The Role of Traditional Medicine in the Etiology and Management of Chronic Kidney Disease in Moshi, Tanzania

by

Joseph Lunyera

Duke Global Health Institute
Duke University

Date:________________________
Approved:

____
Uptal D. Patel, Supervisor

____
John W. Stanifer

____
David L. Boyd

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2015

ABSTRACT

The Role of Traditional Medicine in the Etiology and Management of Chronic Kidney Disease in Moshi, Tanzania

by

Joseph Lunyera

Duke Global Health Institute
Duke University

Date:_______________________
Approved:

____
Uptal D. Patel, Supervisor

____
John W. Stanifer

____
David L. Boyd

An abstract of a thesis submitted in partial
fulfillment of the requirements for the degree
of Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2015

Copyright by
Joseph Lunyera
2015

Abstract

Background: Traditional medicine use is increasingly recognized as a common and important component of healthcare globally. Our study aim was therefore to identify the commonly used traditional medicines in Moshi, Tanzania, the factors influencing their use and associations between traditional medicine use & prevalence of chronic diseases. Methods: We performed a secondary data analysis of a mixed methods study in Moshi, comprising 42 extended interviews and 5 focus group discussions with key informants, and cross-sectional household survey using interviewer-administered questionnaires and field-based diagnostic tests for CKD, diabetes, hypertension and HIV. Results: We identified 168 traditional medicines, of which 15 (8.9%) and 5 (3%) were used to treat chronic diseases and CKD, respectively. Participants reported seeking healthcare advice from medical doctors (97%), family members (52%), pharmacists (24%) and friends or neighbors (14%). In a fully adjusted model, CKD patients were more likely than the non-CKD population to report a history of traditional medicine use (AOR=1.99; p=0.04), and family tradition (OR=1.97), difficulty finding a medical doctor (OR=2.07) and fewer side effects with traditional medicines (OR=2.07) as their reasons for preferring traditional medicines to hospital medicines. Conclusions: Traditional medicine use is high in Moshi, and more so among the CKD population. A history of traditional medicine use is associated with the prevalence of CKD in Moshi. Most of

these traditional medicines have biologically active substances that could potentially be developed into therapeutic and prophylactic therapies for CKD, and CKD-associated co-morbidities.

Dedication

I dedicate this work to my family and friends in my home country of Uganda, and to my friends in the United States, for their hospitality and support in countless ways.

Contents

List of Tables

List of Figures

Acknowledgements

I thank my mentor, Uptal D. Patel, MD, for giving me the opportunity to lead this project, and for shaping my career by exploring and actively supporting my pursuit of professional development opportunities. I am thankful to John W. Stanifer, MD, who led the primary study upon which this secondary analysis was performed, for generously sharing the data from his work, and for providing oversight for this analysis and manuscript preparation. I also thank David L. Boyd, PhD, for sharing his experience and expertise on traditional medicine, and for providing additional oversight for the analysis and manuscript preparation, and for instilling enthusiasm to the team.

I am indebted to the administrative support provided by the program administration of the MSc. Global Health program at the Duke Global Health Institute (DGHI), specifically for coordinating my thesis project and mentorship placements. Without their commitment to my success, I would not have been able to complete this important component of my global health training. I also thank the faculty at DGHI for investing their time to provide additional input on this project.

I also thank our collaborators in Tanzania for providing the *emic* perspective on traditional medicine in Tanzania, which, among other contributions, permitted us to identify the plant remedies in our database. Justin Omolo, PhD, and Francis Karia gave noteworthy contributions to this end.

1. Introduction

The term "Traditional medicine" is defined by the World Health Organization (WHO) as "a wide variety of therapies and practices which may vary greatly from country to country and from region to region." Traditional medicine (TM) is also referred to as, "alternative medicine," "complementary medicine" or "ethno medicine" [1]. In the Indian sub-continent, there are two forms of TM: "Ayurvedic medicine" and "Unani medicine." These TM medical systems comprise the use of herbs, ash and heavy metals, to which a significant part of the rural population in the Indian subcontinent rely on to meet their healthcare needs [2]. Traditional Chinese Medicine (TCM), another form of TM, is used by over 60% of the Chinese population; plant extracts and elements are the main components of the TCM system [2]. TM use in the developed world is also rising; about 10% of US adults reported using herbals in a survey in 1999. A significant proportion of the national expenditure on "dietary supplements" ($US 17.8 billion) in the US in 2001 was in the form of herbs and botanical remedies ($US 4.2 billion) [3], and about $US 5 billion was spent on herbal medicine-derived over-the-counter drugs in Europe in 2003 [4]. In sub-Saharan Africa, up to 80% of the population is estimated to use TM to meet their healthcare needs [5], and about 60% of the Tanzanian population use traditional medicines as their mode of healthcare access [6]. Furthermore, TM practitioners are the first health practitioners to be consulted in up to 80% of cases in some parts of the developing world [7].

TM use is thus increasingly being recognized as an important component of healthcare delivery globally [5]. In the 2008 Beijing Declaration, TMs were formally recognized as pivotal in healthcare service delivery especially in low-income regions like sub-Saharan Africa. The Declaration also recognized the efforts of many governments to integrate TM into their health system, and it urged other member states that have not yet done so to take action (resolution number 3, Beijing declaration on TM, 2008). The congress also further noted that TM should be developed based on research and innovation (resolution number 4) [1].

In Tanzania TMs are used for a number of disease conditions, including both communicable and non-communicable diseases (NCDs). Smart et al. [8] noted that adults admitted with complications of hypertension to their hospital in Western Tanzania often reported a history of TM use prior to coming to the hospital. In a systematic review of TM use for hypertension in SSA, they identified six main reasons for the preference of TMs to Hospital Medicine: perceived failure of hospital medicines (31.73 %), relatively high cost of hospital medicines compared to traditional medicines (23.08 %), social cultural practices and/or herbal knowledge (20.19 %), poor accessibility to medical facilities (19.23 %), safety concerns about hospital medicines (9.62 %), and uncaring attitudes of hospital staff (6.73 %) [8].

NCDs are a growing burden in sub-Saharan Africa. It is estimated that NCDs account for 1 in 4 deaths in some SSA countries [9], and it is likely that traditional medicine use for NCDs is also high in SSA [8]. Given the scarcity of resources for healthcare delivery in SSA, partnerships between hospitals and traditional medicine practices may be important for healthcare delivery for NCDs. However, as noted in the Beijing declaration on TM, these partnerships should be built on research and innovation [1]. Thus the role of TMs in the etiology and management of NCDs in SSA needs to be described, and this should be guided by lessons learned from other parts of the world. Among the NCDs, chronic kidney disease (CKD) is of particular concern because little is known about its etiology in SSA [20] and its etiology has been linked to TM use in other parts of the world [2]. Jha noted that a number of herbs in Ayurvedic medicine, particularly Aristolochia spp., have been implicated in the development of CKD in rural populations in the Indian sub-continent. Elsewhere, the leaves of the Native American shrub creosote bush are used to induce cystic renal disease in rats, and long-term exposure to this plant has been associated with development of renal cysts and renal carcinoma [10].

We therefore aim to explore TM use in Northern Tanzania, to determine the factors influencing their use and to identify associations between TM use and NCDs, including CKD.

2. Methods

This study is a secondary data analysis of a mixed methods study that was recently conducted in Moshi, Tanzania from July 2013 to June 2014. The mixed methods approach had 3 components: extended interviews (EIs), focus group discussions (FGDs) and cross-sectional household survey [16].

2.1 Setting

The setting for this study was Moshi, the capital of the Kilimanjaro region in Northern Tanzania. The Kilimanjaro region is one of Tanzania's 30 administrative units, with a population of 1,640,087 and a population density of 124 people per square kilometer according to the 2012 Tanzanian national census. Moshi has a population of 184,292 according to the 2012 census and covers about 59 square kilometers (23 sq mi), making it the smallest municipality in Tanzania by area [11]. The Chagga and Pare are the two main ethnic groups in Moshi. The urban district of Moshi had the highest literacy of persons older than 15 years in Tanzania in 2005 according to the Tanzania Poverty and Human Development Report 2005 [12]. Moshi has 3 main healthcare institutions: the Kilimanjaro Christian Medical Center is a non-government institution and the largest of the three, it also serves as the zonal referral hospital; Mawenzi Regional Hospital is the primary public hospital in Moshi with 300 beds; the third health institution is the Kilimanjaro Center for Community Ophthalmology, which is dedicated to the elimination of avoidable blindness [13].

2.2 Participants

As previously described by Stanifer et al. [16], the antecedent study was open to all adults (age ≥ 18 years) from the general Moshi population, both men and women. Purposive sampling technique was used to recruit participants for the EIs and FGDs; adults, including traditional healers, were recruited from the general population in Moshi and medical doctors from the Kilimanjaro Christian Medical Center were invited to participate in the FGDs and EIs. EIs and FGDs were conducted until thematic saturation was achieved. Participants for the household survey were selected using a 2-stage cluster sampling strategy, in which households were selected by random probability sampling according to the size of the neighborhood (the smallest administrative unit) followed by random selection of adults older than 18 years of age within sampled households. All sampling procedures were computerized, using the random number generator program.

2.3 Procedures

Field technicians verbally communicated the rationale for the study to the prospective study participants, after which those who elected to participate in the study signed the consent forms. The EIs were administered individually to 16 traditional healers at their places of work and to 26 community members in a rented space in Moshi urban, which was accessible to the general study population selected from the Moshi Municipality Council. The field technicians conducted 5 FGDs with key informants from

Moshi in the same rented space; the key informants for the FGDs were as follows: 2 for men, 2 for women and 1 for physicians. The FGDs had between 8-12 participants per FGD. Both the EIs and FGDs were moderated by natives from the Moshi area. The moderators used discussion guides which were designed from the conceptual framework for traditional medicine use in Tanzania, and were translated into Kiswhahili- the language spoken by all of the study participants. The sessions were recorded using an audio device, translated and transcribed by two independent native field technicians. The transcripts from the two field technicians were reviewed for consistency and accuracy by the moderator. The discussion guide was modified as new themes emerged from the EIs and FGDs.

The cross-sectional survey was conducted using the study instrument (described under the sub-title, "Survey Instrument" in section 2.4.3), and biological samples were drawn for field-based diagnostic tests for CKD, diabetes and HIV; blood pressure was measured during the survey (as described in section 2.4.2 below). The diagnostic tests were carried out at the Kilimanjaro Christian Research Institute Biotechnology Laboratory. The laboratory is known in the region for its high quality results, and it participates fully in international external quality assurance programs including the College of American Pathologists and the United Kingdom External Quality Assessment Service. All laboratory investigations were conducted according to Good Clinical Laboratory Practice standards.

Ethical approval for the study was obtained from the Duke University Institutional Review Board (#Pro00040784), the Kilimanjaro Christian Medical College (KCMC) Ethics Committee (EC#502), and the National Institute for Medical Research in Tanzania [16].

2.4 Measures

This section describes selected measures from the antecedent study that are relevant to this secondary data analysis; a comprehensive account of all the measures from the antecedent study is described elsewhere [16].

2.4.1 CKD Screening

CKD cases were defined according to the Kidney Disease Improving Global Outcomes Working Group (KDIGO) guidelines, which has two criteria for CKD case definition: presence of marker(s) for kidney damage (such as albuminuria) and/or decreased glomerular filtration rate (GFR) [14]. A urine albumin greater than 30 mg/dL in the absence of gross hematuria or an ongoing urinary tract infection as confirmed by urinalysis (Siemens Multistix 10G® Urinalysis test strips) was considered a positive marker for kidney damage. Glomerular filtration rate was estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation without the race factor which has been suggested to be the most accurate estimator of GFR in similar populations [15]. The MDRD equation for estimating GFR is as follows:

$$\text{GFR (mL/min/1.73m}^2\text{)} = 175 \times (\text{Serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$$

A GFR < 60 mL/min/1.73 m^2 was considered CKD. Serum creatinine was measured using the Cobas Integra 400 Plus (Roche Diagnostics; Basel, Switzerland) and urine albumin was detected with a Siemens MicroAlbustix® (Siemens Healthcare Diagnostics, Inc.; Tarrytown, NY) from a mid-stream urine sample.

2.4.2 Diabetes, Hypertension & HIV Screening

Diabetes was defined as a hemoglobin A1C > 7.0%. Blood pressure was measured using an automated sphygmomanometer. Hypertension was defined as two-time systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Blood pressure was taken at least 15 minutes from the initiation of the survey to allow the vitals of the respondent to return to the at-rest values, and a second blood pressure measurement was done at 5-10 minutes' interval from the initial measurement. Participants were screened for HIV using the rapid HIV diagnostic test.

2.4.3 Survey Instrument

The instrument used to administer the cross-sectional household survey was a novel chronic disease assessment tool [16]. This tool was designed specifically for assessing knowledge, attitude and practices for chronic kidney disease, and traditional medicine use in the community. It was a semi-structured questionnaire with both open-ended (to explore types of traditional medicines used) and closed-ended questions (targeting frequencies of use of traditional medicines, modes of healthcare access, reasons for use of traditional medicines, and conditions treated by traditional medicines). The instrument was translated to Kiswahili- the local language in the study setting.

2.5 Analysis

As previously mentioned, the antecedent study was a mixed methods design in which the EIs and FGDs served as formative preliminary designs to develop the survey instrument for the household survey. Thus, to examine the context and deeper meanings of the estimates from the cross-sectional survey, we re-examined the transcripts from EIs and FGDs to identify relevant narratives from the respondents. The transcripts were coded and analyzed as part of the primary data analysis [16] prior to this secondary work.

Survey data were coded in an MS Excel program file for the primary data analysis. We exported the data from the Excel file to STATA 13 software (Stata corp., College Station, Tx) for the secondary data analysis. Survey questions from the instrument are generally considered as exposure variables (unless stated otherwise in subsequent sections of this paper) and screening tests are the corresponding outcome variables. We estimated associations between traditional medicine use parameters from the survey instrument (exposure) and screening tests (outcome), including CKD, using generalized linear models with 95% confidence interval. Because the screening tests that were examined in this secondary data analysis were binary, we used the logit function to estimate prevalence odds ratios, and p-value < 0.05 was considered statistically significant for the association between the exposure ("X") and outcome ("Y"). Fully adjusted models controlling for confounding variables were generated using the "mean squared error" approach to evaluate the validity-precision trade-off, assuming constancy. The constancy assumption was verified using likelihood ratio test (LRT) to compare the full and reduced models. The LRT test was also used to compare this "full" model (main effects only) with models incorporating interaction terms (main effects with interaction terms) to assess for effect modification of exposure-outcome relationships.

We concluded our analysis by identifying and cataloguing the herbal plants that were mentioned in the transcripts from the EIs, FGDs and from the survey responses into an MS Excel program file, using the following variables: diseases/condition for which the herbals are prescribed, their mode of use, plant part used and the local/indigenous names for each herbal in Moshi. An additional variable for the botanical names for the herbals was created after searching the literature using their English and/or local names. We then entered the botanical names as search codes in PubMED and Web of Science to search the literature for published work on these herbals. To characterize the ethnopharmacology of these herbal plants, we entered ethnopharmacological parameters as follows: common uses of the herbal in Moshi, known pharmacological mechanisms/properties (and, whenever possible, the active substances responsible for the pharmacologic properties), adverse effects, potential interactions with biomedicines, and detailed uses of the herbal plant in other communities around the globe as documented in the literature. The "uses elsewhere" variable was further described in terms of indications, plant parts used, modes of use and any other relevant ethnographic data about the plant in these communities.

3. Results

3.1 Characteristics of Study Participants

We screened 481 adults in the cross-sectional household survey, of whom 57 (11.85%) had CKD. Most of these CKD patients were urban residents (n=54; 95%), women (n=40; 70%), ethnically Chagga (n=37; 65%), attained at least primary school education (n=40; 70%) and worked in a self-employed small business/vendor (n=21; 37%) (**table 1**). The median age was 45 years (Inter-quartile range (IQR): 35-59). Many reported a history of hypertension (n=25; 44%), diabetes (n=17; 30%), heart disease (n=6; 11%) and HIV (n=6; 11%). Most adults with CKD had a history of alcohol intake (n=41; 72%); however, only a few reported a history smoking (n=17; 30%).

3.2.1 Modes of Healthcare Access

The modes of healthcare access included biomedical and traditional healthcare providers, and they varied with CKD diagnosis. The modes of healthcare access with the highest frequencies were medical doctors (461 out of 476 (97%)), family members (247 out of 476 (52%)), pharmacists (112 out of 476 (24%)) and friends or neighbors (66 out of 476 (14%)). CKD patients had a higher frequency of seeking healthcare advice from herbal vendors (12% vs 5%) and traditional healers (23% vs 6%) compared to the non-CKD population (**figure 1 & table 2**).

Table 1 Characteristics of survey respondents by CKD status

Variable	With CKD (n=57)	Without CKD (n=424)	p-value
Gender			
Male	17 (30%)	106 (25%)	0.424
Female	40 (70%)	318 (75%)	ref
Age			
18-39 years old	16 (28%)	156 (37%)	ref
40-59 years old	24 (42%)	167 (39%)	0.462
60+ years old	17 (30%)	101 (24%)	0.139
Setting			
Rural	3 (5%)	108 (25%)	ref
Urban	54 (95%)	316 (75%)	0.007
Ethnicity			
Chagga	37 (65%)	251 (59%)	ref
Pare	7 (12%)	59 (14%)	0.638
Sambaa	4 (7%)	23 (5%)	0.757
Other‡	9 (16%)	91 (21%)	0.383
Education			
None	4 (7%)	27 (6%)	ref
Primary	40 (70%)	309 (73%)	0.810
Secondary	7 (12%)	67 (16%)	0.533
Post-Secondary	6 (11%)	21 (5%)	0.184
Occupation			
Unemployed#	10 (17%)	64 (15%)	ref
Farmer/Wage Earner	14 (25%)	185 (44%)	0.006
Small Business/Vendors	21 (37%)	137 (32%)	0.942
Professional†	12 (21%)	38 (9%)	0.168
History of Smoking	17 (30%)	101 (24%)	0.349
History of alcohol intake	41 (72%)	276 (65%)	0.364
Self-Reported Medical History			
Hypertension	25 (44%)	109 (26%)	0.006
Diabetes	17 (30%)	44 (10%)	<0.001
Heart Disease*	6 (11%)	12 (3%)	0.225
HIV	6 (11%)	15 (4%)	0.012
Stroke	2 (4%)	6 (1%)	0.196
COPD	0 (0%)	8 (2%)	0.99

Includes housewives and students
† Professional includes any salaried position (e.g. nurse, teacher, government employee, etc.) and retired persons
* Heart Disease includes coronary disease, heart failure, or structural diseases
‡ Includes Maasai

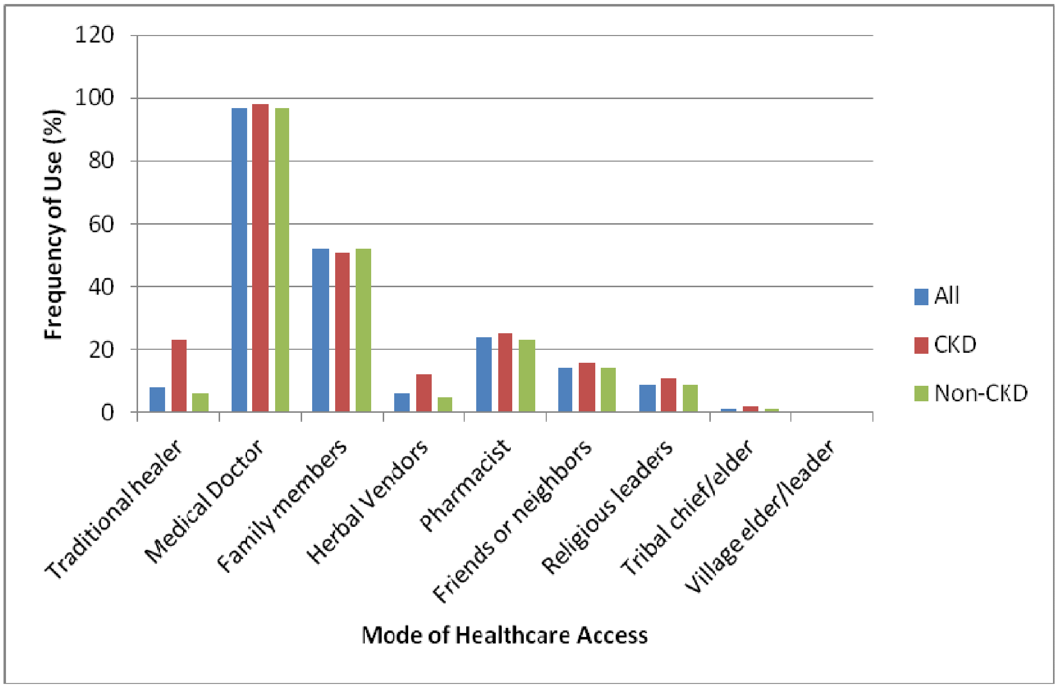

Figure 1: Histogram demonstrating mode of healthcare accessed by CKD status

In a univariate predictive model (**table 2**), CKD patients were more likely than the general study population to report seeking care from traditional healers (OR= 4.66; p-value< 0.001) and herbal vendors (OR= 2.79; p-value= 0.027). After adjusting for confounders (the derivation of the optimal adjustment model is described in section 3.2.2 below), CKD patients were still more likely to report seeking healthcare from a traditional healer (AOR= 4.61; p-value<0.001) and an herbal vendor (AOR= 2.93; p-value= 0.042) than the general study population. In this fully adjusted predictive model, being unemployed was a negative predictor for seeking healthcare from traditional healers (AOR=0.29, p=0.40) and herbal vendors (AOR=0.27, p=0.030) among CKD patients.

Table 2: Modes of healthcare access in Moshi, Tanzania

Mode of Healthcare Access	All (N=476) Freq (%)	CKD (N=57) Freq (%)	Non-CKD (N=419) Freq (%)	Odds Ratio (p-value)	Confidence Interval (95%)
Traditional healer	28 (8%)	13 (23%)	25 (6%)	4.66*	2.22, 9.75
Medical Doctor	461 (97%)	56 (98%)	405 (97%)	1.94	0.25, 15.01
Family members	247 (52%)	29 (51%)	218 (52%)	0.95	0.55, 1.66
Herbal Vendors	27 (6%)	7 (12%)	20 (5%)	2.79#	1.12, 6.94
Pharmacist	112 (24%)	14 (25%)	98 (23%)	1.07	0.56, 2.03
Friends or neighbors	66 (14%)	9 (16%)	57 (14%)	1.19	0.55, 2.56
Religious leaders	44 (9%)	6 (11%)	38 (9%)	1.18	0.48, 2.93
Tribal chief/elder	5 (1%)	1 (2%)	4 (1%)	1.85	0.20, 16.87
Village elder/leader	2 (0.4%)	0 (0%)	2 (0.5%)	0	-
Multivariate models					
Traditional healer				4.61*ǂ	1.96, 10.81
Herbal vendors				2.93#ǂ	1.04, 8.24

*p< 0.01; #p< 0.05; ǂadjusted odds ratio (AOR)

3.2.2 Modeling the minimally sufficient adjustment set

The full set of potential confounders were identified from univariate regression models between the potential confounding variable and CKD; these potential confounders included: residing in urban areas, occupation, self-reported history of kidney disease, HIV/AIDS, high blood pressure, DM and “heart attack”, and history of using medicines for blood pressure and orthopedic conditions. Age and gender, identified using *a priori* knowledge about CKD and TM, were also included in this full set. The model without self-reported history of kidney disease and HIV, and history of using medicines for orthopedic conditions offers the highest gain in precision (confidence limit range 8.85 vs 10.81 for the “full” model) and the least penalty in bias (mean squared error = 4.07) among the “reduced” models. Thus we selected this model as the minimally sufficient set for confounding adjustment in the multivariate analysis (see appendix A for the complete stepwise evaluation of the validity-precision trade-off).

Because of the low numbers of survey respondents who reported a history of kidney disease (14 out of 475 (3%)), we could not fit an interaction term between self-reported history of kidney disease and traditional medicine to use to examine effect modification of the association between traditional medicine use and CKD by self-reported history of kidney disease.

3.2.3 Modes of healthcare access and screening tests

CKD and hypertension, but not DM and obesity, were associated with modes of healthcare access (**table 3**). Although CKD was significantly positively associated with modes of healthcare access (traditional healers and herbal vendors), hypertension was significantly negatively associated with seeking healthcare from a religious leader (unadjusted OR=0.45; p=0.048). Furthermore, in the fully adjusted model, CKD, but not hypertension, remained significantly associated with modes of healthcare access; hypertension was not associated with seeking healthcare from religious leaders in the multivariate model (AOR=0.63, p=0.35) (**table 3**).

Table 3: Modes of healthcare access by screening test results in Moshi

Mode of healthcare access	CKD Odds Ratio	Diabetes Odds Ratio	Hypertension Odds Ratio	Obesity Odds Ratio
Traditional healer	4.66*	1.68	1.28	0.44
Medical Doctor	1.94	0.76	0.69	1.62
Family members	0.96	1.10	0.88	1.11
Herbal Vendors	2.79#	2.63	1.52	0.70
Pharmacist	1.07	1.30	0.82	1.12
Friends or neighbors	1.19	0.51	0.85	1.64
Religious leaders	1.18	0.84	0.45#	1.66
Tribal chief/elder	1.85	0	0.54	1.68
Village elder/leader	0	0	0	2.51

* $p<0.01$; # $p<0.05$

3.2.4 Community perspectives on the definition of CKD

To understand what the phrase “self reported medical history” meant to study participants, specifically in the context of CKD, we identified the relevant themes from the EIs and FGDs transcripts.

When asked what they thought the symptoms of CKD were, EI participants gave responses like: "I went to test (for kidney disease) at KCMC hospital...after I experience (d) some symptoms like frequent urination that made me think I have kidney problems," (EI 02). "...I have not experienced any symptoms I heard in relation to kidney problems like pain during urination," (EI 01). "...your foot will swell because of kidney problems..," (EI 04). "...pain in (the) ribs area," (EI 05). Frequent urination and pain during urination are, however, symptoms of sexually transmitted infections (STIs), not CKD.

Regarding risk factors of kidney disease, respondents gave responses like: "...when they (Moshi community members) hear that someone has kidney problem they will perceive it as among the STI's of which it is not true." S/he added, "…only through drinking of more liquor and alcohol in general can affect the kidneys ability to perform their work in the body," (EI 06). "From what I know kidney disease is a disease that affects much those people who are taking alcoholic drinks," (FGM1 – 12). "…most of us have never attended hospital checkup (for) kidney problems," (EI 03). Respondent "EI 06" correctly distinguished between CKD and STIs; however, s/he believes that alcohol is the main risk factor for CKD. This belief seems to be shared by other community members as well, as suggested by a respondent from the men's focus group (FGM1).

3.2.5 Factors influencing modes of healthcare access

When asked why they might access healthcare from traditional healers instead of medical doctors, some of the EIs and FGD participants gave the following reasons.

For some, affordability was the reason. For example, some comments included: "(TMs are) cheap compared to hospital medicines; I know someone who used them and he was cured, another benefit is that they are easy to access as some are found in our nearby homes," (FGM2- 02). For others, accessibility was an important determinant of mode of healthcare access "(traditional healers are) very close... (to)...the community than hospital as in some case(s) (a) traditional doctor can be your neighbor," (EI 07). In addition to the physical proximity of traditional healers, some respondents tied accessibility to advertisement of services by traditional healers. "...but also the hospital might be available but local healer(s) are very powerful in advertising their herbals compared to hospitals." "...the influence of media by allowing the herbal doctor's advertising their medicine on expense of hospital medicines by showing their side effects to human body without much oversee from the government," (FGM1 – 02). For others side effects of hospital medicines were an important barrier to accessing healthcare from hospitals. "Our elders…taught us that (hospital) medicine has a lot of chemicals, in any home area I know some people who (have) used hospital medication and get some side effects," (FGM2 08). Thus greater affordability and accessibility, according to these respondents, are important reasons for TM use. Additionally, some respondents attribute the greater accessibility of TM to the advertising of TM services.

On the other hand, there were a number of participants who spoke against accessing healthcare from traditional healers. A common theme among most of these respondents was the diagnostic services offered in hospitals, and the ability to dose hospital medications. Some of the responses included: "...medical doctors have testing tools that can make them know what is going on in my body," (EI 01). "Hospital medication has a lot of guidelines on how to use with regard to the dose and time to use. While traditional medicine does not have those, For example when you are taking hospital dose sometimes they instruct you not to eat some food or taking some drinks like alcohol and milk while when using traditional medication you are not allowed to be involved on these," (FGM1-07). “I can’t go to the traditional healers because they don’t have special dosage or measurement in relation to the extent of the problem I have,” (EI 02). “It is absolutely possible because in hospital you can get tested and also have special medications that can help (you) get treated.” S/he added, “I don’t prefer the use of (TM) because they don’t have special measurement,” (EI 02). Thus, although affordability and accessibility may be a barrier to hospital-based care, some community members are still drawn to it because of the conventional nature of biomedicines.

3.4 Herbal Plant Use for Traditional Medicine

Among the general study participants, 276 (58%) reported a history of herbal plant use for traditional medicine over the last one year. However, among the participants with CKD, 42 (74%) reported a history of using herbal plants at least once (unadjusted OR=2.21, p=0.01). In the fully adjusted model, CKD patients were still more likely than the non-CKD population to report using herbal plants (AOR=1.99, p=0.041) over the prior one year interval to the survey (**table 4**).

Table 4: Traditional medicine use in Moshi, Tanzania

Traditional medicine use	All N (%)	CKD N (%)	Odds Ratio	p-value	Confidence Interval
Univariate model					
None	200 (42%)	15 (26%)	ref		
Atleast once	276 (58%)	42 (74%)	2.21	0.012	1.19, 4.12
Multivariate model					
None			ref		
Atleast once			1.99	0.041	1.03, 3.87

3.4.1 Reasons for herbal plant use

The four main reasons for use of traditional medicines (**table 5**) among the CKD population were because herbals are more affordable (58%), failure of hospital medicines (58%), belief that TMs work better (56%) and belief that TMs are easier to obtain (53%). This was similar to the four main reasons given by the non-CKD population for TM use (60%, 58%, 60% and 56%, respectively). However, in a fully adjusted model, CKD patients were more likely than the non-CKD population to report that family tradition (OR=1.97; p=0.035), difficulty finding a medical doctor (OR=2.07; p=0.031) and fewer side effects with TMs (OR=2.07; p=0.028) as their reasons for preferring traditional medicines to hospital medicines. Additionally, CKD patients were also more likely than the non-CKD population to report “too many chemicals in hospital medicines” as their reason for preference of TMs in the unadjusted model (unadjusted OR=1.79; p=0.044).

Table 5: Reasons for traditional medicine use in Moshi, Tanzania

Reasons for traditional medicine use	All (N=469) Freq (%)	CKD (N=57) Freq (%)	Non-CKD (N=420) Freq (%)	Odds Ratio (p-value)	Confidence Interval (95%)
more affordable	284 (60%)	33 (58%)	251 (60%)	0.92	0.49, 1.73
too hard to find a medical doctor	103 (22%)	19 (33%)	84 (20%)	2.07*	1.07, 4.01
failure of hospital medicines	278 (58%)	33 (58%)	245 (58%)	1.04	0.56, 1.94
TMs are safer	132 (28%)	18 (32%)	114 (27%)	1.33	0.69, 2.58
TMs work better	282 (59%)	32 (56%)	250 (60%)	1.22	0.66, 2.25
family tradition	145 (30%)	25 (44%)	120 (29%)	1.97*	1.05, 3.71
religious reasons	31 (7%)	3 (5%)	28 (7%)	0.59	0.16, 2.25
TMs are easier to obtain	265 (56%)	30 (53%)	235 (56%)	0.96	0.52, 1.79
TMs are more traditional	126 (26%)	17 (30%)	109 (26%)	1.34	0.69, 2.62
TMs are found naturally	157 (33%)	22 (39%)	135 (32%)	1.38	0.72, 2.62
too many chemicals in hosp meds	145 (30%)	24 (42%)	121 (29%)	1.77	0.94, 3.31
TMs have fewer side effects	139 (29%)	24 (42%)	115 (27%)	2.07*	1.08, 3.96

* $p< 0.05$

3.5 Traditional medicines used for Kidney Disease

We identified 168 herbal plants (a major component of TM) from the EIs, FGDs and cross-sectional survey; five (5) of these plant remedies are used to treat kidney disease in Moshi: Commifora, Aloe barbadensis, Cympogon citrullus, Zanthoxylun chalybeum and Persea americana (**table 6**). Globally, including neighboring East African countries of Uganda and Kenya, these herbals are used to treat various illnesses including both communicable and non-communicable diseases in these communities. Most of the herbals have pharmacologically active compounds with a wide spectrum of effects including lipid-lowering, anti-microbial, anti-inflammatory and anti-oxidant effects. Toxicities of these herbals include gastro-intestinal upsets (e.g. loose-stools), allergy and hypersensitivity reactions, increased risks of bleeding and damage to visceral organs (kidneys, liver and stomach). These herbals have clinically significant drug interactions with hospital medicines, including propranolol & diltiazem (decreases bioavailability), anti-coagulants (increases bleeding risks), digoxin, non-potassium sparing diuretics, insulin and laxatives.

Table 6: Herbal plants used for kidney disease in Moshi

Name: Botanical (local)	Uses in other global communities	Pharmacology of active compounds	Side-effects/ Toxicity	Drug Interactions
Commifora (Loduwa)	Indian ayurvedic medicine: lipid-lowering agent[24]	Guggulsterone: lipid-lowering efects (binds to farsenoid & bile acid receptors) [23]	inhibits platelet aggregation and increases fibrinolysis[23,32]	Decreases the bioavailability of propranolol and diltiazem[23, 33]
	Egypt: antischistosomial agent[24]		GI upsets/loose stools[24]	May increase bleeding risks with anti-coagulants[23, 32]
	TCM: trauma, arthritis, fractures[24]		Hypersensitivity[23]	
Aloe barbadensis (Aloe vera)	Ayurvedic medicine: a laxative, anti-helminthic, hemorrhoid remedy, eczema & psoriasis, & uterine stimulant (menstrual regulator)[34]	glucomanan- skin mosturizer; acemanan- immune-modulator; bradikininase- anti-inflammatory; aloesin- antioxidant[34, 36, 37, 38]	Dehydration & electrolyte imbalance[61, 62,63] Aloe-emodin induces apoptosis of HK-2 cells in proximal renal tubules[60]	Digoxin, non-K sparing diuretics, insulin, laxatives[34, 35, 40, 41]
	TCM: constipation (WHO approved)[34]	B-cell stimulant[34, 39]	Hypoglycemia[34]	
	Neuropaths: renal stones[34]			
Cymbopogon Citrullus (Mchaichai)	Brazilian folk medicine: sedative & hypnotic, analgesic, anti-emetic, antispasmodic & remedy for stomach & intestinal ailments[29]	Essential oils have antimicrobial effects on both gram+/- bacteria & food-spoilage fungi[45]	At a high dose or chronic low dose: eGFR decrease; may be followed by a decline in the other renal function indices too [30]	
	Mauritius & Malay peninsula: common cold, pneumonia, fever & gastric problems[29, 42, 43]	Anti-trypanosomal and anti-plasmodial activity[42]	Dose- and time-dependent decline in GFR [30]	
	Nigeria: antipyretic, stimulant & antispasmodic[29]	Anti-oxidant[45]	Hepatic & gastric injury at dose> 1500mg in rats[47]	
	Angola & India: anti-tussigen, anti-emetic, antiseptic and anti-rheumatic[29]	insecticidal effects[46]		
	Indonesia: diuretic[29, 44]			
Zanthoxylun chalybeum (Murungurungu)	Kenya: anti-malarial[50]	Anti-plasmodial[50]	skimmianine- epherine-like & antihistamine effects	
	Uganda: dental caries & toothache[48]	antiviral (measles)		
	Machakos and Makueni counties in Kenya: chronic joint pains[49]	Antibacterial activity on S. typhi, P. aeruginosa, S. aureus[48, 51]	lethal to rats with intra-peritoneal injection[52]	
Persea Americana (Avocado seed)	Nigeria: anti-diarrheal/anti-diabetic[53, 55]	Anti-oxidant effects- hepato-protective[59]	Risk of bleeding[56]	Enhances the effects of aspirin and other anti-platelet agents[56]
	several countries in S. America, West Indies & Africa: dengue vector control, diarrhea, sore throat, hemorrhage & menstrual stimulation/regulation[58]	anti-diabetic[54]- inhibits aplha amylase and glucoronidase enzymes[57]	sluggishness & facial/orbital swelling in rats at doses>5000mg/kg body weight[55]	
		acetogenins inhibit platelet aggregation[56]		
		larvicidal to A. aegypti[59]		

4. Discussion

Our mixed methods study demonstrated a high prevalence of traditional medicine use in Moshi, Tanzania. The four main reasons described for TM use among our study population in Moshi were greater affordability and access of TM, as well as beliefs about the failure of hospital medicines and that TMs work better.

4.1 Implications for policy and practice

Most, if not all, of the participants in the FGDs and EIs did not have an accurate knowledge of the definition and risk factors for CKD. For example some participants mentioned urinary symptoms like frequent urination, painful urination, etc as symptoms of CKD; however, these are symptoms of urinary tract infections, not CKD. Similarly, some participants mentioned alcohol intake as the leading risk factor for CKD; although this observation is not unreasonable in this region, we are not aware of findings in the medical literature suggesting that alcohol may play a role in the etiology of CKD. Furthermore, only 3% of survey respondents reported having a medical history of kidney disease yet the prevalence of CKD from the screening test was about 12%. Thus it could be that survey respondents who had CKD (diagnosed from the screening test) were unaware of their CKD-status (self-reported medical history of kidney disease). This probably suggests that healthcare providers in hospitals and local health centers are not talking about CKD to their patients, and probably not screening their at-risk patients for CKD. Healthcare providers are probably not taking about CKD to their patients because they are not aware of the prevalence and risks for CKD among their patients or it could be due to communication barriers such that patients do not understand the diagnosis. Given that CKD often progresses to kidney failure without symptoms, it is particularly important to raise awareness about the disease and to screen at-risk community members for CKD, which will permit early recognition of CKD cases and initiation of interventions to slow disease progression and to prevent CKD-associated co-morbidities [25].

4.2 Implications for further research

Some of the TMs that are prescribed by TM practitioners in Moshi are also used in other global communities, and these medicines have pharmacologically active molecules; however, the effects of most of these substances have been described largely in animal experiments but not in human subjects. Therefore future research should be designed to test the effects of these substances in human subjects under close regulation by the drug development agencies. Such research should seek to describe the clinical applications of these pharmacologically active substances, in terms of their toxicity, interactions with biomedicines, and their therapeutic/prophylactic actions. Preliminary data from our literature search suggests that some of these substances can potentially be developed into drug regimens; for example Aloe barbadensis, which is prescribed for kidney disease in Moshi, was approved by the WHO as a laxative for constipation. Cymbopogon Citrullus and Zanthoxylun chalybeum, locally referred to as "Mchaichai" and “Mrungurungu,” respectively, have been shown in animal experiments to possess significant anti-microbial activity; further research on their effects in human subjects could potentially lead to the discovery of new anti-microbial agents.

The pharmacological data for the TMs used to treat kidney disease in Moshi may also give insights into the mechanisms underlying the observed association between TM use and kidney disease in the present study, which is consistent with previous reports linking TM use and kidney disease in other parts of the world [2, 25, 26]. The postulated mechanisms for nephrotoxicity of TMs include renal tubular damage, electrolyte disturbances, hypertension, renal papillary necrosis, renal cysts and kidney stones formation, etc. The active compounds responsible for these kidney effects have been described for some of these nephrotoxic effects: aristolochic acid (renal tubular defects & interstitial nephritis), nordihydroguaiaretic acid (renal cysts), ephedrine, djenkolic acid & oxalic acid (kidney stones & obstructive CKD), yohimbine (lupus nephritis), and glycrrhizin (hypokalemic nephropathy) [2, 25]. Aloe barbadensis, approved by the WHO as a laxative for constipation, has toxic effects that are potentially detrimental to the kidneys. It causes dehydration and electrolyte imbalances (including potassium depletion) in experimental rats. Dehydration has been shown to cause kidney scarring leading to kidney failure in rats [27], and hypokalemia (potassium depletion) is postulated as the mechanism by which glycrrhizin, the active compound in Glycrrhiza glabra, induces CKD in humans following long-term consumption of the plant [28, 2].

Cymbopogon citrullus, known as “Mchaichai” (the name reflects its use as a medicinal beverage in Tanzania) in the native language in Moshi, has essential oils with anti-microbial properties. However, its toxic effects include decline in kidney function with chronic use [30]. Ekpenyong et al. investigated the effects of daily oral intake of infusions of Cymbopogon leaves on kidney function in humans; after 30 days of daily intake, they observed a statistically significant dose- and time-dependent decline in eGFR[30]. Studies in experimental rats have suggested that the active substances in Cymbopogon leaf extracts are the anti-oxidants tannins, saponins and flavinoids, which have furosemide-like diuretic and natriuretic effects on the kidneys [31]. It’s therefore likely that long-term consumption of Cymbopogon leaves results in decline in kidney function due to recurrent volume depletion and electrolyte imbalance, similar to the mechanism by which Aloe barbedensis induces CKD.

4.3 Study strengths and limitations

Traditional medicine use is deeply rooted in socio-cultural dynamics, which vary across age groups, ethnicities, and cultures. This, therefore, calls for the use of multi-level approaches that emphasizes real-life contextual understandings, multi-level perspectives, and cultural influences to investigate the complex determinants of traditional medicine in communities. Accordingly, our study draws on theoretical frameworks from the social, behavioral and biological sciences. For example, the constructs in the initial guides for the EIs and FGDs were framed by integrating theories from the social and behavioral science perspectives (particularly social determinants of health) with the biological theories of health. Thus, on the one hand, the inductive qualitative component provided insights into the contexts and meanings of the experiences of the study population regarding TM use, and the deductive approach of the quantitative aspect, on the other hand, permitted us to test these theories or hypotheses, gather descriptive information about individual constructs and to examine relationships among these constructs by applying statistical analyses.

Our study design, despite the above strengths, has limitations too. We are not in position to make causal inferences from the measures of association derived from the cross-sectional quantitative study design, despite the strengths of the associations observed in the present study. Thus we could not examine the causal relationship for the observed association between TM use and CKD. Given the gaps in our current understanding of the spectrum of CKD in SSA [20] and other parts of the world [21, 22], future research should be designed to examine the potential role of TM use in the etiology of CKD, as already posited elsewhere [2, 10]. Furthermore, a comprehensive profiling of the toxicities of TMs used in Moshi will likely provide further insights on the mechanisms by which TMs contribute to the etiology of NCDs, including CKD.

5. Conclusion

Traditional medicine use is high in Moshi, especially among the CKD population. In addition, a history of traditional medicine use is associated with the prevalence of CKD in Moshi. The four main reasons described for TM use among our study population in Moshi were greater affordability and access of TM, as well as beliefs about the failure of hospital medicines and that TMs work better. The plant remedies used as traditional medicines for kidney disease in Moshi are also used in other parts of the world; however, they are prescribed for different conditions in different parts of the world. These plant remedies have biologically active substances that could potentially be developed into therapeutic and prophylactic therapies for CKD.

Appendix A

Table comparing "full" and "reduced" models for confounding variables

Model	OR	95% CI	CLR	Bias^2	Variance	MSE
Full	5.47	2.28, 13.09	10.81			
remove BP medicine use	5.45	2.27, 13.06	10.79	0.0000185	5.9049	5.9049
remove orthopedic medicine use (1)	5.32	2.23, 12.65	10.42	0.0008066	5.5225	5.5233
remove history of "heart attack"	5.53	2.32, 13.18	10.86	0.0001061	6.0025	6.0026
remove history of high BP	5.4	2.27, 12.88	10.61	0.0001823	5.7121	5.7123
remove history of DM	5.42	2.27, 12.99	10.72	9.604E-05	5.8564	5.8565
remove history of HIV (2)	4.91	2.06, 11.69	9.63	0.011794	4.7089	4.7207
remove history of kidney disease (3)	5.31	2.22, 12.67	10.45	0.0009181	5.5696	5.5705
remove residence	5.66	2.38, 13.49	11.11	0.0011223	6.3001	6.3012
remove occupation*	5.42	2.34, 12.57	10.23	9.604E-05	5.4289	5.429
remove (1), (2) and (3)	4.61	1.96, 10.81	8.85	0.0294809	4.0401	4.0696

* LRT test was significant: $X^2 = 12.60$, p=0.027. OR= odds ratio; CI= confidence interval; CLR= confidence interval range; MSE= mean squared error.

References

1. WHO Congress on Traditional Medicine, Beijing, China, November 2008. http://www.who.int/medicines/areas/traditional/TRM_BeijingDeclarationEN.pdf?ua=1

2. Jha, V. (2010). Herbal medicines and chronic kidney disease. Nephrology, 15, 10-17. doi: 10.1111/j.1440-1797.2010.01305.x

3. Straus SE. Herbal medicines – What's in the bottle? N. Engl. J. Med. 2002; 347: 1997–8.

4. De Smet PA. Herbal medicine in Europe – relaxing regulatory standards. N. Engl. J. Med. 2005; 352: 1176–8.

5. World Health Organization. Traditional Medicine Strategy, 2002-2005. WHO/EDM/TRM/2002.1.

6. Kisangau DP, Lyaruu HV, Hosea KM, Joseph CC., Use of traditional medicines in the management of HIV/AIDS opportunistic infections in Tanzania: a case in the Bukoba rural district. J Ethnobiol Ethnomed. 2007 Jul 10; 3:29.

7. Maroyi A., An ethnobotanical survey of medicinal plants used by the people in Nhema communal area, Zimbabwe. J Ethnopharmacol. 2011 Jun 22; 136(2): 347-54. doi: 10.1016/j.jep.2011.05.003.

8. Anthony C. Liwa, Luke R. Smart, Amara Frumkin, Helen-Ann B. Epstein, Daniel W. Fitzgerald, Robert N. Peck: Traditional Herbal Medicine Use Among Hypertensive Patients in Sub-Saharan Africa: A Systematic Review. Curr Hypertens Rep (2014) 16: 437.

9. Gerald S Bloomfield, Rajesh Vedanthan, Lavanya Vasudevan, Anne Kithei, Martin Were, Eric J Velazquez: Mobile health for non-communicable diseases in Sub-Saharan Africa: a systematic review of the literature and strategic framework for research. Globalization and Health 2014 10: 49.

10. Smith AY, Feddersen RM, Gardner KD Jr, Davis CJ Jr. Cystic renal cell carcinoma and acquired renal cystic disease associated with consumption of chaparral tea: a case report. J Urol. 1994 Dec; 152(6 Pt 1): 2089-91.

11. Population Distribution by Administrative Units; United Republic of Tanzania, 2013.

12. Tanzania Poverty and Human Development Report 2005, The Research and Analysis Working Group of the Poverty Monitoring System, Dar Es Salaam, pages 104, 106, 108.

13. Tanzania Demographic and Health Survey 2010, National Bureau of Statistics, Dar es Salaam, published April 2011.

14. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2: 1–138.

15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A More Accurate Method to Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Ann Intern Med. 1999; 130:461–470.

16. Stanifer, John, Francis Karia, Corrine Voils, Elizabeth Turner, Venance Maro, Dionis Shimbi, Humphrey Kilawe, Matayo Lazaro, Uptal Patel. "Development and Validation of a Cross-Cultural Knowledge, Attitudes, and Practices Survey Instrument for Chronic Kidney Disease in a Swahili-Speaking Population." (Under review).

17. Christopher J.L. Murray, Julio Frenk, A framework for assessing the performance of health systems. Bulletin of the World Health Organization, 2000, 78 (6).

18. Frenk J (2010), The Global Health System: Strengthening National Health Systems as the Next Step for Global Progress. PLoS Med 7(1): e1000089. doi:10.1371/journal.pmed.1000089.

19. Julio Frenk, Bridging the divide: global lessons from evidence-based health policy in Mexico. Lancet 2006; 368: 954–61.

20. Stanifer JW, Jing B, Tolan S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Global Health 2014; published online Feb 10. http://dx.doi.org/10.1016/S2214-109X (14)70002-6.

21. Cuadra S, Jakobsson K, Hogstedt C, Wesseling C. Chronic Kidney Disease in Central America. Chronic Kidney Disease: Assessment of Current Knowledge

and Feasibility for Regional Research Collaboration in Central America, Section 1, vol 2. Heredia, Costa Rica: SALTRA.

22. Redmon et al.: Additional perspectives on chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka – lessons learned from the WHO CKDu population prevalence study. BMC Nephrology 2014 15:125.

23. Ulbricht, C, Basch, E, Szapary, P, Hammerness, P, Axentsev, S, Boon, H, Woods, J. (2005). Guggul for hyperlipidemia: a review by the Natural Standard Research Collaboration. Complement Ther Med, 13(4), 279-290. doi: 10.1016/j.ctim.2005.08.003.

24. Shen, T., Li, G. H., Wang, X. N., & Lou, H. X. (2012). The genus Commiphora: a review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol, 142(2), 319-330. doi: 10.1016/j.jep.2012.05.025.

25. Vivekanand Jha, Guillermo Garcia-Garcia, Kunitoshi Iseki, Chronic kidney disease: global dimension and perspectives. Lancet 2013; 382: 260–72.

26. Yifei Zhong, Yueyi Deng, Yiping Chen, Peter Y. Chuang, John Cijiang He, Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. Kidney International (2013) 84, 1108–1118; doi:10.1038/ki.2013.276; published online 17 July 2013.

27. Carlos, A.R.J., Fructokinase activity mediates dehydration-induced renal injury, 2013. Kidney International advance online publication, 11 December 2013.

28. Ishikawa S, Kato M, Tokuda T et al. Licorice-induced hypokalemic myopathy and hypokalemic renal tubular damage in anorexia nervosa. Int. J. Eat. Disord. 1999; 26: 111–14.

29. Carlini, E. A., Contar, J. d. D. P., Silva-Filho, A. R., da Silveira-Filho, N. G., Frochtengarten, M. L., & Bueno, O. F. (1986). Pharmacology of lemongrass (Cymbopogon citratus Stapf). I. Effects of teas prepared from the leaves on laboratory animals. J Ethnopharmacol, 17(1), 37-64.

30. Ekpenyong, C. E., Daniel, N. E., & Antai, A. B. (2014). Effect of Lemongrass Tea Consumption on Estimated Glomerular Filtration Rate and Creatinine Clearance Rate. J Ren Nutr. doi: 10.1053/j.jrn.2014.08.005.

31. Jouad A, Lacaille-Dubois MA, Eddouks M. Chronic diuretic effect of the water extract of Spergularia purpurea in normal rats. J Ethnopharmacol. 2001; 75: 219-223.

32. Gaur SP, Garg RK, Kar AM. Gugulipid, a new hypolipidaemic agent, in patients of acute ischaemic stroke: effect on clinical outcome, platelet function and serum lipids. Asia Pacif J Pharm 1997; 12:65—9.

33. Dalvi SS, Nayak VK, Pohujani SM, Desai NK, Kshirsagar NA, Gupta KC. Effect of gugulipid on bioavailability of diltiazem and propranolol. J Assoc Physicians India 1994; 42(6):454—5.

34. Ulbricht, C., Armstrong, J., Basch, E., Basch, S., Bent, S., Dacey, C., . . . Weissner, W. (2007). An evidence-based systematic review of Aloe vera by the natural standard research collaboration. *J Herb Pharmacother, 7*(3-4), 279-323.

35. Odes HS, Madar Z. A double-blind trial of a celandin, aloevera and psyllium laxative preparation in adult patients with constipation. *Digestion,* 1991; 49(2): 65–71.

36. Pugh N, Ross SA, ElSohly MA, Pasco DS. Characterization of aloeride, a new high-molecular-weight polysaccharide from aloe vera with potent immunostimulatory activity. J Agric Food Chem. 2001; 49(2):1030–4.

37. Yagi A, Kabash A, Mizuno K, Moustafa SM, Khalifa TI, Tsuji H, Radical scavenging glycoprotein inhibiting cyclooxygenase-2 and thromboxane A2 synthase from aloe vera gel. Planta Med. 2003 Mar; 69(3):269-71.

38. Singh RP, Dhanalakshmi S, Rao AR. Chemomodulatory action of aloe vera on the profiles of enzymes associated with carcinogen metabolism and antioxidant status regulation in mice. Phytomedicine. 2000; 7(3): 209–19.

39. Beppu H, Nagamura Y, Fujita K. Hypoglycemic and antidiabetic effects in mice of aloe-arborescens miller var natalensis berger. *Phytother Res.* 1993; 7:S37–S42.

40. Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, et al. Antidiabetic activity of aloe vera L. juice. I Clinical trial in new cases of diabetes mellitus. Phytomedicine. 1996; 3(3):241–3.

41. Bunyapraphatsara N, Yongchaiyudha S, Rungpitarangsi V, et al. Antidiabetic activity of aloe vera L. juice. II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. Phytomedicine. 1996; 3(3):245–8.

42. Kpoviessi, S., Bero, J., Agbani, P., Gbaguidi, F., Kpadonou-Kpoviessi, B., Sinsin, B., . . . Quetin-Leclercq, J. (2014). Chemical composition, cytotoxicity and in vitro antitrypanosomal and antiplasmodial activity of the essential oils of four Cymbopogon species from Benin. *J Ethnopharmacol, 151*(1), 652-659. doi: 10.1016/j.jep.2013.11.027

43. Fook, W.T. The Medicinal Plants of Mauritius. ENDA Publication: document 10, March 1980, p. 17.

44. Hirschhorn, H.H. (1983) Botanical remedies of the former Dutch East Indies (Indonesia). Part I: Eumycetes, pteridophyta, gymnospermae, angiospermae (Monocotyledones only). Journal of Ethnop~armacology 7, 123-156.

45. Martins Mdo, R., Arantes, S., Candeias, F., Tinoco, M. T., & Cruz-Morais, J. (2014). Antioxidant, antimicrobial and toxicological properties of Schinus molle L. essential oils. *J Ethnopharmacol, 151*(1), 485-492. doi: 10.1016/j.jep.2013.10.063

46. Lópeza A, Castrob S, Andinaa MJ, Uresa X, Munguíaa B, Llabotb JM, Elderc H, Dellacassad E, Insecticidal activity of microencapsulated Schinus molle essential oil. Industrial Crops and Products 53 (2014) 209– 216

47. Fandohan, P., Gnonlonfin, B., Laleye, A., Gbenou, J. D., Darboux, R., & Moudachirou, M. (2008). Toxicity and gastric tolerance of essential oils from Cymbopogon citratus, Ocimum gratissimum and Ocimum basilicum in Wistar rats. *Food Chem Toxicol, 46*(7), 2493-2497. doi: 10.1016/j.fct.2008.04.006

48. Ocheng, F., Bwanga, F., Joloba, M., Borg-Karlson, A. K., Gustafsson, A., & Obua, C. (2014). Antibacterial activities of extracts from Ugandan medicinal plants used for oral care. *J Ethnopharmacol, 155*(1), 852-855. doi: 10.1016/j.jep.2014.06.027

49. Wambugu, S. N., Mathiu, P. M., Gakuya, D. W., Kanui, T. I., Kabasa, J. D., & Kiama, S. G. (2011). Medicinal plants used in the management of chronic joint pains in Machakos and Makueni counties, Kenya. *J Ethnopharmacol, 137*(2), 945-955. doi: 10.1016/j.jep.2011.06.038

50. Kirira, P. G., Rukunga, G. M., Wanyonyi, A. W., Muregi, F. M., Gathirwa, J. W., Muthaura, C. N., . . . Ndiege, I. O. (2006). Anti-plasmodial activity and toxicity of extracts of plants used in traditional malaria therapy in Meru and Kilifi Districts of Kenya. *J Ethnopharmacol, 106*(3), 403-407. doi: 10.1016/j.jep.2006.01.017

51. Mugiraneza JP, Munyabuhoro S, Bajyana SE, In vitro antimicrobial investigation of Zanthoxylum chalybeum stem bark. Academic Journals Vol. 7(21), pp. 1577-1579, 3 June, 2013 DOI: 10.5897/JMPR12.1231

52. Muganga, R., Angenot, L., Tits, M., & Frederich, M. (2014). In vitro and in vivo antiplasmodial activity of three Rwandan medicinal plants and identification of their active compounds. *Planta Med, 80*(6), 482-489. doi: 10.1055/s-0034-1368322

53. Ezuruike UF, Prieto JM, The use of plants in the traditional management of diabetes in Nigeria: Pharmacological and toxicological considerations. Journal of Ethnopharmacology 155 (2014) 857–924

54. Brai, B. I., Odetola, A. A., & Agomo, P. U. (2007). Hypoglycemic and hypocholesterolemic potential of Persea americana leaf extracts. *J Med Food, 10*(2), 356-360. doi: 10.1089/jmf.2006.291

55. Christian, E. O., Okwesili Fc, N., Parker, E. J., & Okechukwu Pc, U. (2014). Acute Toxicity Investigation and Anti-diarrhoeal Effect of the Chloroform-Methanol Extract of the Leaves of Persea americana. *Iran J Pharm Res, 13*(2), 651-658.

56. Rodriguez-Sanchez, D. G., Flores-Garcia, M., Silva-Platas, C., Rizzo, S., Torre-Amione, G., De la Pena-Diaz, A., . . . Garcia-Rivas, G. (2014). Isolation and chemical identification of lipid derivatives from avocado (Persea americana) pulp with antiplatelet and antithrombotic activities. *Food Funct*. doi: 10.1039/c4fo00610k

57. Oboh, G., Isaac, A. T., Akinyemi, A. J., & Ajani, R. A. (2014). Inhibition of key enzymes linked to type 2 diabetes and sodium nitroprusside induced lipid peroxidation in rats' pancreas by phenolic extracts of avocado pear leaves and fruit. *Int J Biomed Sci, 10*(3), 208-216

58. Dabas, D., Shegog, R. M., Ziegler, G. R., & Lambert, J. D. (2013). Avocado (Persea americana) seed as a source of bioactive phytochemicals. *Curr Pharm Des, 19*(34), 6133-6140.

59. Torres, R. C., Garbo, A. G., & Walde, R. Z. (2014). Larvicidal activity of Persea americana Mill. against Aedes aegypti. *Asian Pac J Trop Med, 7s1*, S167-170. doi: 10.1016/s1995-7645(14)60225-x

60. Zhu S, Jin J, Wang Y, Ouyang Z, Xi C, Li J, Qiu Y, Wan J, Huang M, Huang Z, The endoplasmic reticulum stress response is involved in apoptosis induced by aloe-emodin in HK-2 cells. Food Chem Toxicol. 2012 Mar;50(3-4):1149-58. doi: 10.1016/j.fct.2011.12.018. Epub 2011 Dec 21.

61. Kirdpon S, Kirdpon W, Airarat W, Thepsuthammarat K, Nanakorn S. Changes in urinary compositions among children after consuming prepared oral doses of aloe (Aloe vera Linn) J Med Assoc Thai. 2006;89:199–205.

62. Kirdpon S, Kirdpon W, Airarat W, Trevanich A, Nanakorn S. Effect of aloe (Aloe vera Linn.) on healthy adult volunteers: Changes in urinary composition. J Med Assoc Thai. 2006;89:S9–14.

63. Saka W, Akhigbe R, Popoola O, Oyekunle O, Changes in Serum Electrolytes, Urea, and Creatinine in Aloe Vera-treated Rats. J Young Pharm. 2012 Apr;4(2):78-81. doi: 10.4103/0975-1483.96620.