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**Concurrent use of traditional medicine and prescribed antibiotics
and/or antiviral medicines and their effects on antimicrobial resistance
and treatment failure in Ilembe district, Kwazulu-Natal province,
South Africa.**

BY

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of Master of Pharmacy by research in the Discipline of Pharmaceuticals Sciences,
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PREFACE

This dissertation is presented in a format of manuscripts. The findings of the study are presented in chapters 3 and 4 in a manuscript format as required by the new regulations of the University of KwaZulu-Natal. A systematic review protocol has been submitted for publication to the journal BMC Systematic Reviews. Two manuscripts emanated from data collected. One of the two manuscripts has been submitted for publication to the African Journal of Biomedical Research. Another manuscript has been submitted for publication to the journal BMC Complementary and Alternative Medicine. The reference list is cited according to the instructions for authors as required by the journals where manuscripts have been submitted and according to the required reference style of each journal. A complete reference list is included at the end of chapter one and the synthesis chapter.

The dissertation consists of 5 chapters as follows:

- Chapter 1: Provides a background and a brief overview of literature of the proposed study. This chapter highlights an overview of the rationale of the study, research questions, the aim, and objectives of the study. A general methodology has been included to achieve aim and different objectives of the study.
- Chapter 2: Consists of a systematic review protocol submitted to Bio Med Central, Systematic review journal under the title “Mapping evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance in sub-Saharan Africa: A systematic review protocol”.
- Chapter 3: Provides an original manuscript article submitted to the African Journal of Biomedical Research, under the title “Perspectives on the concurrent use of traditional and prescribed antimicrobial medicines for infectious diseases: a triangulation study involving biomedically trained healthcare professionals, outpatients, traditional health practitioners and their patients
- Chapter 4: Comprises an original manuscript article submitted to the journal BMC Complementary and Alternative medicine under the title “Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review”.
- Chapter 5: Provides the synthesis which includes general conclusions, strengths and limitations of the study then recommendations.

DECLARATION 1 – PLAGIARISM

I, Mukanda Gedeon Kadima, declare that:

1. The research reported in this dissertation, except where otherwise indicated, is my original work.
2. This dissertation has not been submitted for any degree or examination at any other university.
3. This dissertation does not contain other persons' data, pictures, graphs or other information unless specifically acknowledged as being sourced from other persons. Where other written resources have been quoted, then:
 - i) Their words have been re-written but the general information attributed to them has been referenced.
 - ii) Where their exact words have been used, then their writing has been placed inside quotation marks, and referenced.
4. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the reference sections.

Signed _____

Date _____

This is to certify that the contents of this dissertation are the original work of Mr. Mukanda Gedeon Kadima and as the candidate's supervisor, I have approved this thesis for submission.

Signed: _____ Name: Dr Manimbulu Nloto Date: _____

DECLARATION 2 - ETHICS APPROVAL

A Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE 476/17) – (Appendix 1). Permission was obtained from the KwaZulu-Natal Provincial department of health to conduct this study in two healthcare facilities (Appendix 2).

DECLARATION 3 – CONTRIBUTION TO MANUSCRIPTS

1. My contribution to the project was as follows:

Mukanda Gedeon Kadima: First author – Contributed to the project by performing all literature reviews, data collection, statistical analysis and interpretation of the results as well as manuscript preparation and writing of dissertation.

2. The contributions of other authors to the project were as follows:

Aganze Gloire-Aime Mushebenge assisted with drafting the discussion part of the second manuscript included in this dissertation.

Dr Manimbulu Nloto conceptualized and designed the study project. He supervised data collection, revised all the manuscripts for their intellectual contents and accepted the final version of each manuscript before submission to journals for publication.

DEDICATION

I dedicate this Masters of Pharmacy dissertation to MUPELA NTENGU JP, a soul I lost on the 27th March 2018. He was my uncle and an adviser to me and a way or passage that Lord God had planned for my life. This is the harvest of his encouragements and efforts that began at the dawn of his silent exit. I know that in a near future we will be reunited in heaven.

May his soul rest in peace Uncle!

A heartfelt thank you!

RESEARCH OUTPUTS

A. Manuscripts submitted for publication

1. “Mapping evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance in sub-Saharan Africa: A systematic review protocol” Manuscript submitted to the BMC Systematic Reviews.
2. “Perspectives on the concurrent use of traditional and prescribed antimicrobial medicines for infectious diseases: a triangulation study involving biomedically trained healthcare professionals, outpatients, traditional health practitioners and their patients. Manuscript submitted to the African Journal of Biomedical Research (AJBR).
3. “Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review” Manuscript submitted to the journal BMC Complementary and Alternative medicines.

B. Conferences

1. **Oral presentation** “Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review” – International Conference on Promoting ecohealth Research in Africa: *Towards the establishment of an African Chapter of ecohealth international* – ICC Durban, South Africa, 13 – 14 November 2018 (See appendices XIV and XV).
2. The same abstract above has also been accepted for an oral presentation at the 1st Joint International Conference on the potential ethnopharmacology and traditional medicine. Dakar, Senegal, 30 November – 02 December, 2018 (See appendix XVI).

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LIST OF ABBREVIATION/ACRONYMS

AMR – Antimicrobial Resistance

AOR – Adjusted Odd Ratio

ART – Antiretroviral therapy

ARV – Antiviral medicines

ATB – Antibacterial

ATM – Antimicrobial medicines

BHP – Biomedically Healthcare Professionals

CI – Confidence Interval

CYP450 – Cytochrome P450

FDC – Fixed Dose combination

HIV/AIDS – Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome

MMAT – Mixed method appraisal tool

OPD – Out Patients Department

PICOS – Population, Intervention, Comparison, Outcomes and study setting

PLWA – People Leaving with AIDS

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SPSS – Statistical package for the social sciences

TB – Tuberculosis

THP – Traditional Health Practitioners

TM – Traditional medicine

UKZN – University of KwaZulu-Natal

USA – United States of America

WHO – World Health Organization

GENERAL ABSTRACT

Background: Traditional herbal mixtures are generally available, affordable and commonly utilized in developing and developed countries and usually utilized as self-care treatments. However, its incorrect use can lead to fatal outcomes. Antimicrobial resistance (AMR) is driven by many factors such as the careless use of prescribed antimicrobial medicines and the use of traditional medicine, with the result that there is always the danger of misadministration, interaction, and toxicity. AMR is also considered as the major cause of treatment failure and is largely responsible for the declining in eradication rates of infectious diseases worldwide. Individuals may consult both traditional healer practitioners (THPs) and biomedically trained healthcare professionals (BHPs) for the treatment of their bacterial and viral infections. This study aimed at determining whether any antimicrobial resistance and treatment failure could occur among patients, attending outpatient departments of selected healthcare facilities, who used concurrently prescribed antimicrobial medicines and traditional medicine in the Ilembe district, South Africa

Methods: This study was a cross-sectional descriptive study using a mixed method approach. First phase was a qualitative study using an interview face to face with a questionnaire. One hundred and thirty two respondents were included with four (4) types of participants: Traditional health practitioners (THPs), Patients seen by THPs, biomedically healthcare professionals (BHPs) and outpatients. Second phase was a quantitative study using a medical chart review of 400 patients' medical records and who attended the outpatient department in two public healthcare facilities between February and March 2018. Antimicrobials prescribed alone or in association with other medicines and concurrent use of traditional medicine were assessed and reported using descriptive statistics. Where applicable, associations were carried out; a p-value <0.05 was estimated as statistically significant.

Results: This study found a small number of medicinal plants used by traditional healer practitioners for treating infectious diseases of patients seen by them. The majority of traditional healer practitioners and their patients (21/32, 65.62%) mixed different herbs for the treatment of infectious diseases. Traditional healer practitioners and patients seen by them agreed that the combination of both traditional medicines and prescribed medicines for infectious diseases may lead to interactions, adverse effects; infectious diseases may get worse if the time lapses between the two medicines do not exist. However, biomedically healthcare professionals and outpatients reported that combing traditional with prescribed medicines for infectious diseases may result in drug resistance, especially resistance to antibiotics and they highlighted that the majority of

patients came to the clinic with several complications such as kidney failure, vomiting, diarrhoea and jaundice after using either TM alone or in combination with prescribed medicines.

Besides the perception phase of this study, 400 outpatients' medical records were documented from two different municipalities, many participants had viral infections (194/400, 48.50%). Overall, 12% of participants (48/400) had documented negative clinical outcomes with adverse effects (30/48) and interactions (18/48). A few participants (15/400, 3.75%) had used traditional medicine in conjunction with prescribed medicines. Among those who used both traditional medicine and prescribed medicines, the majority (80%, 12/15) had documented adverse effects due to the concurrent use of traditional medicine and prescribed medicines. After adjustment, documented adverse effects and interactions were significantly more likely due to the use of traditional medicine (AOR = 0.01, 95% CI = 0.001-0.05) and (AOR = 0.21, 95% CI = 0.37-1.23) respectively.

Conclusion: From perceptions stated by respondents in this study, the concurrent use of conventional and traditional herbal medicines may interfere or result in damaging some organs, failure of therapeutic effects and modification of pharmacological actions of administered medicines. Traditional medicine was sparingly used in conjunction with prescribed antimicrobials for viral and bacterial/fungal infectious diseases. However, adverse effects and interactions such as herbal intoxication, persistent rashes, and treatment failure were documented in few medical chart records among outpatients attending the two selected healthcare facilities. Further studies are needed to investigate the effects of concurrent use of traditional medicine and prescribed medicines in other parts of South Africa.

CHAPTER 1: INTRODUCTION

This chapter provides a background and a brief overview of literature of the proposed study. It includes the rational of the study, research questions, the aim, and objectives of the study. A general methodology has been included to achieve aim and different objectives of the study.

1.1 Background

Antibiotic-resistant microorganisms is considered as nightmare bacteria that pose disastrous threat to people around the world (WHO, 2013). Infections from resistant bacteria are currently common; some pathogens have become resistant to multiple classes of antimicrobial medicines (Ledingham and Warrell, 2000). Antimicrobial resistance is a microbial adaptation which allows microbes to persist despite the presence of the antibiotic or antiviral and which reduce the potential human health benefit derived from antibiotics and/or antiviral medicines (Hunt et al., 2013).

Antimicrobial drug resistance is a major cause of treatment failure and is largely responsible for the declining in eradication rates (Megraud, 2007). According to World Health Organization (WHO) infectious and non-infectious diseases are invariably treated with antibiotics and this poor practice is leading to the inappropriate use of antimicrobials (WHO, 2011). Viruses and bacteria cause a significant proportion of infections in Africa; the WHO reported that bacterial infections death rate has been estimated at 45% in Africa and South-East Asia (WHO, 2014) while they were reported to be responsible for 48% of premature deaths worldwide (Sosa et al., 2009). According to the Joint United Nations Programme on HIV(Human immunodeficiency virus) and AIDS (Acquired immune deficiency syndrome) (UNAIDS, 2014), 69% of HIV infected people are living in Sub-Sahara Africa and since 2000, about 25.3 million deaths of people living with HIV/AIDS (PLWA) were registered in the world.

South Africa is not an exception to wide spread of antimicrobial resistance. It has been faced with a high burden of antimicrobial resistance such as drug resistant tuberculosis, drug resistant HIV and antibiotic resistance (Hunt et al., 2013). HIV infection is reported to be responsible for the high rate of deaths 31.2% in the total of 6.4 million of PLWA (People Living with HIV/AIDS) in South Africa (Shisana et al., 2014); however the rate of PLWA increased from 6.8 million in 2014 (UNAIDS, 2014) to 7.52 million in 2018 (Statistics, 2018). A report of WHO has shown that 30% of bacteria were resistant to common antibiotics used to treat bacterial infectious diseases (WHO, 2014). The problem of antimicrobial resistance is extremely serious, some bacteria and viruses are becoming resistant because there is either only antimicrobial of last resort or infections are untreatable (Galea, 2015). Antimicrobial resistance (AMR) in South Africa is driven by many factors which include the careless use of prescribed antimicrobial medicines and the use of traditional medicine (TM), with the result that always the danger of misadministration, interaction and toxicity can happen (Goff et al., 2017, Fennell et al., 2004).

Traditional medicine has been defined by the WHO as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness (WHO, 2004)." Thus, Plants are considered as one of the most promising sources for new antimicrobial medicines discovery (ATMs); more than hundreds of plants in the world are used in TM as primary health care needs by up to 80% of the population in Asia, Africa, Latin America and the middle-East for the treatment of virus and bacterial infections (Yuan et al., 2016, Mukul et al., 2016, Fyhrquist et al., 2002). In the European Union, 100 million people believed also in the use of TM (WHO, 2011).

It is estimated that approximately 27 million South Africans, including PLWA and bacteria infected patients still rely on traditional medicine for their primary health care needs (Street et al., 2008). It is relatively due to good accessibility of plants, affordability, confidentiality of health information between the patient and practitioner (Hoyler et al., 2018, Ballabh et al., 2008); medicinal plants are also believed to fight against specific symptoms even diseases such as weight loss, skin disorders, lack of energy, lack of appetite, diarrhea, nausea and vomiting, treatment of side effects of antiretroviral medicines (ARVs) as well as dizziness, fungal infections, pain and stomach upsets (Petzer and Mngqundaniso, 2008, Richter, 2004).

McLay et al., (2017) reported that 44.9% of the study participants have used concurrently traditional medicine with different prescribed medicines. Of whom, 12.7% women with the potential to increase the risk of postpartum haemorrhage, alter maternal haemodynamics, and enhance maternal/fetal central nervous system depression (McLay et al., 2017). Furthermore, another study revealed that less than 20% of participants co-used TM and ARV (Hughes et al., 2012). In addition, 45% of participants in a study were co-users of conventional drugs and herbs, while a sizable proportion of the General Practitioner's patients who co-used herbs with conventional drugs reported interaction potential or additive effects like anticoagulants and garlic. The low disclosure of herbal use to their General Practitioner, poly herbacy and the risk of interactions in vulnerable groups like elderly and chronically ill patients, warrant increased awareness among General Practitioners (Djuv et al., 2013).

TM is commonly used in combination with conventional medicines, mostly with satisfactory results but in some case, the effect of the two associated treatments may be magnified, interacted and/or opposed (Duru et al., 2016, Fugh-Berman, 2000). Different patient groups are known to use herbal remedies and conventional drugs concomitantly (co-use). This causes a serious risk of herb-drug interaction through altering the drug's pharmacokinetics or pharmacodynamics. Little

information have been reported in literature regarding the co-use among patients in general practice. Patients used TM concurrently with conventional medicine and thus interactions might pose a risk at any step of absorption, distribution and elimination phases of the pharmaceutical disposition, which could affect the pharmacokinetic of the medicine in the body (Müller and Kanfer, 2011). Medicinal Plants such as *Taraxacum officinale*, *Echinacea purpurea*, *Hypoxis hemerocallidea*, *Moringa oleifera*, and *Lessertia frutescens* induce the inhibition of the cytochrome CYP450 enzymes which can modify the metabolism of antibacterial (ATB) or ARVs and leading to lack of efficacy and adverse effects experienced by PLWA as well as to those who using simultaneously TM with ARVs (Mills et al., 2005, Müller and Kanfer, 2011). Individuals may consult both Traditional Healer practitioners (THPs) and biomedically trained healthcare professionals (BHPs) for bacterial and viral infections. However, a limited knowledge of interactions remains about the concurrent use of TM and prescribed medicines for bacterial and viral infections.

1.2 Literature review

This is a brief overview of the literature. Relevant literature review has been included in each of manuscripts included in this dissertation.

1.2.1 Concepts on Antimicrobial resistance (AMR)

1.2.1.1 Definition

After the use of antimicrobials in human medicine and animal manufacturing, the pressure of selection increased and resistance genes were produced in various bacterial groups (JETACAR, 1999). Microorganisms change over time so that they can defend themselves against the harmful effects of medicine (Davies, 1994). This protection inevitably leads to drug resistance, certainly due to the human use of antibiotics, and consequently they produce compounds that lead to the development of resistance as a means of survival in the presence of their own products and conflicting species; microbial resistance occurs when antibiotic-inactivating enzymes appear, which can modify the structure of receptors, improve efflux through medicine transporters and reduce cell wall permeability to antimicrobials (Trevor et al., 2010).

1.2.1.2 Emergency of AMR

After sulphonamides were introduced in 1937, the appearance of specific resistance mechanisms was shown to be the first effective antimicrobials (ATMs) (Kampmeier, 1983) but after few years in 1940, Abraham and Chain identified penicillinase (enzyme) several years before the use of penicillin as a therapeutic compound. *S. Pneumococcus aureus pneumonia* was the first bug

discovered against penicillin thereafter, *Enterococcus faecium* bacterium that caused intestinal infection in 1983 was finally considered also as one of the bugs that outwitting penicillin (Lewis, 1995). Streptomycin was found arising during the treatment when introduced for the treatment of mutant strains of *Mycobacterium tuberculosis* resistant to therapeutic concentrations of the antibiotic and to the treatment of tuberculosis (Shah et al., 2007). After the rapid emerging resistance of penicillin for the treatment of infections caused by organisms intrinsically resistant to penicillin, chloramphenicol, erythromycin and vancomycin were finally introduced (Klugman, 1994).

1.2.1.3 Factors contributing to AMR

In the development of antimicrobial resistance, factors such as behaviour and environment are the more implicated (Larson, 2007). Behavioural factors include improper use of antibiotics, such as prescription for nonbacterial infections and self-prescription of antimicrobials in the community (Chatterjee et al., 2016). Most of the time the contact with animals, contaminated products, crowding, impaired cleanliness of the skin, integrity and failure to vaccinate diseases also lead to antimicrobial resistance (WHO, 2010). The lack or poor sanitation in hospitals and in the community increases the rapid dissemination of resistant bacteria in vulnerable patients or in the community (Cars et al., 2008). Contaminated food by resistant bacteria and contaminated animals can easily spread antibiotic resistance to people and animals (Butaye et al., 2006).

The improper use of traditional medicines or practices was described by WHO to have a fatal effect and that, further studies are needed to assess the safety and effectiveness " of different practices and plants used by traditional medicine systems (WHO, 2004).

1.2.3.4 Treatment with traditional medicine

Traditional medicine, commonly known as indigenous or folk medicine, includes medical aspects of traditional knowledge that developed in different cultures over years before the era of conventional medicine (WHO, 2004). The WHO (2004) defines traditional medicine as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness."

Traditional medicines are relied by, up to 80% (WHO, 2002) of the population in some Asian and African countries for their primary health needs. It is often called alternative medicine when adopted outside of its traditional culture (WHO, 2004) and includes some practices known as Ayurveda, Siddha medicine, Unani, ancient Iranian medicine, Islamic medicine, traditional

Chinese medicine, traditional Korean medicine, acupuncture, Muti, Ifa, and African traditional medicine (WHO, 2002).

Traditional medicine (TM) includes a variety of health practices, knowledge, methods and philosophies containing plant, animal and mineral medicines, manual techniques, exercises and divine therapies for well - being and treatment, diagnosis or disease prevention (WHO, 2002).

1.2.3.4.1 Benefit effect of using TM

TM therapies can have less adverse effects than conventional therapies; they are generally available, affordable and widely used in developed countries (WHO, 2002). The advantages of TM are its diversity and flexibility, its availability and cost efficiency in many parts of the world, its widespread recognition in low- and middle - income countries, its relatively low cost and the relatively low level of technology. As a result, TM therapies can help to improve the healthcare system in several countries (WHO, 2002).

Approximately 27 million South Africans, including PLWA and infected bacteria, are estimated to rely on traditional medicine for their primary health needs (Street et al., 2008). This is relative because of good plant accessibility, affordability, confidentiality of health information between patients and practitioners and the high cost of synthetic medicines medicinal plants are also believed to combat certain symptoms, including weight loss, skin disorders, energy shortages, lack of appetite, diarrhea, nausea and vomiting, treatment of side effects of ARVs as well as dizziness, fungal infections, pain and stomach upsets (Petzer and Mngqundaniso, 2008; Richter, 2004).

Scientific studies in many TM therapies have shown that the use of medicinal plants was effective in patients with HIV / AIDS and cancer (Carlsson et al., 2001; Power et al., 2002). Although some plant extracts like *Psidium guajava*, *Artemisia afra* and *Erythrina lysistemon* have not been scientifically investigated, traditional healers have used them to treat the growth of bacteria, viruses and other microbes (Mativandlela, 2007) and especially to treat certain types of wounds, abscesses, arthritis, diarrhea, and influenza (Van Wyk and Gericke, 2000).

1.2.3.4.2 Risk of using TM

Incorrect use of TM can lead to terrible outcomes. Traditional medicine therapies are usually used as self - care treatments. However, TM products are poorly regulated in many countries, so many of the risks to consumers concern the safety and quality of TM products (Mills et al., 2005; Moss, 2001, Eisenberg et al., 1998).

For example, the Chinese herb ma huang (*Ephedra sinica*) containing ephedrine is used for respiratory problems and can cause heart attacks. (Ang-Lee et al., 2001); Kava can cause serious liver damage in the long term use (Stevinson et al., 2002); and ginkgo used to stimulate peripheral circulation may lead to bleeding during operation (Ang-Lee et al., 2001). Interactions may pose a risk to patients who use TM at the same time with conventional medicines. Studies revealed that many patients used TM concurrently with conventional medicine, often without informing their health care provider; thus it is important to be aware of the possibility of interactions that may result from the concurrent use of several TM medication therapies and/or conventional medicines (Eisenberg et al., 1998; Yuan et al., 2016).

1.2.3.4.3 Treatment failure

A standard definition of treatment failure does not exist, but measurements can be defined clinically, virologically and immunologically. Since the main expected effect of antimicrobial therapy is ~~mainly~~ to reduce viral load by viral suppression (antiretroviral) and manage infectious disease by killing or injuring bacteria (antibiotics). A treatment failure occurs when the infection cannot be controlled by an antiviral or antibiotic. Drug resistance, drug toxicity and poor adherence to antimicrobial treatment are the most contributing factors to treatment failure (Aldous and Haubrich, 2009). The decision to change the treatment pattern does not mean that the next one will be successful; however, it is correct to find out why the previous therapy has failed. Most of the time the response may reveal that the treatment was not taken on time or in the prescribed manner or that the treatment was completely stopped. Furthermore, It may also happen because of drug resistance or because of treatment that was not powerful enough or because the drug was poorly absorbed (Farup et al., 2011).

For example, a study showed that the primary health care community in South Africa used *Hypoxis hemerocallidea* as an immunostimulant in HIV / AIDS patients (Albrecht et al., 1995). Nevertheless, A study done on the same plant showed that up to 86% of normal CYP 3A4 isoform activity was inhibited. P-glycoprotein showed moderate activity from exposure to hypoxis, with an activity strength of 42–51% compared to the known P-gp verapamil inhibitor. Hypoxis exposure resulted in almost 2-fold PXR activation ($p < 0.05$). After an in vitro study, the concentration used for experimentation was relatively high; hypoxis revealed a high potential to interact with enzymes that metabolize HIV drugs and subsequently could lead to treatment failure as well as drug resistance and drug toxicity (Mills et al., 2005). However the treatment failure due to the concurrent use of both TM and prescribed medicines is not yet properly highlighted.

1.3 Rationale of the study

The indiscriminate use of antimicrobials has led to drug resistance and treatment failure of many bacterial strains; the emergency of microbial resistance becomes a medical disaster (Jia et al., 2016, Martini and Eloff, 1998). The appearance of antimicrobial resistance has been directly linked to the use and overuse of antimicrobials and may therefore also be linked to poor knowledge of the use of traditional medicine at the same time with prescribed antibiotic and/or antiviral medicines. Traditional medicine can play a major role in cutting down the spread of microbial infection but also can contribute to its treatment failure (Martini and Eloff, 1998).

The effects of various medicinal plants used simultaneously with prescribed medicine can therefore be improved, opposed and/or interacted. (Fugh-Berman, 2000; Kamatou et al., 2006). It is also known that the irrational use of antimicrobials can lead to the failure of treatment and the adaptation of micro - organisms to persist with antiviral and/or antibacterial medicines, while the synergistic effect of antibiotic and plant extracts against resistant pathogens confronts problems of toxicity and overdose (Goff et al., 2017, Nascimento et al., 2000, Russel, 1998).

M (2009) showed that the prevalence of concurrent use of TM and standard medicines in Nsukka, Nigeria was high, out of 278 surveyed patients, 193 patients (69.4%) were at high risk due to population demographic and socio - economic characteristics (MO, 2009). Kadhim et al. (2015) also conducted a similar study in Iraq, showing that the consumption of TM with prescribed medicines by Iraqi patients was quite high. In a total of 367 patients, 73.6% consumed 21 types of TM (crude or refined) either alone or in combination with conventional medicine. Furthermore, in two healthcare facilities in southwestern Nigeria, Chukwuemeka et al. (2017) found that 42.7% of HIV outpatients in a total of 351 recruited HIV - positive patients used herbal medicines simultaneously with ARVs, then it was statistically significant upon cross-tabulation. The HIV treatment was improved but also the interaction between TM and standard medicine was potentially life threatening. In South Africa, Sibanda et al. (2016) reported that the prevalence of concurrent use of ARV and TM by PLWA was quite low, such as 4, 98% in a total of 281(14/281) compared to, 65 % (185/281) of participants who used TM and ART before diagnosis of HIV. However, the need of further study is important, because the limited knowledge of interactions in the treatment of viral and bacterial infections through concurrent use of TM and conventional medicines remains from both, THPs and BHPs.

1.4 Research Questions, Aim and Objectives

1.4.1 Research questions

The general question that this study aimed to answer was as follows: “Is there any antimicrobial resistance and or treatment failure among patients attending out-patient departments (OPD) in selected healthcare facilities namely Stanger Hospital and Umphumulo Hospital and who use concurrently traditional medicine, antibiotics and antiviral medicines?”

The specific questions of this study were as follows:

1. What is the prevalence of Sexually Transmitted Diseases and Respiratory infections (with emphasis on Tuberculosis) in patients/clients seen by THPs for antibacterial and antiviral treatments around healthcare facilities in Ilembe district?
2. Do patients attending out –patient departments in healthcare facilities use concurrently TM, prescribed ATB and ARVs for viral and bacterial infections?
3. How do THPs and biomedically trained healthcare professionals perceive interactions between TM and prescribed ATB and ARVs for viral and bacterial infections?
4. What types of TM are used by THPs to treat viral and bacterial infections in their practices?
5. What types of prescribed ATB and ARVs are used by those patients who combined both prescribed medicines and TM?
6. What are the types of interactions found including treatment failure and AMR among those patients who use prescribed ATB, ARVs and TM?

1.4.2 Aim

This study aimed to determine whether any antimicrobial resistance and treatment failure occur among patients attending out-patient departments in selected healthcare facilities and who use concurrently traditional medicine, antibiotics and antiviral medicines in Ilembe district, KwaZulu- Natal.

1.4.3 Hypothesis

Indiscriminate use of traditional medicine in conjunction with prescribed antimicrobials can lead to treatment failure and antimicrobial resistance.

1.4.4 Objectives

The specific objectives of this study were as follows:

1. To determine the prevalence of Sexually Transmitted Diseases and Respiratory infections (with emphasis on Tuberculosis) in patients/clients seen by THPs for antibacterial and antiviral treatments around healthcare facilities in Ilembe district.
2. To assess whether patients attending out –patient departments in healthcare facilities use concurrently TM, prescribed ATB and ARVs for viral and bacterial infections.
3. To explore the way THPs and biomedically trained healthcare professionals perceive interactions between TM and standard prescribed ATB and ARVs for viral and bacterial infections.
4. To determine types of TM used by THPs to treat viral and bacterial infections in their practices.
5. To evaluate types of prescribed ATB and ARVs are used by those patients who combined both prescribed medicines and TM.
6. To explore the types of interactions found including treatment failure and AMR among those patients who use prescribed ATB, ARVs and TM.

1.5 General Methodology

1.5 1 Study design

This study was a cross –sectional descriptive study, based on an exploratory mixed- method approach. The study was carried out in two phases as follows:

Phase 1

This was a survey based on a qualitative descriptive study with four parts in using purposive sampling method described by Patton (2002):

- **Phase 1.A**, Survey among THPs.
- **Phase 1.B**, Survey among patients seen by the same THPs approached in phase 1A.
- **Phase 1.C**, Survey among BHPs consisted of doctors and professional nurses.
- **Phase 1.D**, Survey among outpatients seen by both THPs and BHPs

Phase 2

This phase consisted of a quantitative analytical study, using a medical chart review among outpatients seen by both THPs and BHPs described in phase 1C.

1.5.2 Study area

This study was conducted in the Ilembe District located in KwaDukuza on the East coast of the province, bordering the Indian Ocean and comprises four municipalities: Mandeni, Ndwedwe, KwaDukuza, and Maphumulo. The district covers 3 269 km², the smallest provincial district in KwaZulu-Natal, with a population size of 630 464 people and it is approximately 75 km from Durban with a population including 90.8% of black African, 2.4% of the white population and 6.8% of others. The majority of the population in the district consists of native isiZulu speakers (82%) followed by native English speakers (9.6%), native Xhosa speakers (3.3%) and others (5.5%) (KZNHealth, 2017). The district comprises four local municipalities located between Durban and Richards Bay: Mandeni, KwaDukuza, Maphumulo, and Ndwedwe with a small urban area in which the majority of the area is rural. The district's rural and traditional areas are characterized by low educational levels, high unemployment rates, and a severe lack of basic services (KZNHealth, 2017).

Ilembe Health District has four hospitals: Montebello District hospital, Stanger Provincial hospital, Umphumulo District hospital, and Untunjambili District hospital. This study included two Hospitals, Stanger Provincial hospital, and Umphumulo District hospital. Both hospitals belong to the Ilembe health department in the public sector.

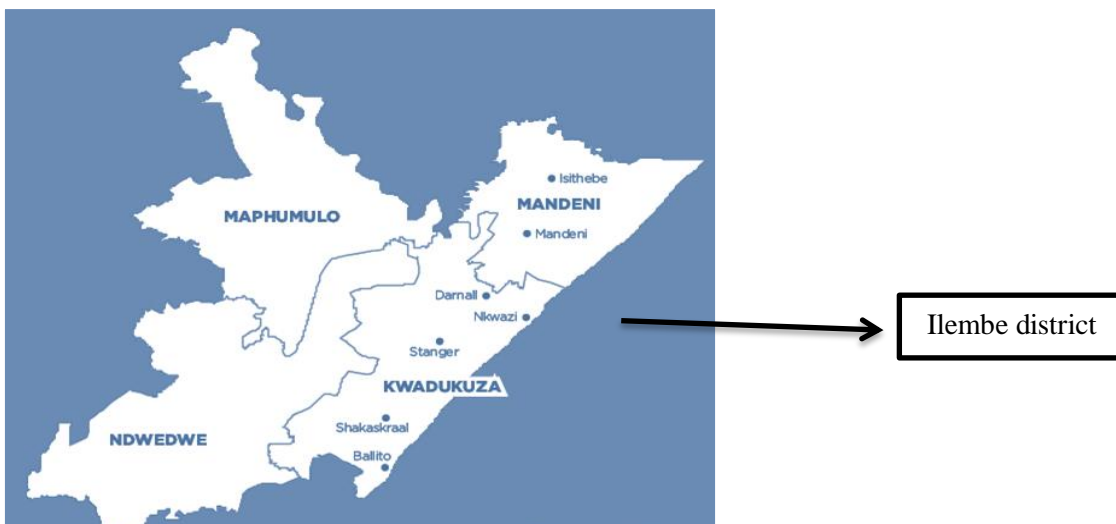


Fig. 1.1: Map of study area (<http://www.kznhealth.gov.za/ilembe.htm>).

1.5.3 Study population, inclusion and exclusion criteria and Sample size

1.5.3.1 Study population

The population of this study comprised participant such as THPs and their patients, BHPs consisting of doctors and professional nurses and finally out-patients attending public healthcare facilities in Ilembe district, KwaZulu-Natal province.

1.5.3.2 Inclusion and exclusion criteria

This study involved THPs and BHPs as well as patients seen by them, aged 18 years old and above. BHPs who have had treated bacterial and viral infections in the past three months as well as outpatients referred by them were included in this study. Other outpatients attending the outpatient department (OPD) of the two healthcare facilities were as well included in this study. THPs, BHPs and patients less than 18 years old were excluded in this study. BHPs who have had not treated bacterial or viral infections in the last three months were excluded in this study.

1.5.4 Recruitment and selection of participants

Participants were recruited according to our inclusion and exclusion criteria pertinent to the study research questions. A researcher had to find a sample that matched his established criteria.

Phase 1

- **Phase 1A (THPs)**: THPs were recruited purposively using snow ball technique. They were approached at their workplace during their business hours. Community head and leaders of traditional organizations were approached to assist with the identification of traditional healers operating in the Ilembe district.
- **Phase 1B** (Patients seen by THPs): after interviews with THPs, with their permission (consent), we had to speak to the patients seen by them. Snowball sampling technique was used as well. After our conversation with patients seen by THPs, they were asked whether they had used at the same time traditional and conventional medicine; to those that the answer was “yes”, they were asked if they could indicate which healthcare facility they have attended to in Ilembe district.
- **Phase 1C** (BHPs): they were mostly recruited during their lunch time at the Hospitals besides those recruited according to the indications got from their patients treated as well by THPs.
- **Phase 1D**: patients seen by both THPs and BHPs as identified in phase 1B were recruited and selected during clinic business operating hours. The intention to include this category of patients was to allow having access to their medical charts.

Phase 2

This second phase implicated a medical chart review of patients seen by both THPs and BHPs at the Hospitals identified in phase 1B.

1.5.5 Sample size and sampling technique

Phase 1

This phase was a qualitative descriptive study, based on the principle of saturation. The sample size calculation is based on the assumption that in a qualitative study the principle of saturation is often used whereby a researcher cannot gather new information after a maximum of 50 participants (Fusch and Ness, 2015, Hennink et al., 2017, Saunders et al., 2018).

- ***Phase 1A***

The sampling method was the purposive sampling using snow ball technique for identifying THPs, a maximum of fifty participants was required.

- ***Phase 1B***

After seeing THPs in phase 1A, through snowball technique, patients seen by them were recruited. The calculation for sample size for patients was based on the “*principle of saturation*” of the Ilembe population which utilized simultaneously both Traditional medicine and prescribed medicines. A minimum of fifty participants was interviewed.

Phase 1C

A minimum of fifty of BHPs was included in this phase, using a purposive sampling. This minimum sample size was equally divided into the two hospitals (Stanger Provincial hospital and Umphumulo District hospital) included in the study.

- ***Phase 1D***

A minimum of fifty of outpatients was included in this phase, using a purposive sampling. This minimum sample size was equally divided into the two hospitals (Stanger Provincial hospital and Umphumulo District hospital)

Phase 2

This phase was a quantitative descriptive study, including a minimum of 400 outpatients' medical records. The calculation for sample size for patients was based on the assumption of the normal distribution; 50% as an equal distribution with 95% of confidence interval, 5% of margin error of the Ilembe population which used simultaneously both Traditional medicine and prescribed medicines.

1.5.6 Data collection techniques and Tools

The data collection method adopted in this study was as follows:

Phase 1: This phase consisted of researcher administered interviews.

This phase was an explorative study with semi-structured interviews with 132 informants (THPs, Patients seen by THPs, BHPs and patients seen either by BHPs alone or by both THPs and BHPs) was conducted on January 2018. A total of 17 THPs and 15 patients seen by them were initially identified and interviewed by snowball sampling technique; while 100 participants including 50 BHPs and 50 outpatients attending the two selected healthcare facilities. An interview face to face was used and the questionnaire form used for data collection was specifically developed for the study in which were included in section A the participants' address, age, gender, marital status, educational level, language spoken, occupation as well as in section B, information relating to the use of TM and their related conditions and in section C, information on any clinical outcomes including treatment failure and antimicrobial drug resistance from the concomitant use of TM and prescribed medicines.

Data collection had four (4) phases. The first phase was done with THPs which were recruited purposively using snowball technique. Some of them were approached at their workplace during their business hours and other at their households and the only tool used was an interview questionnaire (Appendix 8). Phase two was done with patients seen by THPs using snowball technique with their permission (see Appendix 9 and 12); they were asked whether they had used at the same time traditional and conventional medicine; to those that the answer was "yes", they were asked if they could indicate which healthcare facility they had attended in Ilembe district. The third phase of the interview was with BHPs (Appendix 6), they were recruited at the hospitals. BHPs were recruited purposively in the two selected healthcare facilities during their business operating hours. Finally, the fourth phase was conducted among outpatient, only those who were consulted by both THPs and BHPs and those who were attending the outpatient department (Appendix 7).

From phase 1.A to phase 1.D, a researcher administered interview using a questionnaire. Data was collected 4 days per week during seven weeks as data collection period. The questionnaire was translated from the English into IsiZulu by an expert for content validity.

Phase 2: This second phase was a medical chart review.

Medical chart records of adult patients, aged 18 years and above, irrespective of gender were selected at the OPD of the two selected healthcare facilities as well as at their respective tuberculosis (TB) and HIV clinics during clinic visit hours. Patients' medical records from January 2017 to January 2018 were assessed and selected according to the study's inclusion and exclusion criteria during the data collection period between February and March 2018. Records of patients who used concurrently TM and prescribed antimicrobials as well as who developed any side effects and/or interactions were reviewed in details.

1.6 Layout of the dissertation/ structure of the dissertation

The dissertation is entitled: "Concurrent use of traditional medicine and prescribed antibiotics and/or antiviral medicines and their effects on antimicrobial resistance and treatment failure in Ilembe district, Kwazulu-Natal province, South Africa.

This study using a mixed method approach has been conducted in the community and in two different healthcare facilities namely Stanger hospital and Umphumulo hospital in the Ilembe district, KwaZulu-Natal province, South Africa.

The dissertation consists of :

- Chapter 1: Provides a background and a brief overview of literature of the proposed study. This chapter highlights an overview of the rationale of the study, research questions, the aim, and objectives of the study. A general methodology has been included to achieve aim and different objectives of the study.
- Chapter 2: Consists of a systematic review protocol submitted to Bio Med Central, Systematic review journal under the title "Mapping evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance in sub-Saharan Africa: A systematic review protocol"
- Chapter 3: Provides an original manuscript article submitted to the African Journal of Biomedical Research, under the title "Perspectives on the concurrent use of traditional and prescribed antimicrobial medicines for infectious diseases: a triangulation study involving biomedically trained healthcare professionals, outpatients, traditional health practitioners and their patients.

- Chapter 4: Comprises an original manuscript article submitted to the journal BMC, Complementary and Alternative medicine under the title “Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review”
- Chapter 5: Provides the Synthesis which includes general conclusions, strengths and limitations of the study then recommendations.

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A systematic review protocol was written to establish the evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in order to assess the reduction of antimicrobial resistance. This chapter is presented in a manuscript format, it has been prepared and submitted following the authors guidelines of the journal BMC Systematic Reviews. This manuscript is under review and it is registered under reference number: SYSR-D-18-00185.

CHAPTER 2: FIRST MANUSCRIPT SUBMITTED FOR PUBLICATION

TITLE: Mapping evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance in sub-Saharan Africa: A systematic review protocol.

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ABSTRACT

Background

The overuse of prescribed antimicrobials, concurrent use of both traditional medicine and prescribed antimicrobials has been shown to lead to antimicrobial resistance. The absence of collaboration between traditional health practitioners and biomedically trained healthcare professionals can contribute to antimicrobial resistance, treatment failure, overdose, toxicity and misadministration. This scoping review explores evidence on collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance and treatment failure in bacterial and viral diseases.

Methods/design

We will search electronic databases such as Science Direct, Google scholar, PubMed, MEDLINE via EBSCOhost. We will also search reference lists of included studies. A two-stage mapping procedure will be carried out. Stage one (1) will consist of title, abstracts and full article screening, respectively. A piloted screening form guided by the defined eligibility criteria will be used. Stage two (2), data will be extracted from the included studies. Parallel screening and data extraction will be conducted by two reviewers. Mixed methods appraisal tool (MMAT) will be used to assess the quality of the included studies. NVIVO version 11 will be employed to aid pertinent thematic analysis. The outcomes of interest will be as follows: Primary outcome will be the prevention and the reduction of antimicrobial resistance. Secondary outcomes: Effective collaboration between traditional healthcare practitioners and biomedically healthcare professionals.

Discussion

This review anticipates uncovering pertinent publications reporting the evidence of collaboration between traditional health practitioners and biomedically trained healthcare professionals in the reduction of antimicrobial resistance in sub-Saharan Africa. The sum up of evidence acquired from the included studies will help guide for future research. The result from the research will be print and electronically exposed.

Systematic review registration: PROSPERO CRD42017072952

Keywords: Traditional Health Practitioners - Collaboration - Absence - Prevention - Effective - sub-Sahara Africa.

Background

Traditional treatment or indigenous health system cannot be considered to be of a lower quality than the mainstream healthcare system, in contrast it is thought to be desirable and needful in treating a range of several health troubles or difficulties that mainstream healthcare system fails to cure sufficiently [1, 2]. In the view of Qi and Kelley [2], traditional herbal mixtures are a reliable, believable and dignified source of health care. Bacterial and viral infections are currently common; some pathogens have become resistant to multiple classes of antimicrobials [3]. Microbial adaptation allows microbes to persist despite the presence of an antibiotic or antiviral agent; this reduces the potential human health benefit derived from antibiotics and/or antiviral medicines [4, 5].

The ratio of traditional health practitioners and biomedically trained professionals to the general population in the sub-Saharan of Africa is approximately 1:500 and 1:40000, respectively [6]. In addition to their modern biomedical treatment, up to 70 percent of South Africans are usually consulted by an estimated 200 000 indigenous traditional healers [6, 7]. Approximately 27 million South Africans, including people living with HIV/AIDS and bacteria infected people depend on traditional medicine (TM), for their primary health care needs [8]. STIs such as Tshofela/drop (gonorrhoea), Thosola (syphilis), some other specific bacterial infections and assumed HIV/AIDS are the most common treated conditions and problems by THPs [9]. This is probably due to good accessibility of plants, affordability, confidentiality of health information between the patient and practitioner and the high cost of synthetic medicines [10]. Furthermore, consumers believe that certain infections such as acne, warts, shingles and STIs cannot be treated with western medicine by BHPs but rather by THPs [11, 12]. Medicinal plants are effective, cheap, readily available and used for cultural reasons.

In South Africa, antimicrobial resistance (AMR) is extremely prevalent, some bacteria and/or viruses are becoming so resistant that there is either only antimicrobial of last resort or infections are untreatable [13]. AMR in South Africa is driven by many factors such as the careless use of prescribed antimicrobials, the use of traditional medicine (TM) currently not regulated, the lack of collaboration between traditional health practitioners (THPs) and biomedically trained healthcare professionals (BHPs), with the result of treatment failure, misadministration, interactions and toxicity [14]. With a view

to conceptualizing the conditions for collaboration between the two systems, Pretorius [15] proposed the analogical model of the Biomedical/Traditional Medical Relationship, this model shows clearly that each aspect of the traditional medicine system may be linked to the western medicine system such as mutual referral. In addition, the WHO have adopted strategies to ensure the integration of collaboration between research institutions and THPs based on research and management of patients; and between THPs and BHPs in human immuno deficiency virus and acquired immune deficiency syndrome (HIV/AIDS) prevention and sexually transmitted infections (STIs)/tuberculosis programs [16].

Although the use of TM has increased, not currently regulated, with the result of enhancement of the activities of standard medicines when used concurrently with TM [17]. Nascimento et al., reported that the danger of misadministration, drug interactions, overdose, toxicity, especially the problem of drug resistance and treatment failure can occur when TM and prescribed antimicrobials are simultaneously and indiscriminately used [18]. This review aims to map the evidence on the collaboration between THPs and BHPs in the reduction of antimicrobial resistance in sub-Saharan Africa.

Methodology

Scoping review

A scoping review of peer-reviewed literature will be conducted on the following specific points: concurrent use of traditional medicines and prescribed antimicrobials, collaboration between THPs and BHPs and treatment of bacterial and viral diseases. Selection of scoping review method was to make easy the mapping of the topic under study and to build evidence around the related subject [19]. This review will use the framework developed by Arksey and O'Malley [20]. This framework stipulated the following steps (a) identification of research questions, (b) identification of pertinent studies, (c) charting the data, and (d) collation, summary and report of findings.

Identifying the research questions, aim and objectives

The general research question of this study is “What is the evidence of collaboration between THPs and BHPs in the reduction of antimicrobial resistance in bacterial and viral diseases?” The specific research questions to answer the general question are as follows:

1. What is the prevalence of patients/clients seen by THPs for antibacterial and antiviral treatments?
2. What is the evidence of the concurrent use of TM, prescribed ATB and ARVs medicine for viral and bacterial infections?
3. What is the evidence of the perceptions of TPHs and BHPs about interaction between TM and prescribed ATB and ARV medicine for viral and bacterial infections?
4. Is there a bidirectional referral of patients between THPs and BHPs in the management of bacterial and viral diseases?

Aim

To map the evidence of collaboration between THPs and BHPs in the reduction of antimicrobial resistance and treatment failure in bacterial and viral diseases.

Objectives

1. To assess the prevalence of patients/clients seen by THPs for antibacterial and antiviral treatments.
2. To determine the evidence of the concurrent use of TM, prescribed ATB and ARVs medicine for viral and bacterial infections.
3. To map the evidence of the perceptions of TPHs and BHPs about interaction between TM and prescribed ATB and ARV medicine for viral and bacterial infections.
4. To determine whether there is any bidirectional referral of patients between THPs and BHPs in the management of bacterial and viral diseases.

Eligibility criteria for research questions

The study will use an amended Population, Intervention, Comparison, Outcomes and Study setting (PICOS) framework to evaluate the eligibility of research questions (Table 1).

Table 2. 1 PICOS framework for determination of eligibility of review question

Criteria	Determinants
Population	THPs and BHPs.
Intervention	Collaboration between traditional and biomedically healthcare workers.
Comparison	Absence of collaboration between THPs and BHPs.
Outcomes	Primary outcome: Prevention and reduction of antimicrobial resistance Secondary outcomes: Effective collaboration.
Setting	Sub-Sahara Africa.

Identification of pertinent studies

Studies that utilize mixed methods, qualitative and quantitative published in peer-reviewed journals and grey literature, from January 2005 to May 2018, addressing the above research questions will be included. Different types of study designs will be used during the process of screening data. Electronic search will be conducted from the following electronic databases: Science Direct; Google Scholar PubMed and; MEDLINE via EBSCOhost. Internet sites such as the World Health Organization (WHO) and government internet sites will be explored for reports and policies on collaboration of healthcare workers, measures on antimicrobial resistance, safe use of traditional medicine, concurrent use of both traditional medicine and prescribed medicines. Through “Cited by”, other articles will also be searched in the reference lists of selected articles. The keywords for the search will include Traditional Health Practitioners, collaboration, absence, prevention, effective and sub-Sahara Africa.

Study selection

To be certain that the included studies have the specific information according to the eligibility criteria, they should respond to the questions on the evidence of collaboration between THPs and BHPs in the reduction of antimicrobial resistance and treatment failure in bacterial and viral diseases.

Eligibility criteria

Inclusion criteria

For the inclusion of publications in this study, they should match with the undermentioned criteria:

- There will be a language restriction (English and French) on the inclusion of studies.
- Focus on strategies of collaboration between THPs and BHPs.
- Publications from January 2005 to May 2018.
- Report on cases of treatment failure, drug-interactions, drug-resistance and antimicrobial stewardship.
- Publications on the use of traditional medicine in conjunction with prescribed antimicrobials by community members of 18 years and above.
- Reports on death causes worldwide, with special emphasis on sub-Saharan Africa.

Exclusion criteria

Studies will be excluded if they meet the following characteristics:

- Articles published before 2005 and after May 2018.
- Articles that they do not report on the use of TM for the management of bacterial and viral diseases.
- Articles that report on other diseases than infectious diseases.

A pilot study will be carried out to check the appropriateness of the chosen studies, keywords and databases. Selected articles will be shared between two reviewers using research manager software such as Endnote library or Mendeley. A comprehensive title screening according to the eligibility criteria will be conducted by both first and second

reviewer. Eligible publications will be exported using either Endnote management software or Mendeley library. Articles will be checked for duplication using EndNote program or Mendeley.

Table (2) below presents how publications will be recorded. Full articles and abstracts of studies will be screened according to the eligible criteria. A third reviewer of the study will be considered in case of non-accordance between the two previous reviewers. In case of difficulty to find some articles, the assistance of the UKZN library will be needed. However, for authors whose publications will be cited and difficult to retrieve, they will be asked for assistance through a correspondence letter. If they do not respond to the correspondence, then their articles will be excluded.

Table 2. 2 Electronic search record

Keyword search: Search engine used	Number of articles or publications selected
Mainstream healthcare system	
Traditional herbal mixtures	
Microbial adaptation	
Mutual referral	
Concurrent use	
Bacterial	
Viral	
HIV/AIDS	
Infectious diseases	
Collaboration	

Fig.2.1 illustrates a PRISMA chart used for the selection of study strategies. The undermentioned procedure will be followed:

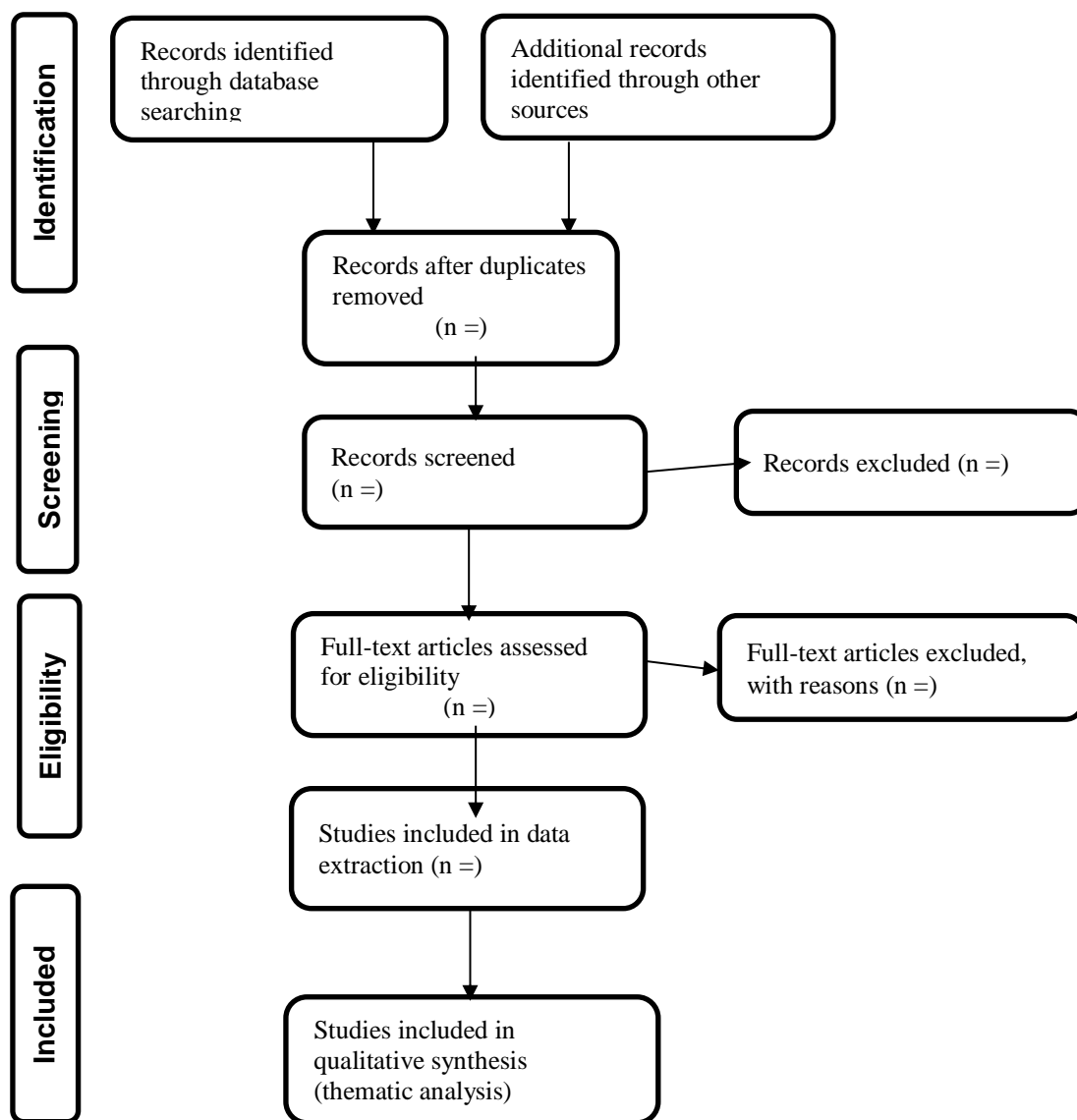


Fig. 2.1 Study selection procedure.

Charting the data

Table (3) presents the flow or the charting of included studies. A data charting form will be conceived and piloted. Variables to include in order to summarize the included articles are shown in Table 3.

Table 2.3 Form for Data charting

Author and date
Article or study title
Journal full reference
Aims or main research question
Characteristics of participants
Recruitment context (e.g. where participants were recruited)
Sampling method
Study method or design
Theoretical background
Data collection (what data collection methods were used?)
Data analysis (how was the data analyzed?)
Intervention
Intervention outcome
Most relevant findings
Conclusions
Comments

Summarizing, collation and reporting of findings

This study aims at mapping the evidence of collaboration between THPs and BHPs in the reduction of antimicrobial resistance and treatment failure in bacterial and viral diseases in sub-Saharan Africa and to summarize the results as found from the included studies. Following data extraction, thematic content analysis will be carried out to code the data according to the following themes: types of interactions registered in publications; causes of treatment failure, approach system and medicinal plants used by THPs to treat infectious diseases; barriers and facilitators towards collaboration between THPs and BHPs and; types of infectious disease not cured by western medicine. Emerging theme

will also be coded. NVIVO software version 11 will be employed to assist with coding of the themes [21].

- Coding data from the included articles
- Categorizing the codes into major themes
- Displaying the data
- Identification of key patterns in the data and identification of subthemes
- Summarizing

Synthesis

Resulting themes will be analyzed and critically examined in relationship with the research questions. The meanings of the results in reference to the aim of the research and the implications of these results for the forthcoming research, practice and policy will be analyzed by reviewers.

Quality appraisal

The mixed method appraisal tool (MMAT)-Version 2011 will be used to evaluate the quality of the included studies [22]. We will assess the appropriateness of the aim of the study, adequacy and methodology, study design, participant recruitment, data collection, data analysis, presentation of findings, authors' discussions and conclusions.

Discussion

This scoping review will be carried out as a first part of a larger study on the evidence of collaboration between THPs and BHPs in the reduction of antimicrobial resistance and treatment failure in bacterial and viral diseases in sub-Saharan Africa. This review will identify types of interactions registered in publications, causes of treatment failure, approach system and medicinal plants used by THPs to treat infectious diseases, barriers and facilitators towards collaboration between THPs and BHPs, types of infectious disease not cured by western medicine. Although there is a growing acknowledgement that healthcare systems are encouraging ways of collaboration between THPs and BHPs [23-26], but the paucity of knowledge about collaboration between THPs and BHPs still with regard to antimicrobial resistance, treatment failure or other interactions. In addition, the existence of challenges related to the availability of relevant full text articles.

Articles that report on other diseases than infectious diseases will be excluded because this study is focused on the use of prescribed antimicrobials and TM in the treatment of infectious diseases. This review excludes all studies that do not report on the use of TM for the management of bacterial and viral diseases. All the reports on deaths that are not caused by infectious diseases and those are not reporting cases of interaction either in TM alone, prescribed antimicrobials alone or in the concurrent use of both TM and prescribed antimicrobials will be excluded.

Results from this study will be of benefit to researchers by highlighting gaps in evidence that may need further investigation. Study findings will be disseminated by peer reviewed publications.

Abbreviations

THP: traditional healer practitioners **BHP:** biomedically healthcare professionals
PICOS: population, intervention, comparison, outcomes and study setting. **MMAT:** Mixed Methods Appraisal Tool **HIV/AIDS:** Human Immunodeficiency Virus/ Acquired immunodeficiency deficiency Syndrome. **TM:** Traditional Medicine.

Declarations

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Funding

The University of KwaZulu-Natal, College of Health Sciences Scholarship Award (CHS Scholarship) will fund this research study.

Availability of data and material

All data generated or analyzed during this study will be included in the published scoping review.

Authors' contributions

MGK drafted this manuscript. MN and TPM-T and MN revised the manuscript for its intellectual content, technical compliance and accepted the final version of the manuscript for publication. All three authors agreed with the publication of the manuscript.

Competing interests

No any competing interests are declared by the authors.

Consent for publication

Not applicable

Ethics approval and consent to participate

Not applicable

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In order to evaluate perceptions about the concurrent use of prescribed antimicrobial and traditional medicines, four (4) types of participants namely traditional healer practitioners, patients seen by them, biomedically healthcare professionals and outpatients have been interviewed on the concurrent use of traditional and prescribed medicines for infectious diseases and their effect on antimicrobial resistance and treatment failure. This chapter is presented in a manuscript format, it has been prepared and submitted following the authors guidelines of the journal **African Journal of Biomedical Research (AJBR)**. This manuscript is under review.

CHAPTER 3: SECOND MANUSCRIPT SUBMITTED FOR PUBLICATION

TITLE: Perspectives on the concurrent use of traditional and prescribed antimicrobial medicines for infectious diseases: a triangulation study involving biomedically trained healthcare professionals, outpatients, traditional health practitioners and their patients.”

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ABSTRACT

Background: Traditional medicines are generally available, affordable and commonly used as self-care treatments. However, their incorrect use lead to fatal outcomes. Individuals may consult both traditional healer practitioners (THPs) and biomedically trained healthcare professionals (BHPs) for their infections. This study aimed at determining whether any antimicrobial resistance and treatment failure could occur among patients, attending outpatient departments of selected healthcare facilities, who used concurrently prescribed antimicrobial and traditional medicines.

Methods: A survey was conducted using a questionnaire to assess the perceptions of respondents on the concurrent use of traditional and prescribed medicines for infections. One hundred and thirty two respondents were included namely THPs, patients seen by them, BHPs and outpatients.

Results: A small number of medicinal plants were used in the treatment of infections and 65.62% of THPs and their patients (21/32) mixed different herbs for the treatment of infections. Respondents agreed that the combination of traditional and prescribed medicines for infections may lead to interactions, adverse effects; infectious diseases may get worse if the time lapses between the two medicines is not used. However, BHPs and outpatients reported that combining traditional with prescribed medicines for infectious diseases may result in drug resistance, especially resistance to antibiotics and they highlighted that the majority of patients came to the clinic with several complications such as kidney failure, vomiting, diarrhea and jaundice.

Conclusions: The concurrent use of conventional and traditional herbal medicines may interfere or result in damaging some organs, failure of therapeutic effects and modification of pharmacological actions of administered medicines.

KEYWORDS: Concurrent, traditional medicine, infectious diseases, prescribed medicines, interactions.

Introduction

Treatment with traditional medicine

Traditional medicine (TM), commonly referred to as indigenous or folk medicine, comprises medical and traditional knowledge formulated in several communities over generations prior to the modern medicine era (WHO, 2004). The World Health Organization (WHO) describes traditional medicine as "the sum of knowledge, abilities, and practices based on indigenous concepts, philosophies, and experiences of various cultures, whether explained or not, it is used to maintain well-being, prevent and treat, diagnose, improve physical and mental illness"(WHO, 2000). Traditional medicines include different practices, commonly known as herbal Ayurveda, traditional African medicine, Siddha medicine, Unani, Muti, Ifa, ancient Iranian medicine, acupuncture, traditional Chinese medicine in Islamic medicine and traditional Korean medicine (WHO, 2002).

Many people around the world choose traditional medicines or herbal products as a curative agent, either alone or in combination with others, to maintain their health. In some Asian and African countries, up to 80% (WHO, 2002) of the population depends on traditional medicine for their primary medical needs. In different traditional medical systems, plants are always the main source of medicines or treatment strategy. Some traditional Chinese medicine, such as Coumarin, Aescin, and Liu-jun-zi-tang, is used to improve postoperative side effects such as tiredness, pain, appetite, diarrhea, nausea, vomiting, and lymphedema at certain stages of cancer lesions (Qi et al., 2015).

• Benefit effect of using TM

TM treatments are frequently used in developed and developing countries where they are generally available and sustainable. TM treatments can have less adverse effects than conventional therapies (WHO, 2002). The benefits of TM include its diversity and flexibility, its availability and cost-effectiveness in many parts of the world; it is widely accepted in low- and middle - income countries and the relatively low level of technological input required. As a result, TM therapies can significantly contribute to the improvement of the healthcare system in many countries (WHO, 2002).

Approximately 27 million South Africans, including PLWA and infected bacteria, are estimated to rely on traditional medicine for their primary health needs(Street et al., 2008). This is relative because of good plant accessibility, affordability, confidentiality of health information between patients and practitioners and the high cost of synthetic medicines (Ballabh et al., 2008); medicinal plants are also believed to combat certain symptoms, including weight loss, skin disorders, energy shortages, lack of appetite, diarrhea, nausea and vomiting, treatment of side effects of antiretroviral medicines (ARVs) as well as dizziness, fungal infections, pain and stomach upsets (Richter, 2004, Petzer and Mngqundaniso, 2008).

Scientific studies in many TM therapies have shown that the use of medicinal plants is effective in patients with HIV / AIDS and cancer (Power et al., 2002, Carlsson et al., 2001). Although some plant extracts like *Psidium guajava*, *Artemisia afra* and *Erythrina lysistemon* have not been scientifically investigated, traditional healers have used them to treat the growth of bacteria, viruses and other microbes (Mativandlela, 2007) and especially to treat certain types of wounds, abscesses, arthritis, diarrhea, and influenza (Van Wyk and Gericke, 2000). The use of Jiangzhi in association with atorvastatin

showed a synergistic effect in the improvement of lipid level of the blood without serious adverse effects (Wang et al., 2012).

- **Risk of using TM**

Traditional medical therapies are usually used as self-care therapies, and their improper use can lead to serious outcomes. TM products are, however, poorly regulated in many countries, and many of the risks to consumers concern their safety and quality products (Mills et al., 2005; Moss, 2001; Eisenberg et al., 1998). The combination of certain Chinese herbal preparations commonly used in cardiovascular diseases showed different interactions with cytochrome CYP450, either an induction effect with Ginkgo Tablet or an inhibition effect with compound danshen Tablet. In addition, a narrow therapeutic window and the accumulation of medicines in the body when using herbal medicines can lead to an increase of medicine concentration in the blood that leads to serious adverse effects as a consequence (Wang, 2015). The Chinese herb ma huang (*Ephedra sinica*), for example, which contains ephedrine, can lead to heart attacks as respiratory problems; as well as long-term use of kava (*Piper methysticum*) can lead to fatal liver injury and ginkgo (*Ginkgo biloba*) used to boost peripheral circulation may lead to bleeding during surgery (Ang-Lee et al., 2001). Interactions can be a risk for patients using TM with conventional medicines at the same time. Studies have shown that many patients use TM at the same time as conventional medicine, often without informing their health care provider; thus it is important to be aware of the possibility of interactions that may result from the concurrent use of several TM medication therapies and/or conventional medicines (Eisenberg et al., 1998).

TM is commonly used in combination with conventional medicines, with most satisfactory results, but in some cases, the effect of the two treatments may be magnified, interacted and/or opposed (Fugh-Berman, 2000, Ramadan, 2017). Studies have shown that many patients used TM in conjunction with conventional medicine and therefore interactions could pose a risk at any stage of absorption, distribution, and elimination of pharmaceutical disposal, which could affect the pharmacokinetics of the medicine in the body (Müller and Kanfer, 2011, Di Minno et al., 2017). Medicinal plants such as *Taraxacum officinale*, *Echinacea purpurea*, *Hypoxis hemerocallidea*, *Moringa oleifera* and *Lessertia frutescens* induce the inhibition of cytochrome CYP450 enzymes that can alter antibacterial metabolism (ATB) or (ARV)s which lead to lack of efficacy and adverse effects experienced by PLWA and using simultaneously TM with ARVs (Müller and Kanfer, 2011, Mills et al., 2005). Individuals may consult both Traditional Healer practitioners (THPs) and biomedically trained healthcare professionals for bacterial and viral infections.

However, there is a limited knowledge of interactions about the concurrent use of TM and prescribed medicines for bacterial and viral infections. This study aimed at determining whether any antimicrobial resistance and treatment failure could occur among patients, attending outpatient departments of selected healthcare facilities, who used concurrently prescribed antimicrobial medicines and traditional medicine in the Ilembe district, South Africa.

Methods

Setting and design

This study was conducted in the Ilembe District. It is located in KwaDukuza on the east coast of the province, bordering the Indian Ocean and comprises four municipalities: Mandeni, Ndwedwe, KwaDukuza, and Maphumulo. The district covers 3 269 km², the smallest provincial district in KwaZulu-Natal, with a population size of 630 464 people and it is approximately 75 km from Durban with a population including 90.8% of black African, 2.4% of the white population and 6.8% of others. The majority of the population in the district consists of native isiZulu speakers (82%) followed by native English speakers (9.6%), native Xhosa speakers (3.3%) and others (5.5%) (KZNHealth, 2017). The district comprises four local municipalities located between Durban and Richards Bay: Mandeni, KwaDukuza, Maphumulo, and Ndwedwe with a small urban area in which the majority of the area is rural. The district's rural and traditional areas are characterized by low educational levels, high unemployment rates, and a severe lack of basic services (KZNHealth, 2017).

Ilembe Health District has four hospitals: Montebello District hospital, Stanger Provincial hospital, Umphumulo District hospital, and Untunjambili District hospital. The study included two Hospitals, Stanger Provincial hospital, and Umphumulo District hospital. Both hospitals belong to the Ilembe health department in the public sector.

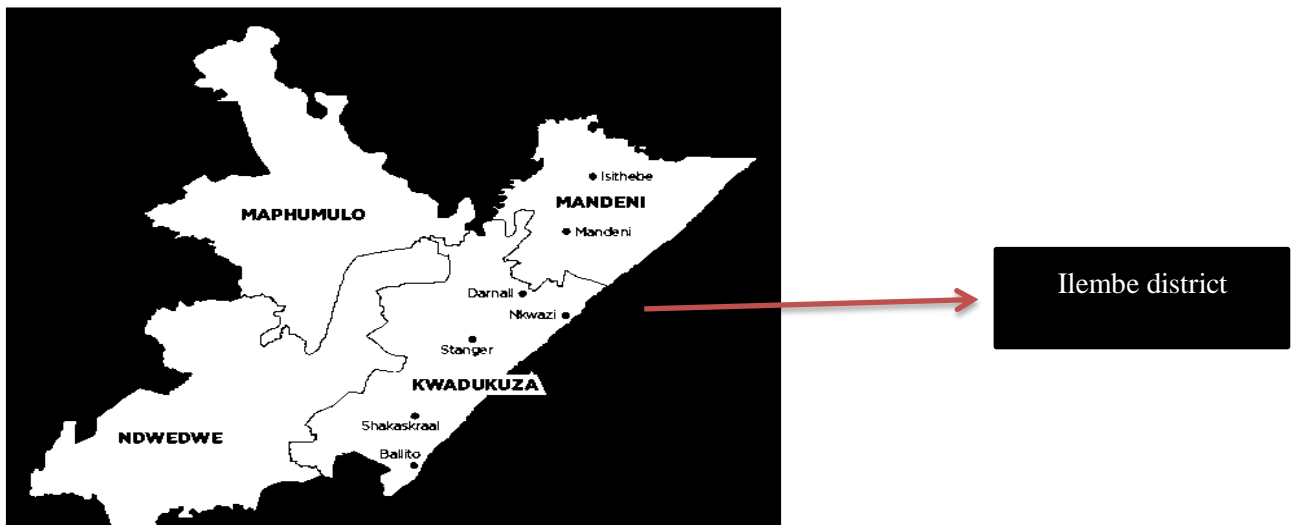


Figure 3.1 Map of the study area (<http://www.kznhealth.gov.za/ilembe.htm>).

Data collection

An explorative study using a semi-structured interviews with 132 informants (THPs, Patients seen by THPs, BHPs and patients seen either by BHPs alone or by both THPs and BHPs) was conducted on January 2018. A total of 17 THPs and 15 patients seen by them were initially identified and interviewed by snowball sampling technique; while 100 participants including 50 BHPs and 50 outpatients attending the two selected healthcare facilities. An interview face to face was used and the questionnaire form used for data

collection was specifically developed for the study in which were included in section A the participants' address, age, gender, marital status, educational level, language spoken, occupation as well as in section B, information relating to the use of TM and their related conditions and in section C, information on any clinical outcomes including treatment failure and antimicrobial drug resistance from the concomitant use of TM and prescribed medicines.

Data collection had three (3) phases. The first phase was done with THPs which were recruited purposively using snowball technique. Some of them were approached at their workplace during their business hours and other at their households and the only tool used was an interview questionnaire. Phase two was done with patients seen by THPs using snowball technique with their permission; they were asked whether they had used at the same time traditional and conventional medicine; to those that the answer was "yes", they were asked if they could indicate which healthcare facility they had attended to in Ilembe district. The third phase of the interview was with BHPs, they were recruited at the Clinic. BHPs were recruited purposively in the two selected healthcare facilities during their business operating hours. Finally, the fourth phase was conducted among outpatient, only those who were consulted by both THPs and BHPs and those who were attending the outpatient department.

Statistical analysis

Data collected from participants by interview were firstly entered and captured into Excel spreadsheets then all the responses from participants were grouped into thematic and then later analysed using Statistical Package for Social Sciences (SPSS), software version 25. Descriptive statistics including frequency and percentage were used to describe socio-demographic characteristics of study participants and for expressing different variables or questions.

Results

Response rate

This study enrolled 132 participants out of a targeted maximum of 150, yielding a response rate of 88.0%. Respondents consisted of 17 out of 25 THPs, 15 out 25 patients seen by THPs, 50 BHPs and 50 outpatients seen by both THPs and BHPs in the two selected healthcare facilities.

1. Socio-demographic characteristics of participants

Table1 presents the socio-demographic characteristics of participants included in this study. Overall, the majority of participants included in this study were black African (116/132, 87.88%), female (86/132, 65.15%), unmarried (89/132, 67.42%), employed (84/132, 63.64%) and had attended at least secondary school (55/132, 41.66%). The median age was 35 years old with a standard deviation of 12.031(35 years old \pm 12.031), while the minimum and maximum age were 18 and 76 respectively (Range 18 – 76).

Table 3.1 Socio-demographic characteristics of participants

Variables	Sub category	Frequency of THPs n=17 (%)	Frequency of Patients seen by THPs n=15 (%)	Frequency of BHPs n=50 (%)	Frequency of Out patients seen by BHPs, n=50, (%)	Total, N=132 (%) [95% CI]
Ilembe district	Municipality A	17	15	25(50.0)	25(50.0)	82(62.12)[53.84 - 70.4]
	Municipality B	None	None	25(50.0)	25(50.0)	50(37.88)[29.6 - 46.16]
Gender	Female	7(41.18)	12(80.0)	39(78.0)	28(56.0)	86(65.15)[57.02 - 73.28]
	Male	10(58.82)	3(20.0)	11(22.0)	22(44.0)	46(34.85)[26.72 - 42.98]
Race	Black African	16(94.12)	15(100.0)	36(72.0)	49(98.0)	116(87.88)[82.31 - 93.45]
	Indian	1(5.82)	None	11(22.0)	1(2.0)	13(9.85)[4.77 - 14.93]
	White	None	None	2(4.0)	None	2(1.52)[-0.57 - 3.61]
	Mixed race	None	None	1(2.0)	None	1(0.76)[-0.72 - 2.24]
Occupation	Employed	1(5.82)	9(60.0)	48 (96.0)	26(52.0)	84(63.64)[55.43 - 71.85]
	Unemployed	16(94.12)	6(40.0)	2(4.0)	24(48.0)	48(36.36)[28.15 - 44.57]
Marital status	Married	9(52.94)	2(13.33)	24(48.0)	5(10.0)	40(37.82)[29.55 - 46.09]
	Unmarried	8(47.06)	13(86.67)	25(50.0)	43(86.0)	89(67.42)[59.42 - 75.42]
	Widowed	None	None	1(2.0)	2(4.0)	3(2.27)[0.27 - 4.81]
Educational level	Illiterate	7(41.18)	2(13.33)	None	1(2.0)	10(7.57)[3.06 - 12.08]
	Primary Sc.	6(35.3)	10(66.67)	None	23(46.0)	39(29.54)[21.76 - 37.32]
	Secondary Sc.	3(17.65)	3(20.0)	24(48.0)	25(50.0)	55(41.66)[33.25 - 50.07]
	Tertiary	1(5.82)	None	26(52.0)	1(2.0)	28(21.21)[14.24 - 28.18]
Language spoken	IsiZulu	14(82.35)	15(100.0)	35(70.0)	49(98.0)	113(85.6)[79.61 - 91.59]
	Xhosa	2(11.76)	None	1(2.0)	None	3(2.27)[-0.27 - 4.81]
	English &/ Afrikaans	1(5.82)	None	14(28.0)	1(2.0)	16(12.12)[6.55 - 17.69]
	Total					100%

2. Disease conditions treated and African traditional medicine used by THPs

Table 2 presents self-reported disease conditions and African traditional medicines used by THPs for treating patients seen by them. The majority of THPs (64.70%, 11/17) have treated either one or more disease conditions such as period pains/abdominal cramps (Isibibho) and headache (Ubuhlungu ikhanda) (THP2, 3, 4, 6, 7, 8, 9, 10, 11, 14, 15). The following medicinal plants were reported by these eleven THPs for the management of the disease conditions above: Gumtree (Ugum-tree), *Ikhowa* mushroom (Umsilinga), *Hypoxis hemerocallidea* (Magic muthi or inkomfe), *Senegalia burkei* (Umkhaya), *Hilliardiella aristata* (Isibhaha), *Spirostachys Africana sond* (umtumbothi), *Sutherlandia Frutescens subspecies Microphylla* (Insiswa or Unwele).

Table 3. 2 Self-reported disease conditions and African traditional medicine treated by THPs

Variables	Self-reported disease conditions treated	Self-reported African traditional medicine used
THP1	Open a person's womb (Isizalo), Fits (Isifo sokuwa), Shingles (Ibhande), Tuberculosis (Isifo sofuba), influenza (Imfuluwenza), Gastritis (Ubuhlungu isisu), HIV infection (Igcwane lengculazi)	Sutherlandia Frutescens subspecies Microphylla (Insiswa or Unwele) (boost the immune system), Isijula (Consider carefully deep: direct to the infection), Umbola (defeat the infection and makes it weak)
THP2	Diarrhea (Isifo sohudo), stroke (unhlangothi), period pains/abdominal cramps/ (Isibhobo)	Gumtree (Ugum-tree), Ikhowa mushroom (Umsilinga), goat (imbuzi), Inhambanella henriquesii (Umathungulu), marula tree, Sclerocarya birrea (Unganu), Aloe sp (Inhlaba)
THP3	Shingles (Ibhande), period pains/abdominal cramps/ (Isibhobo), Stroke (unhlangothi)	Umsindo (Directed to the care of pain)
THP4	Headache (Ubuhlungu ikhanda), period pains/abdominal cramps/ (Isibhobo), Shingles (Ibhande), HIV infection (Igcwane lengculazi), punishment, assault (ukushangwa)	English name (Ikhanda Eligatswayo), Hypoxis hemerocallidea (Magic muthi or inkomfe)
THP5	Fits (Isifo sokuwa), Mego vuvukal kongawo, isisu segazi, Fufunyani (demons), Bladder or Abd. Pains (Ubuhlungu besisu)	Not shared
THP6	Headache (Ubuhlungu ikhanda), Body itching/ sores on the body (Sores on the part the penis) (Uma unezilonda esithweni sangasese)	Isilwane (animal, beast), Senegalia burkei (Umkhaya) and Setaria verticillata (Isinama), Sutherlandia Frutescens subspecies Microphylla (Insiswa or Unwele)
THP7	Shingles (Ibhande), menorrhea (Isisu), Headache (Ubuhlungu ikhanda), Mental trouble (Ukuhlushwa), ralwani	Not shared
THP8	period pains/abdominal cramps/ (Isibhobo), Inkwanju (cramps), amajagamba	Animal skin (sheddings of a snake, crocodile), Hilliardia aristata (Isibhaha), Spirostachys Africana sond (umtumbothi)
THP9	Bilharzia (Umkhaza isichnene), period pains/abdominal cramps/ (Isibhobo), Headache (Ubuhlungu ikhanda),	Imkwangu, Hilliardia aristata (isibhaha)
THP10	Stroke (Unhlangothi), Shingles (Ibhande), Help clear womb to bare kids, Headache (Ubuhlungu ikhanda)	Not shared
THP11	Crazy people (Isifo sengqondo), Headache (Ubuhlungu ikhanda), (where female is Bewitched and bleeds endlessly), urinary infections (Phayipi lomchamo)	Mangifera indica (Ukwango=Umango), Sutherlandia Frutescens subspecies Microphylla (Insiswa or Unwele)
THP12	Psychotic people (crazy) (Isifo sengqondo) and most emotional trips, and others diseases as, Gonorrhea, Cancer, Cold & Flu (Umkhuhlane)	Carpobrotus dimidiatus (Ikhambi)
THP13	HIV infection (Igcwane lengculazi) and Cancer even crazy people	Hypoxis hemerocallidea (Magic muthi or inkomfe), Liliaceae lancifolium spp, Wild (ilabatheka)
THP14	Stomach Ulcers (Ubuhlungu isisu), Rashes (Ukuqubuka), sores, Headache (Ubuhlungu ikhanda), Diarrhea (Isifo sohudo), any diseases	Spirostachys africana sond (Umtombothi), Sclerocarya birrea (Unganu),
THP15	Problem with urinating, Headache (Ubuhlungu ikhanda), period pains/abdominal cramps/ (Isibhobo), Wounds (Isilofida)	Inguduze, insumbili (help for witchcraft), Spirostachys Africana sond (Umtombothi), Hilliardia aristata (Isibhaha) (help for isibhobo), Umushlwa help for wounds
THP16	Flu & cold (Umkhuhlane), Diarrhea (Isifo sohudo), Vomiting (Uyahlanza) & nausea, Infections, Any diseases	Spiritual water used after praying, Liliaceae lancifolium Spp, Wild (Ilabatheka), Dombeya Rotundifolia, (Unhliziyo omkulu), Tetrademia ripania, Kamiaceae, (Ibozane: Ginger bush)
THP17	Diabetes (Isifo sikashukela), Bilharzia (Umkhaza isichnene), HIV infection (Igcwane lengculazi), Bronchitis, Asthma, Bad spirits (Isifo sengqondo)	isibunge, Khalimusi, Hilliardia aristata (Isibhaha), Ginger, Imboziso (help against flu), Hypoxis hemerocallidea (Magic muthi or inkomfe)

Translation of IsiZulu names taken from articles published by (Hutchings, 1996); (Pooley, 1993); (Ndlovu, 2009); (Ndlovu, 2013) and the website: pza.sanbi.org (Plantzafrica.com)

3. Self-reported disease conditions reported by patients seen by THPs

Table 3 presents self-reported disease conditions reported by patients seen by THPS. The majority of patients (4/15) reported that they had cutaneous conditions such as sores on the body, body itching, wounds infection and rashes (Patients 5, 11, 12, 13). Three patients out of fifteen reported having respiratory problems such as chest pain and coughing (Patients 7, 9, 10).

Table 3. 3 Self-reported disease conditions by patients seen by THPs

Participants	Self-reported disease conditions	Self-reported African medicines used
Patient 1	Leg problem, foot was swollen	Not shared
Patient 2	Weakness	Not shared
Patient 3	Headache, no appetite	Not shared
Patient 4	Stressed out, Unbearable anxiety	Water and prayer
Patient 5	Sores on the body	Prayer & Herbal medicine not shared
Patient 6	Abdominal pain	Herbal medicine not shared
Patient 7	Coughing with blood, Chest pain	Not shared
Patient 8	Diarrhea, vomiting	Herbal medicine not shared
Patient 9	Stomach-ache, Coughing	Herbal medicine not shared
Patient 10	Respiratory problem, Chest pain, Coughing, Body pain	Herbal mixtures (Plant, powder) not shared
Patient 11	Body itching, Headache	Herbal medicine not shared
Patient 12	Body itching	Not shared
Patient 13	Wounds, Rashes	Herbal mixtures (Plant, powder) not shared
Patient 14	I was just sick, unwell	Herbal mixtures (Plant, powder) not shared
Patient 15	I was just sick, unwell	Herbal mixtures (Plant, powder) not shared

4. Self-reported disease conditions and prescribed medicines by BHPs and outpatients

Table 4 presents the frequency of disease conditions and prescribed medicines self-reported by BHPs and outpatients. In total, 181 diseases were self-reported by respondents with almost half by BHPs (96/181, 53.04%) while the remainder of disease conditions were self-reported by outpatients (85/180, 46.96%). Overall, TB infection accounted for 28.18% (51/181) of all cases reported. Out of this proportion, 60.78% (31/51) were reported by the BHPs and 39.22% (20/51) were reported by outpatients. HIV infection accounted for 23.20% (42/181) of all cases reported overall. Out of this proportion, 35.71% (15/42) were reported by BHPs and 64.29% (27/42) were reported by outpatients.

Table 3.4 Frequency of self-reported disease conditions and prescribed medicines by BHPs and outpatients

Self-reported disease conditions	Frequency of self-reported disease conditions		Total (N=181)	Self-reported prescribed medicine used
	Reported by BHPs	Reported by Outpatients		
TB(Pulmonary, abdominal & meningitis)	31(17.13)	20(11.05)	51(28.18)	Rifafour (Ethambutol, Rifampicin, Pyrazinamide, Isoniazid), Pyridoxine
HIV infection	15(8.29)	27(14.92)	42(23.21)	FDC (TDF, EFV, 3TC/ABC, 3TC)
Scabies	8(4.42)	4(2.21)	12(6.63)	Fluconazole, Augmentin (Amoxicillin + Clavulanate), Benzyl benzoate
Wound infections & Rashes	6(3.31)	3(1.65)	9(4.97)	Clotrimazole cream, Fluconazole, Gentamycin, ciprofloxacin, Metronidazole
Meningitis	5(2.76)	3(1.65)	8(4.42)	Amphotericin B, Augmentin(Amoxicillin + Clavulanate), cephalixin, ceftriaxone
Malaria	4(2.21)	None	4(2.21)	Artesunate (2), CoArtem(2), Metronidazole, Bactrim (Trimethoprim and sulfamethoxazole, cotrimoxazole),
Pneumonia	3(1.65)	4(2.21)	7(3.87)	Ceftriaxone, Augmentin(Amoxicillin + Clavulanate), amikacin, tazocin (Piperacillin-tazobactam), Imipenem, meropenem, azithromycin,
Respiratory problem, Coughing with blood, Chest infection	3(1.65)	4(2.21)	7(3.87)	Augmentin(Amoxicillin + Clavulanate), Ceftriaxone, Ampicillin
UTI	2(1.10)	None	2(1.10)	Augmentin(Amoxicillin + Clavulanate), ciprofloxacin, ceftriaxone
STI	2(1.10)	3(1.66)	5(2.76)	Azithromycin
LRTI	2(1.10)	None	2(1.10)	Azithromycin, Augmentin(Amoxicillin + Clavulanate), Ceftriaxone
Herpes zoster	2(1.10)	None	2(1.10)	Acyclovir, Augmentin (Amoxicillin + Clavulanate), ciprofloxacin
Diarrhea, weakness & vomiting	1(0.55)	8(4.44)	9(4.97)	Metronidazole, ciprofloxacin, Sorol citrate
Body itching/ sores on the body(Sores on the part the penis)	1(0.55)	2(1.11)	3(1.65)	Augmentin(Amoxicillin + Clavulanate), Fluconazole
Skin disease	1 (0.55)	None	1(0.55)	Augmentin(Amoxicillin + Clavulanate), cloxacillin
URTI	1(0.55)	None	1(0.55)	Amoxicillin
Influenza infection	1(0.55)	None	1(0.55)	Augmentin(Amoxicillin + Clavulanate), ceftriaxone, cephalixin
Measles	1(0.55)	None	1(0.55)	Fluconazole
Herpes snapper	1(0.55)	None	1(0.55)	Acyclovir
Chickenpox	1(0.55)	None	1(0.55)	Amikacin
Others(Non-communicable diseases: Headache, Epilepsy)	5(2.76)	6(3.31)	11(6.10)	Non prescribed antimicrobials(Panado, Allergex)
None response	None	1 (0.55)		None
Total	96(53.0.4%)	85(46.96%)	181(100%)	

NB: *There was more than one condition or disease reported by participants.

Keynote: FDC: Fixed dose combination; BHP: biomedically healthcare professionals; TB: Tuberculosis, HIV: Human immunodeficiency virus; UTI: Urinary tract infection; LRTI: Lower respiratory tract infection; STI: Sexually transmitted infection; URTI: Upper respiratory tract infection.

5. Perception of BHPs and outpatients on the use of TM and prescribed medicines

Table 5 presents the frequencies of responses obtained from respondents on the use of TM. To the question “*Have you ever treated infectious diseases in the past 3 months? / have you had infectious diseases in the past 3 months?*” Overall, 89% (89/100) of respondents (BHPs (39/100, 39%) and outpatients (50/100, 50%) have reported infectious diseases. Out of this proportion, 43.82% of treated infectious diseases were reported by BHPs (39/89) and the remainder of infectious diseases were reported by outpatients (50/89, 56.18%). To the question “*Are your patients satisfied with the treatment received for the above infectious diseases? / Are you satisfied with the treatment received for the above infectious diseases?*” the majority of respondents (90/100, 90%) either BHPs (46/90, 51.11%) and outpatients (44/90, 48.88%) responded that they were satisfied with the treatment. This question was asked to respondents “*What do you think about the treatment administered to patients? / what do you think about the treatment administered to you?*” overall 88% of both BHPs and outpatients (88/100) responded that the treatment was “Effective”

To the question “*Have you ever treated other patients referred to you by THPs? / Have you ever used traditional medicine in the past 3 months?*” A few numbers of respondents (BHPs and outpatients) (29/100, 29%) that they received patients referred from THPs (BHPs) and a few other numbers of outpatients reported that they have been referred from THPs to BHPs. Furthermore, to next question asked only to outpatients “*Can TM fight infectious diseases?*” Half of them responded affirmatively (25/50, 50%) and only 34% of outpatients (17/50) responded that “sometime”. Another question was asked only to outpatients “*What do you think about the use of TM to treat your infectious diseases?*” Overall 30% of outpatients (15/50) responded that “TM can fight infectious diseases if using the right dose and the right medicinal plant.” To the question asked only to outpatients “*What do you think of combining various medicines to treat the same infectious diseases?*” The majority of them (14/50, 28%) responded that “They can fight both completely the same disease” another question was asked to outpatients “*Have you ever combined at the same time TM and prescribed medicines?*” Overall 20% of outpatients (10/50) responded that “I stopped with TM when I started with prescribed medicine” and 20% other outpatients (10/50) responded that “Doctor or THP could not allow the use of both”

The following question was addressed only to BHPs “*What do you think about drug-drug interactions for those patients using concurrently TM and prescribed antimicrobial medicines?*” The majority of BHPs (10/50, 20%) responded that “This could result in drug resistance especially resistance to antibiotics” and 18% of them (9/50) responded that “Most of the patients came to the clinic with several complications such as kidneys failure or liver failure, vomiting, diarrhea and jaundice after using either TM alone or in combination with prescribed medicine, since TM is not safe at all.” Another question was asked only to BHPs “*Can I talk to the concerned patients using both TM and prescribed antimicrobial medicines?*” the majority of BHPs (37/50, 74%) did not give their agreement.

Table 3. 5 Perception of BHPs and outpatients on the use of TM and prescribed medicines

Questions	Responses	BHPs (n=50)	Outpatients (n=50)	Total (N=100)
Have you ever treated infectious diseases in the past 3 months? / Have you had infectious diseases in the past 3 months?	Yes	39	50	89
	No	11	None	11
Are your patients satisfied with the treatment received for the above infectious diseases? / Are you satisfied with the treatment received for the above infectious diseases?	Yes	46	44	90
	No	4	6	10
What do you think about the treatment administered to patients? / What do you think about the treatment administered to you?	Effective	40	44	88
	No effective	4	6	10
	According to guidelines	6	None	6
Have you ever treated other patients referred to you by THPs? / Have you ever used traditional medicine in the past 3 months?	Yes	7	22	29
	No	43	28	71
Can TM fight infectious diseases?	Yes	NA	25	25
	No	NA	8	8
	Sometimes	NA	17	17
What do you think about the use of TM to treat your infectious diseases?	TM can fight infectious diseases if using the right dose and the right medicinal plant	NA	15(30%)	15
	It can heal but not for infectious diseases like HIV or TB	NA	11(22%)	11
	It depends on the believing	NA	6	6
	It is so strong and harmful, then it can bring any Intoxication or damage to the body	NA	6	6
	No, it cannot cure infectious diseases	NA	4	4
	As African, we believe in TM	NA	2	2
	It can treat but with many side effects	NA	1	1
	I advise both TM and prescribed, but THP and BHP must be in touch to avoid any side effect	NA	1	1
	I do not believe in TM as a Christian	NA	1	1
	Only qualified doctors can treat Infectious diseases	NA	1	1
	No idea	NA	2	2
What do you think about combining various medicines to treat the same infectious diseases?	They can fight both completely the same disease	NA	14(28%)	14
	Since it is the doctor's idea then it is fine	NA	11(22%)	11
	At the hospital they give us various medicine for only one disease, then combining is good	NA	5	5
	Not good, the treatment can fail or any Intoxication	NA	5	5
	Many side effects and complications can happen	NA	4	4
	It depends on everyone's believes	NA	3	3
	Medicines can interact with each other	NA	3	3
	It depends on everyone's experience(THP or BHP)	NA	2	2
	The disease can become worse	NA	1	1
	No idea	NA	2	2
I stopped with TM when I started with prescribed medicine	NA	10 (20%)	10	

Have you ever combine at the same time TM and prescribed medicines for infectious diseases?nes	Doctor or THP cannot allow the use of both	NA	10(20%)	20
	I never combine since TM brought bad effect, I stopped immediately	NA	9	9
	I never used both	NA	9	9
	I stopped TM before to start with prescribed medicines	NA	2	2
	I stopped with TM when I started with HIV medicine	NA	2	2
	I stopped TM before since it did not heal me	NA	2	2
	They must be used separated with a gap of time	NA	2	2
	I could not combine since they can bring many complications	NA	1	1
	I stopped TM when I got diarrhea	NA	1	1
	I stopped with TM when I knew my HIV status	NA	1	1
I used TM alone for Diarrhoea	NA	1	1	
What do you think about drug-drug interactions for those patients using concurrently TM and prescribed antimicrobial medicines?	Can result in drug resistance especially resistance to antibiotics	10(20%)	NA	10
	Most of the patients come to the clinic with several complications such as Kidneys failure (liver failure), vomiting, Diarrhoea, and jaundice after using either TM alone or in combination with prescribed medicine, Since TM is not safe at all.	9(18%)	NA	9
	Combing TM with Western medicines must be discouraged since the desired effect of medicines can be increased in producing many complications.	6	NA	6
	Delay of the healing process with prescribed medicines because of TM used (Drug-interaction)	5	NA	5
	Both can inhibit each other, so treatment failure can happen	4	NA	4
	I think any interaction like toxicity or Treatment failure can happen	2	NA	2
	Awareness should be given to the patient when combining	2	NA	2
	Use either TM alone or western medicines alone.	2	NA	2
	Since it is a free country, then patients are free to use medication of their choice according to their different cultural background	2	NA	2
	Collaboration might be between THPs and BHPs to avoid any intoxication	2	NA	2
	Use either TM alone or western medicines alone	1	NA	1
	THPs must be registered before giving medicine to patients	1	NA	1
	Difficult to assess notice as patients do not report herbal use	1	NA	1
	Drug resistance can happen because TM is not registered in MCC	1	NA	1
HIV or TB patients who take both, their viral load became high	1	NA	1	
I never encounter, come across those patients	1	NA	1	
Can I talk to the concerned patients using both TM and prescribed antimicrobial medicines?	Yes	13 (26%)	NA	13
	No	37	NA	37

6. Self-reports of clinical outcomes following concurrent use of both TM and prescribed medicines by BHPs and outpatients

Table 6 presents clinical outcomes reported by BHPs and Outpatients following the concurrent use of both TM and prescribed medicines.

To the question asked only to BHPs “*Are you aware of patients using both THPs and BHPs for infectious diseases?*” The majority of BHPs affirmed that they were aware of patients using both TM and prescribed medicines (38/50, 76%). A question was asked to respondents “*Have you ever registered some cases of drug-drug interactions (TM and prescribed medicines)?*” A minority of respondents including both BHPs and outpatients (28/100, 28%) indicated that they had registered some cases of drug-drug interactions. Another question was asked to respondents about “*types of interactions found between TM and prescribed medicines*”. Only 11% of BHPs and outpatients (11/100) responded that “The desired effect increases”.

To the question “*Have you ever registered some cases of adverse effects when combining both TM and prescribed medicines?*” A small number (25/100, 25%) of both respondents BHPs and outpatients (75/100) registered some cases of adverse effects. A question was further asked to probe the types of adverse effects experienced by patients for combining both TM and prescribed medicines. Diarrhea (11/100, 11%) and kidney failure (7/100, 7%) were mainly reported as adverse effects experienced by respondents. The majority of BHPs and outpatients responded that “Drug interactions, resistance to treatment, failure of TM and intoxication could occur when combining TM and prescribed medicines.” Furthermore, they said that medicines would interact with each other and patients became very ill with symptoms such as convulsion and unconsciousness (16/100, 16%)”.

Table 3.6 Perceptions of BHPs and outpatients on the clinical outcomes from the use of both TM and prescribed medicines

Questions	Responses	BHPs (n=50)	Outpatients (n=50)	Total (N=100)
Are you aware of patients using both THPs and BHPs for infectious diseases?	Yes	38(76%)	NA	38
	No	12 (24%)	NA	12
Have you ever registered some cases of drug-drug interactions when combining both TM and prescribed medicines?	Yes	17 (17%)	11 (11%)	28 (28%)
	No	33 (33%)	39(39%)	72(72%)
If yes, which medicines (TM and prescribed medicines) were involved?	Not determined	33 (33%)	40(40%)	73(100%)
	TM	17(17%)	8(8.0%)	25(25%)
	HIV medicine	None	1(1.0%)	1(1.0%)
	TB medicine	None	1(1.0%)	1(1.0%)
Types of interactions between TM and prescribed medicines	The desired effect increases	11(11%)	None	11
	The desired effect decreases	6(6.0%)	1	7
	Intoxication	2	5(5.0)	7
	MDR	None	2	2
	Treatment failure of TM	None	3	3
Have you ever registered some cases of adverse effects when combining both TM and prescribed medicines?	Yes	13	12	25
	No	37	38	75
If yes, which medicines (TM and prescribed medicines) were involved?	TM	NA	7	7
	TB medicines	NA	2	2
	HIV medicines	NA	1	1
	HIV medicines associated with TB medicines	NA	1	1
	HIV medicines associated with Painkillers	NA	1	1
Kind of adverse effects	Diarrhea	7	4	11
	kidneys failure (liver injury)	7	None	7
	Jaundice	6	None	6
	Vomiting and weakness	4	6	10
	Rashes	3	2	5
	Tiredness and loss of energy	2	2	4
	Loss of appetite	2	2	4
	Electrolyte in balance	1	None	1
	Confusion	1	None	1
	Convulsion	1	None	1
	A headache	1	1	2
	Dizziness	None	1	1
	Penis part changed color	None	1	1
	Drug interaction or drug resistance (Failure of TM, any intoxication), medicines will interact with each other and patients become very ill (Convulsion, unconsciousness)	16	None	16
	Never experienced because patients hide the use of TM	12	None	12
	Kidneys failure (renal failure), drug-induced, diarrhea, vomiting, and death	11	None	11
	Delay of treatment, unsatisfactory of treatment, less effectiveness of treatment and death	11	None	11
	Qualified doctors can explain it well	None	7	7

What is the effect experienced by patients for combining both TM and prescribed medicines? / What is the effect experienced by you for combining both TM and prescribed medicines?	I will not recover if combining	None	6	6
	Interaction can occur between TM prescribed medicines	None	6	6
	The medicine effect can increase and damage the body	None	6	6
	To avoid any Intoxication, this must not be allowed	None	6	6
	The disease can become worse	None	5	5
	They can interact with each other	None	5	5
	TM was not used at the same time with western medicine	None	1	1
	No idea	None	8	8

7. Perceptions of THPs and patients seen by them on the use of TM

Table 7 presents the perceptions of both THPs and their patients on the use of TM. A question on diagnosis was asked to THPs *“How do you decide whether you are treating a viral or bacterial infection?”* Overall 35.29% of THPs (6/17) responded that “spiritual search, dreams and ancestor guidance (Idlozi)” were the way for them to determine whether it was about viral or bacterial infection. Furthermore, four THPs (4/17, 23.52%) out of those number responded that “they did not cure viral infections, after seeing their patients’ symptoms they referred them to the hospital”.

To the question *“What basic ideas (philosophy) are you using before you decide on the treatment pattern?”* A few THPs (5/17, 29.41%) indicated that they learned from ancestors and elders. Dreams and calling from ancestors were as well reported as a way to determine their treatment pattern (3/17, 17.64%). Furthermore, another question was asked to THPs about *“Are your patient(s) satisfied with your healing?”* Most of THPs (14/17, 82.35%) responded that their patients were satisfied with the treatment received. More than half of patients seen by THPs (8/15, 53.33%) have confirmed that they felt relieved by the treatment received from THPs. Another question asked to THPs *“Can I talk to your patient(s)?”* The majority of THPs (11/17, 64.70%) did not agree and gave as a reason that their patients' life was private and confidential (7/11, 63.63%).

To the question asked to patients *“Why did you choose TM for your condition?”* Almost half of the patients (6/15, 40%) seen by THPs responded that “TM healed them before, they believed in it then it was fast and less costly”. Furthermore, a small number of same patients (3/15, 20%) seen by THPs responded that “They were told about TM as well as because the hospital was far”. A similar question was asked to patients *“Did you use traditional medicine previously?”* The majority of patients (11/15, 73.33%) seen by THPs agreed that they used TM before. In addition, another question was asked to patients about *“Did the THPs use some prayers, things, songs, spiritual rituals in addition?”* Most of the patients seen by THPs (11/15, 73.33%) affirmed that THPs did some rituals upon them such as *“Prayer to ancestors”* (6/15, 40%).

Table 3. 7 Perceptions of THPs and patients seen by them on the use of TM

Questions	Responses	THPs	Patients
How do you decide whether you are treating a viral or bacterial infection?	Spiritual search, dreams and ancestor guidance (Idlozi)	6	NA
	Symptoms from patients then I do not cure viral infection, in case I refer to the hospital	4	NA
	Certain explanations, symptoms, medical records, examination (Ukuhlola) from the patients	3	NA
	First I send people to the hospital for the blood test, then I treat according to the hospital results	2	NA
	Symbols showed by ancestors	1	NA
	Disease revealed by the holy spirit	1	NA
What basic ideas (philosophy) are you using before you decide on the treatment pattern?	I learned from ancestors and elders	5	NA
	Dreams and calling from ancestors	3	NA
	Practical experience for many years and traditional searching	2	NA
	Talents and ancestors calling	2	NA
	The philosophy is to talk to elders that have passed away	2	NA
	Revelation from the holy spirit	1	NA
	First seek help from the hospital then here(THP)	1	NA
	There is a school where we are taught	1	NA
Do your patient(s) satisfied with your healing?	Yes	14	NA
	Not at the exact time	3	NA
Can I talk to your patient(s)?	Yes	6	NA
	No	11	NA
Any reason(if the answer is NO)	My patients' life are private and confidential	7	NA
	I lost their contacts	4	NA
Why did you choose TM for your condition?	TM healed me before, I believe in it then it is fast and less costly	NA	6
	I was told about it	NA	3
	The hospital was far	NA	3
	THPs are more confident than doctors, then the healing is fast	NA	2
	Because the doctor failed to heal me	NA	1
Did you use traditional medicine previously?	Yes	NA	11
	No	NA	4
Did the THPs use some prayer, things, songs, spiritual rituals in addition?	Yes	NA	11
	No	NA	4
Specify those practices	Prayer to ancestors	NA	6
	He screamed to the spirit and sung	NA	1
	He kept quiet for a moment when he prayed	NA	1
	He rang the bell then prayed	NA	1
	He turned around by singing	NA	1
	Attended the services, when they praise and pray	NA	1
	None	NA	4
How do you feel after treatment (the issue)?	Relieved	NA	8
	Unwell	NA	4
	Relieved but with side effect	NA	2
	Nothing changed, he referred me to the hospital	NA	1

8. Self-report of clinical outcomes following concomitant use of TM with prescribed medicines by THPs and Patients seen by them

Table 8 presents the general perception of THPs and patients seen by them on the use of TM. To the question “*What type of treatment are you using to treat your patients with infectious diseases?*” A small number of THPs (5/17, 29.41%) responded that their information was “*confidential*” and the same question was also asked patients (9/15, 60%) seen by them who also indicated that they did not know the medicines used by their THPs since THPs did not share their knowledge. The following question was asked to respondents “*Do both THPs and their patients' mix sometimes different herbs for treatment in case of different infectious diseases?*” Overall, of both THPs and their Patients (22/32, 68.75 %) affirmed that they mixed different herbs in case of infectious diseases. To the question about any reason for mixing different herbs, the majority of THPs (10/17, 58.82%) responded that “each illness had its own plants”, so they could be combined. Each Ikhambi (medicinal plant) had its own condition /infection; the intakes are different so medicines do not interfere; THPs could combine until they find a solution; people came with certain different cases, then THPs must treat by mixing herbs”. Moreover, another question asked to both THPs and patient “*Do your patients combined TM with prescribed medicines?*” Most of them (21/32, 65.62%) responded that they were aware that their patients used to combine TM with prescribed medicines. Patients seen by THPs were asked the following question: “*Do you consult also BHPs for the same problem?*” Less than half of patients seen by THPs (6/15, 40%) responded that they consulted both THPs and BHPs.

To the question about any reason for “*combining TM with prescribed medicines for infectious diseases*”, less than half of THPs (8/17, 47.05%) responded that in case of any interaction such as vomiting and coughing they did refer patients to BHPs. In case of treatment failure or any other complications, THPs referred 100% of their patients to BHPs. In addition, in case of any medicine from THPs did not work; THPs are not allowed to donate water or blood or any other treatment that may lead to death of patients. Thus it is good to work hand to hand or to collaborate between BHPs and THPs.

To the question “*Do you ever register some cases of adverse effects after mixing TM with prescribed medicines for infectious diseases?*” Less than half of THPs and patients (14/32, 43.75%) responded that they had experienced adverse effects. Vomiting, dizziness, diarrhea, and weakness were some of the adverse effects reported by THPs (3/17, 17.64%) and one patient (1/15, 6.66%). The following question was asked to THPs “*What is your thought about interactions for using at the same time TM with conventional medicines?*” Few THPs (3/17, 17.64%) responded that “*interactions were good especially when you are not sure with one medicine*”, the same question was asked to patients seen by THPs, a few patients (4/15, 26.66%) responded that “*disease could get worst.*” Another question was asked to THPs “*According to you, what can occur if the patient takes at the same time TM and conventional medicine?*” Less than half of THPs (6/17, 35.29%) responded that “nothing bad could happen if patients respected the time lapse between the two treatments”.

Table 3. 8 Perceptions of THPs and patients seen by them on the clinical outcomes from the use of both TM and prescribed medicines

Questions	Answers	THPs	Patients	Total
What type of treatment are you using to treat your patients?/ Which type of TM, your THP has used to treat you?	Confidential	5	None	5
	Plants and animal parts	4	None	4
	Not using plants	3	None	3
	It depends of the problem	2	None	2
	Most of the knowledge the ancestors had, it was from plants (Leaves, crops,...)	1	None	1
	crops, leaves	1	None	1
	Leaves, roots	1	None	1
	He used herbal (Muthi), but I do not know	None	9	9
	No idea, it is THPs own secret	None	3	3
	I was unconscious, I cannot know	None	1	1
	Wangi caba (cut with a bleed), herbs, impepo, pleading with ancestors	None	1	1
Water and prayer	None	1	1	
In case of a different problem, does the THP mix also different herb to treat you? Are you also sometimes mixing different herbs for your patient in case of a different problem?	Yes	11	11	22
	No	6	4	10
Reasons for mixing both TM and prescribed medicines for infectious diseases	Each illness has its own plant, so they can be combined	2	NA	2
	Each khambi has its own things/infection	2	NA	2
	The intakes are different so medicines do not interfere	2	NA	2
	I can combine until I find a solution	2	NA	2
	People come with certain different cases of the problem, then you must treat by mixing herbs	2	NA	2
	Each medicine has its place to work	1	NA	1
	I mix 3 or 4 medicines when I am not sure with the diagnostic	1	NA	1
	When I am not sure with the patient's problem	1	NA	1
None	4	NA	4	
Do your patients combined TM and prescribed medicines for infectious diseases? / Do you use to consult also BHPs for the same problem?	Yes	15	6	21 (65.62%)
	No	2	5	7
	Yes but not for the same problem	None	1	1
	Yes I did before to consult the THP	None	1	1
	Yes Referred by the THP	None	2	2
Reasons for combining both TM and prescribed medicines for infectious diseases	In case of any interaction (vomiting or coughing), I do refer them	1	NA	1
	In case of treatment failure or complication, I refer 100% of patients to doctors	1	NA	1
	In case that THP's medicine does not work	1	NA	1
	It is a norm now. We were taught, we cannot donate water or blood that leading to death	1	NA	1
	It is good to work hand to hand(a collaboration between BHP and THP)	1	NA	1
	They do combine but not for the same problem	1	NA	1
	only in case of over illnesses	1	NA	1
	There are medicines only for specific disease, so prescribed medicine will not work after using TM	1	NA	1
None	9	NA	9	

Do you ever register some case of adverse effects after mixing that?	Yes	8	6	14
	No	9	9	18
(If Yes) List them	Weakness and vomiting	3	1	4
	Dizziness and weakness	2	1	3
	Diarrhea and vomiting	2	None	2
	Allergies	1	None	1
	Chest pain	None	1	1
	The disease went worst	None	1	1
	loose of sight	None	1	1
	Nausea	None	1	1
	None	9	9	18
What is your thought about interaction when using at the same time TM and Conventional medicine for infectious diseases?	The disease can get worst	None	4	4
	They can interact with each other	None	2	2
	The medicines effect can either increase or decrease	None	1	1
	The treatment can either be successful or fail	None	1	1
	There must be a time gap in their use	None	1	1
	They both treat and they do not clash	None	1	1
	Side effects can occur	None	1	1
	You can get intoxicate	None	1	1
	Interaction is good especially when you are not sure with one medicine	3	None	3
	A mutual relationship is good. We do not have the equipment to check the minor things that play a big role in a person life	2	None	2
	It is good for fighting completely the diseases but this treatment must be stopped in case of adverse effect	2	None	2
	The interaction is good as long as there is a time lapse	2	None	2
	Patients must not take both, at least his BHP and THP must be in known.	1	None	1
	Since we do not have the same knowledge, we should help each other(TM and Prescribed medicine)	1	None	1
	No idea	3	3	6
	Patients get heal but there must be a mutual relationship between THP and BHP	1	None	1
	The interaction is good. BHP cannot treat a specific disease that needs an ancestor intervention.	1	None	1
We cannot heal disease instantly, there is a process. So BHP and THP must collaborate	1	None	1	
According to you, what can occur if the patient takes at the same time TM with conventional medicine?	If they respect the time lapse, nothing bad can happen	6	NA	6
	Intoxication	3	NA	3
	It depends on their dosage, but any complication must be avoided	3	NA	3
	Medicines can interact	3	NA	3
	No Idea	1	NA	1
	There must be a mutual relationship, there is something that I can heal and some other that the doctor can also heal	1	NA	1

DISCUSSION OF THE RESULTS

THPs and their Patients

This study was conducted in the ILembe district, South Africa on experiences from BHPs, outpatients, THPs and patients seen by them. The aim of the study was to establish whether any antimicrobial resistance and treatment failure could occur among patients, attending outpatient departments of selected healthcare facilities, who used concurrently prescribed antimicrobial medicines and TM.

This study found a small number of medicinal plants used by THPs such as *Spirostachys Africana sond* (Umtomboti), *Hypoxis hemerocallidea* (magic muthi or inkofe) and *Sutherlandia frutescens* (Insiswa or Unwele). Although the majority of THPs could not reveal the specific recipe used for each disease condition treated with the listed plants above; a few THPs indicated that they used *Sutherlandia Frutescens* for “boosting the immune system.” THPs in this study also used *Hypoxis hemerocallidea* and *Sclerocarya birrea* (Unganu) for treating diarrhea (*Isifo sohudo*) and HIV infection (*Igciwane lengculazi*). The use of *Hypoxis hemerocallidea* against infectious diseases has been reported previously in another study for the treatment of sexually transmitted infections (De Wet et al., 2012). Another study reported the use of *Hypoxis hemerocallidea* and *Sutherlandia frutescens* for enhancing the immune system and may have antiviral properties (Awortwe et al., 2013, Mugomeri et al., 2016). *Sclerocarya birrea* (Unganu plant) has been reported having a pharmacological property against sexually transmitted infections such as *gonorrhoea* (De Wet et al., 2012). In some African countries, the same plant was used in the management of human ailments, such as diarrhea, dysentery, and others (Louis et al., 2018).

This study found that 65.62% of THPs and their patients (21/32) mixed different herbs for the treatment of infectious diseases. This finding may be supported by another study conducted in Portugal (Freitas et al., 2013) which reported the synergistic enhancement of antimicrobial compounds from medicinal plants. However, respondents from this study reported that *they had experienced adverse effects such as vomiting, dizziness, diarrhea, and weakness when mixing different herbs for the management of their infectious diseases*. Compared to another study, respondents expressed negative attitudes towards the use of TM in conjunction with prescribed medicines by showing that TMs were most of the time harmful especially when mixing them with ARVs, they ended to death or any other complications (Weintraub et al., 2018).

In this study, respondents agreed that when combining both TM and prescribed medicines for infectious diseases, interactions and adverse effects may result and if there is no respect of time lapses between the two medicines, the infectious disease may get worse. Perceptions from respondents in this study may be supported by statements such as TM and prescribed medicines could coexist and complement each other (Giovannini et al., 2011, Calvet-Mir et al., 2008). In the same line, another study done in Brazil reported that people in the local community relied on both TM and prescribed medicines to treat diseases of all categories including infectious diseases (Zank and Hanazaki, 2017).

BHPs and outpatients

This study found that the majority of disease conditions were infectious diseases (169/180, 93.88%) with mainly TB infection (51/181, 28.33%) and HIV infection

(42/180, 23.33%) reported in Table 4 above. This may be supported by a previous study done in KwaZulu-Natal province which found that KwaZulu-Natal province had the highest prevalence of HIV infection in South Africa (Gómez-Olivé et al., 2013); a recently published report on the prevalence of HIV infection in South Africa showed that KwaZulu-Natal province was the most prevalent province (Approximately 26.6 %) among the top four high HIV-prevalent provinces in South Africa (Statistics South Africa, 2018).

Respondents (30%, 15/50) from this study perceived that TM can fight infectious diseases if using the right dose and the right medicinal plant; in addition, they responded that TM is associated with prescribed medicines could fight completely infectious diseases. In contrast, Weintraub et al.,(2018) disagreed in showing that the majority of respondents in his study opposed the concurrent use of TM and prescribed medicines for the management of HIV infection and they believed that ARVs were the most effective option for treating HIV infection. In line with the findings of this study, TM remains the framework and cannot be ignored against the management of infections. Accordingly, many authors suggested for collaboration between BHPs and THPs by respecting local expertise in managing infectious diseases (Green and Ruark, 2016, Gqaleni et al., 2011)

Outpatients (20/50, 40%) in this study reported that they stopped with using TM when started with prescribed medicine or when they knew their HIV status because BHPs would not allow the use of both. A study done previously in 2010 showed that the use of TM usually decreases among patients after ARV initiation (Peltzer et al., 2010); more studies reported that traditional medications provided good results, despite their side effects and toxicity (Leone et al., 2015, Anwar et al., 2007). TM and prescribed medicines if used concurrently should be used wisely per avoidance of any interactions and adverse effects such as kidney failure which mostly reported the present study.

Respondents in this study including BHPs and outpatients reported that combining TM and prescribed medicines for infectious diseases may result in drug resistance especially resistance to antibiotics and they highlighted that the majority of patients came to the clinic with several complications such as kidneys failure, vomiting, diarrhea and jaundice after using either TM alone or in combination with prescribed medicines. Similar studies were conducted in the UK and in Ethiopia showing that the lack of collaboration between health practitioners has an impact on treatment failure. BHPs always have negative perceptions about TM which discourage patients from sharing information on the use of TM which result in adverse effects and interactions on patients health due to the toxicity of TM used (Mekuria et al., 2018, Barnes, 2003). From these experiences stated by respondents in this study, authors may admit that having conventional medicines and TM at the same time may interfere or may result in damaging some organs, failure of the treatment as well as modifying drugs pharmacological action.

Strengths and limitations of the study

This was a mixed method approach study using both qualitative and quantitative as study design. This study was a triangulation study including four (4) types of participants, namely THPs, patients seen by THPs, BHPs, and outpatients. This study had a few limitations. This was a survey with self-reports collected from respondents. There was neither observation of THPs in their practices nor experimentations conducted by researchers. No matching of information between BHPs and patients seen by them; although this study matched information from THPs and a few patients seen by them. The

concurrent use of TM and prescribed antimicrobial was under-reported by participants because of embarrassment or belief that their medical providers were against TM use or their information could be divulged (Puoane et al., 2012). The majority of medicinal plants used by THPs for infectious diseases or other disease conditions were not reported by them and kept as a secret. However, results cannot be generalized to the entire population of THPs, patients seen by them, BHPs and outpatients in the entire province of KwaZulu-Natal and South Africa.

Conclusion

This study presented different perceptions from THPs, BHPs and their patients on medicinal plants used concurrently with prescribed antimicrobial medicines and their effects on antimicrobial resistance and treatment failure. A small number of medicinal plants were reported with antibacterial and/or antiviral properties. THPs and their patients confirmed that they combined medicinal plants for a positive result. Cases of interactions and adverse effects were reportedly referred by THPs to the nearest hospital or clinic. However, patients seen by either BHPs or THPs confirmed that they stopped with TM when they started with prescribed antimicrobial medicines. The majority of BHPs reported that adverse effects such as kidney failure, vomiting, and jaundice were the most common clinical outcomes among patients who used either TM alone or in combination with prescribed medicines. Further studies are needed in other parts of South Africa to investigate the effects of concurrent use of traditional medicine and prescribed antimicrobial medicines. Furthermore, studies are needed to investigate bidirectional referral systems between THPs and BHPs.

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After collecting perceptions on the interactions and side effects following concurrent use of prescribed antimicrobial and traditional medicines for infectious diseases, a medical chart review was carried out in order to assess the clinical outcomes documented in outpatients' medical records. This chapter is presented in a manuscript format, it has been prepared and submitted following the authors' guidelines of the journal **BMC Complementary and Alternative medicines**. The manuscript is currently under review with the registration number: BCAM-D-18-01617R1.

CHAPTER 4: THIRD MANUSCRIPT SUBMITTED FOR PUBLICATION

TITLE: Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review.

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ABSTRACT

Background: Antimicrobial resistance (AMR) is a major origin or cause of treatment failure and is largely responsible for the declining in eradication rates of infectious diseases worldwide. AMR in South Africa is driven by many factors such as the careless use of prescribed antimicrobial medicines and the use of traditional medicine, with the result that there is always the danger of misadministration, interaction, and toxicity. This study aimed at determining whether any antimicrobial resistance and/or treatment failure occurred among patients attending out-patient departments in selected healthcare facilities and who use concurrently traditional medicine with antibiotics and/or antiviral medicines in ILembe district, KwaZulu- Natal.

Methods: This study was a cross-sectional descriptive study using medical chart review among patients attending the outpatient department in two public healthcare facilities between February and March 2018. Antimicrobials prescribed alone or in association with other medicines and concurrent use of traditional medicine were assessed and reported using descriptive statistics. Where applicable, associations were carried out; a p-value <0.05 was estimated as statistically significant.

Results: Four hundred (400) outpatients' medical records were documented from two different municipalities, many participants had viral infections (194/400, 48.50%). Overall, 12% of participants (48/400) had documented negative clinical outcomes with adverse effects (30/48) and interactions (18/48). A few participants (15/400, 3.75%) had used traditional medicine in conjunction with prescribed medicines. Among those who used both traditional medicine and prescribed medicines, the majority (80%, 12/15) had documented adverse effects due to the concurrent use of traditional medicine and prescribed medicines. After adjustment, documented adverse effects and interactions were significantly more likely due to the use of traditional medicine (AOR = 0.01, 95% CI = 0.001-0.05) and (AOR = 0.21, 95% CI = 0.37-1.23) respectively.

Conclusion: Traditional medicine was sparingly used in conjunction with prescribed antimicrobials for viral and bacterial/fungal infectious diseases. However, adverse effects and interactions such as herbal intoxication, persistent rashes, and treatment failure were documented in few medical chart records among outpatients attending the two selected healthcare facilities. Further studies are needed to investigate the effects of concurrent

use of traditional medicine from perspectives of traditional healers and biomedically healthcare professionals.

KEYWORDS: Antimicrobial resistance - Treatment failure- Traditional Medicine - Bacterial and viral infections.

BACKGROUND

Antibiotic-resistant microorganisms as “nightmare bacteria” represent a global menace [1]. Some microorganisms have become resistant to multiple antimicrobial classes, which means that infectious diseases caused by resistant bacteria are now common [2]. Antimicrobial resistance (AMR) is the ability of a microorganism to withstand the effects of antimicrobials namely antiviral, antibiotic and antifungal medicines (AMR) with as a result AMR reduces the potential human health benefit derived from antibiotics and/or antiviral medicines [3]. A report from the World Health Organisation (WHO) has shown that 30% of bacteria were resistant to common antibiotics used to treat bacterial infectious diseases [4]. AMR is a serious burden, some bacteria and/or virus become so resistant that there is either only last resort antimicrobials or infections cannot be treated [5]. AMR is a leading cause of treatment failure and is largely responsible for the reduction in infectious disease extermination rates worldwide [6]. Infectious and non-infectious disease conditions are most of the time treated with antibiotics, which leads to the indiscriminate use of antimicrobials [7]. Virus and bacteria cause a large proportion of infectious diseases in Africa; bacterial infections account for 45% of deaths in Africa and South - East Asia [4] whereas 48% of premature deaths worldwide were caused by these infectious diseases [8]. Actually, due to antiretroviral therapy, the incidence of HIV infection has decreased from 0.40 per 1000 people non-infected with HIV/AIDS in 2005 to 0.26 per 1000 people non-infected with HIV/AIDS worldwide in 2016 [9]. Similarly, from 2000 to 2016, the incidence of TB has decreased by 19 % over a 16-year period from 173 cases per 100 000 population to 140 per 100 000 population respectively. Despite the increase in the incidence of TB infection, drug-resistant TB remains a global menace; as a result among 600 000 registered new cases of TB resistant to rifampicin, there were 490 000 cases of multidrug-resistant [10].

South Africa is no exception to widespread AMR; it confronts a triple AMR burden: drug-resistant tuberculosis, drug-resistant HIV and antibiotic resistance [3]. People living with HIV / AIDS (PLWA) increased from 6.8 million in 2014 [11] to 7.52 million in 2018 [12]. AMR is driven by many factors in South Africa, such as the careless use of prescribed antimicrobial medicines and the use of traditional medicine (TM), with the result that misadministration, interaction, and toxicity are always at risk [13].

Traditional medicine (TM) was defined by the WHO as “the sum of knowledge, skills, and practices based on indigenous theories, beliefs and experiences of different cultures, whether or not explainable, used to maintain health and to prevent, diagnose, improve or treat physical and mental illness” [14]. Thus, plants are considered as one of the most promising sources for new antimicrobial medicines discovery; more than hundreds of plants in the world are used in TM for the treatment of viral and bacterial infections and other disease conditions by up to 80 percent of the population in Asia, Africa, Latin America, and the Middle East [15]. In the European Union, 100 million people believed also in the use of TM [16]. It is estimated that approximately 27 million South Africans, including PLWA depend on TM for their primary health care needs [17]. This is relatively due to good accessibility to plants, affordability, and confidentiality of health information between patients and traditional health practitioners and the high cost of synthetic medicines [18]. Medicinal plants are also believed to combat the specific symptoms of diseases such as weight loss, skin disorders, lack of energy, digestive problems such as lack of appetite, diarrhoea, nausea, vomiting and treatment for side effects from antiretroviral medicines (ARVs) as well as dizziness, fungal infections, pain and stomach upsets [19, 20]. Studies from around the world have shown that people have used concurrently traditional medicine with different prescribed medicines. A study in North - East Scotland showed that women have the potential to increase the risk of postpartum hemorrhage, alter maternal hemodynamic and increase the depression of the central nervous system between mothers and fetuses [21]. In addition, another study showed that less than 20% of participants co-used TM and ARV; however, nearly 80% of participants use TM before contracting HIV infection [22]. Furthermore, 45% of study participants were co-users of conventional drugs and herbs, while a significant proportion of general health practitioners who co-used herbs with conventional drugs for their patients reported potential interactions or adverse effects due to the concomitant use of anticoagulants and

garlic [23]. TM is commonly used in combination with conventional medicines, mainly with satisfactory results, but in some cases, the effect of the two treatments can be increased, interacted and/or opposed [24]. Different patient groups are known to use herbal remedies and conventional drugs concomitantly (co-use). This poses a potential risk of interactions between herbal drugs by changing the pharmacokinetics or pharmacodynamics of the drug. Little is known about AMR among patients who co-use prescribed medicines antibiotic or antiviral medicines with TM. Individuals may consult both traditional healer (THPs) and biomedically trained healthcare professionals (BHPs) for bacterial and viral infections. However, there is a limited knowledge of interactions about the concurrent use of TM and prescribed medicines for bacterial and viral infections. This study aimed at determining whether any antimicrobial resistance and/or treatment failure could occur among patients attending out-patient departments (OPD) in selected healthcare facilities and who used concurrently traditional medicine with antibiotics and/or antiviral medicines in Ilembe district, KwaZulu- Natal.

Methods

Study design

This study was a cross-sectional descriptive study using medical chart review among patients attending OPD in two public healthcare facilities in the Ilembe district, KwaZulu-Natal province, South Africa.

Study setting

This study was carried out in Ilembe district, one of the 11 districts of the province of KwaZulu-Natal in South Africa. Ilembe is the smallest district municipality in the province with a surface area of 3,269 km²; it is approximately 75 km from Durban with a population of 630 464 inhabitants (90.8%), white population (2.4%) and others (6.8%); the majority of the population in the district consists of native isiZulu speakers (82%) followed by native English speakers (9.6%), native Xhosa speakers (3.3%) and others (5.5%) [25]. It is located in KwaDukuza on the east coast of the province, bordering the Indian Ocean and comprises four municipalities: Mandeni, Ndwedwe, KwaDukuza, and Maphumulo.

There are four hospitals in the Ilembe Health District namely: Montebello District Hospital, Stanger Provincial Hospital, Umphumulo District Hospital, and Untunjambili District Hospital. This study involved two hospitals: the Stanger Provincial Hospital in the municipality of KwaDukuza and the Umphumulo District Hospital in the municipality of Maphumulo. Both hospitals belong to the Ilembe health department in the public sector.

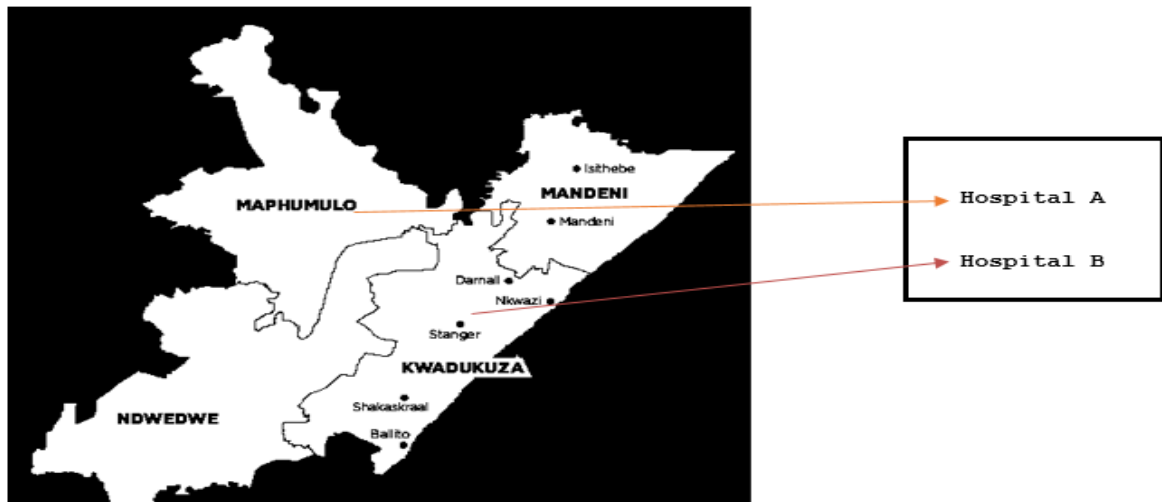


Fig. 4. 1 Map of the study area (<http://www.kznhealth.gov.za/ilembe.htm>).

This map represents the area where data have been collected for this study. The map contains two different arrows that show the two hospitals (Hospital A and B) where the study were conducted.

Sample size calculation assumption

Records or medical chart of patients aged 18 years and older were systematically sampled from January 2018 to March 2018. In general, a margin of precision of $\pm 10\%$ requires a sample size of approximately 100, which increases to approximately 400 for a margin of precision of $\pm 5\%$ and 10,000 for a margin of precision of $\pm 1\%$, for an expected prevalence of approximately 50% for the outcome variable [26], the sample size was determined in respect of the calculation method [27] which stipulated that the sample size would be 377 for a sizeable population of 20,000 with a margin of precision of $\pm 5\%$, 95% CI and within 50% as an equal distribution. Accordingly, Ilembe district has a population size of 630 464. The researcher assumed that the sample size for a large

population of 630 464 was at least 384 [28]. The study was oversampled by a maximum sample to include 400 medical chart reviews.

Ethical approval

Ethical approval to undertake the study was granted by the Biomedical Research Ethics Committee of UKZN (Reference BE476/17). In this phase of the study, no contacts were done with participants. Medical chart records were reviewed; findings of this study have been reported anonymously. No name, no personal identification and file numbers have been reported to protect the privacy and to maintain confidentiality about study participants.

Recruitment process and selection of participants

Medical chart records of adult patients, aged 18 years and above, irrespective of gender were selected at the OPD of the two selected healthcare facilities as well as at their respective TB and HIV clinics during clinic visit hours. Patients' medical records from January 2017 to January 2018 were assessed and selected according to the study's inclusion and exclusion criteria during the data collection period between February and March 2018. Records of patients who used concurrently TM and prescribed antimicrobials as well as who developed any side effects and/or interactions were reviewed in details.

Data collection technique and instruments

A medical chart review was conducted during four weeks between February and March 2018. Data from four hundred (400) outpatients were collected manually by the researcher since there were no computerized records in the OPD. A data extraction form was specifically developed for the study. The form included the following information: patient's address, age, gender, marital status, educational level, language spoken, occupation as well as viral infectious diseases, bacterial and/or fungal infectious diseases. Moreover, the details of any antimicrobials prescribed alone (antiretroviral, antibiotics and/or antifungals) or in association with other prescribed medicines, the use of traditional medicine, any adverse effects and interactions registered were assessed. The data extraction form was prepared in the English language. Thus, all the patient's

information needed for this study was recorded for every eligible out-patient in both hospitals.

Statistical analysis

Descriptive statistics using frequency and percentage were used to describe socio-demographic characteristics of study participants. Data deriving from medical records using medical chart reviews were transferred into Excel spreadsheets, and then later analyzed using Statistical Package for Social Sciences (SPSS), software version 25. Categorical data were presented as tables. Prevalence of HIV infection, TB (Tuberculosis) infections, and other respiratory infectious disease were reported as a percentage with 95% confidence intervals (95% CI). Prevalence of use of traditional medicine and prescribed antimicrobials medicines were as well reported as a percentage with 95% CI. Associations between variables were carried out using Pearson Chi-Square tests. For multivariate analysis, a binary logistic regression analysis (adjusted odds ratio, AOR) was used. In addition, a separate multivariate logistic regression model was built to determine the association between use of TM and clinical outcomes. A P-value ≤ 0.05 was considered as statistically significant. Logistic regression analyses were used to calculate odds ratios for adverse effects and interactions regards to traditional medicine used.

RESULTS

This study reviewed 400 documented patients' medical records in two different municipalities in Ilembe district, KwaZulu Natal, South Africa.

1. Socio-demographic characteristics of study participants

Table 1 presents the socio-demographic characteristics of the study participants. Overall, the majority of participants were black African (339/400, 84.80% [95%CI, 81-89]), female (218/400, 54.50% [95%CI, 50-60]), and unmarried (314/400, 78.50% [95%CI, 74-82]). Most of the participants were employed (228/400, 57% [95%CI, 52-62]) and had attended at least primary school (174/400, 48.30% [95%CI, 43-53]). The median age was 33 years old with a standard deviation of 16.42 (33 years old \pm 16.42), range 18-93 years.

Table 4.1 Socio-demographic characteristics of participants

Category	Sub-category	N (%) [95% CI]
District ILembe	Municipality A	200(50.0)[45-55]
	Municipality B	
	Total	400(100)
Gender	Female	218(54.50)[50-60]
	Male	182(45.50)[41-51]
	Total	400(100)
Race	Black African	339(84.75)[81-89]
	Indian	31(7.75)[5-10]
	(Mixed race)	18(4.50)[3-7]
	White	12(3.0)[2-5]
	Total	400(100)
Occupation	Employed	228(57.0)[52-62]
	Unemployed	172(43.0)[38-48]
	Total	400(100)
Marital status	Married	62(15.50)[12-20]
	Unmarried	314(78.50)[74-82]
	Widowed	24(6.0)[4-8]
	Total	400(100)
Educational level	Illiterate	23(5.75)[4-8]
	Primary School	193(48.25)[43-53]
	Secondary School	174(43.50)[39-49]
	Tertiary	10(2.5)[1-4]
	Total	400(100)
Language spoken	English & Afrikaans	43(10.75)[8-14]
	IsiZulu	340(85.0)[81-88]
	IsiZulu & English	17(4.25)[2-6]
	Total	400(100)

Key: CI: Confidence Interval

2. Prevalence of infectious diseases associated with HIV and TB among study participants

Table 2 presents the prevalence of HIV, TB and other associated diseases or comorbidities among study participants. The majority of participants (194/400, 48.50% [95%CI, 43.6-53.4]) had either HIV infection alone (49/194, 25.26% [95%CI, 19.15-31.37]) or a co-infection of HIV and tuberculosis (61/194, 31.44% [95%CI, 25.19-38.31]) and finally HIV with other diseases (84/194, 43.30% [95%CI, 36.33-50.27]). Tuberculosis was documented either alone (35/49, 71.42% [95%CI, 58.77-84.07]) or in combination with other infections excluding HIV infection reported above (14/49, 28.57% [95%CI, 15.92-41.22]). Overall, seventeen percent of participants had other respiratory infections excluding TB (67/400, 16.75% [95%CI, 13.03-20.41]). Besides HIV infection, TB either alone or associated with other comorbidities, other infectious diseases were documented in almost seven and a half percent (30/400, 7.50% [95%CI, 4.92-10.08]) while the

remainder of participants had non-communicable diseases (63/400, 15.75% [95%CI, 12.18-19.32]).

Table 4.2 Frequency of communicable and non-communicable infectious diseases associated to HIV and Tuberculosis

Category	Sub-category	Frequency documented diseases (%)	P value, AOR (95% CI)
HIV infection	HIV infection alone	49(12.25)	P < 0.001 0.073(0.039-0.14)
	HIV with Tuberculosis	61(15.25)	
	HIV with other bacterial infectious diseases (Pneumonia (3), meningitis (2) and other (12))	21(5.25)	
	HIV with Fungal infectious diseases non-identified	6(1.5)	
	HIV with other Sexually Transmitted Diseases (10) and three viral infectious diseases (shingles(1), genital warts (2))	13(3.25)	
	HIV with Non communicable diseases (Hypertension (6), Assault (injury) (5), renal failure (5) and other (28))	44(11)	
Subtotal		194	
Tuberculosis infection	Tuberculosis infection alone	35	8.75(6.1 – 11.4)
	Tuberculosis with other Bacterial infectious diseases(Pneumonia (3), Meningitis(2)), one fungal infection (candidiasis) and one viral infectious disease(Hepatitis B) and with two others	9	2.25(0.88 – 3.62)
	Tuberculosis with non-communicable diseases (Gastroenteritis acute (2), asthma (1) and two others diseases	5	1.25(0.27 – 2.23)
Subtotal		49	
Respiratory infection	Respiratory infections alone (Pneumonia (3), Upper respiratory tract infection (3), Pharyngitis (2) and other (6))	14	3.5(1.83 – 5.17)
	Respiratory infection with other infectious diseases: Pneumonia with lower respiratory tract infection (1), Upper respiratory tract infection with diarrhea(1), Upper respiratory tract infection with Tinea pedis (1) and Other diseases (4)	7	1.75 (0.79 - 2.71)
	Respiratory infection with non-communicable diseases(Lower respiratory tract infection with Acute gastroenteritis (4), Pneumonia with Asthma (4) and other diseases (35))	43	10.75(7.69 – 13.81)
Subtotal		64	
Other infectious diseases alone (Urinary tract infection (3), one herpes simplex and other infectious diseases alone (26))		30	7.5(5.01 – 9.99)
Non-communicable diseases (Hypertension (11), Diabetes (5) and other diseases (47))		63	15.75(12.26 – 19.24)
Total		400	100%

Key: AOR: Adjusted odds ratio that is obtained from binary logistic regression, CI: confidence interval, HIV: human immunodeficiency virus

3. Documented medicines prescribed (antimicrobial and non-antimicrobials) by BHPs

Table 3 presents the frequency of documented antimicrobial medicines prescribed by biomedically trained healthcare professionals. Most of the medical records reviewed for study participants contained prescribed antimicrobials (356/400, 89.0% [95%CI, 85.93-92.07]) while the remainder had other prescribed medicines than antimicrobials 44/400, 11.0% [95%CI, 7.93-14.07]).

Overall, 1497 medicines were identified within study participants' medical chart records. Although the majority of medical records contained infectious diseases and the appropriate antimicrobial treatment; non-antimicrobial medicines (808/1497, 53.97% [95%CI, 51.45-56.49]) were predominantly prescribed in conjunction with antimicrobials (689/1497, 46.03% [95%CI, 43.51-48.55]). Those non-antimicrobials consisted mainly of Paracetamol in combination with other painkillers (Paracetamol + Codeine + Potassium sorbate), which accounted for at least sixteen percent (131/808, 16.21% [95%CI, 13.67-18.75]). Antimicrobial medicines were mainly common antibiotics or antifungals (389/689, 56% [95%CI, 52.29-59.71]) such as Augmentin® (Amoxicillin + Clavulanate), or Bactrim® (Sulfamethoxazole + Trimethoprim), Flagyl® (Metronidazole), and Fluconazole. They were followed by antiretroviral medicines (190/689, 27.58% [95%CI, 24.24-30.92]) in a fixed-dose combination antiretroviral containing either Tenofovir + Emtricitabine + Efavirenz or Abacavir + Lamivudine + Lopinavir; and finally followed by anti-tuberculosis medicines (110/689, 15.97% [95%CI, 13.23-18.71]) consisting of a fixed dose combination Rifafour® made of Rifampicin + Ethambutol + Isoniazid + Pyrazinamide.

Table 4.3 Documented medicines prescribed (antimicrobial and non-antimicrobials) by BHPs

Frequency of participants (N=400, %)		Frequency of prescribed medicines used N=1497, (%)		
Prescribed antiretroviral Fixed dose combination (FDC) Tenofovir + Emtracitabine + Efavirenz or Abacavir + Lamivudine + Lopinavir	FDC (alone)	31(7.75)	FDC (alone)	31(2.07)
	FDC with Rifafour® consisting of a fixed dose combination (Rifampicin + Ethambutol + Isoniazid + Pyrazinamide)	31(7.75)	FDC(31) with Rifafour® consisting of a fixed dose combination (Rifampicin + Ethambutol + Isoniazid + Pyrazinamide)(31)	62(4.14)
	FDC with other prescribed antibiotics(Augmentin (amoxicillin + Clavulanate) (9) and to other medicines (74)	83(20.75)	FDC(83) with other prescribed antibiotics(Augmentin (amoxicillin + Clavulanate) (9) and to other medicines(74)	166(11.08)
	FDC with prescribed antifungals(Cotrimazole(3), prescribed antibiotics and other prescribed medicines(23)	26(6.5)	FDC(26) with prescribed antifungals(Cotrimazole(3), prescribed antibiotics and other prescribed medicines(23)	75(5.01)
	FDC with other prescribed medicines(Amlodipine(3), Hydrochlorothiazide(2) and other (14)	19(4.75)	FDC with other prescribed medicines(Amlodipine(3), Hydrochlorothiazide(2) and other (14)	38(2.53)
Other antiviral used(Acyclovir) associated to 8 other prescribed medicines		4(1)	Other antiviral used(Acyclovir) associated to 8 other prescribed medicines	
Subtotal		194(48.5)	384(25.62)	
Prescribed antibiotics	Rifafour (Rifampicin +Ethambutol+ Isoniazid + Pyrazinamide) with other prescribed antibiotics(Augmentin (amoxicillin + Clavulanate)(10), Bactrim(sulfamethoxazole + trimethoprim)(8) and others(61)	79(19.75)	Rifafour (Rifampicin +Ethambutol+ Isoniazid + Pyrazinamide) with other prescribed antibiotics(Augmentin (amoxicillin + Clavulanate)(10), Bactrim(sulfamethoxazole + trimethoprim)(8) and others(61)	158(10.55)
	Other prescribed antibiotics used alone Flagyl (Metronidazole)(4), Praziquantel (2) and other (13)	19(4.75)	Other prescribed antibiotics used alone Flagyl (Metronidazole)(4), Praziquantel (2) and other (13)	19(1.27)
	Other combination between prescribed antibiotics(Amoxicillin with metronidazole(8), Clotrimazole with Fluconazole (4) and other (52)	64(16.0)	Other combination between prescribed antibiotics(Amoxicillin with metronidazole(8), Clotrimazole with Fluconazole (4) and other (52)	128(8.55)
Subtotal		162(40.5)	305(20.37)	
Other prescribed medicines (Panado: Paracetamol +Codeine + Potassium sorbate)(131), Pyridoxine(113), Multivitamin (49), Brufen (Ibuprofen(43) and other (472)		44(11)	Other prescribed medicines (Panado: Paracetamol +Codeine + Potassium sorbate)(131), Pyridoxine(113), Multivitamin (49), Brufen (Ibuprofen(43) and other (472)	
Total		400(100)	1497(100)	

4. Documented clinical outcomes of the concurrent use of TM and prescribed medicines among study participants

Table 4 presents the documented concurrent use of TM and prescribed medicines among study participants. Overall very few participants (15/400, 3.75% [95%CI, 1.89-5.61]) used TM with their prescribed medicines whose clinical outcomes were also documented in their medical chart records. Eight out of fifteen documented cases (8/15, 53.33% [95%CI, 28.08-78.58]) consisted mainly of treatment failure and drug resistance to the first line ARV treatment and a persistent rash to conventional treatment, loss of scrotum pigmentation, diarrhea, nausea, vomiting, body pain, headache, and renal impairment. Twelve cases (12/33, 36.36% [95%CI, 19.95-52.77]) were documented having drug resistance and treatment failure either from the first line or the second line of antiretroviral therapy, severe renal impairment, rashes, kidney pain, jaundice, painful lower limbs, weakness, and vomiting.

Table 4. 4 Documented clinical outcomes of the concurrent use of TM and prescribed medicines

Use of TM (N=15)				Non-use of TM(N= 385)			
Conditions	Prescribed medicines used	Documented interactions	Documented adverse effects	Conditions	Prescribed medicines used	Documented interactions	Documented adverse effects
HIV infection disease	FDC, Aminophylline, Bactrim (Cotrimoxazole or sulfamethoxazole + trimethoprim), Panado(Paracetamol +Codeine + Potassium sorbate)	Herbal intoxication(1), Treatment failure(to the first line)	Unconsciousness due to overdose (1), Nausea(1) and headache(1)	HIV infection alone	FDC, Bactrim (Cotrimoxazole or sulfamethoxazole + trimethoprim), Fluconazole, Clotrimazole, Multivitamin	Drug resistance and treatment failure(7) either of the first line or the second line of FDC	Missed of period(1), Shingles, and sores(1), Genital warts(1), vomiting(2), Dizziness(2), Loss of balance, Headache(1), Weakness(1), Stomach cramps
HIV with TB and/or other disease	FDC, Rifafour(Rifampicin + Ethambutol + Isoniazid + Pyrazinamide), Bactrim (Cotrimoxazole or sulfamethoxazole + trimethoprim), Augmentin (Amoxicillin + Clavulanate potassium), Multivitamin, Fluconazole, Verofer(Iron sucrose) , Rocephin (Ceftriaxon), Azythromycin, Clexane(Enoxaparin) , FeSO4, Paracold(Paracetamol + Codeine phosphate), Voltaren(Diclofenac Sodium) , Betamethasone, Brufen(Ibuprofen), Allergex, Sorol Citrate, Ampicillin, Prednisolone, Clotrimazole cream, Flucox(Flucloxacillin), Aciclovir	Herbal intoxication (1), Treatment failure(3) and Drug resistance (to the first line ARV regimen)(1), and persistent Rashes to conventional treatment	Loss of scrotum pigmentation(1), Diarrhea(2), Rash resistant(2), Nausea(1), Diarrhea(1), body pain(1), Headache(1), Rashes, Renal impairment(2)	HIV with Tuberculosis infection	FDC, Rifafour(Rifampicin + Ethambutol + Isoniazid + Pyrazinamide), Augmentin (Amoxicillin + Clavulanate potassium), Bactrim Cotrimoxazole or sulfamethoxazole + trimethoprim),, Norfloxacin, Pyridoxine, Panado(Paracetamol +Codeine + Potassium sorbate), Dapsone, Multivitamin, Vitamin BCo, Vitamain C	Drug resistance(2) and treatment failure(1) either of the first line or the second line of FDC	Severe renal impairment(2), Rashes(1), Kidney pain(2), Jaundice bloods(1), Painful lower lmb(1), Weakness(1) , Diarrhea (1) and Vomitting(2)
Tuberculosis infection alone	Rifafour(Rifampicin + Ethambutol + Isoniazid + Pyrazinamide), Pyridoxin,	None	None	HIV with Mouth ulcer and other diseases	FDC, Bactrim Cotrimoxazole or sulfamethoxazole + trimethoprim),, Flucloxacillin, Flagyl(Metronidazole),	Drug resistance(1) and treatment failure either of the first line	Diarrhea(1), Vomitting (1) and Kidney failure (1)

	Panado(Paracetamol +Codeine + Potassium sorbate), Multivitamin				Lansoloc(Lansoprazole), Brufen(Ibuprofen), Buscopan (hyoscine butylbromide), Fluconazole, Clotrimazole	or the second line of FDC	
Abdominal pain(Renal impairment)	Buscopan (hyoscine butylbromide) and ringer lactate	Herbal intoxication(1)	Abdominal pain(1), vomiting(1), body weakness(1)	TB with AGE	Rifafour(Rifampicin + Ethambutol + Isoniazid + Pyrazinamide), Augmentin(Amoxicillin + Clavulanate potassium), Rocephin(Ceftriaxone), Clotrimazole, Nystatin, Maxolon (metoclopramide), Sorol Citrate, Allergex, Pyridoxine, Panado(Paracetamol +Codeine + Potassium sorbate), Multivitamin	None	Vomitting and abdominal pain(2)
Gastritis and Septicemia	Augmentin (Amoxicillin + Clavulanate potassium), Rocephin (Ceftriaxone), Flagyl(Metronidazole), Maxolon(Metoclopramide), Lansoprazol	None	Vomitting and weakness	TB with Pneumonia	Rifafour(Rifampicin + Ethambutol + Isoniazid + Pyrazinamide), Augmentin(Amoxicillin + Clavulanate potassium), Azythromycin, Rocephin(Ceftriaxone), Pyridoxine, Panado(Paracetamol +Codeine + Potassium sorbate), Vit C	None	Loss of energy and Headache

Key: ARV: antiretroviral medicines, FDC: Fixed dose combination, TM: traditional medicine, HIV: human immunodeficiency virus, TB: tuberculosis.

5. Association between the use of traditional medicine and documented adverse effects and interactions.

Table 5 presents an association between the use of TM and adverse effects and/or interactions. Overall, less than ten percent of patients had documented adverse effects (7.5%, 30/400 [95% CI, 4.92-10.08]). A small percentage of participants (15/400, 3.75% [95% CI, 1.89-5.61]) have reportedly used TM, only twelve out of fifteen (12/15, 80% [95% CI, 59.76-100.24]) had adverse effects due to the use of TM (Renal impairment, diarrhea, vomiting, abdominal pain, and weakness), 4.5% of patients had reported interactions (18/400, [95% CI, 2.47-6.53]); seven out of eighteen had reportedly used TM (38.89% (intoxication and treatment failure), while seven out of fifteen (7/15, 46.67% [95% CI, 21.42-71.92]) of documented interactions were related to the use of traditional medicine (7/15). Of those 15 participants, 60% were female (9/15, [95% CI, 35.21-84.79]), 73.33% had attended at least primary school (11/15, [95% CI, 50.95-95.71]), and were employed (12/15, 80% [95% CI, 59.76-100.24]).

Documented interactions and adverse effects were significantly associated with the use of TM in combination with prescribed medicines using Pearson Chi-square ($p < 0.001$). Using multiple logistic regression models, the risk estimate of using of TM alongside with prescribed medicines was higher among females gender compared to males (AOR= 0.93; 95% CI [0.34-2.54]). After adjustment, documented adverse effects and interactions were significantly more likely to the use of traditional medicine (AOR = 0.01, 95% CI [0.001-0.05]) and (AOR = 0.21, 95% CI [0.37-1.23]), respectively.

Table 4.5 Association between the use of traditional medicine and documented adverse effects and interactions.

Variables (N=400)		Use of TM (N=15)			P-Value (χ^2)	AOR (95% CI)
		No	Yes	Total		
Gender	Female	209 (52.25%)	9 (2.25%)	218 (54.50%)	P=0.886	1.07(0.3-2.9)
	Male (Ref.)	176 (44%)	6 (1.50%)	182 (45.50%)		
Educational Level	Illiterate	23 (5.75%)	0	23 (5.75%)	P=0.199	0.2(0.02-2.1)
	Primary Sc.	182 (45.50%)	11 (2.75%)	193 (48.25%)		
	Secondary Sc.	170 (42.50%)	4 (1.00%)	174 (43.50%)		
	Tertiary (Ref.)	9 (2.25%)	1 (0.25%)	10 (2.50%)		
Documented Adverse effects	No	367 (91.75%)	3 (0.75%)	370 (92.50%)	P=0.000	0.01(0.001-0.05)*
	Yes (Ref.)	18 (4.50%)	12 (3.00%)	30 (7.50%)		
Documented Interactions	No	374 (93.50)	8 (2.00%)	382 (95.50%)	P=0.000	0.21(0.37-1.23)*
	Yes (Ref.)	11 (2.75%)	7 (1.75%)	18 (4.50%)		
Total		400				

Key: AOR: Adjusted odds ratio that is obtained from binary logistic regression, TM: traditional medicine

Discussion

This study aimed at determining whether any antimicrobial resistance and/or treatment failure occurred among patients who used concurrently traditional medicine with antibiotics and/or antiviral medicines, and attending out-patient departments in selected healthcare facilities in ILembe district, KwaZulu- Natal.

This study found that a few participants had a documented concurrent use of TM with prescribed medicines (15/400, 3.75%). Traditional medicine was not commonly used by the study participants 385/400 (96.25%) as showed in Table 5. This finding is in agreement with another study carried out in eThekweni municipality [29] which showed a quite low use of ARV in conjunction with TM (4.98%). A study done by Hughes et al., (2012) revealed that less than 20% of participants co-used TM and ARV [22, 30]. However other studies done in Nigeria [31] and in North-East Scotland [21] indicated in contrast a high prevalence (69.4% and 44.9% respectively) of the concurrent use of both TM and prescribed medicines. According to the WHO [32], this trend may be attributed to accessibility, affordability, and availability of traditional medicines in the world.

In this study, there was no statistically significant association between use of TM and gender (P value=0.886) and level of education (P value=0.199). The majority of those who used TM were female participants (9/15, 60%). This was in agreement with other studies carried out in Iraq [33] and in Nigeria [34] which stated that 52.9% and 72.4% respectively of female participants used more TM concurrently with their prescribed medicines than males. The preponderance of female proportion in this study (9/15) was similar to other studies that reported that female gender was a predictor of traditional medicine use amongst people living with AIDS [22, 35].

This study found a few cases of documented adverse effects (30/400) and interactions (18/400) as clinical outcomes; among those who had adverse effects, 40% (12/30) used concurrently TM while 38.89% (7/18) had interactions and used concurrently TM. After adjustment in this study, documented adverse effects and interactions were significantly more likely to the use of traditional medicine (AOR = 0.01, 95% CI = 0.001-0.05) and (AOR = 0.21, 95% CI = 0.37-1.23) respectively. These results were in agreement with similar studies conducted in Norway [23] which showed that patients who used concurrently conventional medicines with TM, had significantly ($p < 0.05$) increased

odds of having experienced adverse effects (AOR 37.5); in the same way McLay et al., [21] showed that pregnant women who co-used TM and conventional medicines had postpartum hemorrhage and altered maternal hemodynamic. Interactions between TM and prescribed medicines can occur and may lead to negative clinical consequences. However, the results of this study were in contradiction with other studies carried out in Portugal and around the world which showed that antimicrobial compounds from plants have revealed to be synergistic enhancers in that though they may not possess any antimicrobial properties alone, but when used concurrently with prescribed medicines they enhance the activity of the medicine and co-users of both TM and prescribed medicine feel quality of life improved [36, 37] .

This study found a high prevalence of HIV infection (47.5%, 190/400). This finding is in agreement with a published report on the high prevalence of HIV infection in KwaZulu-Natal as well as the most prevalent province (Approximatively 26.6 %) among the top four high HIV-prevalent provinces [12]. Shah et al. [38] showed in their report that of 404 participants, 311 (77%) had HIV infection in KwaZulu Natal. The South African government has highlighted earlier that aspects of poverty in townships such as inadequate sanitation and food, unemployment and poor education, violence, and crime have been associated with increased HIV transmission [39].

Strengths and limitations of the study

This phase of the study was a medical chart review; no direct contacts were made with patients reportedly using concurrently TM and prescribed medicines. Some more information could have been collected by talking directly to patients themselves. The findings of this study should be interpreted with caution. They cannot be generalized to the entire province of KwaZulu-Natal and to South Africa. Further studies are needed in other districts of KwaZulu-Natal and the rest of South Africa. There was a difficulty of finding data that revealed the type of TM used since documented patient medical records do not highlight it properly. In addition, studies involving direct interactions with patients, BHPs and THPs are warranted to gather more information on the problem under study.

Conclusion

The findings from the present study revealed a low documented use of traditional medicine in conjunction with prescribed antibiotic and/or antiviral medicines. Patients had a high prevalence of viral infections (with emphasis on HIV infection) and bacterial infections (with emphasis on tuberculosis infection and other respiratory infectious diseases). Few documented adverse effects and interactions were documented among those who used concurrently TM and prescribed medicines in the healthcare facilities included in this study. Further studies are needed to investigate the effects of concurrent use of TM and prescribed medicines on antimicrobial resistance and/or treatment failure in other parts of South Africa.

Abbreviations

AOR: adjusted odds ratio; CI: Confidence Interval; SPSS: Statistical package for the social sciences; PLWA: People living with HIV/AIDS; HIV: Human immunodeficiency virus; AIDS: Acquired immune deficiency syndrome; TM: traditional medicine; ARV: antiretroviral medicine; ATB: Antibacterial; THP: Traditional Healer practitioners; BHP: Biomedically trained healthcare professionals; OPD: Outpatient department; TB: Tuberculosis; UKZN: University of KwaZulu-Natal; FDC: Fixed Dose combination.

Ethical approval and consent to participate

Ethical approval to undertake the study was granted by the Biomedical Research Ethics Committee of UKZN (Reference BE476/17). In this phase of the study, no contacts were done with participants. Medical chart records were reviewed after obtaining gate-keeper permission at the study site.

Consent for publication

Not applicable.

Availability of data and materials

The materials and data of his study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests. MGK received a stipend and running expenses from the College of Health Sciences, University of KwaZulu-Natal. However, the college does not impose where to publish findings of this study.

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Authors' contributions

MN conceptualized the study and its design, he revised the manuscript and accepted the final version of this publication as the senior author. MGK collected data and wrote the first draft of the manuscript. All authors have read critically the manuscript for its substantial intellectual content and approved the final manuscript.

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5.1 Synthesis and discussion – Significance of major findings

This chapter highlights the major findings of this study, it gives a general conclusion drawn from the study and provides recommendations for future investigations.

5.1.1 Perceptions from THPs, patients seen by them, BHPs and outpatients about the concurrent use of traditional medicines and prescribed antimicrobial medicines for infectious diseases

The phase one of this study was a qualitative study using a face to face interview with four (4) types of participants namely: THPs, patients seen by THPs, BHPs and outpatients.

- i. This study found a small number of medicinal plants used by THPs such as *Spirostachys Africana sond* (Umtombothi), *Hypoxis hemerocallidea* (magic muthi or inkofe) and *Sutherlandia frutescens* (Insiswa or Unwele) for infectious diseases. A similar study conducted in Mpoza, South Africa reported that among seventeen plant species identified for the management of HIV and other related infectious diseases, *Hypoxis hemerocallidea* (85%) was the most frequently used medicinal plants (Gail et al., 2015); in the same line, another study reported that *Hypoxis hemerocallidea* and *Plectranthus amboinicus* were the herbal medicines used not only for boosting the immunity but also in the management of HIV infection and bacterial infections (Maroyi, 2014).

In this study the majority of THPs could not reveal the specific recipe used for each disease condition treated with the listed plants above; a few THPs indicated that they used *Sutherlandia frutescens* for “boosting the immune system.” THPs in this study also used *Hypoxis hemerocallidea* and *Sclerocarya birrea* (Umganu) for treating diarrhea (Isifo sohudo) and HIV infection (Igcwane lengculazi). Similarly, another study in Namibia reported that medicinal plants and other recipes used to manage HIV infection and other opportunistic infectious diseases were not disclosed by THPs at all because they were values and indigenous knowledge; THPs preferred to keep this knowledge as a secret for themselves (Chinsembu et al., 2015).

- ii. This study found that 65.62% of THPs and their patients (21/32) mixed different herbs for the treatment of infectious diseases; moreover, respondents in this study agreed that when combining both TM and prescribed medicines for infectious diseases, interactions and adverse effects may result and if there is no respect of time lapses between the two medicines,

the infectious disease may get worse. For supporting these findings, synergistic and antagonistic interactions were noted among six Southern African medicinal plants when associated with seven prescribed antimicrobial medicines in a study conducted in South Africa (Hübsch et al., 2014). Medicinal plants may contain multiple ingredients and when used simultaneously with prescribed medicines, either therapeutic effects may occur or side effects and treatment failure may also happen. In contrast, a very little attention was given to the safety of TM because only a small number of interactions between TM and conventional medicines were found by the Brazilian Unified Public Health System (Mazzari and Prieto, 2014); in the same line, a study conducted in the East Asian part concluded that the use of TM can be associated with prescribed medicines but this depends to the medical systems of each country (Shim, 2016).

- iii. Outpatients (30%, 15/50) in this study reported that TM can fight infectious diseases if using the right dose and the right medicinal plant; in addition, they responded that TM if associated with prescribed medicines could fight completely infectious diseases and then some of them (20/50, 40%) reported that they stopped with using TM when started with prescribed medicine or when they knew their HIV status because BHPs would not allow the use of both. Another study reported that TM could fight infectious diseases such as symptoms of HIV infection, tuberculosis, diarrhoea, skin rashes and other opportunistic infections. The frequent plant parts used were leaves, fruits and seeds mainly through oral administration (Gurrapu and Mamidala, 2016). Perspectives from respondents in this study were supported by a study done in Mozambique which reported that the majority of PLWA (62%) went to see first their THPs for only some strange symptoms status; secondly, without knowing their HIV status, they just join the clinic only when the symptoms persist (Audet et al., 2014). The delay in diagnosis and treatment of HIV infection is registered when there is no early referral from THPs to BHPs. However the use of TM is hardly reported by patients to BHPs ; a study done in Kenya reported that only 12.5 % of pregnant women revealed to their BHPs the use of TM alone or in association with prescribed medicine for same disease conditions (Mothupi, 2014).

Respondents in this study including BHPs and outpatients reported that combining TM and prescribed medicines for infectious diseases may result in drug resistance especially resistance to antibiotics and they highlighted that the majority of patients came to the clinic with several complications such as kidneys failure, vomiting, diarrhea and jaundice after using either TM alone or in combination with prescribed medicines. A study agreed that medicinal plants contain different compounds in one mixture that constitute a challenge regards to side effects and interactions with enzymes of medicines metabolism when they

are used in conjunction with prescribed medicines (Thomford et al., 2015). In addition, a clinical study conducted in USA, found that PLWA combined TM treatment to ARVs and developed side effects such as viral resistance and inhibition of medicines metabolism that lead to toxicity. Many medicinal plants are able in their mechanism of action to inhibit the action of enzymes of medicines metabolism; thus it would be necessary for BHPs, THPs and patients to be aware of interactions and side effects per avoiding the consumption at the same time of TM and ART (Fasinu et al., 2016). From these experiences stated by respondents in this study, concurrent use of conventional medicines and TM at the same time may interfere or may result in damaging of some organs, failure of the treatment as well as modifying drugs pharmacological action.

5.1.2 Clinical outcomes from a medical chart review following the concurrent use of prescribed antimicrobial and traditional medicines

This second phase of the study was a quantitative approach using a medical chart review of outpatients attended Stanger hospital and Umphumulo hospital and who used concurrently TM and prescribed medicines for their infectious diseases conditions.

- i. Traditional medicine was not commonly documented in medical chart records of study participants. This study found that a few participants had a documented concurrent use of TM with prescribed medicines (15/400, 3.75%). A similar study reported a small number of participants (20%) that co-used TM with prescribed antimicrobial medicines for their infectious diseases (Abou-Rizk et al., 2016). Furthermore, another study done in Kenya by Mothupi (2014) reported that 12.5% of pregnant women disclosed the use of TM to their BHPs, and only 20% used TM at the same time with prescribed medicines for their disease conditions such as malaria, respiratory tract infections and other infectious diseases; while serious adverse effects were noted in a study conducted by Izzo et al(2016) among pregnant women who used TM for cystitis prevention, nausea, hypertension, migraine and other conditions, although clinical results for side events showed that TM was more tolerated by pregnant women than conventional medicines (Mothupi, 2014; Izzo et al., 2016). However, a study done in Nigeria had reported in contrast a high rate (69.4%) of concomitant use of TM and prescribed medicines for disease conditions such as malaria, typhoid fever and other (MO, 2009).
- ii. This study found a few cases of documented adverse effects (30/400) and interactions (18/400) as clinical outcomes; among those who had adverse effects, 40% (12/30) used concurrently TM while 38.89% (7/18) had interactions and used concurrently TM. This was

supported by a study that showed the production of an antagonistic effect against *P. mirabilis* and *E. faecalis* when medicinal plants associated with prescribed antimicrobial medicines while a synergistic effect was produced against *P. aeruginosa* (Ofokansi et al., 2013). In addition, a clinical case report study showed potential interaction on HIV infected women who used concurrently TM and ARVs; the most developed adverse effects were liver injury and jaundice (Mateo-Carrasco, 2013). Documented adverse effects and interactions were significantly more likely to the use of traditional medicine after adjustment (AOR = 0.01, 95% CI = 0.001-0.05) and (AOR = 0.21, 95% CI = 0.37-1.23) respectively. In contrast, Darwish and Aburjai (2010) reported in their findings a possibility of combining prescribed antibiotics with medicinal plants for managing infectious diseases caused by *E. coli*. In the same line, Shim (2016) reported the promote of the East Asian medicines on the concomitant use of TM with prescribed medicines but this depends to the medical systems of each country (Shim, 2016).

5. 2 General Conclusions drawn from the study findings

This study was conducted in the ILembe district, KwaZulu-Natal province, South Africa and aimed to investigate whether antimicrobial resistance or treatment failure could occur among patients attending out-patient department of selected healthcare facilities, who used concurrently traditional medicine and prescribed antimicrobial medicines.

In this study, a mixed approach method was used which firstly included face to face interviews with THPs and patients seen by them; thereafter interviews were conducted with BHPs, and lastly with outpatients seen by both THPs and BHPs attending the outpatient department in the two selected healthcare facilities namely Stanger Hospital and Umphumulo Hospital. Secondly, Phase two consisted of a medical chart review of outpatients who came from THPs and files of those other outpatients who used concurrently TM and prescribed antimicrobial medicines.

This study demonstrated different perceptions from THPs, BHPs and their treated patients with medicinal plants used concurrently with prescribed antimicrobial medicines and their effects on antimicrobial resistance and treatment failure. A small number of medicinal plants were reported with antibacterial and antiviral properties. THPs and their patients confirmed that they have combined medicinal plants for a positive result. Cases of interactions and adverse effects were referred by THPs to the nearest hospital. However, 40 percent of the interviewed outpatients (20/50) in this study confirmed that they stopped with TM when they started with prescribed antimicrobial medicines. The majority of BHPs reported that adverse effects such as kidney

failure, vomiting, diarrhoea and jaundice were the most common clinical outcomes among patients who used either TM alone or in combination with prescribed medicines.

Besides perceptions from participants, the findings from the present study revealed as well a low documented use of traditional medicine in conjunction with prescribed antibiotic and/or antiviral medicines. Patients had a high prevalence of viral infections (with emphasis on HIV infection) and bacterial infections (with emphasis on tuberculosis infection and other respiratory infectious diseases). Few documented adverse effects and interactions were documented among those who used concurrently TM and prescribed medicines in the healthcare facilities included in this study. Documented interactions and adverse effects were significantly associated with the use of TM in combination with prescribed medicines using Pearson Chi-square ($p < 0.001$). Using multiple logistic regression models, the risk estimate of using of TM alongside with prescribed medicines was higher among females gender compared to males (AOR= 0.93; 95%CI [0.34- 2.54]). After adjustment, documented adverse effects and interactions were significantly more likely to the use of traditional medicine (AOR = 0.01, 95% CI [0.001-0.05]) and (AOR = 0.21, 95% CI [0.37- 1.23]), respectively.

Strengths and limitations of the study

This was a mixed method approach study using both qualitative and quantitative as study design. This study was a triangulation study including four (4) types of participants, namely THPs, patients seen by THPs, BHPs and outpatients. This study had its strength when revealing that the use of both TM and prescribed antimicrobial medicines for patients who had bacterial, viral and/or fungal infections developed adverse effects and interactions.

This study had a few limitations. This was a survey in its first phase with self-reports collected from respondents. There was neither observation of THPs in their practices nor experimentations conducted by researchers. Among outpatients, there were very few cases referred by BHPs for the concurrent use of prescribed antimicrobial and traditional medicines. Although this study matched information from THPs and a few patients seen by them, there was no documented evidences about self-reports received either by THPs or patients seen by them. The concurrent use of TM and prescribed antimicrobial medicines was under-reported by participants because of embarrassment or belief that their medical providers were against TM use or their information could be divulged (Puoane et al., 2012). The majority of medicinal plants used by THPs for infectious diseases or other disease conditions were not reported by them and kept as secret. There was also a limitation of finding documented patients' medical records that revealed the type of TM used, since documented patient medical records do not highlight it properly in the phase two. However, this results should be interpreted with caution and cannot be generalized to the entire

population of THPs, patients seen by them, BHPs and outpatients in the entire province of KwaZulu-Natal and South Africa.

5.3 Recommendations

Results from this study are of benefit to researchers by highlighting gaps in evidence that may need further investigation. Further studies are needed in other parts of South Africa to investigate the effects of concurrent use of traditional medicine and prescribed antimicrobial medicines and to implement any bidirectional referral between THPs and BHPs in the reduction of any interactions and adverse effects occurring when patients use both TM and prescribed antimicrobial medicines. In addition, experimental studies can also be run by using those medicinal plants used in combination with prescribed medicines. Future experimental and well-designed studies would be beneficial in terms of outcomes and in the perspective of counselling or advising the two parties involved (THPs and BHPs) on the change in their respective practices for the improvement of the health of patients using both traditional and western medicines. Bidirectional referral between THPs and BHPs and an implementation or creation of medical records for patients seen by THPs will be required for the documentation of their information. Further studies are also needed to depict intrinsic and extrinsic factors contributing to the success or failure of treatment. Bidirectional referral between THPs and BHPs and an implementation or creation of medical records for patients seen by THPs will be required for the documentation of their information.

With a view of conceptualizing the conditions for collaboration between the two systems, an earlier concept was suggested by Pretorius (Pretorius, 1991) in which he proposed the analogical model of the Biomedical/Traditional Medical Relationship, this model shows clearly that each aspect of the traditional medicine system may be linked to the western medicine system such as mutual referral. In addition, the WHO has adopted the strategies to ensure the integration of collaboration between research institutions and THPs based on research and management of patients; and between THPs and BHPs in human immunodeficiency virus and acquired immune deficiency syndrome (HIV/ AIDS) prevention and sexually transmitted infections (STIs)/tuberculosis programs (Busia and Kasilo, 2010).

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APPENDIX I: Final approval from the Biomedical Research Ethics Committee



Mr MG Kadima (217032995)
School of Health Sciences
College of Health Sciences
gedeonkadima@gmail.com

Dear Mr Kadima

Protocol: Concurrent use of traditional medicine and prescribed antibacterial and/or antiviral medicines and their effect on antimicrobial resistance and treatment failure

Degree: Master in Pharmacy

BREC Ref No: BE476/17

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 25 July 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 12 January 2018 to BREC correspondence dated 13 December 2017 has been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 23 January 2018. **Please send support letters from hospitals.**

This approval is valid for one year from **23 January 2018**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **13 February 2018**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: nlotoo@ukzn.ac.za
cc postgraduate administrator: nep1@ukzn.ac.za

Biomedical Research Ethics Committee

Professor J Tsoka-Gwegweni (Chair)

Westville Campus, Govan Mbeki Building

Postal Address: Private Bag X54001, Durban 4000

Telephone: +27 (0) 31 260 2486 Facsimile: +27 (0) 31 260 4609 Email: brec@ukzn.ac.za

Website: <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>

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APPENDIX II: Gate keeper letter from the Provincial department of Health



health
Department:
Health
PROVINCE OF KWAZULU-NATAL

330 Langalibalele street,
Private Bag X9051 PMB, 3200
Tel: 033 395 2805/3189/3123 Fax: 033 394 3782
Email: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:

Health Research & Knowledge
Management (HRKM)

Reference: HRKM474/17
KZ_201711_032

15 January 2018

Dear Mr M G Kadima
(UKZN)

Subject: Approval of a Research Proposal

1. The research proposal titled '**Concurrent use of traditional medicine, prescribed antibiotics and/or antiviral medicines and their effect on antimicrobial resistance and treatment failure in Ilembe district, KwaZulu-Natal**' was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

The proposal is hereby **approved** for research to be undertaken at Stanger Hospital, Untunjambili and Umphumulo Hospitals.

2. You are requested to take note of the following:
 - a. Make the necessary arrangement with the identified facilities before commencing with your research project.
 - b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.
3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

Dr E Lutge

Chairperson, Health Research Committee

Date: 17/01/18

Fighting Disease, Fighting Poverty, Giving Hope

APPENDIX III: Support letter from Stanger Hospital



health

Department:
Health
PROVINCE OF KWAZULU-NATAL

NAME OF INSTITUTION/DISTRICT/COMPONENT
Postal Address: Private Bag x10609, Stanger 4450

Tel: 0324376015 Fax. 0867567812
Email: gustavo.lopez@kznhealth.gov.za
www.kznhealth.gov.za

OFFICE OF THE SENIOR MANAGER: MEDICAL SERVICES

Enquiries: Dr. G. Lopez
EXT: 6015
DATE: 19/10/2017

Mr. Mukanda Gedeon Kadima

RE: PERMISSION TO CONDUCT RESEARCH AT STANGER HOSPITAL.

Dear Mr.

I have pleasure in informing you that permission has been granted to you by Stanger Hospital to conduct research on: "Concurrent use of traditional medicine and prescribed antibacterial and/or antiviral medicines and their effect on antimicrobial resistance and treatment failure."

Please note the following:

1. Please ensure that you adhere to all policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Please ensure this office is informed before you commence your research.
4. Stanger Hospital will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to Stanger Hospital.

Thanking you;


Senior Manager, Medical Services
Stanger Hospital

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

APPENDIX IV: Support letter from Umphumulo Hospital



Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
MANAGEMENT

UMPHUMULO HOSPITAL
R74 Greytown Road
Private Bag X9219
MAPHUMULO, 4470
Tel: 032 481 4198 Fax: 032 481 4166 Email: nomzamo.gumedede@kznhealth.gov.za
www.kznhealth.gov.za

04/01/2018

TO: GEDEON KADIMA
UNIVERSITY OF KWAZULU NATAL

FROM: DR N N GUMEDE
CEO UMPHUMULO HOSPITAL

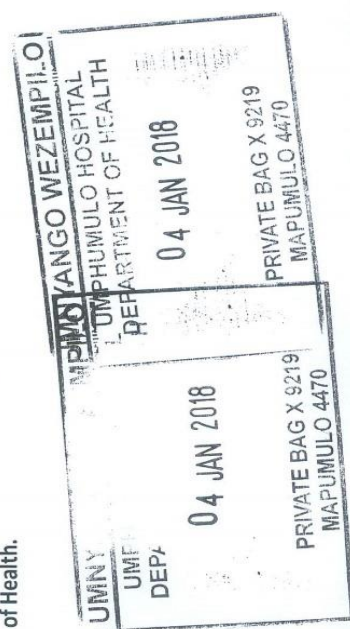
RE: PERMISSION TO CONDUCT RESEARCH STUDY

Good morning

Following your request to conduct a study in our facility, kindly note that permission is hereby granted to perform this study in the institution. Kindly notify us timeously when you will be coming for the research. Kindly adhere to all the principles and ethics of conducting research as set out by the University of Kwazulu Natal and the Kwazulu Natal Department of Health.

Always happy to be of assistance

Regards
Dr N N GUMEDE
CEO



APPENDIX V: Permission letter to the healthcare facility

To the Senior Manager

Institution

Location

Dear Sir/Madam,

RE: Application for support to conduct a study in your Facility

I am a master's student in the Discipline of Pharmaceutical Sciences at the University of KwaZulu-Natal. I would like to request your permission and support in order to successfully conduct my study under your responsibility. The title of the study is: *"Concurrent use of traditional medicine and prescribed antibacterial and/or antiviral medicines and their effect on antimicrobial resistance and treatment failure in Ilembe district, South Africa."*

I would like to conduct a survey among healthcare workers and patients at your health facility. For this, I require your assistance and permission in order to enter the premises of the health facility under your facility and management.

This study is entirely reviewed and approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal before the starting of the research project. This research study is registered with the postgraduate office of School of Health Sciences at the University of KwaZulu-Natal, Westville Campus. For further information and clarity, you may contact the postgraduate office at the School of Health Sciences: Ms. Phindile Nene (Telephone: 031 260 82 80) as well as my Supervisor, Dr. Manimbulu Nlooto (Telephone: 031 260 70 30 or Email: Nlooto@ukzn.ac.za) in the Discipline of Pharmaceutical Sciences.

Yours Faithfully,

Mr. Mukanda Gedeon Kadima (Student number: 217032995)

APPENDIX VI: BHP's Questionnaire

SECTION A																
District			Code of Clinical type(R/U)					Code of informant								
Sex		Age		Marital status				Race								
M	F	Years		Married		Unmarried		Widowed		Bantu		White		Asiatic		Coloured
Language spoken								Religion								
Zulu		Xhosa		English		Afrikaans		Other		Christian		Muslim		Hinduism		Other
Occupation				Educational level												
Employed		Unemployed		Illiterate		Primary Sc.		Secondary Sc.			University Gr.					
Name of interviewer:								Start and end time								

SECTION B	
Questions	Answers
Have you ever treated infectious diseases in the past 3 months?	
Which kind of infectious diseases have you ever treated in the past 3 months?	
Which prescribed medicines (antimicrobial) did you use to treat the above infectious diseases?	
Through which route did you administered it to them?	
Are your patients satisfied with the treatment received for the above infectious diseases?	
What do you think about the treatment administered to patients?	
Have you ever treated other patients referred to you by THPs?	
Are you aware of patients using both THPs and BHPs for the above diseases?	a. Yes..... No..... b. If yes please list

SECTION C	
What is the effect experienced by patients for combining both TM and prescribed medicines?	
Have you ever registered some case of drug-drug interactions(TM and prescribed medicines)?	a. Yes..... No..... b. If the answer is yes, please list
If yes, which medicines(TM and prescribed medicines) were involved? Please list	
Which kind of interaction?	a. The desired effects was reduced b. The effects was increased c. There was adverse effects (unnecessary pain, allergic reaction, fever, rashes d. Others,(specify).....
What do you think about drug-drug interactions for those patients using concurrently TM and prescribed antimicrobial medicines?	
Can I talk to the concerned patients using both TM and prescribed antimicrobial medicines?	
Alternatively, can I check their files?	
Are these patients still in your care?	

APPENDIX VII: Questionnaire on out patients seen by both THPs and BHPs

SECTION A																
District			Code of Clinical type(R/U)					Code of informant								
Sex		Age		Marital status				Race								
M	F	Years		Married		Unmarried		Widowed		Bantu		White		Astatic		Coloured
Language spoken								Religion								
Zulu		Xhosa		English		Afrikaans		Other		Christian		Muslim		Hinduism		Other
Occupation				Educational level												
Employed		Unemployed		Illiterate		Primary Sc.		Secondary Sc.		University Gr.						
Name of interviewer:								Start and end time								

SECTION B		
Questions	Answers	Observation
Which kind of infectious diseases have you had in the past 3 months?		
Which prescribed medicines (antimicrobial) did you use to treat the above infectious diseases?		
Where do you get them?	a. BHP b. THP(African traditional healer) c. Community pharmacy d. Health shop e. Others, please specify	
How do you administer them and for how long?		
Are you currently taking any antiviral or antibacterial medicine? If yes, please list		
Are you satisfied with the treatment received for the above infectious diseases?		
What do you think about the treatment administered to you?		
Have you ever used traditional medicine in the past 3 months? If yes, please list		
Have you ever used both TM and any antiviral or antibiotic medicines at the same time? If yes, please list them(TM and prescribed medicines used concurrently)		
What do you think of combining various medicines to treat the same infectious diseases?		
What do you think about the use of TM to treat your infectious diseases?		
Did the THP do some practices upon you? /can you explain?		

SECTION C		
Questions	Answers	Observation
What is the effect experienced by you for combining both TM and prescribed medicines?		
Have you ever registered some case of drug-drug interactions(TM and prescribed medicines)?	a. Yes..... No..... b. If the answer is yes, please list	
If yes, which medicines(TM and prescribed medicines) were involved? Please list,		
Which kind of interaction?	a. The desired effects was reduced b. The effects was increased c. There was adverse effects (unnecessary pain, allergic reaction, fever, rashes d. Others, (specify).....	

APPENDIX VIII: THP's Questionnaire

SECTION A											
<u>District</u>			<u>Address</u>						<u>Code of informant</u>		
<u>Sex</u>		<u>Age</u>		<u>Marital status</u>				<u>Race</u>			
<u>M</u>	<u>F</u>	<u>Years</u>		<u>Married</u>	<u>Unmarried</u>	<u>Widowed</u>	<u>Bantu</u>	<u>White</u>	<u>Asiatic</u>	<u>Coloured</u>	
<u>Language spoken</u>						<u>Religion</u>					
<u>Zulu</u>	<u>Xhosa</u>	<u>English</u>	<u>Afrikaans</u>	<u>Other</u>	<u>Christian</u>	<u>Muslim</u>	<u>Hinduism</u>	<u>Other</u>			
<u>Occupation</u>				<u>Educational level</u>							
<u>Employed</u>	<u>Unemployed</u>	<u>Illiterate</u>	<u>Primary Sc.</u>	<u>Secondary Sc.</u>	<u>University Gr.</u>						
<u>Name of interviewer:</u>							<u>Start and end time</u>				

SECTION B		
Questions	Answers	Observations
Which type of illness are you treating?		
How do you decide that it is about viral or bacterial infection (diagnosis)?		
What types of medicinal plants are using to treat them?		
Can you enumerate them?		
What basic ideas (philosophy) are you using before to decide on the treatment pattern?		
SECTION C		
Do your patients combining sometime TM and prescribed medicines?		
Are you also sometime mixing different herbs for your patient if he has different problems?		
Do you already register some case of adverse effect after mixing that? (if yes, enumerate them)		
What is your thought or your opinion about interaction of medicine?		
According to you, what can occur if the patient takes at the same time TM and conventional medicine?		
Do your patient(s) satisfied to your healing?		
Can I talk to your patient(s)?		

APPENDIX IX: Questionnaire of Patients seen by THPs

SECTION A											
<u>District</u>			<u>Address</u>					<u>Code of informant</u>			
<u>Sex</u>		<u>Age</u>		<u>Marital status</u>				<u>Race</u>			
<u>M</u>	<u>F</u>	<u>Years</u>	<u>Married</u>	<u>Unmarried</u>	<u>Widowed</u>	<u>Bantu</u>	<u>White</u>	<u>Asiatic</u>	<u>Coloured</u>		
<u>Language spoken</u>						<u>Religion</u>					
<u>Zulu</u>	<u>Xhosa</u>	<u>English</u>	<u>Afrikaans</u>	<u>Other</u>	<u>Christian</u>	<u>Muslim</u>	<u>Hinduism</u>	<u>Other</u>			
<u>Occupation</u>				<u>Educational level</u>							
<u>Employed</u>	<u>Unemployed</u>	<u>Illiterate</u>	<u>Primary Sc.</u>	<u>Secondary Sc.</u>	<u>University Gr.</u>						
<u>Name of interviewer:</u>						<u>Start and end time</u>					

SECTION B		
<u>Questions</u>	<u>Answers</u>	<u>Observations</u>
What problem (illness) do you have?		
Why did you choose TM to heal you?		
Did you use traditional medicine previously?		
Which type of TM, your THP has used to heal you?		
Did he use some prayer, things, songs, spiritual rituals in addition?		
How do you felt after treatment (the issue)?		
Does it bring to you some adverse effect?		
(If Yes) can you enumerate them?		
In case of different problem, does the ATH mix also different herb to treat you?		
(If Yes) which kind of plant and for which problems?		
Do you use to consult also <u>biomedically trained healthcare professionals</u> for the same problem?		
(if Yes) Does he give you prescribed medicines?		
If yes, can you enumerate them?		
SECTION C		
Did you combine at the same time TM from THP and prescribed medicines from biomedically trained healthcare practitioners?		
(if Yes) How is the result, or does it helped you?		
Does it bring to you some adverse effect?		
(If Yes) enumerate them?		
What is your thought about interaction in using at the same time TM and Conventional medicine?		
Can I talk to your biomedically trained healthcare		

APPENDIX X: Medical chart review form

SECTION A												
District			Code of Clinical type(R/U)						Code of informant			
Sex		Age		Marital status				Race				
M	F	Years		Married	Unmarried	Widowed	Bantu	White	Asiatic	Coloured		
Language spoken							Religion					
Zulu	Xhosa	English	Afrikaans	Other	Christian	Muslim	Hinduism	Other				
Occupation				Educational level								
Employed	Unemployed	Illiterate	Primary Sc.	Secondary Sc.	University Gr.							
Name of interviewer:							Start and end time					



Infectious disease			
Use of prescribed antimicrobials	Yes.....	No.....	If yes, list of medicines used
Use of Traditional medicines	Yes.....	No.....	If yes, list of TM
Combining both TM and prescribed antimicrobials	Yes.....	No.....	
Interactions found			
Adverse effects found			
Outcome of treatment	Satisfied.....	Unsatisfied.....	Other

APPENDIX XI: Information Sheet

Information Sheet

Date:

Greeting:

My name is MUKANDA GEDEON KADIMA from the University of KwaZulu Natal, School of health Sciences, Discipline of Pharmaceutical Sciences/ Contacts: gedeonkadima@gmail.com(081 096 61 06), nlooto@ukzn.ac.za (076 091 1427)

You are being invited to consider participating in a study that involves research on the concurrent use of traditional medicine and prescribed antibiotic and/or antiviral medicines and their effect on antimicrobial resistance and treatment failure. The aim and purpose of this research is to determine whether any antimicrobial resistance and or treatment failure occurs among patients attending out-patient departments in selected healthcare facilities and who use concurrently traditional medicine, antibiotics and antiviral medicines in ILembe district, KwaZulu- Natal.

The study is expected to enrol approximately 818 participants in total composed by 50 traditional healer practitioners, 384 Patients (seen by traditional health practitioners) and 384 biomedically trained healthcare professionals in different facilities in KwaZulu Natal. It will involve the following procedures; A research-administered face-to-face interviews will be carried out in phase 1 of this study while phase 2 will consist of a medical chart review as data collection technique method. Data will be collected four days a week during the data collection period. The duration of your participation if you choose to enrol and remain in the study is expected to be (an hour). The study is funded by the School of Health Sciences/CHS scholarship.

The study may involve a minimum risk and/or discomforts. In the case of discomfort, the PI or the researcher will refer participants with discomfort to seek a proper care with an authorized clinician. This study will not provide direct benefits to participants but a feedback to community members can be given on the management of infectious diseases. Findings of the research will be written in a final thesis and peer-reviewed publications related to our specific objectives. Anonymity will be maintained and participants will be guaranteed confidentiality. No name, no ID of participants will be disclosed to third party or displayed on questionnaires and data collection forms.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number _____).

In the event of any problems or concerns/questions you may contact the researcher at (Tel.081 096 61 06) or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

APPENDIX XII: Consent form to participate into the study

Consent to participate into the study

CONSENT (Edit as required)

I have been informed about the study entitled the concurrent use of traditional medicine, prescribed antibacterial and/or antiviral medicines and their effect on the antimicrobial resistance and treatment failure.by (provide name of researcher/fieldworker).....

I understand the purpose and procedures of the study (add these again if appropriate).

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

I have been informed about any available compensation or medical treatment if injury occurs to me as a result of study-related procedures.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at (provide details).

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001

Durban

4000|

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

APPENDIX XIII: Ethics Certificate



**Zertifikat
Certificat**

**Certificado
Certificate**

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants



Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Mukanda Gedeon Kadima

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

mars 7, 2017
CID : Ub2KV1fFK

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator



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European and Developing Countries Clinical Trials Partnership (EDCTP) (www.edctp.org) - Swiss National Science Foundation (www.snf.ch) - Canadian Institutes of Health Research (<http://www.cihr-irsc.gc.ca/e/2891.html>) - Swiss Academy of Medical Science (SAMS/ASSM/SAMW) (www.samw.ch) - Commission for Research Partnerships with Developing Countries (www.kfpe.ch)

[REV : 20170310]



ecohealth international

Presentation title: Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review.

Candidate/Student: Mukanda Gedeon Kadima

Supervisor: Dr. Manimbulu Nlooto

ABSTRACT

Background

Antimicrobial resistance (AMR) is a major origin or cause of treatment failure and is largely responsible for the declining in eradication rates of infectious diseases worldwide. AMR in South Africa is driven by many factors such as the careless use of prescribed antimicrobial medicines and the use of traditional medicine, with the result that there is always the danger of misadministration, interaction and toxicity. This study aimed at determining whether any antimicrobial resistance and/or treatment failure occurred among patients attending out-patient departments in selected healthcare facilities and who use concurrently traditional medicine with antibiotics and/or antiviral medicines in Ilembe district, KwaZulu- Natal.

Methods

This study was a cross –sectional descriptive study using medical chart review among patients attending outpatient department in two public healthcare facilities between February and March 2018. Antimicrobials prescribed alone or in association with other medicines and concurrent use of traditional medicine were assessed and reported using descriptive statistics. Where applicable, associations were carried out; a p value <0.05 was estimated as statistically significant.

Results

400 outpatients' medical records were documented from two different municipalities, many participants had viral infections (194/400, 48.50%). Overall, 12% of participants (48/400) had documented negative clinical outcomes with adverse effects (30/48) and interactions (18/48). A few participants (15/400, 3.75%) had used traditional medicine in conjunction with prescribed medicines. Among those who used both traditional medicine and prescribed medicines, the majority (80%, 12/15) had documented adverse effects due to the concurrent use of traditional medicine and prescribed medicines. After adjustment, documented adverse effects and interactions were significantly more likely due to the use of traditional medicine (AOR = 0.01, 95% CI = 0.001-0.05) and (AOR = 0.21, 95% CI = 0.37-1.23) respectively.

Conclusion

Traditional medicine was sparingly used in conjunction with prescribed antimicrobials for viral and bacterial/fungal infectious diseases. However, adverse effects and interactions such as herbal intoxication, persistent rashes and treatment failure were documented in few medical chart records among outpatients attending the two selected healthcare facilities. Further studies are needed to investigate the effects of concurrent use of traditional medicine from perspectives of traditional healers and biomedically.

APPENDIX XV: Program of oral presentation, International Conference on Promoting ecohealth Research in Africa: *Towards the establishment of an African Chapter of ecohealth international*

**“International Conference on Promoting ecohealth Research in Africa:
Towards the establishment of an African Chapter of ecohealth
international” Programme
13 and 14 November 2018**

Plenary - Day 1

TIME	Activity	Presenter	Chair
08:00-10:00	Registration	Secretariat	
10:00-10:30	Welcome Tea	All	Professor Moses Chimbari
10:30-11:00	Welcome, introduction of VIP and opening Address	Professor Busi Ncama	
11:00-11:30	Role of Ecohealth in Current Global Health and Environmental Challenges	Dr Jonathan Sleeman	
11:30-11:50	Principles and general methodology of ecohealth	Professor Moses Chimbari	
11:50-12:45	Lunch		
DAY 1 BREAKAWAY SESSIONS			
SESSION 1: MAIN HALL (THEME 1: ECOHEALTH AND EXPLOITATION OF NATURAL RESOURCES (MINING, AGRICULTURE AND TOURISM))			
13:00-13:20	Contribution of forest ecosystem services towards food security and nutrition	Cliff Dlamini	Dr Cliff Dlamini
13:20-13:35	Village chicken eggs used for sustainability to overcome food insecurity	Thando Tenza	
13:35-13:50	A protocol for community-based forest enterprises: The case of non-timber forest products (NTFPs)	Leyla Nkosi	
13:50-14:05	Occurrence of trypanosome infections in cattle in relation to season, livestock movement and management practices of Maasai pastoralists in Northern Tanzania	Esther G. Kimaro	
14:05-14:20	Life history traits of <i>Bulinus globosus</i> , post resuscitation from aestivation	Chester Kalinda	
14:20-14:35	Influence of distance to water source on productivity of Nguni weaners and does	Cresswell Mseleku	

14:35-14:50	Exploration of nutrient dense traditional dishes as a possible intervention for child malnutrition	Maria Nnyepi	
14:50-15:05	Increasing the resilience to water-related risks in the UK fresh fruit and vegetable system	Mlungisi Shabalala	
15:05-15:10	Effects of decentralised wastewater treatment effluent on taro and banana, soil and the environment	William Musazura	
15:10-15:25	Quorum sensing inhibitory potential of biologically-active compounds from <i>Bulbine natalensis</i> (Baker)	Olusola Bodede	
15:25-15:40	Is plastics contamination a concern in Durban harbour?	Refilwe Mofokeng	
15:40-15:55	Sanitation Safety Plans for the use of human excreta fertilizers in crop production	Sharon Migeri	
15:55-16:10	Evaluating the use of recovered nutrients from a ultrafiltration membrane toilet effluent for crop production in urban agriculture	Sisekelo Sihlongonyane	
Poster Presentation			
16:10-16:15	Can crocodile meal used for poverty alleviation?	Rendani Luthada-Raswiswi	
SESSION 2: BREAKAWAY ROOM (ECOHEALTH AND LOCAL KNOWLEDGE SYSTEMS-AN AFRICAN PERSPECTIVE)			
13:00-13:20	Ecohealth” approach in the control and prevention of Neglected Zoonotic Diseases-An African perspective	Samson Mukaratirwa	Dr Elizabeth Ojewole
13:20-13:35	The cost implications of the National Health Insurance and traditional healing and medicine in South Africa	Naseema Vawda	
13:35-13:50	Prevalence and risk factors of schistosomiasis and soil-transmitted helminthiasis among preschool children aged (1-5 years) in rural KwaZulu-Natal	Hlengiwe Sacolo	
13:50-14:05	Ethno-botanical study on the indigenous knowledge on malaria in the Gwanda district, Zimbabwe	Margaret Macherera	
14:05-14:20	Evaluation of concomitant use of prescribed antiviral, antibacterial and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review	Mukanda Gedeon	

14:20-14:35	Village chicken eggs used for sustainability to overcome food insecurity	Thando Tenza	
14:35-14:50	Exploitation of indigenous knowledge in controlling gastrointestinal nematodes in chickens	Nkanyiso Majola	
14:50-15:05	Achieving EcoHealth principles through community engagement	Rosemary Musesengwa	
15:05-15:20	Community engagement campaign toward a pilot small-scale mosquito sterile insect technique (SIT) release programme in Jozini KwaZulu-Natal, South Africa	Thabo Mashatola	
15:20-15:35	Knowledge and documentation of patient health information amongst traditional health practitioners in urban and peri-urban in Durban, KwaZulu-Natal province, South Africa	Tracy Zhandire	
15:35-15:50	Up-regulation of hippocampal synaptophysin expression, GFAP cell count and mGluR3 immunoreactivity in a pilocarpine rat model of epilepsy	Oluwole Alese	
15:50-16:05	Molecular identification of hookworm isolates from stray dogs, humans and selected wildlife from KwaZulu-Natal and Mpumalanga provinces of South Africa.	Philile Ncamphalala	
Poster Presentations			
16:20-16:25	Of women, goats, chickens and blankets: gender intersectionality insights from the Botswana Ecohealth Project	Barbara Ntombi Ngwenya	
16:25-16:30	Combination anthelmintic therapy: an adaptation from nature	Fomum Sylvester	
16:30-17:00	Afternoon tea		
17:00-18:30	FORMATION AND LAUNCH OF THE AFRICAN CHAPTER	Professor Chimbari and Dr Sleeman	Professor Samson Mukaratirwa
18:30-Late	DINNER		

APPENDIX XVI: Acceptance letter for attending the 1st Joint International Conference on the potential Ethnopharmacology and traditional medicine. Dakar, Senegal, 30 November – 02 December, 2018

**1ST JOINT INTERNATIONAL CONFERENCE ON POTENTIAL OF
ETHNOPHARMACOLOGY AND TRADITIONAL MEDICINE
(JIC-PEPTM)**



1st Joint International Conference
Potential of Ethnopharmacology and Traditional Medicine



1^{ère} Conférence Internationale Conjointe
Potentiel de l'Éthnopharmacologie et de Médecine Traditionnelle

<http://JIC-PEPTM2018.org/>
30 November – 02 December, 2018
VENUE: Dakar, Senegal
Conference Theme

***"Natural Products-based Drug Discovery and Development: Basic research
and Clinical Applications of Recent Research findings for Sustainable
Development"***

07 November 2018

Abstract Acceptance letter

To: Mr Mukanda Gedeon Kadima
Discipline of Pharmaceutical Sciences
Westville Campus, University of KwaZulu –Natal
Durban 4000, South Africa

Greetings!!

The Organizing Committee of the 1st Joint International Conference on the ***"Potential of Ethno pharmacology and Traditional Medicine"*** (1st JIC-PEPTM 2018) invite you to attend this event which will be held in Dakar (Senegal), during 30 November – 02 December 2018.

We are glad to inform you that after peer review by our scientific committee, your abstract titled: **" Evaluation of concomitant use of prescribed antiviral, antibacterial**

and/or antifungal medicines with traditional medicine in Ilembe district, South Africa: A medical chart review” has been accepted for **oral presentation**.

This event is a **three-day international conference** which will feature plenary/parallel sessions, oral/poster presentations and workshops on selected topics by leaders in the field from academia and industry.

As an author of the accepted abstract, you are advised to register, make payment (*Choose the right option available on the conference website*), attend and present your work at one of the conference sessions (tracks) which will be communicated to you.

We hope that through this conference, stronger ties between the scientists and industries from the different regions of the world can be fostered.

For more details please visit: <http://JIC-PEPTM2018.org/>

On behalf of the Conference Scientific Committee, we look forward to seeing you in Dakar at the conference (UCAD)

With Thanks,



Prof Kensese S. Mossanda
Conference Chairman

Email: Kensese.Mossanda@gmail.com

Mobile : [+1-905-616-4021](tel:+1-905-616-4021) (using also WhatsApp)