old children in the Eastern Cape of South Africa. J Hypertens. 2018; 36: p e320. (abstract) doi: 10.1097/01. hjh.0000549306.63999.c8.

7. Mbombela V, Sewani-Rusike C, Musaruwa H, Nkeh-Chungag BN. Relationship between CD4 count and creatinine/albumin ratio in HIV-positive patients: Clin Chem Lab Med. 2018. 56:eA115 (abstract)

8. Sekokotla AM, Nkeh-Chungag BN, Iputo JE. Overweight and obese adolescents from Mthatha – South Africa may have a greater risk of hypertension and pre-hypertension. Appetite. 2015; 89: 313. (abstract)

9. Nkeh-Chungag BN, Sekokotla AM, Iputo JE. Influence of BMI, hip and waist circumferences on serum hs-CRP levels and blood pressure in adolescents living in Mthatha". Journal of Diabetic Research and Clinical Practice: Diabetes Research and Clinical Practice. 2014; 103: S43 (abstract). DOI: https://doi.org/10.1016/ S0168-8227(14)70142-1

10. Nkeh-Chungag BN, Sekokotla AM & Iputo JE. Influence of BMI, waist and hip circumferences on some risk markers for cardiovascular diseases in adolescents living in Mthatha. Journal of Obesity and Weight Loss Therapy. 2013, 3:7

(abstract). DOI:1 0.4172/2165-7904.S1.010

11. Mbombela V, Sewani-Rusike CR, Musaruwa H and Nkeh-Chungag B. 2018. Relationship between Cd4 count and creatinine/ albumin ratio in HIV-positive patients: p10. Clinical Chemistry and Laboratory Medicine, 56(6), p.eA115. (Abstract) 10.1016/j. appet.2014.12.042.

CONFERENCE PRESENTATION

ORAL AND POSTER PRESENTATIONS AT ACADEMIC CONFERENCES

1. Nkeh-Chungag BN. Are anthropometric normative reference values established in one population useful for obesity screening in another? (Plenary) AAPS-PSSA Online Congress, 12-15 September 2021.

2. Nkeh-Chungag BN, Walter Sisulu University, SA: Association of indoor air particulate matter count with obesity and blood pressure parameters in 10-14 year old children. Child Health Paradox Conference. Insbruck – Austria 10-11 November 2020.

3. Mbombela V Sewani-Rusike, CR and Nkeh-Chungag BN. 2019. The association between erectile function and markers of metabolic syndrome in newly diagnosed HIV positive and HIV negative men in Mthatha, South Africa. SAMRC Symposium 2019, ICC East London, 29-31 August, 2019.

4. Chungag A, Sewani-Rusike CR, Nkeh-Chungag BN. Urban and rural differences in exposure and effects of micro air particles on blood pressure parameters. (American Heart Association Conference 6-9 September 2018, Chicago, USA).

5. Matjuda EN, Sewani-Rusike CR, Nkeh-Chungag BN. Relationship between endothelial function and blood pressure in 6-8 year old children in the Eastern Cape of South Africa. (International Hypertension Society 20-23 September 2018, Beijing-China).

6. Mbombela VS, Msarurwa H, Sewani-Rusike CR, BN Nkeh-Chungag. Relationship between CD4 count and creatinine/albumin ratio in HIV-positive patients. Graz-Austria, ISMD2018. May 31st and June 2, 2018.

7. Tata CM, Sewani-Rusike CR, Oyedeji OO, Nkeh-Chungag BN. Differential acute toxicity, antioxidant and antihypertensive effects of chemical fractions of Senecio serratuloides. Basel – Switzerland from 3-7 September 2017.

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9. Chungag A, Tata CM, Sewani-Rusike CR, Matjuda EN, Chingombe W, Nel W, Nkeh-Chungag BN. Is there a possible relationship between BMI, ankle circumference and blood pressure? 28-29 November 2017, Polokwane South Africa.

10. Aremu OO, Tata CM, Sewani-Rusike C, Matewu M, Oyedeji AO, Oyedeji OO, and Nkeh-Chungag B.N. Acute and sub-chronic antihypertensive properties of Taraxacum officinale in L-NAME-induced hypertensive rats. 44th Congress of the Physiological Society of Southern Africa.

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12. Nkeh-Chungag BN, Sekokotla AM, Iputo JE. Comparison of some cardiometabolic risk factors in peri-urban adolescent school learners in Mthatha, South Africa 4th International Conference and Exhibition on Obesity & Weight Management. 7 – 9 December 2015 (Atlanta – USA).

13. Nkeh-Chungag BN. Are adolescents at greater risk of hypertension today than they were in the last two decades? Congress of the Physiological Society of Southern Africa. 14 – 17 September 2014 (Durban – South Africa).

14. Sekokotla AM, Nkeh-Chungag BN and Iputo JE. Overweight and obese adolescents from Mthatha – South Africa may have a greater risk of hypertension and pre-hypertension. Annual Conference of the European Childhood Obesity Group 13 – 15 November 2014 (Salzburg – Austria).

15. Nkeh-Chungag BN, Sekokotla AM, Iputo JE. Influence of BMI, hip and waist circumferences on serum hs-CRP levels and blood pressure in adolescents living in Mthatha". 25 – 28 February 2014 (Yaoundé – Cameroon).

16. Nkeh-Chungag BN, Sekokotla AM & Iputo JE. Influence of BMI, waist and hip circumferences on some risk markers for cardiovascular diseases in adolescents living in Mthatha. 02-04 December 2013 (Las Vegas – USA).

17. Aremu O, Nkeh-Chungag BN, Ndebai JE, Iputo JE. The effects of Cordia platythyrsa on various experimental models of pain and

carrageenan induced inflammation. 01- 06 December 2013 (East London – South Africa).

18. Nkeh-Chungag BN, Sekokotla AM, Sewani-Rusike CR, Iputo JE. Does culturally acceptable overweight/obesity contribute to the risk of cardiovascular diseases in peri-urban female adolescents? 15-18 September 2013 (Pretoria – South Africa).

19. Nkeh-Chungag BN, Ndebia EJ, Opeoluwa O. Oyedeji and Adebola O. Oyedeji. Anti-inflammatory and membrane stabilizing properties of two semi-synthetic derivatives of oleanolic acid. 2nd Biotechnology World Congress. 18-21 February 2013. (Dubai-UAE).

20. Nkeh-Chungag BN, Sekokotla AM, CR Rusike, Iputo JE. Determination of some risk factors for CVDs in adolescents aged 13-17 years old living in Mthatha. Congress of the Physiological Society of Southern Africa. 10-23 September 2012. (Stellenbosch – South Africa).

21. Sekokotla MA, Nkeh-Chungag BN, Iputo JE. Association of serum adiponectin levels and waist/hip circumferences with higher blood pressures in adolescents living in Mthatha. Congress of the Physiological Society of Southern Africa. 10-23 September 2012. (Stellenbosch – South Africa).

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23. Kamadyaapa D, Rusike C, Nkeh-Chungag BN. Evaluation of antioxidant and antihyperglycemic effects of ethanolic leaf extract of Erythrina abyssinica. Congress of the Physiological Society of Southern Africa. 10-23 September 2012. (Stellenbosch – South Africa).

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25. Mxhosa TH, Mgoduka NP and Nkeh-Chungag BN. Influence of waist and hip circumferences on the blood pressure of Walter Sisulu University students. WSU International Research Conference. 21-24 August 2012. (East London – South Africa).

26. Mgoduka NP, Mxhosa T and Nkeh-Chungag BN. Perceptions and knowledge of some risk factors of hypertension among Walter Sisulu University students. WSU International Research Conference. 21-24 August 2012. (East London – South Africa).

27. Kamadyaapa D, Sewani-Rusike C and Nkeh-Chungag BN (2012). Evaluation of the antioxidant and antihyperglycemic effects of ethanolic leaf extract of Erythrina abyssinica. WSU International Research Conference. 21-24 August 2012. (East London– South Africa).

28. Sekokotla AM Nkeh-Chungag BN and Iputo JE (2012). Dietary preferences in adolescents aged 13-17 years old living in Mthatha. WSU International Research Conference. 21-24 August 2012. (East London– South Africa).

29. Nkeh-Chungag BN, Namugowa A, Sewani-Rusike C and Iputo JE. Influence of obesity on peripheral and central blood pressure components in female students of African ancestry from Walter Sisulu University. International Society of Hypertension – teaching seminar. 6-7 October 2011. (Maputo – Mozambique).

30. Nkeh-Chungag BN, Njamen D, Tchoukouegno DS, Mvondo MA, Tagne J. Estrogenic properties of ethanolic stem bark extracts of Fernandoa adolfi-friderici (Bignoniaceae). TWOWS 4th General Assembly and International Conference. 27-30 June 2010 (Beijing – China).

31. Nkeh-Chungag BN, Sewani-Rusike C, Chungag A. Physiological aspects of geophagia. International Conference on Geophagia. 19-24 October 2008. (Bloemfontein – South Africa).

32. Nkeh-Chungag BN, Ndebia EJ, Mpholwane M. Peripheral analgesic properties of a lignan isolated from Oxyanthus uniloculatis. Congress of the Physiological Society of Southern Africa.16-19 September 2008. (Pretoria – South Africa).

33. Bekwa PCM, Ndebia EJ, Nkeh-Chungag BN. Analgesic properties of Oxyanthus unilocularis. Congress of the Physiological Society of Southern Africa.16-19 September 2008. (Pretoria – South Africa).

34. Nkeh-Chungag BN, Sibanda Z, Songca N (2008). Toxicity studies of some commonly used medicinal plants of the Mthatha area. 1st WSU International Research Symposium. 2008. (Mthatha – South Africa).

35. Ndebia EJ, Bekwa PCM, Nkeh-Chungag BN (2008). In vivo analgesic and anti-inflammatory activities of Oxyanthus unilocularis. 1st WSU International Research Symposium. 2008. (Mthatha – South Africa).

36. Gasa ZP, Jafta V, Bekwa PCM, Ndebia EJ, Nkeh-Chungag B (2008). Investigation of the analgesic properties of the methanol extract of

Cordia platythyrsa. 1st WSU International Research Symposium. 2008. (Mthatha – South Africa).

37. Nkeh-ChungagAnye BN and Kingue S. Gender-dependent influence of age, BMI and waist-to-hip ratio on SBP in a sub-urban African population. Panafrican Hypertension Meeting Cameroon. 2-5 December 2005. (Yaoundé Cameroon).

38. Nkeh B, Woodiwiss AJ, Samani NJ, Badenhorst D, Maseko M, Tiago A, Candy GP, Dube H, Libhaber E, Sareli P, Brooksbank R, Norton GR. Functional varaints of the angiotensinogen gene determine anti-hypertensive response to angiotensin-converting enzyme inhibitors in subjects of African ancestry. Physiology Society of Southern African. 13-15 September 2004. (Coffee Bay – South Africa).

39. Nkeh B, Badenhorst, AD Tiago, GP Candy, M Maseko, GR Norton, AJ Woodiwiss. The role of the angiotensiongen gene as a risk factor for hypertension in subjects of African ancestry. Congress of the South African Hypertension Society. 7-9 March 2003. (Johannesburg– South Africa).

40. Norton GR, Tiago A, Bardenhorst D, Nkeh B, Candy G, Sareli P and Woodiwiss A. Independent association of an aldosterone synthase gene variant with ambulatory and office blood pressure in recently diagnosed hypertensives. Congress of the South African Hypertension Society. 7-9 March 2003. (Johannesburg – South Africa).

41. Dube H, Nkeh B, Badenhorst B, Tiago A, Brooksbank R, Maseko M, Sareli P, Woodiwiss A, Norton G. An interaction between functional promoter region variant of the angiotensinogen gene and risk of hypertension in black South Africans. Congress of the South African Hypertension Society. 7-9 March 2003. (Johannesburg – South Africa).

42. Maseko M, Nkeh B, Badenhorst B, Tiago D, Brooksbank R, Dube H, Sareli P, Woodiwiss A, Norton G. An interaction between functional promoter region variants of the angiotensiongengen determines blood pressure in black South Africans. Congress of the South African Hypertension Society. 7-9 March 2003. (Johannesburg – South Africa).

43. Woodiwiss A, Nkeh B, Badenhorst D, Tiago A, Candy G, Sareli P, Woodiwiss A, Norton G. A stimulatory guanosine triphsophate protein gene variant is associated with hypertension and blood pressure in black South Africans. Congress of the South African Hypertension Society. 7-9 March 2003. (Johannesburg – South Africa).

44. Nkeh B, Badenhorst D, Dube H, Brooksbank R, Woodiwiss A, Norton G. Association between angiotensinogen gene promoter region and hypertension in black South Africans. Congress of the Physiological Society of Southern Africa. 2002. (Stellenbosch – South Africa).

45. Nkeh B, Badenhorst D, Dube H, Tiago AD, Brooksbank R, Maseko M, Serali P, Woodiwiss AJ, Norton GR. A promoter region variant of the angiotensinogen genes is associated with hypertension in female black South Africans. Congress of the Physiological Society of Southern Africa. 2002. (Stellenbosch – South Africa).

46. Nkeh B, Tiago AD, Badenhorst D, Candy G, Libhaber H, Libhaber C, Serali P, Norton GR, Woodiwiss AJ. Angiotensinogen gene variant modifies the impact of ambulatory blood pressure on left ventricular mass in hypertension. Congress of the Physiological Society of Southern Africa. 2002. (Stellenbosch – South Africa).

47. Nkeh B, Badenhorst D, Tiago AD, Candy GP, Serali P, Norton GR, Woodiwiss AJ. Inhibitory and excitatory Guanosine triphosphate protein gene variants modify the impact of body size on blood pressure in hypertension. Congress of the Physiological Society of Southern Africa. 2002. (Stellenbosch – South Africa).

48. Nkeh B, Tiago A, Badenhorst D, Candy G, Libhaber E, Sliwa K, Deftereos D, Brooksbank R, Serali P, Woodiwiss A, Norton G. Impact of epistasis between G protein and angiotensinogen gene polymorphisms increases their penetrance in human hypertension. International Immunopharmacology Congress (2001) (Sun City – South Africa).

49. Nkeh B, Woodiwiss A, Tiago A, Badenhorst D, Candy GP, Radevski IV, Deftereos D, Brooksbank R, Samani NJ, Serali P, Norton GR. Independent association of G protein gene polymorphisms with hypertension in black South Africans. International Immunopharmacology Congress. 2001. (Sun city – South Africa).

50. Nkeh B, Woodiwiss A, Tiago A, Badenhorst D, Candy GP, Radevski IV, Deftereos D, Brooksbank R, Samani NJ, Serali P, Norton GR. Lack of an independent association of an epithelial sodium channel gene with hypertension in black South Africans. International Immunopharmacology Congress (2001). (Sun city – South Africa).

51. Nkeh B, GR Norton, A Tiago, R Brooksbank, GP Candy, Radevski IV, P Serali, AJ Woodiwiss (2000). Gs alpha protein gene variant is associated with essential hypertension. Congress of the African Association of Physiological Sciences. 2000 (Pretoria – South Africa).

52. Tiago A, Nkeh B, Candy GP, Badenhorst D, Deftereos D, Netjhardt M, Luker F, Samani N, A Woodiwiss, G Norton. Association study of eight candidate genes with renin status in mild to-moderate hypertension in patients of African ancestry. Congress of the African Association of Physiological Sciences. 2000. (Pretoria – South Africa).

FELLOWSHIPS AND RESEARCH AWARDS

WSU Vice Chancellor's award for Community Engagement	2019
WSU Vice Chancellor's Award for Research and Innovation	2019
Paul Dudley White Award in recognition of research output (AHA)	2018
National Research Foundation Rated Scientist (C3)	2010 to date
WSU Vice Chancellor's Award for researcher who attracted most funds in 2017	2017
Winner of the YK Seedat prize for the best oral presentation at the 13th Congress of the South African Hypertension Society,	2003
Third World Organization for Women in Science (TWOWS) fellowship for PhD	2000-2003

Professorial Inaugural Presentation

by
Professor Benedicta Ngwenchi Nkeh-Chungag

ARE CARDIOVASCULAR DISEASES A CAUSE FOR CONCERN IN PEOPLE OF AFRICAN ANCESTRY?

ABSTRACT

Hypertension is a multifactorial condition and the most important risk factor for cardiovascular diseases (CVDs). Hypertension in people of African ancestry is characterized by an earlier onset, poor control and greater severity compared to other races. This is a clear indication that genetic differences across ethnic populations may be implicated in the etiology of the disease. Twin studies have, however, shown that environmental factors, especially those associated with lifestyle changes, play an important role in the risk for hypertension and consequently CVDs. Sub-Saharan Africa is undergoing rapid urbanization accompanied by lifestyle changes which have an impact on the gene expression of people of African ancestry making them susceptible to chronic diseases such as hypertension and CVDs. Therefore, addressing hypertension and its risk factors such as obesity and stress will greatly contribute to reducing the risk of CVDs in this population. I will in this Professorial Inaugural Lecture demonstrate how my studies have evolved from some genetic aspects of hypertension to the assessment of CVD risk factors in South African children of African ancestry and how medicinal plants may play a role in the management of hypertension. I will also explore the possibility that currently used normative reference values for diagnosing obesity, a risk factor for hypertension, may not be adequate in people of African ancestry.

Citation

"If it had not been the LORD who was on my side,"
Let Benedicta now say—
"If it had not been the LORD who was on my side,…
My help *is* in the name of the LORD,
Who made heaven and earth. Psalm 124: 1,2,8

ACKNOWLEDGEMENTS

My utmost gratitude goes to the Lord God Almighty, maker of the Heavens and Earth. Indeed, 'If it had not been for You, where would I be …? You are Lord.

I am grateful to Walter Sisulu University for giving me the opportunity to grow and pursue my passion.

Sincere gratitude to the Vice Chancellor and Principal of Walter Sisulu University, Prof Rushiella Songca for her vision and leadership. Thank you for reinstituting Professorial Inaugural Lectures in this university. It is a great privilege to be the first one in this new dispensation to present my Professorial Inaugural Lecture.

I have received enormous support from the top management of the university. My Mzolisi Payi – thank you for ensuring that my family members are able to physically participate in this ceremony. I am grateful to the Senior Director of Research, Prof Wilson Akpan, the Senior Director of Marketing, Mrs Yonela Tukwayo and her division, my Campus Rectorate – Mr Francis Kwahene and Prof Elphina Cishe who supported in many ways and ensured that all activities are on track. Thank you.

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To my spouse Dr Chungag Anye, thank you for your selflessness and boundless support and for always encouraging me to scale heights. Thank you to our children, Dr Samuel Nkeh Chungag Anye, Benjamen Fon, Paul Chungag Anye, Joseph Alma Chunga Anye. You make life worth living.

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Thank you to all who have supported me in one way or the other. I am grateful for your well-wishes and prayers.

PREFACE

I was very young when my mother's health started failing. It was said that she had hypertension. I somehow hoped that like malaria, which was rampant, she would take some medications and get well and our lives would return to normal. She faithfully took her medication but the disease instead of improving, rather progressed. I remember as a child leaning on her shoulder, I told her, 'Mami I will study very hard and find a cure for hypertension so that you would not be sick anymore'. My mother hugged me and said, 'I believe you. Even if I do not live to see you do this, I want you to keep your promise and help others who would be affected by hypertension'. She understood the ways of life better than my childhood brain could fathom. She passed away before I could start pursuing this dream.

My research career started in a rather interesting way. Although the desire to learn more about hypertension was burning in my heart, I lacked the opportunity to do so. I therefore started where I could – intestinal motility. God knows the desires of our hearts and grants them. I was later given the opportunity to study in the university of the Witwatersrand, where I started researching on the genetic determinants of hypertension in people of African ancestry. These were my first steps in the direction of trying to keep the promise to my mother.

I have worked with colleagues on various topics while maintaining my interest in hypertension. The real breakthrough came when I received a grant from the MRC to investigate the risk factors for hypertension in adolescents of African ancestry in 2010. Research opportunities have since then hurtled over one another and I have been kept very busy trying to find the cause(s) of hypertension in people of African ancestry.

I wish I could at this time say, 'Mami, this is what I have found!'. Alas, there have been several challenges on the way. It is my ardent desire that sooner rather than later a plant-based medication for hypertension would be developed from my studies. To complement this would be the description of the risk profile in children that would predict hypertension in adulthood.

In this booklet, I summarise the research work that I have done in chapters, each with a specific theme. The themes range from some genetic aspects of hypertension, hypertension risk in children, mechanisms associated obesity with hypertension and the use of medicinal plants for the management of pain & inflammation and hypertension & metabolic syndrome and erectile dysfunction.

I trust you will be able to wrap your head around this presentation and draw some useful lessons to share with others.

CONTENTS

Chapter 1

Aspects of the genetic determinants of hypertension in people of African ancestry

Abstract

Blood pressure (BP) is a heritable trait and thus primary hypertension tends to have a strong genetic component. There is evidence that hypertension and BP control in people of African ancestry are distinct in many respects compared to other races. Thus, my research focus in this chapter is to explore the role of gene candidates associated with BP measures/ hypertension in people of African ancestry. Single nucleotide polymorphisms (SNPs) associated with hypertension in African and non-African populations were explored. The contribution of selected SNPs to response to antihypertensive therapy was also studied in this cohort. Some of the studied SNPs showed associations with hypertension in people of African ancestry. We also showed that Africans living in the diaspora did not have the same phenotype as populations in Africa. We also revealed that genetic changes may influence the antihypertensive response to medications in people of African ancestry.

1.1 Introduction

Hypertension is one of the leading causes of death globally, and a primary risk factor for cardiovascular diseases (Kearney et al., 2005). As a multifactorial disease, hypertension occurs as a consequence of the complex interplay between environmental risk factors with multiple genetic factors (Fadlalmula et al., 2021). Genetic factors give an insight to the predisposition of an individual to the disease (Virdis et al., 2010). Pre-adolescent children of Caucasian and African ancestry have similar BPs though the increase in BP accompanying post-pubertal years is greater in young adults of Africans (Rabinowitz et al., 1993).

Some genes have been associated with essential hypertension (EHT) and the mode of impact of these genes on BP has been identified. There is documentary evidence that suggests association of certain candidate genes with hypertension. The genes reported herein are the epithelial sodium channel (ENaC), renin angiotensin aldosterone system (RAAS) (Woodiwiss et al., 2006;). Angiotensin converting enzyme (ACE), Angiotensinogen (AGT) and aldosterone synthase (*CYP11B2*) gene variants have also been shown to produce an effect on BP in human subjects (Tiago et al., 2003). The severity of hypertension is of prognostic importance and thus, knowledge of the impact of candidate genes on BP in hypertension is of great significance. Individual responsiveness to BP following antihypertensive therapy is variable (Bidiville, 1988). Studies have suggested that genetic variation may be responsible for this difference and could serve as a useful marker to predict the therapeutic efficacy of hypertensive medication (Kurland et al., 2004). The aim of these studies was to identify SNPs described in other populations and then to determine their association with BP and hypertension in a large cohort of people of African descent.

1.2 Methods

Deoxyribonucleic acid (DNA) was extracted from whole blood by red blood cell lysis and digestion of the remaining white cell pellet with proteinase K (Lahiri et al 1992). Primer pairs for target DNA sequences were designed and DNA amplified using polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP)-based techniques. In a subset of participants, either an open label ACEI or calcium channel blocker was administered, or impact of SNPs on antihypertensive response was assessed.

1.3 Results

The results are summarized in Table 1 below. The Table shows the association of the SNPs with hypertension and risk factors of hypertension in a population of African ancestry.

Table 1: Summary of impact of polymorphisms on risk for hypertension

	Objectives	Findings	Reference
1.	To determine the prevalence and role of the T594M variant of the β-subunit of the ENaC gene in hypertension in South African individuals of African ancestry	• No differences in frequency distribution of the T594M • There were no differences in clinic or ambulatory (day/night) BP in cases and controls. • Results did not support an important role for the T594M polymorphism of the ENaC β-subunit gene in contributing to either the development or severity of hypertension in subjects of African descent	Nkeh et al., 2003
2.	To determine whether the angiotensinogen (AGT) gene polymorphisms influence hypertension risk and ambulatory blood pressure (ABP) in people of African ancestry	• The -217G→A polymorphism was only modestly associated with hypertension risk. • Interactions between the -217G→A and -20A→C polymorphisms influenced both hypertension risk and ABP • The impact of the -217G→A polymorphism on hypertension risk and ABP was abolished in those subjects with at least one copy of the -20C allele.	Nkeh et al., 2005
3.	To investigate the relationship between the Atrial Natriuretic Peptide (ANP) gene polymorphism and Blood Pressure in people of African Ancestry	• No relationship between the exon 3 polymorphism on either the presence or severity of hypertension was noted • The intron 2 polymorphism occurred at a low frequency in the control group but was almost absent in the hypertensive group. • A relationship between normal BP and the intron 2 polymorphism was noted.	Nkeh et al., 2002
4.	To determine whether genetic variants within the angiotensinogen (AGT) gene may influence patients' response on monotherapy with angiotensin-converting enzyme inhibitor (ACEI) or a calcium channel blocker	• ACEIs in patients with the AA genotype of the -217G→A polymorphism failed to elicit an antihypertensive response. • Patients with at least one copy of the -217G allele showed some response ACEI administration. • Patients who had the AA genotype for both polymorphisms failed to develop an antihypertensive response to ACEIs whereas patients with at least one copy of both the -217G allele and the -20C allele developed substantial decreases in ABP following ACEI therapy. • Patients with at least one copy of the –217G allele demonstrated a significant reduction in aldosterone-to-renin ratio.	Woodiwiss et al., 2006
5.	To evaluate the impact of Renin-Angiotensin-Aldosterone System (RAAS) gene variants on BP in newly diagnosed hypertensive patients	• Severity of hypertension was associated with the *CYP11B2* locus in patients of African ancestry. • Both the angiotensin-converting enzyme (ACE) insertion/deletion and AGT gene polymorphisms were associated with ambulatory and office SBP or DBP. • The *CYP11B2* gene polymorphism was associated with both ambulatory and office BP.	Tiago et al., 2003
6.	To assess whether variants of genes that encode for substances that directly or indirectly modulate the RAAS activity can account for RAA system variance in black HTs from South Africa.	• We observed that plasma renin-aldosterone (PRA) values tended to be lower in patients homozygous for the G-6A variant while aldosterone (ALD) values tended to be lower in patients with the C825 allele of the GNB3 gene variant. • The ACE, AGT, GNB3, *CYPIIB2,* ANP exon 3 and α-adducin were not significantly associated with either RA, ALD, or ALD-to-PRA ratios assuming either recessive or dominant inheritance models. • The results obtained do not support a clinically meaningful role for any single gene candidate examined in South Africans hypertensives of African ancestry.	Tiago et al., 2001

1.4 Discussion

There is evidence that blood pressure and hypertension have a strong genetic component. However, it will take time to unravel the contribution of each genetic mutation to the development of the disease. Being a multifactorial trait, it is agreed that no single gene polymorphism can explain the susceptibility of people of African ancestry to hypertension and its secondary effect. The more plausible explanation would lie in multiple gene interaction and interaction with the environment. In my studies, I explored the possible interaction of SNPs within the same gene loci and how these could affect blood pressure levels and severity of hypertension. Indeed, our studies show that interactions between the -217G →A and -20A→C polymorphisms account for a substantial portion of the risk for hypertension and ambulatory blood pressure in hypertension.

The effects of the -217G→A and the -20A→C polymorphisms, as well as their influence on BP and responses to ACEI therapy can be explained by their impact on extra renal AGT production and consequently RAAS activity. The -217G→A polymorphism has been shown to enhance AGT gene transcription (Jain et al., 2002). On the other hand, the -20A→C polymorphism has been shown to play a role in the transcription of angiotensinogen (Zhao et al., 1999). This explains why ACEI therapy, does not prevent patients with the –217AA genotype and/or the – 20AA from producing large amounts of angiotensinogen (Husain, 1993). The findings in this study showing that the aldosterone-to-renin ratio was not reduced in subjects with the –217AA genotype are consistent with this possibility.

Our studies showed that a functional polymorphism of the GNB3 gene (Siffert et al., 1998) has a marked influence on the impact of body size on BP. The relation between body size and SBP in hypertensives was noted only in those patients homozygous for the risk allele (825T), but not in patients with at least one copy of the 825C allele. It was also noted that although the 825C→T polymorphism did not produce an independent effect on either BP in hypertensives, or the risk for hypertension, it accounted for body size differences between subjects. Body size ultimately would affect blood pressure. This SNP clearly demonstrates the fact that a risk genotype may not act on blood pressure directly but may affect one of the risk factors which in turn affects blood pressure.

The T594M polymorphism of the ENaC gene which was thought could explain the high prevalence of salt sensitive hypertension in people of African ancestry was neither associated with the presence of hypertension, nor with BP in hypertensive and normotensive subjects.

Also described is the role of the ANP locus on the development of hypertension in individuals of African descent. This polymorphism showed protective effects against hypertension though the frequency of the allele was very low.

1.5 Highlights

- The prevalence of the T594M variant was not different between hypertensive and non-hypertensive participants. Furthermore, the T594M variant was not associated with the presence of hypertension in people of African ancestry.

- Studies on the functional polymorphisms of the AGT showed that the -217G→A polymorphism was only modestly associated with hypertension risk though interactions between the -217G→A and - 20A→C polymorphisms influenced both the hypertension risk and ambulatory blood pressure (ABP).

- Studies on the functional variants of the AGT gene contribute towards the variability of ABP responses to ACEI therapy in patients of African origin. Patients with at least one copy of both -217G→A and -20A→C allele developed substantial decreases in ABP.

1.6 Conclusion

Certain genes involved in blood pressure regulation could influence the risk of hypertension development while other genes could determine response to antihypertensive therapy.

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Chapter 2

Hypertension and Cardiovascular Risk in South African Children of African Ancestry

Abstract

Cardiovascular diseases (CVDs) are a worldwide problem with increased morbidity and mortality. CVD risk factors are known to begin early in life and track to adulthood as there is growing prevalence in children population across the world. However, limited data on these prevailing risk factors is available for South African of African ancestry. To investigate the presence of CVD risk factors, we conducted several studies utilising cross-sectional, case-control and descriptive comparative studies in children, adolescent and adult population. Our findings showed that cardiovascular risk factors including obesity, metabolic syndrome, oxidative stress, chronic low-grade inflammation, albuminuria and hypertension were prevalent in children and adolescent population. These risk factors were associated with hypertension and vascular dysfunction. Apart from the metabolic risk factors, HIV, antiretroviral treatment and air pollution were associated with cardiovascular risk factors. These findings suggest that South African children of African ancestry may be at risk of developing CVDs in future. Therefore, intervention strategies are necessary for the prevention of CVD development in this population.

2.1 Introduction

Cardiovascular diseases (CVDs) are a worldwide problem. Over 17.9 million deaths due to CVDs were recorded globally in 2019 with about 18% of all deaths in South Africa (WHO, 2021). South Africa is undergoing transition to urbanization adopting western diets and sedentary lifestyles which may be accountable for the increased prevalence of obesity. Due to the heightened risk of cardio–metabolic diseases, there is need for accurate assessment of obesity. Obesity, characterized by excess fat stored in the adipose tissue has been reported to induce inflammation, which is strongly associated with T2D, metabolic syndrome (MetS) and vascular dysfunction (Reisinger et al., 2021). Also, obesity-induced inflammation can lead to oxidative stress by generating reactive oxygen species (ROS) (Engwa et al., 2020a) which may reduce NO levels leading to endothelial dysfunction, an early initiator to the development of atherosclerotic diseases (Park et al., 2015). More so, a reduced level of NO can impair endothelium-dependent vascular relaxation, thereby increasing vascular contraction causing hypertension. On the other hand, hypertension is a known risk of renal dysfunction characterized by elevated creatinine and albumin (Lin, 2013). Apart from metabolic CVD risk factors, HIV/ART (Abrahams et al., 2015) and air pollutants particularly particulate matter (PM) (Lederer et al., 2021) have been associated with increased risk of CVD development. Despite the growing prevalence of CVDs in SSA population, there is paucity of information on the prevailing risk factors for hypertension and CVD in South Africans of African ancestry especially children and adolescents. We therefore, investigated the prevalence of risk factors associated with hypertension in people of African ancestry and attempted to verify the validity of the use of current WHO body mass index cut off points in separating adolescents of African ancestry into lean and overweight and obese categories.

2.2 Methods

Cross-sectional, descriptive comparative and/or case-control studies were conducted in the Eastern Cape Province of South Africa wherein the prevalence of cardiovascular risk factors including obesity, hypertension, metabolic syndrome, microalbuminuria etc were determined. Also, anthropometric measures were compared using receiver operating characteristic (ROC) to assessed obesity screening tools in adolescents (Engwa et al., 2021; Nkeh-Chungag et al., 2015a). In another cross-sectional study, obesity screening tools and cardio–metabolic risk were compared with subcutaneous adipose tissue (Schmid-Zalaudek et al., 2021).

Further, three cross-sectional studies assessed the relationship between obesity (weight, height and waist circumferences) and blood pressure (diastolic blood pressure, systolic blood pressure, heart rate)/metabolic syndrome parameters (lipid profile, blood glucose) (Chungag et al., 2019; Sekokotla et al., 2017, Nkeh-Chungag et al., 2015b). Five studies investigated the relationship of obesity and blood pressure with other cardiovascular risk factors including low-grade inflammation, vascular function, renal function, and oxidative stress (Matjuda et al., 2020a; Matjuda et al., 2021a; Letswalo et al., 2021; Sekokotla et al., 2021; Matjuda et al., 2020b) while one study assessed the relationship between oxidative stress parameters and renal function indices (Matjuda et al., 2022). A study investigated the relationship of HIV and anti-retroviral treatment (ART) with cardiovascular risk factors in adults (Nkeh-Chungag et al., 2021) while a comparative descriptive study assessed the relationship of anthropometric parameters and blood pressure parameters with indoor air particulate matter in school children (Chungag et al., 2021b).

2.3 Results

The prevalence of cardiovascular risk factors: obesity/overweight, pre-hypertension/hypertension, albuminuria and metabolic syndrome ranged 20-40%, 22-42%, 14% and 6.1% respectively and varied across children and adolescents and between boys and girls as summarized in Table 2. Obesity screening tools were assessed in three studies. A study revealed that WHtR and BMI percentile were the most sensitive obesity screening tools in adolescents and ROC analysis revealed that the cut-off value for BMI percentile in this South African adolescent population was lower than the CDC and WHO recommended references (Engwa et al., 2021). Moreover, another study showed that BMI was less accurate than sub-cutaneous fat

measurement in diagnosis obesity in children and adolescent (Schmid-Zalaudek et al., 2021). Several studies showed an association between obesity and blood pressure in children and adolescents (Letswalo et al., 2021; Chungag et al., 2019; Nkeh-Chungag et al., 2015a; (Nkeh-Chungag et al., 2015b).

Six studies reported on the relationship between anthropometric measures with other cardiovascular risk and vascular function. A study showed that obesity and hypertension were associated ($p < 0.05$) with renal-cardiovascular disease risk (increased albumin-to-creatinine ratio (ACR), and/or vascular dysfunction (ADMA and PWV) as well as with oxidative stress in another study (Matjuda et al., 2022; Matjuda et al., 2020a) in children. It was revealed in a study that cardiovascular risk factors (obesity, dyslipidaemia, fasting glucose, hypertension) were associated ($p < 0.05$) with vascular dysfunction (increased PWV and/or ADMA)) in children (Matjuda et al., 2021a) and adolescents (Letswalo et al., 2021). Another study showed that blood pressure parameters were associated with microalbuminuria (Matjuda et al., 2020b). A study revealed that obesity was associated with low-grade inflammation (Sekokotla et al., 2021). HIV patients on ART showed evidence of dyslipidaemia, higher response to flow mediated dilation (Nkeh-Chungag et al., 2021) while $PM_{2.5}$, PM_5 and PM_{10} were positively associated ($p < 0.05$) with obesity in children (Chungag et al., 2021b).

Table 2: Prevalence of Cardiovascular risk factors in children in the Eastern Cape Province.

Year	Type of study	Population type	Sample size	Cardiovascular risk marker	Prevalence (%)	Citation
2022	Cross-sectional	Children	306	Albuminuria	14.05	Matjuda et al., 2022
2021	Cross sectional	Adolescents	1144	obesity based on pBMI	15.5	Engwa et al., 2021
2021	Cross-sectional	Adolescents	244	Overweight/obesity	33	Letswalo et al., 2021
				Pre-HT/HT	38.8	
2020	Cross-sectional	Children	306	E-BP	32.3	Matjuda et al., 2020b
				H-BP	10.5	
				Microalbuminuria	10.1	
2020	Cross-sectional	Children	306	Overweight/obesity by pBMI	19.28	Matjuda et al., 2020a
				Pre-HT /HT	42.16	
2019	Cross-sectional	Adolescents	540	Overweight	10.9	Chungag et al., 2019
				Obesity	14.3	
2017	Cross-sectional	Adolescents	371	Overweight/Obesity	40.2	Sekokotla et al., 2017
				pre-HT/ HT	32.6	
				MetS	4.0	
2015	Cross-sectional	Adolescents	216	Pre-HT/ HT	40.2	Nkeh-Chungag et al., 2015a

Legend: Body mass index (BMI), BMI percentiles (pBMI), elevated blood pressure (E-BP), High blood pressure (H-BP), Metabolic syndrome (MetS), Pre-hypertension (Pre-HT), Hypertension (HT), waist to height ratio (WHtR),

2.4 Discussion

CVD risk factors are known to begin early in life and track into adulthood. This calls for public health concern as it increases the risk of CVD development. The prevalence of obesity was as high as 19% in children and 40 % in adolescents. We further showed a lower BMI cut-off value for screening obesity in a South African adolescent population, different from the CDC recommended cut-off, (Engwa et al., 2021) establishing that obesity screening in children may be ethnic/race specific. The prevalence of hypertension was about 10% in children and increased in adolescents to 42%. Also, children had 6% and 14% prevalence of metabolic syndrome and microalbuminuria, respectively. The increased cardiovascular risk factors may be attributed to the rapid urbanization and lifestyle changes in this population where western diets and sedentary lifestyle has been adopted.

Obesity has been reported to be linked with vascular dysfunction which may be induced by low grade inflammation. Our studies showed an association of obesity with low-grade inflammation (Sekokotla et al., 2021) and vascular dysfunction (Mutjuda et al., 2020a). These findings corroborate with previous studies that have shown obesity to induce vascular dysfunction. Further, vascular dysfunction was associated with hypertension in children and adolescents (Matjuda et al., 2020a). More so, obesity, hypertension, oxidative stress and microalbuminuria were associated with vascular dysfunction (Matjuda et al., 2021a). These findings suggest the early presence of vascular dysfunction in children of African ancestry.

Hypertension is a diseases of public health concern which is strongly associated with obesity as observed in some of our studies. Increased blood pressure may cause renal impairment by damaging the glomerular endothelium of the kidney

(Takase et al., 2015). Our studies in children showed that hypertension was associated with microalbuminuria (Matjuda et al., 2020b) as previously reported (Okpere et al., 2012) while oxidative stress was associated with albuminuria (Matjuda et al., 2022). These findings indicate that hypertension as well as oxidative stress may be implicated in the development of microalbuminuria, a risk for renal disease and CVD development. Apart from metabolic factors, ART was associated with dyslipidaemia in hypertensive South Africans of African ancestry living with HIV concurring with previous studies (Crane et al., 2011). We also observed that high concentration of PMs was positively associated with obesity in children (Chungag et al., 2021b). These findings indicate that there is increased cardiovascular risk in South African children of African ancestry.

2.5 Highlights

- The cut-off value for BMI percentile for obesity screening in South African adolescent population was lower and different from the CDC and WHO recommended references.
- There is increased prevalence of cardiovascular risk factors in South African children of African ancestry.
- Cardiovascular risk factors including obesity, low-grade inflammation, metabolic syndrome, oxidative stress and microalbuminuria are associated with hypertension and vascular dysfunction South African children of African ancestry.
- HIV/ART and particulate matter air pollution are associated with cardiovascular risk factors in people of African ancestry.

2.6 Conclusion

Cardiovascular risk factors including obesity, metabolic syndrome, oxidative stress and microalbuminuria are prevalent and associated with hypertension and vascular dysfunction in South African children of African ancestry.

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Chapter 3

How obesity may be associated with inflammation, oxidative stress and cardiovascular diseases.

3.1 Introduction

Increased inflammation and oxidative stress are known risk factors for endothelial dysfunction. Endothelial dysfunction is in turn an early marker for CVDs (Bottino et, 2015). We have shown that raised blood pressure and hypertension are associated with obesity in children and adults of African ancestry.

3.2 Mechanism of inflammation in adipose tissue

The increasing adoption of urban lifestyles explains the obesity pandemic. When more food is consumed than is burnt up for energy needs, the excess energy is converted to fats and stored in the body.

Under normal circumstances, in lean people, white adipose tissue (WAT) houses M2 macrophages whose roles include tissue surveillance, remodeling, and secretion of anti-inflammatory adipokines such as adiponectin, interleukin 10 and Secreted frizzled-related protein 5 (SFRP5) (Gustafson et al, 2007).

Weight gain results in hypertrophy or hyperplasia of adipose tissue. Hyperplasia being characterized by an increased number of adipocytes while hypertrophy is characterized by engorgement of existing adipocytes with fatty acids. Hyperplasia is generally accompanied by corresponding angiogenesis for proper cell perfusion and oxygenation. On the other hand, hypertrophy occurs rapidly and surpasses angiogenesis resulting in hypoxia and necrosis. Normally, hyperplastic adipocytes have a high number of M2 macrophages while hypertrophic adipocytes have a high number of M1 macrophages (Figure 1). Necrotized adipocytes are surrounded by M1 macrophages which digest the dead cells. M1 macrophages also secret monocyte chemoattractant proteins to increase the number of monocytes in adipose tissue to clear up dead cell debris.

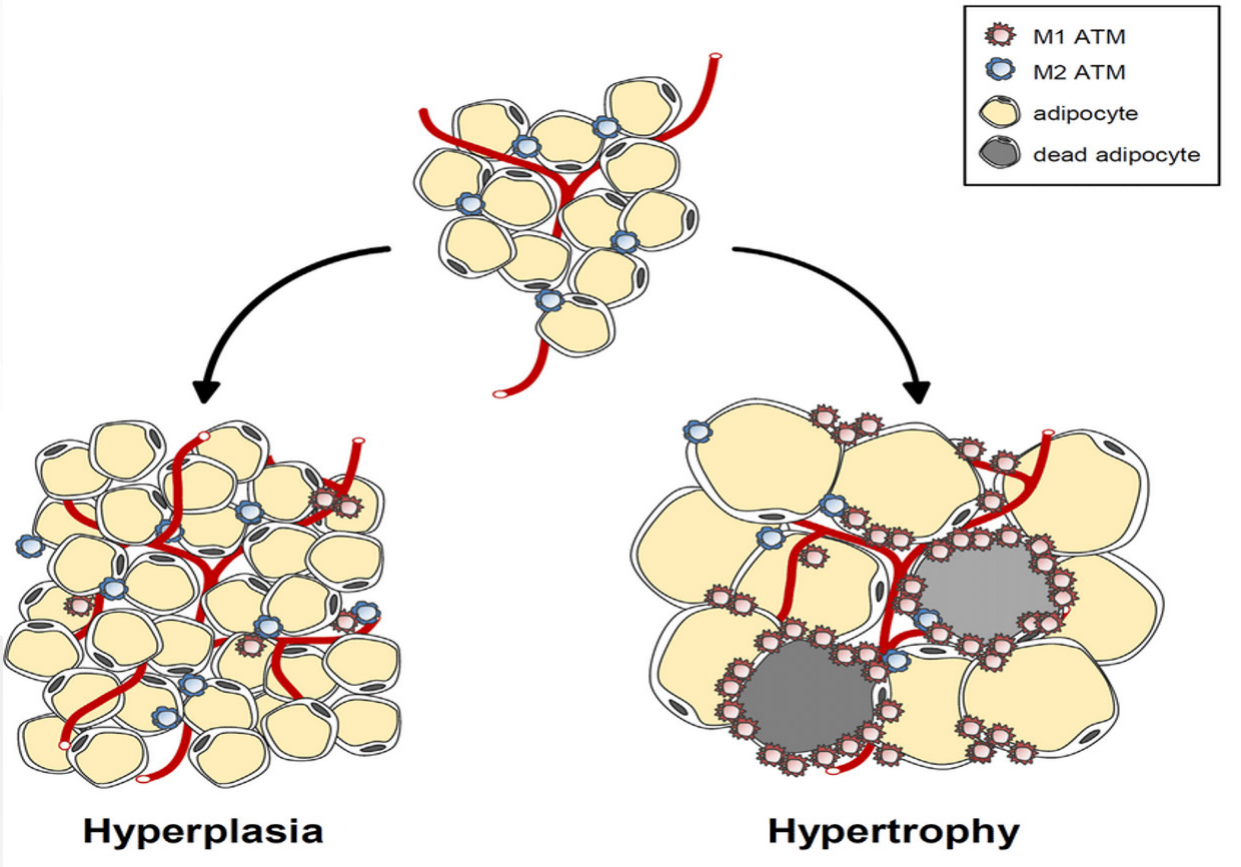

Figure 1: Adipose tissue hyperplasia and hypertrophy (Choe et al, 2016)

Recruited monocytes differentiate into M1 macrophages and attract even more monocytes into the adipose tissue. M1 macrophages in adipose tissue secrete large amounts of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF α), IL 1 and IL 6. Increase in the numbers of M1 macrophages downregulates the numbers of M2 macrophages which results in increased pro-inflammatory signals compared to anti-inflammatory signals moving the tissue into a pro-inflammatory state (Figure 2) (Jung et al, 2014). Prolonged maintenance of the inflammatory state eventually progresses to low-grade systemic inflammation.

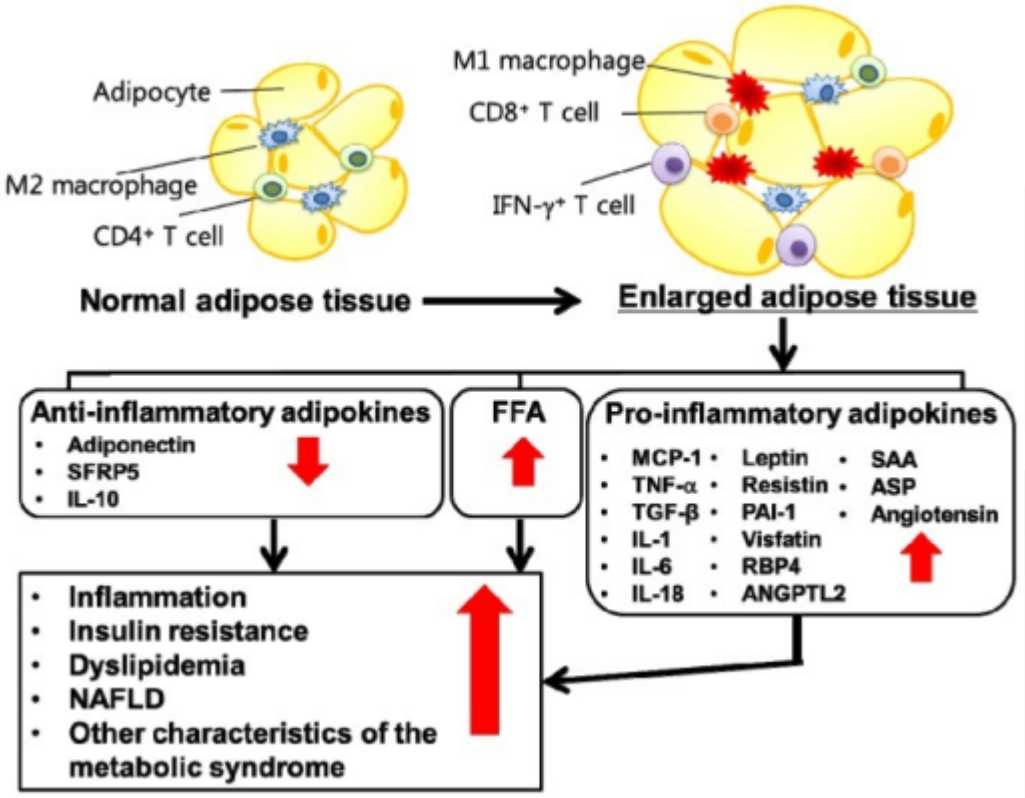

Figure 2: Changes in adipose tissue during weight gain and obesity (Jung et al, 2014)

3.3 Oxidative stress in inflammation

Oxidative stress describes a state of imbalance in which the production of reactive oxygen species (ROS) in the body exceeds the capacity of the antioxidant defense system. Under normal physiological conditions, the body generates ROS (to destroy invaders or for apoptosis) which are neutralized by antioxidants and enzymes such as catalase and superoxide dismutase. ROS has been associated with DNA and tissue damage (Srinivas et al, 2019). Factors that contribute to the accumulation of ROS in the body include chronic overnutrition (obesity), poor diet, alcohol consumption, chronic inflammation and more (Monteiro and Azevedo, 2010).

Our studies have shown that oxidative stress is associated with obesity and high blood pressure in children (Matjuda et al, 2022). Norris et al (2011) showed that overweight and obese children and adolescents have high levels of oxidative stress and inflammation. They further showed that these children had high levels of oxLDL compared to their normal-weight peers.

Chronic inflammation is generally associated with oxidative stress. Inflammatory cytokines contribute greatly to the generation of reactive oxygen species (ROS). Superoxides react rapidly with NO to produce peroxinitrite thus decreasing the bioavailability of NO. ROS decreases NO production by uncoupling the enzyme, endothelial NO synthase (eNOS), depleting the tetrahydrobiopterin (the NOS co-factor) concentration in the cell, and by the accumulation of asymmetrical dimethyl-arginine (ADMA) which inhibit NOS activity (Grande et al., 2011; Dinh et al., 2014; Vaziri, 2008). The uncoupling of eNOS reduces NO bioavailability results in endothelial dysfunction which favours increased total peripheral resistance which may in turn raise blood pressure. Additionally, NO deficiency in the kidney increases vascular resistance and favours sodium and water reabsorption while inhibiting natriuresis, raising blood pressure. Furthermore, NO deficiency in the brain may increase sympathetic activation which can also raise blood pressure (Vaziri, 2008). On the other hand, raised levels of oxidized LDL are associated with inhibition of eNOS activity which would result in a reduced NO production followed by endothelial dysfunction.

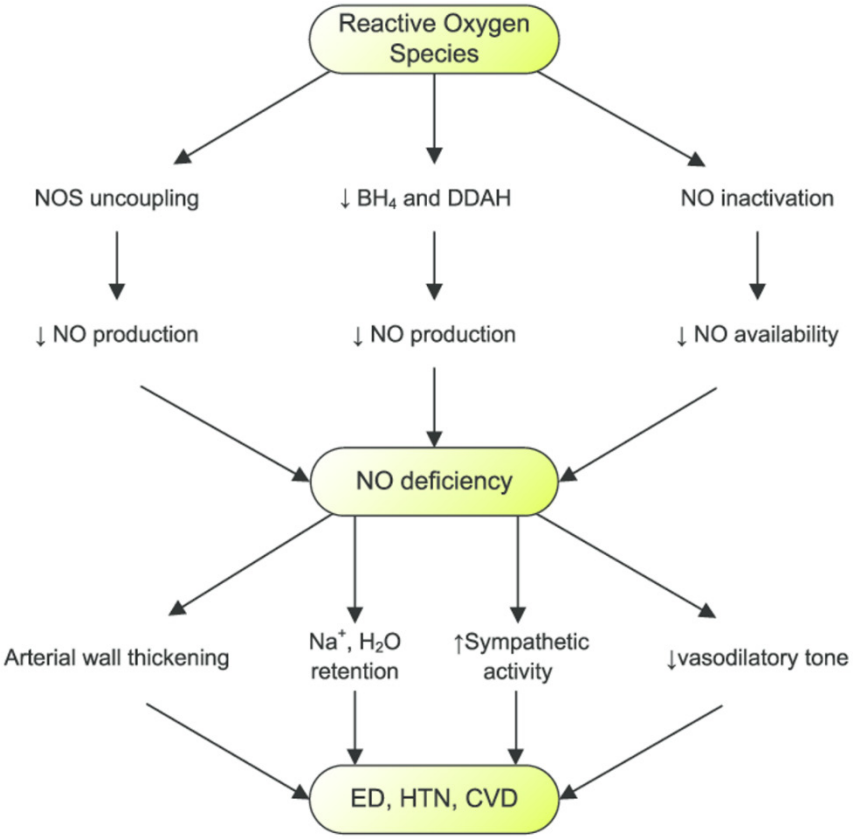

Figure 3: relationship between ROS and endothelial dysfunction (Vaziri, 2008)

3.4 Conclusion

Obesity and overweight are therefore two conditions which increase the risk for hypertension and CVDs through chronic inflammation and oxidative stress.

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Chapter 4

Studies of the analgesic and anti-inflammatory properties of medicinal plants.

Abstract
Pain and inflammation are the most common reasons for hospital visits. Importantly, most chronic diseases have an inflammatory component. Medicinal plants have been used and are still being used globally to manage various types of pain. In this chapter, a synopses of research projects investigating the analgesic and anti-inflammatory properties of medicinal plants we have investigated is presented. Our results corroborate the claims made by traditional healers.

4.1 Introduction

The pathophysiology of chronic diseases like cardiovascular diseases involves inflammation (Ong et.al, 2015). Thus, the treatment of inflammation may be a valuable approach in the prevention of cardiovascular disorders (Golia et al, 2014). Inflammation is generally associated with pain and therefore studies reporting on inflammation also often report on pain. However, the current management of these conditions is highly dependent on cyclo-oxygenase inhibitors which have a toxic effect on organs like the liver and kidney. Traditionally, plants have been used for the treatment of pain (Varrassi *et. al., 2019*). Hence, the need to provide a scientific basis for the folkloric use of plants for the treatment of pain and inflammation. The Eastern Cape Province has an extensive and very diversified flora from which rural communities obtain plants for their healthcare. Many of these plants are yet to be studied for the beneficial effects. We have therefore investigated the scientific basis for the traditional uses of some of these plants.

4.2 Methods

In these studies plants were collected, identified and voucher samples deposited in Herbaria which issued voucher numbers for each specimen. Extractions were done by maceration in different solvents to obtain the crude extracts for testing.
The preliminary qualitative phytochemistry tests were conducted to reveal the phytochemical constituents in some extracts. When constituent compounds were isolated, gas chromatography-mass spectrometer (GCMS) was used to characterize the bioactive components from the extract.
Several experimental models were used to study these plants for their analgesic and anti-inflammatory properties. Models included thermal, mechanical and chemical models of nociception, meanwhile the inflammation models used were carrageenan-and fresh egg albumin-induced paw oedema.

4.3 Results

Table 3 below provides a summary of the findings from these studies. All tested plants show low levels of toxicity, analgesic and anti-inflammatory properties.

Table 3: Result summary of the analgesic and anti-inflammatory properties of medicinal plants.

S/N	Plants	Part used	Models	Activities	References
2.	*Acacia mearnsii*	Stem Bark	Formalin test	Anti-inflammatory and anti- nociceptive	Avoseh et al., 2017.
11.	*Albuca setosa*	Leaves	Dextran- induced paw edema, Carrageenan induced peritonitis	Anti- inflammatory property	Ndebia et al., 2011.
24.	Buchu plant	leaves	Formalin test	Analgesic activity	Chiguvare et al., 2016.
4.	*Chamaemelum nobile*	Whole plant	Tail flick test, formalin test and fresh egg albumin inflammation test	Anti-nociptive and anti-inflammatory properties	Aremu et al., 2018.
1.	*Cordia platythyrsa*	Stem Bark	Acetic acid test, formalin test, tail flick test and carrageenan test	Dose dependent inhibition of pain and inflammation	Nkeh-Chungag et al., 2014
7.	*Cordia platythyrsa*	Stem Bark	Acetic acid-induced writhing, formalin test, carrageenan-induced inflammation test, tail flick test and Von Frey test	Analgesic and anti-inflammatory	Nkeh-Chungag et al., 2014

18.	*Cymbopogon validus*	Leaves and flowers	Fresh egg albumin-induced inflammation.	Anti-inflammatory properties	Rungqu et al., 2016.
9.	*Drypetes molunduana*	Whole Stem	Carrageenan-induced inflammation test and pressure test	Anti-inflammatory and anti-nociceptive properties.	Nkeh et al., 2003.
3.	*Echinacea species*	Leave and root	Carrageenan -induced inflammation test and acetic acid test	Significant anti-inflammatory and analgesic activities	Nyalambisa et al., 2017.
13.	*Gunnera perpensa*	Rhizome	Hot plate test, formalin assay, acetic acid writhing assay, albumin inflammatory pain assay	analgesic and anti-inflammatory properties	Nkomo et al., 2010.
12.	*Heteromorpha arborescens*	Roots	Hot plate test, acetic acid-induced writhing test, formalin test, albumin-induced inflammation, carrageenan-induced inflammation test	analgesic and anti-inflammatory properties	Nkomo et al., 2011.
17	*Heteromorpha arborescens*	Roots	Hot plate test, acetic acid test, formalin test, albumin-induced inflammation, carrageenan-induced inflammation test	analgesic and anti-inflammatory properties	Nkomo et al., 2011.
21	Lobelia flaccida	Leaves	Carrageenan-induced inflammation test	anti-inflammatory activities	Stolom et al., 2016.
15.	*Mallotus oppositifolium*	Leaves	Acetic acid-induced abdominal writhing test, carrageenan-induced inflammation test, pressure induced pain test	Central and peripheral analgesic property and Weak anti-inflammatory properties	Kamgang et al., 2005.
10.	*Mitragyna ciliata*	Stem Bark	5-lipoxygenase assay and Carrageenan-induced rat paw edema	Anti-inflammatory and anti-nociceptive properties.	Dongmo et al., 2003.
20.	*Pentinisia prunelloides*	Leaves and Rhizome	egg albumin-induced paw oedema and paw licking test in mice	Analgesic and anti-inflammatory activities	Mathews et al., 2016.
23	Schinus molle	Seeds	Tail flick, carrageenan-induced inflammation test	Analgesic and anti-inflammatory activities	Taylor et al., 2016.
8.	*Solanum Torvum*	Leaves	Carrageenan-induced inflammation test, pressure test, acetic acid-induced abdominal writhing test	Analgesic and anti-inflammatory activities.	Ndebia et al., 2007.
5.	*Syzygium aromaticum*	Flower buds	Tail flick test, formalin test and raw egg albumin inflammation test	Analgesic and anti-inflammatory	Rali et al., 2016
19.	*Syzygium aromaticum*	Whole plant	serotonin and fresh egg albumin-induced inflammation test	*in vivo* anti-inflammatory properties	Rali et al., 2016.

14.	*Uapaca guineensis*	Stilt root Bark	acetic acid-induced writhing test, formalin test, hot plate test, pressure induced pain test	Centrally acting analgesic	Nkeh-Chungag et al., 2009.
16.	*Uapaca guineensis*	Stilt root Bark	pressure-induced pain test and the hot plate test in the rats, formalin- and acetic acid-induced pain in the mouse	Central analgesic property	Nkeh-Chungag et al., 2009.
6.	*Valerian*	Roots	Carrageenan-induced inflammation test and acetic acid-induced writhing Test	Analgesic and anti-inflammatory	Dyayiya et al., 2016
22	*Valeriana capensis*	Roots	acetic acid-induced writhing test, carrageenan-induced inflammation test	Anti-inflammatory activity but lacked analgesic properties	Dyayiya et al., 2016.

Legend: S/N means serial number

4.4 Discussion

Findings from these studies on pain and inflammation have provided scientific support for their continued use and proposed mechanism of action of the medicinal plants.

Pain and inflammation have been linked to cardiovascular disorders. In fact, researchers are investigating the possibility of using anti-inflammatory plants for the prevention of CVDs (Golia et al, 2014). To fully examine the anti-nociceptive and anti-inflammatory properties of these medicinal plants, it is important to employ different models in accessing the anti-nociceptive and anti-inflammatory activities of new agents. The different models used, explored the different mechanism by which pain and inflammation are induced.

These studies have clearly shown the anti-nociceptive and anti-inflammatory properties of the tested extract in a dose dependent manner through models that may involve the central and the peripheral analgesic systems. The chemical model used are the formalin induced paw licking and writhing test. The acetic acid test lacks specificity in its action mechanism and was therefore complimented by the formalin test (Sanchez-Mateo et al., 2006; Ikeda et al., 2001).

The formalin test presents more like clinical pain compared to the other models of nociception (Tjolsen and Hole, 1997). This model has two phases, the first being the early or neurogenic phase which is believed to be mediated by the central nervous system and the second phase is referred to as the inflammatory phase. Plants that inhibit both phases significantly have analgesic properties through mechanisms mediated by both central and peripheral systems.

The Hot plate and Tail flick tests are used to investigate centrally acting agents with possible narcotic involvements. More so, the pressure-induced pain follows similar pathways as the tail flick and hot plate test.

However, for the anti-inflammatory studies the Carrageenan-induced paw edema and albumin induced-inflammation were employed. The Carrageenan-induced model of inflammation is a suitable model for screening natural products for the anti-inflammatory properties. This model is believed to have two phases, the first phase involves the release of serotonin and histamine while the second phase is mediated by the cyclooxygenase products and prostaglandin (Zhou et al, 2008). Plants that inhibited pain using this model have the ability to prevent the release of inflammatory mediators like histamine and serotonin.

Plant extracts were found to have alkaloids, flavonoids, saponins and terpenoids. Pharmacological activities associated with alkaloids and flavonoids includes their antioxidant properties, anti-nociceptive properties and anti-inflammatory properties (Barbosa et.al, 2006). The individual or combination of the classes of bio-compounds present in the tested extracts may be responsible for the analgesic and anti-inflammatory properties demonstrated in her studies.

4.5 Highlights

All studied plants showed significantly low levels of toxicity indicating that they were safe for internal use. These studies validate the use of the listed medicinal plants for management of pain and inflammation.

4.6 Conclusion

The African medicinal plants assessed in these studies proved to have analgesic and anti-inflammatory properties validating their use in folk medicine for the treatment of pain and inflammation related conditions.

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Chapter 5

Medicinal plants in hypertension and metabolic syndrome

Abstract
Hypertensive and diabetic patients are faced with the challenge of costly medications making it difficult for them to adhere to their treatment regimens. The use of medicinal plants in the treatment of hypertension and diabetes has become common practice in many communities. Medicinal plants have been reported to possess various biological activities which makes them potential alternatives in the treatment of many ailments. We investigated the *in vivo* and *in vitro* potential of *Sclerocarrya birrea*, *Athrixia phyllicoides, Osteospermum imbricatum; Senecio serratuloides, Lupinus albus, Grandis ferruginea, Garcinia Kola* and *Grandis Bridellia* in treating hypertension, diabetes and metabolic syndrome using the rat model. Furthermore, we investigated the possibility of neonatal programming against hypertension and diabetes using *Hypoxis hemerocallidea* and also determined the toxicity of *Raphis australis, Senecio serratuloides, Artemisia afra*, *Leonatis afra* and *Taraxacum officinale* by measuring their LD_{50}. The results showed that *S birrea*, *A phyllicoides, O imbricatum* possess hypolipidemic properties. We found antioxidant, hypolipidemic, antihypertensive, renoprotective and cardioprotective effects in *S serratuloides*. *T officinale* leaf and root extracts were found to possess good antioxidant capacity. *L albus, G ferruginea, G kola, G grandis* and *R australis* were found to have hypoglycaemic properties. The reported hypolipidemic and hypoglycaemic activities of these medicinal plants suggests that they can be used in the treatment of hypertension and diabetes respectively without causing any harmful effects on the patients. *H. hemerocallida* can potentially be used to protect neonates against obesity and metabolic syndrome.

5.1 Introduction
The challenge of costly medicines has made it difficult for diabetics and hypertensives to adhere to their treatment regimens (Armario et al., 2013; Jarari et al., 2016). This has led to an urgent need for the use of natural, medicines which are deemed more affordable and easily accessible. The use of medicinal plants in the treatment of hypertension and diabetes has become common practice in many communities (Joubert et al., 2008) and is premised on their bioactive compounds with different biological activities (Lawal et al., 2009). These bioactive compounds include flavonoids, polyphenols, saponins, alkaloids, tannins, triterpenoids, phytosteroids, and glycosides. Flavonoids scavenge for free radicals (Lee et al., 2013), prevent oxidation of low-density lipoproteins (Lee et al., 2013; Ajiboye et al., 2014), decrease systolic blood pressure (SBP) and heart rates thus reducing cardiovascular risk and mortality (Ajiboye et al., 2014). Saponins block the renin-angiotensin aldosterone system resulting in decreased total peripheral resistance and consequently decrease systemic hypertension (Lee et al., 2013; Ajiboye et al., 2014). Triterpenoids and phytosteroids lower serum lipid levels thus reducing the risk of atherosclerosis and hence hypertension (Ajiboye et al., 2014)

Athrixia phylicoides (Bushman tea) is used as a tea by the indigenous people of South Africa and for the treatment of diabetes and hypertension (Joubert et al., 2008). *Senecio serratuloides* is commonly used in Eastern Cape, South Africa to treat wounds such as cuts, internal and external sores (including those resulting from sexually transmitted infections), burns, swollen gums and chest pain (Gould et al., 2015). Medicinal plants may play a role in the treatment of hypertension diabetes.

5.2 Methods
We explored the *in vivo* and *in vitro* potential of *Sclerocarrya birrea*, *Athrixia phyllicoides, Osteospermum imbricatum, Senecio serratuloides, Lupinus albus, Grandis ferruginea, Garcinia Kola* and *Grandis Bridellia* in treating hypertension, diabetes and metabolic syndrome using the rat model in several studies. In the different studies, obesity was induced by either a high energy diet or high fat diet. Diabetes was induced by streptozotocin, while hypertension was induced by Nω-Nitro-L-arginine methyl ester (L-NAME) at 40 mg/kg/day. Briefly, weekly fasting glucose and body weights of the rats were monitored, while oral glucose tolerance and blood pressure (BP) were measured before and after treatment with the medicinal plants of interest in the different studies. On termination, visceral and liver fat, serum lipid profiles, adiponectin, leptin, insulin, and homeostatic model assessment of insulin resistance (HOMA IR) were determined. Total cholesterol, free fatty acids (FFAs) and adipokine regulation; leptin: adiponectin ratio (LAR) were assessed on serum after treating rats with the medicinal plants. The antihypertensive properties of bioactive compounds from *Senecio serratuloides* were isolated and tested on urine norepinephrine concentration (Tata et al., 2020). Additionally, we investigated the effect of in utero exposure to these medicaments on metabolic-programming outcomes on the offspring later in life. Body weight, oral glucose tolerance was determined for dams on day 20 of gestation and for pups 28 days postpartum after treating them with *H. hemerocallidea*. Serum total antioxidant capacity (TAC), LDL and HDL were determined 28 days postpartum.

5.3 Results
Results of these different studies are summarized in Table 4. *S birrea*, *A phyllicoides, O imbricatum* were shown to possess hypolipidemic properties. Extracts of *S serratuloides* were found to have antioxidant, hypolipidemic, antihypertensive, renoprotective and cardioprotective effects in. *T officinale* leaf and root extracts were found to possess good antioxidant capacity. *L albus, G ferruginea, G kola, G grandis* and *R australis* were found to have hypoglycaemic properties.

Table 4: Summary of medicinal plants in hypertension and diabetes in rat models

Plant	Part	Solvent used in extraction	Biological Activity	Toxicity	Reference
Sclerocarrya birrea	Peels	Methanol, water (1:1)	Hypolipidemic	Nm	Sewani-Rusike et al 2021
Athryxia phyllicoides	leaf	Water	Hypolipidemic Antidiabetic	Nm	Mokwena et al., 2021
Osteopermamum imbricatum	Leaf Roof		Hypolipidemic	Mild toxicity	Tata et al., 2021
Senecio serratuloides	Leaf	Water-Ethanol n-hexane, dichloromethane, ethyl acetate, and methanol.	Antioxidant Hypolipidemic Antihypertensive Renoprotective Cardioprotective	Nontoxic	Tata et al., 2020 Tata et al., 2020 Tata et al., 2020
Artemisia afra	Leaf Root	70% Ethanol	Antihypertensive	Nontoxic	Mungho et al., 2018
Leonortis leonurus	Leaf Root	70% Ethanol	Antihypertensive	Nontoxic	Mungho et al., 2018
Taraxacum officinale	Leaf Root	70% ethanol	Antioxidant	Nm	Aremu et al., 2019 Aremu et al., 2019
Lupinus albus	Leaf		Antidyslipidemia	Nm	Sewani-Rusike et al., 2015
Bridellia ferruginea	Leaf	Methanolic	Hypoglycaemic	Nm	Njamen et al., 2012
Garcinia kola	Seed	Ethanol	Hypoglycaemic Hypolipidemic	Nontoxic	Duze et al., 2012
Bridellia grandis	Stem bark	Methanol	Antidiabetic	Nm	Njamen et al., 2011
Raphis australis	Fruit	70% ethanol	Antioxidant Antihypertensive	Nontoxic	Tata et al., 2022
Hypoxis hemerocallida	Leaf	70% Ethanol	Antioxidant Hypolipidemic	Nm	Sewani-Rusike et al., 2021

Legend: nm means toxicity was not measured in the study.

5.5 Discussion

The reported reduction in body weight, visceral fat and increase in glucose tolerance and serum insulin in obese rats treated with *S. birrea* suggests that *S. birrea* peels possess antiobesity and antilipidemic effects and could prevent dyslipidemia (Sewani-Rusike et al., 2021). *S. birrea* ameliorated inflammation and insulin resistance by stabilizing the leptin: adiponectin balance and lowering food intake which may correspond to lowering glucose load in treated animals.

The efficacy of *S. Serratuloides* against L-NAME induced hypertension suggested that they may have vasoactive properties. This can be attributed to the high phytochemical content of the extracts reported in the study. The phytosterols isolated in the extracts are favourably absorbed in the intestinal lumen in place of cholesterol resulting in the cholesterol being eliminated in feces (Sanclemente et al., 2009). This suggests that *S serratuloides* has hypocholesterolemic and antiatherosclerotic effects.

S. serratuloides exhibited high antioxidant capacity which was evident in its ability to improve total antioxidant capacity and prevent lipid peroxidation. Oxidative stress has a role in the induction of cardiac dysfunction in renal patients (Nuhu et al., 2018). Given that SS extracts had the ability to prevent oxidative stress in the heart and kidneys and previous studies have reported its ability to prevent cardiac hypertrophy, it suggests that it may be important in combating renal dysfunction as well as associated cardiovascular disorders. The observed renoprotective effect of SS in our study could also have been through inhibiting inflammation and oxidative stress.

Our findings showed that SS significantly improved lipid profiles in a dose dependent manner in L-NAME treated animals indicating that HESS inhibited hypertension. This finding was consistent with previous studies (Adaramoye et al., 2012; Berkban et al., 2015) which observed normal levels of nitric oxide (NO) in heart and kidney of L-NAME treated rats.

Insulin resistance, a key phenomenon in the pathogenesis of type 2 diabetes is usually associated with obesity, dyslipidaemia and hypertension. *L. Albus* (LA) extract reduced fasting glucose levels in normal, non-diabetic rats. The extract was

effective in lowering atherogenic cholesterol in both STZ-induced diabetic and non-diabetic rats. Interestingly, LA showed a hypolipidemic effect in STZ-induced diabetic rats. The reduced insulin levels in STZ-induced diabetic rats in this study imply a non-insulin dependent mechanism in LA's hypolipidemic effects. Our study aligns to the previously reported hypolipidemic and anti- atherosclerotic effects of LA (Marchesi et al., 2008).

The ability of *R. Austris* extracts (RAE) to decrease systolic blood pressure and diastolic blood pressure after once off treatment suggested that the phytoconstituents of RAE as well as its metabolites could be effective against hypertension (Tata et al., 2022).

There are reports of evidence that support the role of intrauterine programming that predisposes the offspring to develop metabolic syndrome later in life, associated with under- and over-nutrition, phytochemicals, drugs and stress during pregnancy (Boney et al., 2005). *H. hemerocallidea* improved glucose tolerance of dams treated with both doses. The unique finding in this study was the observed improved glucose tolerance of *H. hemerocallidea* in exposed pups compared to the untreated controls. Studies in humans and animals have demonstrated that maternal gestational diabetes and hyperinsulinemia play a role in programming obesity and insulin resistance in offspring (Wang et al., 2018). This suggests that intrauterine programming for improved glucose tolerance in the offspring might have occurred due to the anti-insulin resistance effects of *H. hemerocallidea* observed after maternal treatment.

5.6 Highlights

- *Sclerocarrya birrea* fruit peel extract and *Athrixia phylicoides* tea can be used to ameliorate obesity and metabolic syndrome.

- The antioxidant and antihypertensive properties found in extracts of *Osteospermum imbricatum, Senecio serratuloides*, *Taraxacum officinale* leaf and *Raphia australis* implies that they can be used to treat oxidative stress-mediated diseases and prevent hypertension.

- *Senecio serratuloides* can be used for antihypertensive drug development.

- *Bridellia ferruginea*, *Bridellia grandis* extract can be used by diabetics to lower blood glucose levels.

- *H. hemerocallidea* may protect insulin resistance, dyslipidaemia and oxidative stress in pups which may have resulted from intrauterine programming during pregnancy.

5.7 Conclusion

The reported hypolipidemic, hypoglycaemic and antihypertensive activities of these medicinal plants in the several studies suggests that they can be used in the treatment of hypertension and diabetes without causing any harmful effects on the patients. *H. hemerocallida* showed that medicinal plants can potentially be used to protect neonates against obesity and metabolic syndrome.

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Chapter 6

Studies on erectile dysfunction

Abstract
Sexual health is a vital component and affects the quality of life and well-being of an individual. Sexual dysfunction including erectile dysfunction in males are critical health problems which may be linked to cardiovascular disease, hypertension, obesity, ageing and diabetes mellitus. Assessment of erectile dysfunction in males demonstrates that *Garcina kola* possesses sexual enhancing activity which may be useful in males with erectile dysfunction associated with endothelial dysfunction and CVDs.

6.1 Introduction

Sexual health is a vital aspect of life that affects the quality of life and well-being of an individual. Erectile dysfunction (ED) negatively affects sexual function and may erode the male essence (Tański et al, 2022). Sexual dysfunction is defined as the difficulty in achieving or maintaining an erection that is sufficient for sexual activity at least 50% of the time for the last 6 months (Laumann et al., 1999). Cardiovascular diseases, hypertension, obesity, ageing and diabetes mellitus are some of the organic etiological factors that contribute towards ED (Heidelbaugh, 2010). Available commercial treatments involve the use of selective phosphodiesterase inhibitors (Kuthe, 2003). However, prohibitive cost of the medication is a huge setback most especially in the developing countries and hence the need for alternatives (Ralebona et al., 2012). From published literature, it is evident that the use of plants to increase sexual performance and pleasure and for the management of ED is very common as shown from various experimental studies (Ralebona et al., 2012; Sewani-Rusike et al., 2015). Traditional herbs have been shown to offer a respite and thus we conducted studies to verify the potential aphrodisiac effects of the seed of *Garcinia kola* in mature male rats.

6.2 Methods

To determine the effect of *Garcinia kola* on erectile dysfunction, exactly twenty four albino rats of 14 weeks old of both sexes were used for the study divided into 3 experimental groups of 8 rats each were used. The first two groups used two doses of 70% ethanolic extract of *G. kola* seeds (200 and 400 mg/kg body weight). The third group was the control group which received 2 ml of distilled water. All groups were treated orally daily for 28 days. In the second phase of the experiment, a third treatment group was fed with 100 mg/kg body weight. On days 28 and 50, mounting frequency (MF), intromission frequency (IF) and ejaculation frequency (EF) were quantified during sexual behavior tests. At termination, body and organ weights, gastric ulceration and cauda epididymal sperm counts were determined.

6.3 Results

A finding involving the effect of *Garcinia kola* on erectile dysfunction, there was increased pre-coital sexual behavior was observed in all *G. kola*-treated rats compared with the control group. The frequency of mount and intromission following treatment with *G. kola* (100, 200 and 400 mg/kg) was significant ($p < 0.01$) compared to control (Figure 4). Lastly, we observed a significant increase ($p < 0.05$) in total serum testosterone levels in all *G. kola*-treated groups compared to controls (Figure 5). Serum luteinizing hormone (LH) and follicle stimulating (FSH) remained similar to controls (not shown).

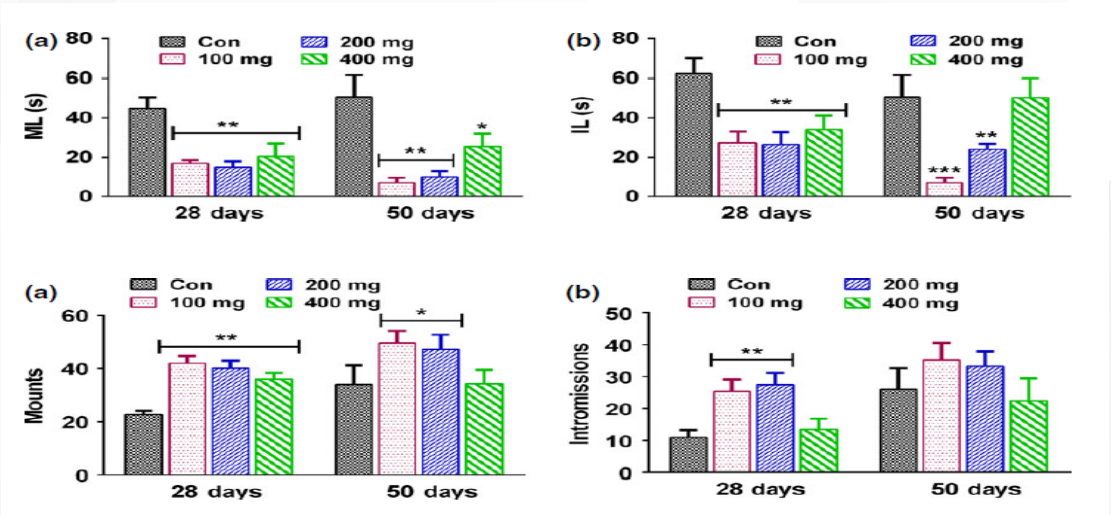

Figure 4: Effect of Garcinia kola treatment on (a) mount frequency and (b) intromission frequency observed after 28 and 50 days of treatment.

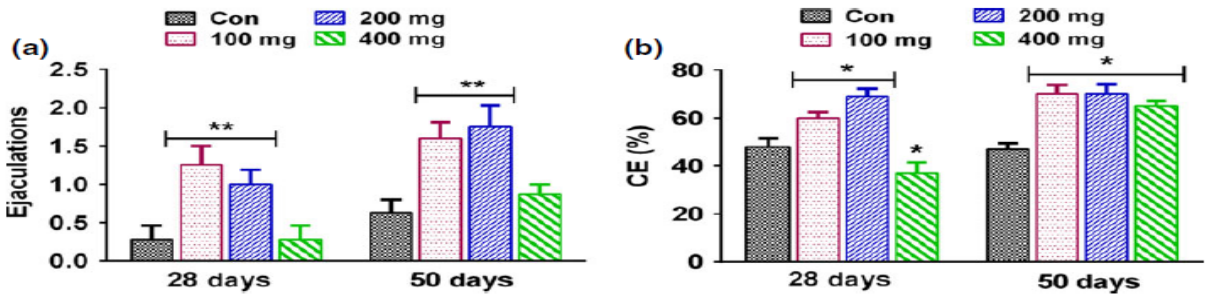

Figure 5: Effect of Garcinia kola treatment on (a) number of ejaculations and (b) copulatory efficiency (%) after 28 and 50 days of treatment.

6.4 Discussion

Libido and potency were measured using mounting (MF) and intromission frequencies (IF), and is an indication of improved sexual arousal and performance (Abdulwaheb et al., 2007). Sexual enhancing effects of *G. kola* were documented as evident by increased IF and MF coupled with increased number of ejaculations over 20 minutes of observation (Ralebona et al., 2012). Therefore, treatment with ethanolic extract of *G. kola* (EEGK) increased both libido and potency in normal rats. Other measures of qualitative pre-coital sexual behavior including sniffing, nosing, chasing and genital grooming were increased in *G. kola*-treated rats (Sewani-Rusike et al., 2015). The treated rats with EEGK were aggressive and persistent in pursuing the females. Similar enhanced pre-coital behavior has been observed in male albino rats following oral treatment with extracts of *Fadogia agrestis* stem (Yakubu et al., 2007). Furthermore, treatment with G. *kola* increased total testosterone levels either by increasing the number of leydig cells or their sensitivity to luteinizing hormone. It can also act centrally to influence levels of gonadotropins (Ralebona et al., 2012; Sewani-Rusike et al., 2015), but further studies are needed to elucidate the probable mechanism required. From our study, the extract caused significant increase in testicular weights (Ralebona et al., 2012), which may imply an increase in spermatogenesis, as the seminiferous tubules forms the bulk of testicular weight (Oyewopo et al., 2011). Also, there was 40% increase in sperm count in *G. kola*-treated rats (Sewani-Rusike et al., 2015). Interestingly, our research demonstrated that long-term treatment, but at higher doses (400 mg/kg) of *G. kola* results in increased testosterone level (Sewani-Rusike et al., 2015). This was confirmed by the low number of ejaculations in the high-dose group. On the other hand, the low-dose treatment groups (100 and 200 mg/kg) showed high copulatory efficiency and corresponding high number of ejaculations.

6.5 Highlights

G. kola nuts have marked aphrodisiac activity with significantly enhanced sexual behaviour parameters and increased testosterone levels in male animals.

6.6 Conclusion

G. kola showed potential for the management of erectile dysfunction in males and could contribute to the prevention of cardiovascular diseases

6.7 References

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Chapter 7

Conclusions and recommendations

The prevalence of cardiovascular diseases in people of African ancestry is on the rise. Obesity and hypertension are the two important modifiable risk factors for CVDs in this population. The increased prevalence of obesity and hypertension have been linked to rapid urbanization which comes with lifestyle changes. Many more Africans live in urban areas and have adopted a sedentary lifestyle and westernized fast foods which are rich in fats and salt. These lifestyle changes have promoted weight gain and obesity in people of African ancestry.

It is reported that people of African ancestry have a greater susceptibility to hypertension and cardiovascular diseases. There is evidence that hypertension is linked to genetic predisposition. Although genetic factors explain the differences in blood pressure levels, studies show that genetic factors alone cannot explain the occurrence and severity of hypertension and cardiovascular diseases in this population.

Recent research has shown a strong link between obesity/overweight and oxidative stress along with chronic low-grade inflammation. Chronic low-grade inflammation results in endothelial dysfunction which is the first step towards the development of cardiovascular diseases. Overweight and oxidative stress have become rampant in people of African ancestry. It is therefore not surprising that the prevalence of hypertension and cardiovascular diseases is increasing in this population.

The management of hypertension and cardiovascular diseases with plants is common practice in developing countries. Several African medicinal plants could be developed for the management of these conditions in people of African ancestry.

It is recommended that people of African ancestry live more active lives and consume more vegetable and fruit rich foods. African medicinal plants which are currently used by traditional healers may provide a solution for the prevention and management of hypertension and related complications.

Notes:

NATIONAL ANTHEM

Nkosi sikelel' iAfrika
Maluphakanyisw' uphondo lwayo,
Yizwa imithandazo yethu,
Nkosi sikelela, thina lusapho lwayo.

Morena boloka setjhaba sa heso,
O fedise dintwa le matshwenyeho,
O se boloke, O se boloke setjhaba sa heso,
Setjhaba sa South Afrika - South Afrika.

Uit die blou van onse hemel,
Uit die diepte van ons see,
Oor ons ewige gebergtes,
Waar die kranse antwoord gee,

Sounds the call to come together,
An united we shall stand,
Let us live and strive for freedom,
In South Africa our land.