

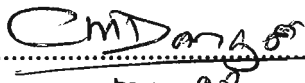
**AN INVESTIGATION OF THE ANTIDIABETIC HERBAL
REMEDIES USED BY TRADITIONAL HEALERS IN
NORTHERN KWAZULU-NATAL AND THEIR EFFECT
ON BLOOD GLUCOSE LEVELS**

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A dissertation submitted to the Faculty of Pharmacy in fulfilment of the requirements
for the doctorate degree - PhD-Pharm, University of Durban-Westville.

1998

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I, Thembelihle Thandekile Ziqubu-Page, hereby declare that this dissertation is based on original work (except where acknowledgements indicate otherwise) and that neither the whole work nor part of it has been or is being submitted elsewhere for another degree.

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To Ayanda and Anele,

my constant sources of inspiration

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ABSTRACT

This research study undertook to investigate and evaluate for efficacy and safety, the herbal remedies used for treating Diabetes mellitus in northern KwaZulu-Natal. In addition, it sought to gain knowledge and better understanding of traditional healing systems and the medicinal use of the natural flora. During the process of assimilating the desired information, the epidemiological and socio-economic factors which determine the form of medicine chosen by rural people in the region, were quantified.

Both aspects of explanatory studies i.e. experimental and observational were used. Firstly, to evaluate the safety of the two herbal remedies, laboratory animals were given an oral dose of the herbal medicine and observed for a period of 14 days. Efficacy was assessed by treating Streptozotocin-induced diabetic rats with the herbal remedies and comparing their effect on blood glucose with that of a conventional sulphonylurea. The second part of the study was observational and it involved monitoring human subjects (patients) for twelve months, who were already taking the herbal preparations (n=56) and comparing their prognoses with that of a group taking conventional medicine (n=97). A third group using both types of medicine (n=42) was included as control measure for a possible confounding factor.

Main outcome measures: Both subjective and objective measures of the perceived health of the diabetic patients were measured, as well as the determinants of using traditional medicine versus conventional medicine.

The battery of toxicity tests which utilises behavioural and functional observations of the laboratory animals, yielded no signs of toxicity or abnormal behaviour. The histopathological examination results of the sample organs from the treated rats also revealed no signs of abnormality that could be attributed to the herbal remedies tested. There was no sex variation recorded in the response. The first HP tested (HP-1) demonstrated minimal hypoglycaemic effect whereas HP-2 significantly lowered the blood glucose of the streptozotocin-induced diabetic rats by an average of 59%. This was comparable to the conventional medicine (Glibenclamide) used in the experiment.

After 12 months of follow-up, 93 % of traditional medicine users (n=56) were convinced that their blood sugar was controlled because of the traditional remedy they were using. The proportion of diabetic cases who used conventional medicine were no better off than those who used traditional medicine or vice versa. Health status and the financial situation (income) of the respondents greatly influenced their choice for diabetic treatment.

The herbal remedies that were investigated were non-toxic and safe for use and internal consumption. One preparation demonstrated a significant hypoglycaemic effect, which was comparable to the conventional allopathic medicine used in treating Diabetes mellitus. This study should serve as a springboard to encourage more pharmacological evaluation of herbal medicines.

GLOSSARY

DEFINITION AND DESCRIPTION OF TERMS

ALLOPATHIC MEDICINE

This refers to medicine practised by western trained practitioners. It is sometimes referred to as modern medicine and it functions within a scientific empirical framework.

ANIMALS

In this study this term refers to Wistar albino rats.

BIOMEDICINE

same as allopathic

CLINIC

A health facility where primary health care needs of the community are rendered. In a rural area, the health team usually consists of nursing sister(s), auxillary staff and an occasional visit by a medical officer.

DECOCTION

The prepared medicinal plant part [leaves, chopped bark or roots etc] is boiled in water for a certain period before use. The supernatant liquid is used for treatment.

HERBAL PREPARATION

This is sometimes referred to as remedy. It is either an infusion, decoction, inhalation, maceration or even poultice, sauna or powder of medicinal plant(s) that purportedly has medicinal or therapeutic value. Various parts of the plant could be used in these preparations depending on the concentration of the active ingredient

HOSPITAL

A health service point where more than primary health care is rendered. This may include secondary level of care and sometimes tertiary. In rural health settings however, the level of care is usually limited to secondary level.

INFUSION

Water is boiled or just heated and poured over the plant(s) [leaves, chopped bark or roots etc] and this is allowed to stand for some time before use.

MEDICAL PRACTITIONERS

Doctors, nurses, paramedics and all providers authorized by law to provide biomedical services to the communities

MODERN (WESTERN) MEDICINE

see allopathic

TRADITIONAL HEALER

There are four different types of healers; the sangoma, a herbalist, a faith healer and traditional birth attendants. In this study the term traditional healer refers to one who uses medicinal plants in treating ailments. He/she is sometimes referred to as traditional practitioner.

TRADITIONAL MEDICINE

These are healing systems practised by indigenous people based on African cosmology and sometimes include supernatural or involve performing certain rituals in addition to ingested medicine. It is founded on personal experience and observations handed down from generation to generation, either verbally or sometimes in writing, and is

used for the diagnosis, prevention or elimination of imbalances in physical, mental or social well-being.

TRADITIONAL PRACTICE (also TRADITIONAL MEDICINE)

This practice involves the use of traditional methods of healing, the medicine, the rituals accompanying the administration of this medicine and the whole approach of treating not only the patient but the including the families and the communities.

TRADITIONAL PRACTITIONER (also see TRADITIONAL HEALER)

He/she provide or use traditional methods in treatment of ailments. Traditional birth attendants, herbalists and diviners fall under this category. There are different classes of practices such as general practitioner and specialists who specialises on certain ailments e.g. Diabetes specialists or STD specialists etc.

CHAPTER 1

1.1. INTRODUCTION AND BACKGROUND

Diabetes mellitus is a metabolic disorder, and a complex chronic disease that has become a leading cause of loss of lower limbs through amputation, renal failure and blindness. The prevalence of Diabetes mellitus has been found to be 8% in South Africa [Levitt et al, 1993 Harris et al, 1987; WHO Expert Comm, 1980] which exceeds the recent rate of 1% recorded in Tanzania (0.8% in rural community before age adjustment) [McLarty et al, 1989; 1990]. In a recent study published by Charlton and co-workers (1997), the prevalence of Diabetes mellitus among the South African Coloured population was found to be 28.7% (95% CI of 21.7-35.7%). This was further classified as 25.7% in men and 30.3% in women. Worldwide, prevalences have been found to be up to 40% [Levitt N et al, 1993; Reubi et al, 1985; Harris et al, 1987; Winegard et al 1990]. In New Zealand, the prevalence was found to be 1.8% with no sex variation observed [Baker et al, 1993]. This means that South Africa has a higher prevalence rate compared to other countries where such studies have been conducted.

Modern medicine does not cure diabetes, but provides symptomatic relief [Goodman & Gilman, 1990; Anokute, 1990; Clarke & Campbell, 1975].

With recent developments in pharmacology and other technologies providing the basis for evaluation and exploitation of natural resources, it is logical

for scientists to continue the search for a cure for diabetes. Many studies, in different parts of the world, have demonstrated the hypoglycaemic effect of certain medicinal plants [Meir & Yaniv, 1985; Leatherdale et al, 1981; Keder et al, 1982; Ibanez-Camacho et al, 1983; Kato & Muira, 1994; Sanchez de Medina et al, 1994; Guntai, 1989; Vad, 1960; Ghannam et al, 1986; Glombitza et al, 1994; Ajabnoor, 1990; Frati-Munari et al, 1988; Ajgaonkar, 1979; Day & Bailey, 1988; Akthar & Alli, 1995; Bailey and Flatt, 1985].

1.2. Indigenous Healing Systems

In the developing countries, the traditional method of health care delivery is mostly based on the use of plant preparations, and this will no doubt continue to predominate as long as most of the population remains rural. It is worth noting that this is not just based on cost benefit analysis, but it is interwoven with the overall beliefs and cultural ways of a rural life [Gumede, 1990; Hedberg and Staugard, 1989; Matte, 1989; Farrand, 1980; Mkhize, 1981; Wessels, 1985; Freeman, 1990; Yangni-Angate, 1991]. The scent, taste, appearance etc, of the plant preparations, and the rituals that often accompany their application, all conform to such life styles and therefore command more trust as effective agents than modern drugs [Abebe, 1990].

Consequently, they are sometimes selected for their religious and symbolic values. They have great importance in an holistic view of healthcare, linking both physical and psychological aspects of health [Akerele, 1987; Aluwihare, 1982; Zeller, 1974; Neki et al, 1985; Young, 1983].

On the other hand, traditional medicine has provided the empirical knowledge and has served as a precursor upon which modern medicine has laid its foundations, since time immemorial [Abebe, 1990; Sussman, 1988; Cunningham, 1988; Pujol, 1990; Yangni-Angate, A; Schlegel, 1986; Bailey, 1989]. The World Health Organization (WHO) recognises herbal medicine and traditional healing as a valuable and readily available resource for primary health care and has endorsed their safe and effective use [WHO Expert Comm, 1980; Bannerman et al, 1983].

1.3 Western Medicine

In this day and era, people all over the world are enjoying precise and state-of-the-art medical techniques such as laser surgeries, organ transplantations and sophisticated microsurgery. The results are generally satisfactory health, well-being and longer life expectancies. In other words, allopathic medicine has undeniably made great strides in terms of development and technology.

However, at the same time, although it has managed to penetrate even the remote

corners of the world, it is not acceptable *in toto* [Hedberg & Staugard, 1989; Zempleni, 1988; Whittaker, 1985; Anyinam, 1987; Ataud, 1985; Farrand 1984; Freeman, 1990]. There are several reasons for this: Firstly, allopathic medicine has brought with it numerous undesirable sequelae such as iatrogenic diseases, allergies and hypersensitivity to certain drugs, and disability due to certain operations [Hedberg and Staugard, 1989; Gbile, 1990; Dauskardt, 1990]. Secondly, the cost of this high technology and advanced health care as a whole has risen so rapidly that few people can afford it [Anyinam, 1987; Farrand, 1980; Mdluli and Msomi, 1989; Gumede, 1990]. Thirdly, highly specialised and technical care is also highly centralised and accessibility is therefore very limited [Farrand, 1980; Anyinam, 1987; Green and Makhubu, 1984; Mkhize, 1981]. People in the rural areas particularly, have very limited access to biomedical institutions and clinics or biomedical practitioners in comparison with those in urban areas. Economic, political and social realities continue to limit the reach of biomedical health systems to all parts of the country. Overwhelming evidence indicates that, for the well being of mankind, allopathic medicine alone cannot cope with the demand for health care for the whole population [Hogle & Prins, 1983; Bannerman et al, 1983; Abdool-Karim et al, 1994; Oyeneeye, 1985]. Despite the endeavours of governments and international organizations to meet the challenge posed by World Health Organization (WHO) in 1978 at Alma Ata with its lofty goal of "Health for all by year 2000", the failure of health services to meet the basic health needs of the third world populations is well known. With

the important discovery of insulin in 1921, there has since been a decline in the use of medicinal plants for the treatment of diabetes, especially in developed countries. Notwithstanding this discovery, there is a growing need for new antidiabetic drugs to serve as an alternative and the medicinal flora is the logical field for such research and exploration.

South Africa's health care system is in a transitional phase at the moment, and obviously the new government will be reviewing and reformulating policies regarding health care delivery. When these policies are considered, it is important that relevant debates and available knowledge on all aspects of health are considered, so that the new health care system may represent the interests of the majority of the people it will serve. It is quite conceivable that in the not too distant future, African Traditional Healing and Biomedicine will not only contribute side by side to improve the health of the South African people, but will also find areas for collaboration with mutual benefit and a resultant improvement of health standards for all [Freeman, 1990; Farrand, 1980; Green and Makhubu, 1984; Oskowitz, 1991; Abebe, 1990; Oyeneye, 1985].

CHAPTER 2

2.1. LITERATURE REVIEW

Simple herbal remedies have been used for illnesses since ancient times.

Theophrastus (circa 370-285BC) a Roman, was the first to systematically compile a document on pharmaceutical botany - *De Historia Plantarum* (History of plants) [Wheelwright, 1974]. In the first century AD, Dioscorides, a Greek physician was the first real medical botanist whose *Materia medica* served as the standard reference on the use of medicinal plants for 1500 years, until the end of the 16th century. The new methods and concepts used by a Swiss-German physician and herbalist, Paracelsus (1439-1541) led to the beginning of chemical research and the development of synthetic products [Dbn. Bot. Gardens,1990; Pujol, 1990]. He abandoned many of Galen's plant prescriptions and started the use of minerals such as zinc and antimony in his remedies [Wheelwright, 1974].

In the industrialised countries, the use of herbal remedies has been largely replaced by synthetic products. However, it is an open secret that even in these affluent societies, there is renewed interest to return to more natural drugs, since these plant products have less or no long lasting side effects [Abebe, 1990; Bannerman et al, 1983; Abdulkadir, 1986; WHO Expert Comm, 1980].

Nevertheless, herbal remedies from plant sources have always been the prime

tools-of-the-trade in the fight against various forms of health problems in the developing nations and yet, they have not been exploited to their full advantage [Cunningham, 1990; Abebe, 1990; Jingfeng, 1987; Freeman, 1991].

Their use has been the source of controversy and scepticism in modern medical practices because of doubts about their efficacy and safety [Pantanowitz, 1991; Xaba-Mokoena, 1991; Richards, 1991; Ojanuga, 1981; Sherwood, 1995; Koff, 1995]. This is because most of the claims have been anecdotal and have not received adequate medical and scientific evaluation. The other reason is that the biomedical sector has only been exposed to the failures of traditional medicine (overdoses, enemas in childhood diarrhoea, etc) whereas the successes are left undocumented [Abdool Karim et al, 1994; Gumede, 1990].

Hogle & Prins (1991) estimated that the African population was 518 000 000 in 1983. There are approximately 1 million Traditional Healers on the continent. This means that the Traditional Healer/population ratio is 1:500 the doctor/population ratio is 1:40 000. In KwaZulu-Natal where this study was conducted, the doctor/population ratio is 1: 17 500 and the traditional healer/population ratio is 1: 600 [Savage, 1985 cited in Cunningham. 1988]. This means that the Traditional Healers are ubiquitous, and therefore readily available

and accessible to the people, to be utilised for health care delivery [Anyinam, 1987].

2.1.1 The quest for new discovery through research

Again, spearheaded by WHO, both developing and developed countries alike, are encouraging and promoting the use of alternative or complementary medicine, be it Chinese Traditional medicine, Unani medicine, Ayurvedic or African Traditional healing. In South Africa, in a similar fashion as in the rest of Africa, Traditional healing, which existed long before biomedicine was introduced, remains a thriving and dynamic cultural feature [Neki et al, 1985; Hutchings et al, 1994; Hedberg and Staugard, 1989; Pujol, 1990; Gumede, 1990]. There is no doubt that African Traditional healers and Traditional medicine will continue to be utilised and this fact cannot be wished away or legislated away. South Africa also has rich flora with many species, some of which contain active principles that are utilised in useful remedies [Cunningham, 1988; 1990; Fourie et al, 1992; Hutchings et al, 1994; Gumede, 1990]. There is a great need to protect our flora whereby overutilisation and exploitation would be avoided and at the same time, optimising the potential benefits that could be derived from it.

There may be modern drugs to cure many diseases, but they are either inaccessible or too expensive for the consumer in the developing world [Gbile, 1990; Abebe, 1990; Hackland, 1987; Maclean, 1982]. Hence the use of plant preparations by approximately 80% of the population [Abdool Karim et al, 1994; Gumede, 1990; Bannerman et al, 1983]. The figures (of this patronage) are comparatively more or less the same for South Africa as for all Sub-Saharan countries. Within the limits of our scientific resources and in view of the pressing health problems, it justly suffices to evaluate some of the widely applied plants to determine their activity and safety in order to render them usable and acceptable in a conventional health care delivery system, particularly at the primary health care level. The Chinese, though not unique in the use of medicinal plants, have shown how to maximise health care coverage by gradually integrating the traditional with modern medicine, and they have discovered over 60 new drugs in the last 37 years from their local medicinal plants [Ho et al, 1983]. In Taiwan alone, there are more than three thousand licenced Doctors of Herbal medicine today [Pujol, 1990], whereby traditional medicine is dispensed alongside allopathic medicine. Studies conducted by Noristan Ethnobotany Research in the late 80's and early 90's suggest that the majority of plants used in traditional medicine in Southern Africa do indeed possess some pharmacological activity. About 31% of the plants tested were found to be highly active therapeutically, 48% moderately active, and 88% were found to be non-toxic [Fourie et al, 1992].

Renewed attention to traditional medicine and natural folk therapies have stimulated a new wave of research interest all over the world. Numerous studies have been documented world wide on the effectiveness of certain medicinal plants in lowering blood glucose levels. South African scientific literature is however lagging far behind in such evaluative studies. A few studies that have been conducted, mostly deal with identification of medicinal and therapeutic value of the plants but lack the comprehensive evaluation of their safety and efficacy. In other countries research on this aspect of traditional remedies has been going on for a long time. Most of these countries have established research centres or departments of Traditional Medicine at universities, Health Ministry departments or as separate institutes. In Tanzania for example, the Department of Traditional Medicine is attached to the Ministry of Health, and they have reported on a number of medicinal plants that have hypoglycaemic effect [Chabra et al, 1984; Hedberg and Staugard, 1983; Abdool Karim et al, 1994; Bannerman et al, 1983; Hogle & Prins, 1991]. In Japan, Hikino and co-workers have isolated and documented several alkaloids from *Japonica* rhizophors that demonstrated hypoglycaemic activity [Hikino et al, 1986]. Similarly, numerous studies have shown the blood glucose lowering effect of *Mormodica* species [Bailey et al, 1986; Day and Bailey, 1988; Leatherdale et al, 1981; Vad, 1960; Meir et al, 1985; Keder et al, 1982]. Some of these studies are done on

experimental diabetic animals, [Ibanez- Camacho et al, 1983; Akthar & Alli, 1995; Guntai et al, 1989; Bailey et al, 1986; Kato & Muira, 1994; Glombitza et al, 1994; Sanchez de Medina et al, 1994; Bone et al, 1985; Ganda et al, 1976; Mordes, 1985], whereas some have been Phase II clinical trials using human as subjects [Mossa, 1985; Ajgaonkar, 1979; Frati-Munari et al, 1988; Ghannam et al, 1986; Haller, 1990; Ajabnoor, 1990]. Ghannam and his co-workers (1986) for instance, reported the hypoglycaemic effect of aloes studied in five patients with non-insulin-dependent diabetes, as well as in alloxan-induced-diabetes Swiss albino mice.

There are a few studies being conducted on in South Africa, at various universities but they are not co-ordinated. Most of them have as their ultimate goal the establishment of: a data base of traditional medicine such as the TRAMED project; a Traditional Medicines' Pharmacopoeia; conservation; or simply concentrate on isolating and identifying the therapeutically active ingredients [Hutchings, 1989; Wainwright, 1977; Savage, 1985; Croom, 1983; Cawe, 1986]. Almost every university now has some form of research relating to traditional medicine in their botany, pharmacology, anthropology, pharmacy, botany or phytochemistry department. Even pharmaceutical companies such as Glaxo are now seeking traditional healers assistance in identifying plants that can be used to manufacture new drugs [Koch, 1995]. There is however a dearth of documented studies that comprehensively evaluate traditional remedies (both

pharmacological and epidemiological) in the treatment of Diabetes mellitus, hence the need and relevance for the present study.

In summary, this thesis argues that traditional medicine has an important role to play in the treatment of diabetes. However, even if the traditional medicine for diabetes may be deemed by some to be merely a 'placebo effect' or 'psychological opium', it remains a fact that more than 80% of the sub-Saharan population patronise it, have faith in it, and may actually derive some benefit from it [Farrand, 1980; Mkhize, 1981; Mankazana, 1994; Simon, 1991]. This should serve as encouragement to the scientists to continue researching all aspects of traditional medicine.

CHAPTER 3

3.1 THE PURPOSE AND AIM OF THE STUDY

In spite of the remarkable advances of allopathic medicine, there is ever increasing evidence that even where biomedical institutions are readily available and accessible, indigenous people continue to utilise the services of African Traditional Healers [Gumede 1990, Maclean, 1982; Wessels, 1985; Mankazana, 1994; Neuman and Lauro, 1982; Simon, 1991; Abdulkadir, 1986]. There are numerous reasons for this and these include “inter alia” a belief that certain diseases can only be cured by biomedical practitioners and vice versa. Chronic diseases such as diabetes, especially, fall under this category. After taking the same medication for extended periods with no “cure”, there is a tendency to look for an alternative.

3.2. Definition and Classification of Diabetes mellitus

Diabetes mellitus is a chronic condition characterised by a lack of insulin secretion and/or increased cellular resistance to insulin resulting in symptomatic glucose intolerance and hyperglycaemia and other metabolic disturbances. The symptoms of Diabetes mellitus include: excessive thirst and hunger, frequent urination, weight loss, blurred vision and recurrent infections; urinary tract and monilial infections. If this hyperglycaemia is not controlled, complications may

set in and these include renal, ocular, cardiovascular or severe neurological complications. Diabetes is classified into three types; Type I which is Insulin-dependent Diabetes mellitus (IDDM), which is sometimes called the juvenile-onset diabetes. This affects approximately 5-10% of the diabetic population and appears, although not always, before the age of 30 years. These patients have no pancreatic reserve of insulin and are solely dependent on exogenous insulin to sustain life. They have a tendency to develop ketoacidosis. The second type is the Non-Insulin dependent Diabetes mellitus (NIDDM) or Type II diabetes. This is characterised by the presence of endogenous insulin, an absence of ketosis and the time of onset which is usually over 30 years; hence the name, adult-onset diabetes. The third category is called the Gestational Diabetes mellitus (GDM) since its symptoms usually appear for the first time during pregnancy. This could be transient, disappearing soon after delivery, or sometimes show signs of permanent disability in the disease state.

The risk factors for NIDDM include: obesity, a family history of diabetes, hypertension, a history of GDM, sex (female being more susceptible), race (Blacks* and Hispanics are more susceptible), degree of urbanisation, upper-segment fat distribution and alcohol abuse [Albertse et al, 1990; Baker et al, 1993; Levitt et al, 1980; Gilman and Gilman, 1990; Nesher et al, 1987; Nutrition SubComm., 1982; Koda-Kimble et al, 1983].

* Blacks in this case in according to the American definition.

3.3. Diagnosis and Treatment of Diabetes mellitus

The diagnosis of diabetes comprise of glucose tests in those patients presenting with symptoms and a standard oral glucose tolerance challenge (OGTT) in individuals that are asymptomatic. Seventy five grams of glucose for an adult and 1.75g/kg for a child is administered orally and the random venous plasma glucose should be less than 9 mmol/l after 2 hours if the patient is normal.

However, if the patient is diabetic this random check of blood glucose should be equal or higher than 11 mmol/l after the same period of administration. The Nutrition sub-Committee of the British Association's Medical Advisory Committee (1982), recommended that those patients that are borderline, sub-clinical and asymptomatic be left untreated because the label "diabetes" has broad social, psychological and economical impacts [Nutr sub-Comm, 1982; WHO Expert Committee, 1980].

The therapeutic goals of treatment, once initiated, are to relieve the immediate symptoms of diabetes (polydypsia, polyuria, weight loss, fatigue and recurrent monilial infections) and control the blood glucose levels as well as to prevent complications and reduce excess mortality. Many studies that have been conducted on the treatment of diabetes suggest that tight control of hyperglycaemic levels (to near normoglycaemia) may help retard the onset of

complications and prevent high morbidity and mortality associated with Diabetes mellitus [Schwartz and Clancy, 1984; Sprafka et al, 1988; Winocour et al, 1990; Melander et al, 1989; Baker et al, 1993; Levitt et al, 1980; Goldstein et al, 1986; Winegard et al, 1990].

There are different modalities of treatment. The first line of treatment is the non-drug modality which involves diet, exercise, reducing and controlling weight and regular monitoring of blood pressure, glucose levels etc. If this then fails to control blood sugar, sulphonylureas have been successfully used for decades in treatment of NIDDM in lowering blood glucose levels by increasing β -cells sensitivity to glucose, to release insulin or exogenous insulin in the case of IDDM. Extra-pancreatic effects such as, improved tissue sensitivity to insulin has been cited as one of the mechanisms of action of some sulphonylureas [Clarke and Campbell, 1975; Asplund et al, 1983; Day & Bailey, 1988; Goodman and Gilman, 1990; Melander et al, 1989]. They however, differ in their pharmacokinetics with different plasma half-lives. Glibenclamide is one of the second generation sulphonylureas and in recent times has become one of the most commonly prescribed drug for NIDDM. It has been suggested that the second generation sulphonylureas may be less susceptible than older agents to displacement by other acidic, highly protein-bound drugs [Melander et al, 1989; Jackson et al, 1981; Balant, 1981]. Sulphonylureas have no beneficial effects on

pancreotomized individuals or Type I diabetics, hence their use is limited to symptomatic NIDDM.

Many studies have demonstrated that the diabetic patient's knowledge and understanding of their disease can have a tremendous positive influence on diabetic control [Skyler, 1978; Bunn, 1981; Balant, 1981; Jackson et al, 1981; Anderson et al, 1990; Melander et al, 1989; Baker et al, 1993]. This encourages the patient to do self-monitoring which is the key to management [Anon, 1991; Skyler, 1982; Nutr SubComm., 1990].

Claims of the effectiveness of herbal remedies are abundant but mostly anecdotal and have not received adequate medical or scientific evaluation [Maurice and Cream, 1989; Maclean & Bannerman, 1982; Ho et al, 1984; Macgregor et al, 1989].

The aim of this study was to determine the safety and effectiveness of some medicinal plant preparations used for the treatment of Diabetes mellitus in the Northern KwaZulu-Natal area as well as explore and seek more understanding of traditional healing systems .

Some specific **research questions** that this project attempted to answer include the following:

- * What are these herbal remedies? From which medicinal plants are the constituent active ingredients derived?

- * Are these herbal remedies efficacious in lowering blood glucose levels?

- * If the herbal remedies are efficacious, what is the duration of their effect or action?

- * How safe are those herbal remedies for human medicinal use?

- * What are the determinants of traditional medicine use?

- * How beneficial is the use of traditional medicine?

To achieve these aims two different studies, a pharmacological and epidemiological approach, were undertaken.

3.4. Objectives

3.4.1 Objectives of the Pharmacological study

- To test the efficacy of these remedies on laboratory rats (laboratory-induced-diabetic rats) using in vitro testing models and comparing the different treatment modalities.
- To test the safety of these remedies by subjecting them to a battery of toxicological tests (acute oral toxicity) using laboratory rats.

3.4.2 Objectives of the Epidemiological study

*. To obtain information and samples of the herbal remedies from the traditional healers as well as the data on established chronic diabetic patients who use them.

This information included the preparation and formulation (parts of the plants used and all other ingredients) and the directions for use by the patient. The diagnosis and treatment of Diabetes mellitus was to be verified by using hospital/clinic records.

*. To identify three groups of diabetic patients (those who use herbal remedies only, those who use herbal remedies concurrently with allopathic medicine and those who use allopathic medicine only) in order to assess the degree of control achieved in the blood glucose levels.

*. To monitor the patients over a period of one year and to compare the prognosis in the three groups.

3.5 FEASIBILITY STUDY

A preliminary investigation was conducted prior to the actual data collection to establish attitudes towards utilisation of indigenous medicinal plants by both the traditional healers and their patients or the community at large.

3.5.1. Objectives:

The main **objectives** of this pilot run were threefold:

1. To determine the feasibility of the project as a whole. African traditional healers are known to be secretive and keep their knowledge to themselves. The consent and willingness of the traditional healers to participate, reveal and to make available their remedies was therefore critical to the study.

2. To test questionnaires on a sample population in order to make the necessary revision and adjustments to the questionnaires for utilisation in the main study prior to actual data collection.

3. To assess and attempt to minimise the extent of logistic problems in tracing patients and traditional healers in a rural setting where communication and contacting people might be difficult. They are often without street addresses, telephone lines and other modern technologies.

3.5.2. Methods:

Five students from University of Durban-Westville (in their second year of study in the Science Faculty) were identified as willing fieldworkers. They were trained by the Principal Investigator in ethnographical interviewing, sensitised to the African traditional customs and briefed on signs, symptoms and treatment of Diabetes mellitus. This training took two weeks and was done prior to the pilot study.

Three meetings were held with the traditional healers; two of which were individual interviews at Hluhluwe and Phongola and the third was a meeting with 11 traditional healers at Hlabisa. Out of the 11 traditional healers present, 5 had and still did treat Diabetes mellitus and were then interviewed individually. Out

of the 7 (five from Hlabisa plus the other two from Hluhluwe and Pongola), two specialised in Diabetes mellitus and the rest were traditional general practitioners, treating a whole variety of diseases or specialising in other areas such as hypertension or kidney diseases etc. A standardised questionnaire was used for these interviews (see Appendix IV) and this was then adjusted and later used for data collection for the main study.

From these interviews, recipes and names of the plants they used in treating diabetes were obtained. All, but one, were willing to give their formulas for preparations or give their already prepared medicines to be used for laboratory tests.

Overall, they all expressed keenness in collaborating in this study, even when it was explained to them that their medicines and their practices would be scrutinised and subjected to scientific evaluation.

3.5.3 Results:

From all 7 traditional healers, a list of the patients treated was obtained. Twenty four of these patients could be traced, their consent sought and they were interviewed at their homes.

Out of the 24, seventeen used the traditional medicine concurrently with allopathic medicine. There were 8 males and 9 females, mostly: unemployed, homemakers or self-employed. Some of these people only kept the allopathic medicine (especially insulin) for emergencies, when the symptoms of hyperglycaemia occurred. They also went to the clinics only to have their blood glucose levels checked. Seven patients believed and strictly controlled their blood glucose levels by taking traditional medicine only. In general, all of them felt that the traditional medicine helped them and that they had better control of the disease due to its use. The reasons they cited for their patronage of traditional healers varied from: difficulties in attending clinics due to distance or lack of transportation; prohibitive costs as some were pensioners or simply unemployed; and waiting periods at the clinics before they are attended.

A third group of patients were interviewed as they came out of the diabetic clinic (Hlabisa hospital). These patients were later used as part of the control group for the study. These patients used allopathic medicine only. The majority of them were sophisticated. Distance or cost was not a problem to them and some had medical aid schemes that absorbed most of their costs.

3.5.4 Limitations of this Study:

Most of the difficulties encountered stemmed from tracing and locating the people; both the traditional healers and their patients. This was rendered more

difficult by the fact that there are no street addresses or phones in the rural area. As a result, a lot of legwork and high transportation costs were incurred. The time spent in locating patients was more than the time spent on interviews. In addition to time delays, financial constraints and inaccessible roads compounded the difficulties in locating patients. The fact that most of the traditional healers themselves do not keep good records, further complicated the matter.

The other problem related to availability of accommodation for the fieldworkers and future studies could become relatively more expensive if fieldworkers from outside town are brought in to collect data.

CHAPTER 4

THE PHARMACOLOGICAL STUDY OF SELECTED TRADITIONAL MEDICINES

4.1 BACKGROUND AND FORMULATION DESCRIPTIONS

The approval of the Ethics Committee of University of Durban-Westville was obtained prior to the commencement of the project (see Annexure I).

Upon interviewing traditional healers, it was realised that all those who are based in one locality or proximity, basically tend to use similar plants (with minor variations in excipients) in their formulation of antidiabetic remedies.

Consequently, it was considered to study the two most widely used preparations.

The premise was that the two preparations were representative of the antidiabetic preparations used in the northern parts KwaZulu-Natal province.

The herbal preparations (HPs) were used as they were prepared and made available by the traditional practitioners themselves. The HP contained numerous plants and other ingredients. Individual plants were not tested for specific activities since the combination could possibly have different effect/s compared to a formulation with only one plant species in use; such as a

potentiation of effect, detoxification or modification of toxic substances, or even attenuation of therapeutic effect. Hutchings (1991), in her studies discovered that certain species have been used and are still used to counteract the harmful effects of others in herbal preparations made from more than one species.

4.1.1 THE FIRST HERBAL PREPARATION (HP-1)

Description

This aqueous preparation or mixture comprised of a piece of the leaf blade of *Aloe arborescens* (umhlaba/inhlaba or inkalane), a whole plant - from the roots to the flower of *Catharanthus roseus* (isisuhlungu or ikhwinini) and the bulbous root of *Hypoxis oligitricha* (ilabatheka).¹ These morphological parts were harvested and boiled together for about five minutes, cooled and sieved. The “other” ingredients that were added depended on the traditional practitioner. These were either additional medicinal plants or minerals. One traditional healer for example added “blue stone” and another added a sour stone called “alum”. Both these stones served as preservatives for the formulation and made the concoction last for an extended period without promoting instability.

4.1.2. THE SECOND HERBAL PREPARATION (HP-2)

Description:

¹ Botanical taxonomical classification was done concurrently with Hutchings [personal comm] and Pujol, 1990

The second Herbal Preparation (HP-2) comprised mainly of *Momordica carifolia*, or *Momordica foetida*, or *Momordica involucrata*, (intshungu) - all three different species were available in different sub-regions of the study site, *Cannabis sativa* - dagga (insangu) and a *Musa sapientum* thyrses (inhliziyo ka Banana).² These were also boiled together, cooled and sieved before bottling. In this preparation, leaves were the main ingredient from all medicinal plants except for the *Musa sapientum* (banana tree - Family Musaceae) whereby the heart-shaped bud that grows in front of the bunch of fruit, was used. Some traditional healers mixed the dagga with cow's milk. Similar to the first preparation, several "other" undisclosed excipients were added in the formulation.

4.1.3 The Streptozotocin model for Diabetes mellitus:

The streptozotocin-induced diabetic rat represents one of the most useful tools available to researchers in testing the effects of anti-diabetic drugs.

Streptozotocin (STZ) possess at least four major biologic properties; its antibiotic, β -cytotoxic, oncolytic as well as oncogenic effects. Ganda et al (1976) who studied different models of experimentally induced diabetes, found (in their microscopic studies) alterations in the tissues signifying these effects. These alterations included mild beta-cell secretory degranulation, nuclear pyknosis and cytoplasmic clumping. With STZ doses higher than 20mg/kg, progressively severe beta-cell necrosis and degranulation were observed. When a high dose of

² Taxonomical classification and identification by Hutchings [personal communication] and references in Pujol, 1990; Gumede, 1990.

streptozotocin is given, irreversible dysfunction of glucose level normalising and insulin secreting abilities is observed. Low doses of streptozocin however, in addition to the disturbances mentioned above, also disturbs organs other than pancreas [Kawada et al, 1986; Ganda et al, 1976; Jacobs et al; 1989]. The mechanism of its diabetogenic activity has been explained by supposing that DNA methylation is closely related to poly (ADP-ribose) synthetase in pancreatic beta-cells. The result of this activity coupled with the beta-cell secretory degranulation, is that insulin secretion is impaired

Portha & Serradas [1991] described a model of STZ-induced diabetic Wistar rats generated by injection of newborn rats with 100mg/kg STZ. As adults these animals exhibit decreased (about 50%) basal plasma insulin level coupled with a deficient insulin response to glucose both in vivo and in vitro; a frank elevation of basal plasma glucose value and impaired glucose tolerance, raised glycosylated haemoglobins, and a marked reduction of pancreatic insulin stores. A modified version of this model was used in this study; Wistar albino rats were injected with 65mg/kg so that the characteristics of their diabetogenicity resembled that of the diabetic human being. These rats exhibited a failure of insulin release in response to glucose but had a relative preservation of the response to other secretagogues.

4.2. METHODOLOGY

4.2.1 Study Design

An experimental study design was used whereby two groups of rats were assigned different treatments (the herbal preparation and a conventional sulphonylurea) for comparison. The third group was used as a control group by assigning it to a placebo treatment. Glibenclamide was chosen for this experiment since in recent times it has become the most commonly prescribed second generation oral antidiabetic drug [Melander et al, 1989; Balant, 1981].

The exact reason of why glibenclamide has become the most popular oral hyperglycaemic drug is not yet known [Koda-Kimble et al, 1983; Asplund et al, 1983].

4.2.2 Acute Oral Toxicity Test (AOTT)

The Organization for Economic Cooperation and Development (OECD) recommended method for acute oral toxicity testing was used. The WHO guidelines were also taken into account when these clinical trials and toxicity tests were conducted [WHO publication, 1974; Hunter et al, 1979; OECD, 1977].

Acute oral toxicity is the adverse effects occurring within a short time of oral administration of a single dose of a substance or multiple doses given within 24 hours [OECD, 1977]. In the assessment and evaluation of the toxic

characteristics of any substance, determination of acute oral toxicity is one of the first steps and especially in this case, since the substance in question is ingested.

Thirty normal and healthy adult Wistar Albino rats ranging from 175g to 250g were divided into three groups of 10, each group consisting of five female and five male rats. They were acclimatised for three days prior to the experiment, in a controlled environment of 22°C, 30-70% humidity and 12 hours of light and dark cycles respectively. Each group was given a specific (once only) dose of the HP by oral intubation and then observed for any behavioural changes from the norm. Table I lists the number and types of observations that were carried out on the animals (see Appendix I for detailed interpretation).

These observations were carried out, initially before dosing, everyday for three days after dosing and then every second day for 14 days starting at Day 1. A special data collecting form was used (see Annexure II). The first group was given 0.6ml of the HP-1 (the normal dose being 0.4ml calculated from the dose given to human subjects and based on HP-1 mls/body wt). The second group was given 1.2mls and the third group was given 2.0 ml respectively. After the 14th day, the rats were euthanised and autopsied. Specimens were harvested, preserved in 10% formalin, and used for histopathological examination. The

organs harvested for these tests were portions of pancreas, liver, kidney and spleen.

Ideally, a control group receiving placebo instead of an herbal preparation should have been included in the study. However, due to financial constraints, this was not possible. Thus, in this study, the effects of lower dose of HP were compared with the effects of the very high dose of HP.

TABLE 1

**FUNCTIONAL/BEHAVIOURAL OBSERVATIONS CARRIED OUT
ON THE STUDY RATS**

HOME CAGE	HANDLING	OPEN FIELD	REFLEX
Clonic Convulsions Palpebral Closure Tonic Convulsions Vocalization Posture	Lacrimation Palpebral Closure Salivation Vocalization Ease of Removal Ease of Handling Piloerection	Arousal Bizarre Behaviour Clonic Convulsions Gait Score Gait Type Mobility Score Rears Sterotype Tonic Convulsions Vocalization Defecation Urination	Air Righting Reflex Pupil Response Object Approach Response Touch Response Click Response Tail Pinch Response

Rating Scale:

- 1 = No Reaction
- 2 = Slight Reaction
- 3 = Normal Reaction
- 4 = Increased Reaction
- 5 = Bizarre Reaction (Jumps, Bites, Attacks)

or, Y/N where possible
See Appendix I for detailed measures

4.2.3. Diabetic Clinical Trial

A total of 30 rats were used, divided into subgroups of 10 with each subgroup comprising of five females and five male rats. On the eighth day after induction of diabetes, the treatment and experimentation began. The first subgroup (X) was treated with Glibenclamide suspension (3mg/kg body wt - a method used by Sanchez de Medina et al, 1994), the second (Y) with Distilled water - the control group and the third group (Z) treated with HP-1. Food and water were available *ad libitum* during the experiment and the animals were housed in well-ventilated individual cages which were cleaned regularly.

Firstly, the glucose levels were determined and recorded using urine dipsticks and glucometers. The weight of each animal was also recorded. The animals were starved overnight, prior to testing. On the test day, and every second day, the urine glucose and blood glucose levels were recorded before the treatment dose for the day was given. The weights were measured every first day of the week. The data was recorded on a form specially designed for this (see Annexure II). After the tests, the animals were fed (with pellet chow) and given water *ad lib*. To prevent possible injury during administration of the treatment dose; which was done daily for a period of twenty six days (HP, Glibenclamide suspension or distilled water) the treatment dose was mixed with a third of the daily ration of standard food. This was devoured in 15-20 minutes. Once that was ingested, the

rest of the daily ration was given to be taken ad lib. This dosage schedule was similar to that of HP and Glibenclamide. The traditional healers encouraged that their patients take half a cup every morning and if the symptoms of high sugar level were not abating, then an additional evening dose was suggested. Similarly, glibenclamide is prescribed as a daily dose that is increased to two daily or one twice a day if necessary.

In all studies, blood samples were taken by tail spin and their blood glucose level were measured by a glucometer (Glucometer Elite) using one drop of blood. The experiment continued until the 26th day when the animals were euthanized and organs harvested for histopathological tests. Portions of the pancreas were homogenised in a solution of 76% ethanol, 1.5% HCl 12 mmol/litre and 22.5% distilled water for a determination of insulin content. The supernatant liquid obtained from these samples were kept at -20°C and the insulin levels determined by double antibody radioimmuno assay (kit by Amersham UK Ltd & Isolab Inc.) within two months of storing these samples.

A similar procedure to 4.2.1. and 4.2.2. above was applied for the HP-2 with group A given HP-2, group B treated with Glibenclamide suspension and group C used as control and given Distilled water respectively.

4.2.4. Oral Glucose Tolerance Test (OGTT)

At the end of the diabetic clinical experiment and before sacrificing the animals, an oral glucose tolerance test was performed on the animals used at 4.2. above. Five rats from each sub-group, two male and three females, were used for this test. The animals were starved overnight and the test, OGTT, performed in the morning after they had been given their daily dose of the relevant treatment (HP, Glibenclamide or Distilled water respectively). Four hours after the treatment, a bolus of glucose solution (0.8g/kg dissolved in 0.2ml/10g body wt of water - a model described by Glombitza et al (1994) and WHO guidelines, was administered by intragastric tubing . Blood glucose levels were again tested before administration, and at 0.5, 1.0, and 2.0 hrs after administration.

4.2.5. Weight Studies

Weights of each animal in the groups studied i.e. X,Y,Z and A,B,C groups, were recorded once a week i. e. every Monday when the experiments were conducted. This made it possible to have a record of three readings for each animal during the study period.

4.2.6. Statistical Analysis

The technicians performing histopathological testing and biochemical assays (the radioimmunoassays - RIAs), were blinded to the treatment groups of the specimen and the type of treatment administered to the animals. The dose given to each group was also not disclosed to the technicians and neither to the statisticians doing the analysis. The statistical analysis used for comparing the three groups was performed by analysis of variance (ANOVA) the Scheffe' F test for the AOTT data, one-way analysis of variance for the diabetic trial [Gould, 1980; Kleinbaum et al, 1988]. The test statistic (H) was computed by using the following formula:

$$H = \frac{12}{n(n+1)} \sum_{j=1}^k \frac{R_j^2}{n_j} - 3(n+1)$$

k = the number of groups.

n_j = the number of observations in the j^{th} group.

n = the number of observations in all groups combined.

R_j = the sum of the ranks in the j^{th} group.

4.3. RESULTS

4.3.1. ACUTE ORAL TOXICITY TEST RESULTS

4.3.1.1. Herbal Preparation-1

4.3.1.1.1. Mortality:

For the first group (AOTT) different dose levels (2.0ml, 1.2ml and 0.6ml) of the HP-1 (groups X, Y and Z) were tested in that order. These were all above the recommended therapeutic dose which is 0.4ml (calculations based on ml/body wt as given to human subjects by traditional healers). No animals died within 24 hours which is the critical period for this test. experiment. They all lived up to the end of the experiment (14 days) when they were necropsied.

No mortality was observed in all three groups, despite the doses used which were above the normal recommended therapeutic doses and no sex variation was observed in the treated groups.

4.3.1.1.2. Behavioural observations:

There was no significant change in the functional or behavioural observations with the exception of four reflex observations; the click response, the tail pinch response, object approach response and the touch response. Even with these

observational changes, there was minimal change from the first day of observation to the last one, i.e. the eighth observation on the fourteenth day. The recorded variation among the groups (i.e. different dose levels) was minimal. This is depicted in Table IIa and IIb and Figure Ia and Ib overleaf. The Tail Pinch scores for example, were slightly higher than normal in all of the three groups, which could be attributed to the fact that the animals were reacting to the attention given to them. As they got used to this attention, their response decreased to be slightly below normal (see Table IIb and Figure 1b). Similarly with the Click Response scores, a minimal change was recorded.

TABLE IIa

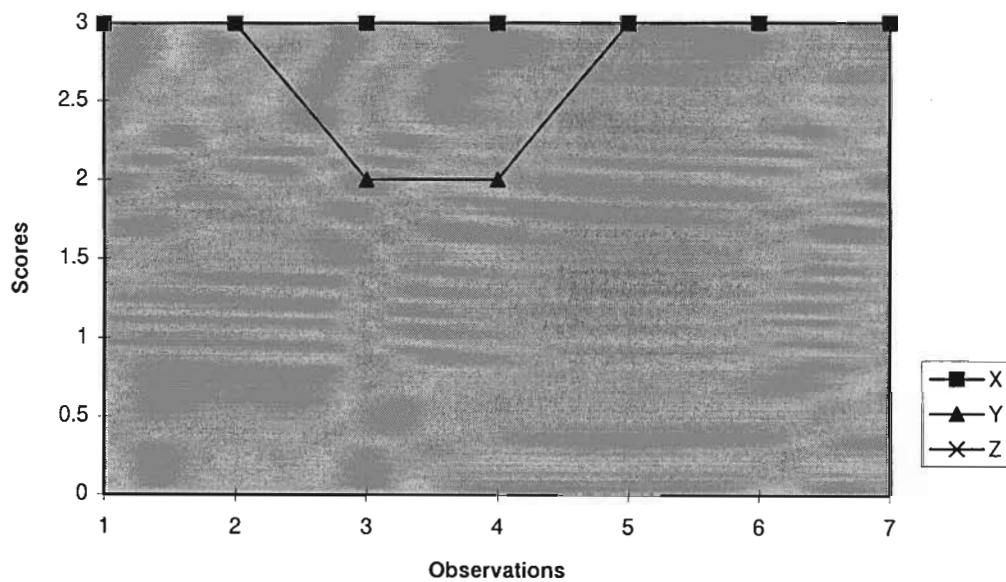
REFLEX OBSERVATION TEST - CLICK RESPONSE MEAN SCORES

Observation Days							
	Day 1	Day 2	Day3	Day 5	Day 7	Day 9	Day 12
Group X	3	3	3	3	3	3	3
Group Y	3	3	2	2	3	3	3
Group Z	3	3	3	3	3	3	3

Key:	1	=	No Reaction
	2	=	Slight Reaction
	3	=	Normal Reaction
	4	=	Increased Reaction
	5	=	Bizarre Reaction (Jumps, Bites, Attacks)

X = 2.0ml dose group
 Y = 1.2ml dose group
 Z = 0.6ml dose group

FIGURE 1 a CLICK RESPONSE SCORE CURVES



Key: 1 = No reaction
2 = Slight reaction
3 = Normal reaction
4 = Increased reaction
5 = Bizarre reaction (Jumps, Bites, Attacks)

See Appendix I for full details on score measurements

X = 2.0ml dose group
Y = 1.2ml dose group
Z = 0.6ml dose group

TABLE IIb

REFLEX OBSERVATION TEST- TAIL PINCHES MEAN SCORES

Observation Days							
	Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 12
GROUP X	4	2	3	3	2	3	3
GROUP Y	3	4	3	3	3	2	3
GROUP Z	3	3	3	3	3	3	3

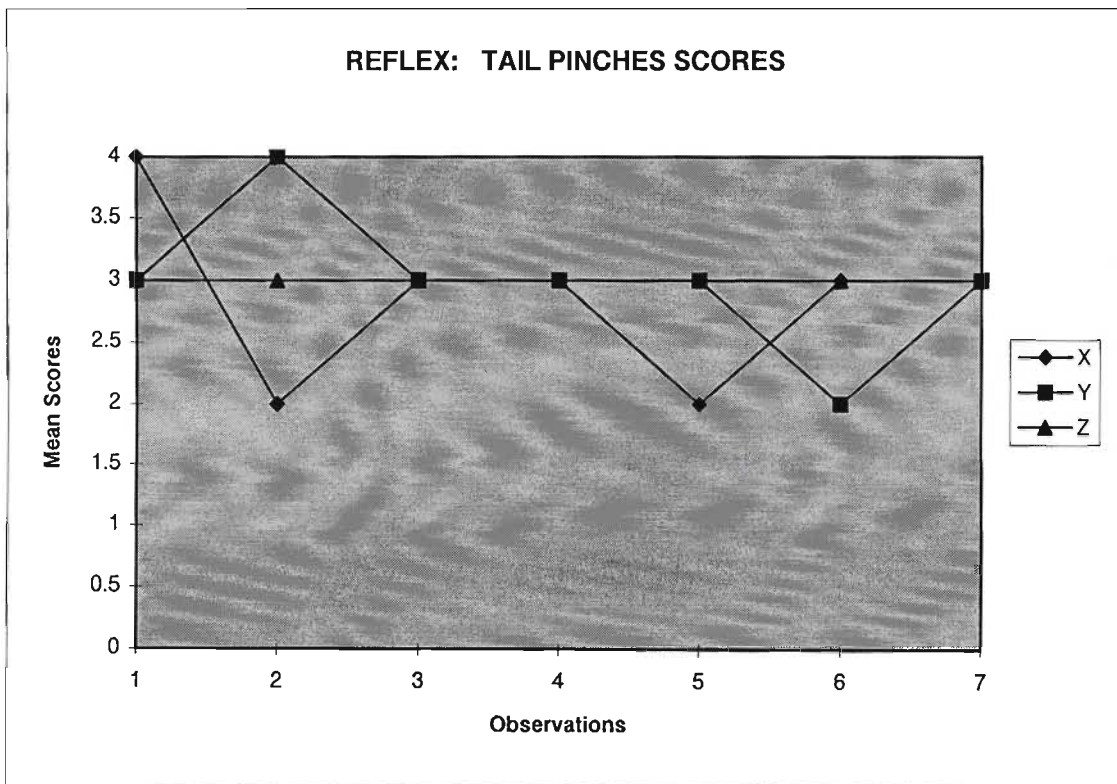
Key:

1	=	No Reaction
2	=	Slight Reaction
3	=	Normal Reaction
4	=	Increased Reaction
5	=	Bizarre Reaction (Jumps, Bites, Attacks)

See Appendix I for full details on score measurements

X = 2.0ml dose group
Y = 1.2ml dose group
Z = 0.6ml dose group

FIGURE 1b



Key:

- 1 = No Reaction**
- 2 = Slight Reaction**
- 3 = Normal Reaction**
- 4 = Increased Reaction**
- 5 = Bizarre Reaction (Jumps, Bites, Attacks)**

X = 2.0ml dose group
Y = 1.2ml dose group
Z = 0.6ml dose group

4.3.1.1.3. Statistical Report

The Click Response is used here as an example. Each of the behavioural observations was assigned a score of 1 through 5. The score of 1 indicated normality and that of 5 indicated total abnormality. In some cases, a score of 1 indicated no reaction with 5 indicating a totally bizarre and unusual reaction (again, the full explanation is in Appendix I). The mean scores obtained in 4.3.1.1.2 above ranged from 2.3 to 3.1. This was the score that was entered in the analysis. A non-significant difference ($p\text{-value} = 0.372$) was observed between groups and within groups ($p\text{-value} = 0.294$) both at the beginning and at the end of the experiment. The following Table IIc illustrates these results.

TABLE IIc. ANOVA RESULTS OF CLICK RESPONSE SCORE (HP-1)

<u>SOURCE</u>	<u>SS*</u>	<u>df</u>	<u>MS**</u>	<u>V.R.***</u>	<u>p-Value</u>
Among groups	1.0014	2	0.5006	5.2529	$0.05 > p > 0.025$
Within groups	1.7143	18	0.0953		
TOTAL	2.7157	20			

*SS = Sum of Squares, **MS=Mean squares, *** V.R. = variance ratio

4.3.1.1.4. Histopathological Results

No abnormal lesions were detected by the histopathologists (see Appendix II for detailed report). The minor morphological changes detected were symptoms of the onset of chronic nephropathy, which is consistent and is a known characteristic of the laboratory animals used. The difference in the doses did not produce any difference in the histopathological examination. The results of acute oral toxicity studies of HP-1 indicate that it is non-toxic to rats.

4.3.1.2. Herbal Preparation-2

Similar to the first groups (X, Y and Z); 0.6, 1.2 and 2.0ml were the doses used in group A, B and C, respectively, in testing acute oral toxicity of HP-2.

4.3.1.2.1 Mortality:

No mortality was recorded within the critical period of the first 24 hours and none of the animals died until they were euthanized after 14 days of observation.

4.3.1.2.2. Behavioural Observations:

Similar to the HP-1 groups, there was minimal change (from normality) from the first observation to the last day, as well as the variation among the three groups (with three different dose levels) was minimal. The Click Response and Tail Pinch response were chosen as an example also in HP-2 to provide consistency in the comparison. Table IIIa and IIIb and Figure 2a and 2b depicts the results of the observations made in the laboratory where a change occurred in the observations.

TABLE IIIa**REFLEX OBSERVATION TEST- CLICK RESPONSE MEAN SCORES**

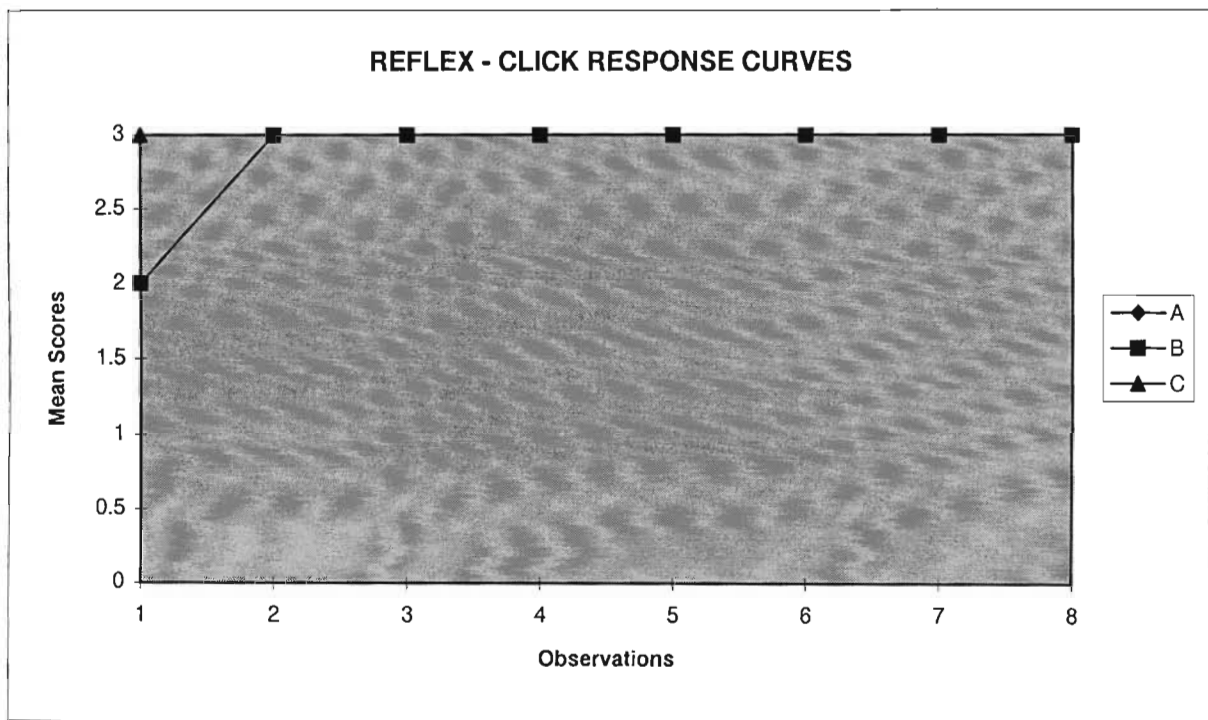
Observation Days								
	Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 12	Day 14
GROUPS A	2	3	3	3	3	3	3	3
GROUPS B	2	3	3	3	3	3	3	3
GROUPS C	3	3	3	3	3	3	3	3

Key:

1	=	No Reaction
2	=	Slight Reaction
3	=	Normal Reaction
4	=	Increased Reaction
5	=	Bizarre Reaction (Jumps, Bites, Attacks)

A= 0.6ml dose group
B= 1.2ml dose group
C= 2.0ml dose group

FIGURE 2a



Key:

- 1 = No Reaction
- 2 = Slight Reaction
- 3 = Normal Reaction
- 4 = Increased Reaction
- 5 = Bizarre Reaction (Jumps, Bites, Attacks)

A = 0.6ml dose group
B = 1.2ml dose group
C = 2.0ml dose group

TABLE IIIb

REFLEX OBSERVATION TEST - TAIL PINCH RESPONSE (MEAN SCORES)

		Observation Days							
		Day 1	Day 2	Day 3	Day 5	Day 7	Day 9	Day 12	Day 14
GROUPS A		3	4	3	3	3	3	3	3
GROUPS B		3	3	3	3	3	4	3	3
GROUPS C		3	3	3	3	3	4	3	3

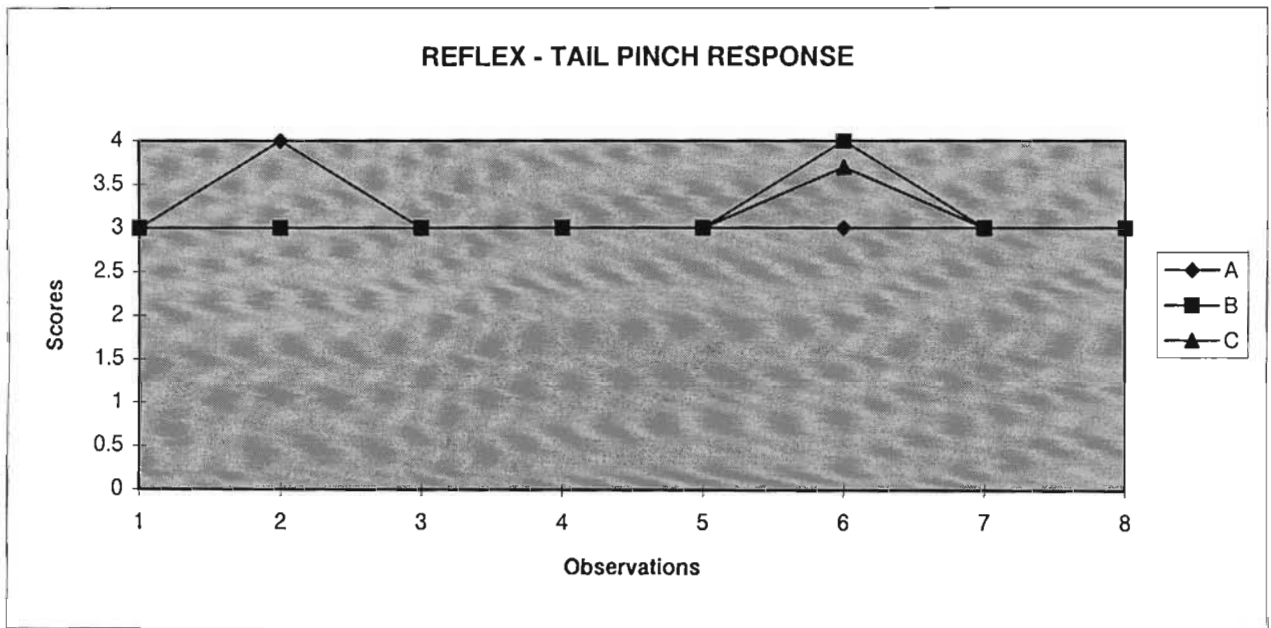
Key:

1	=	No Reaction
2	=	Slight Reaction
3	=	Normal Reaction
4	=	Increased Reaction
5	=	Bizarre Reaction (Jumps, Bites, Attacks)

See Appendix I for details on score measurements

A = 0.6ml dose group
 B = 1.2ml dose group
 C = 2.0ml dose group

FIGURE II b



Key:

- 1 = No Reaction
- 2 = Slight Reaction
- 3 = Normal Reaction
- 4 = Increased Reaction
- 5 = Bizarre Reaction (Jumps, Bites, Attacks)

A = 0.6ml dose group
B = 1.2ml dose group
C = 2.0ml dose group

4.3.1.2.3. Statistical Report

Similar to 4.3.1.1.3. above, each behavioural observation was assigned a score of 1 to 5; with score 1 indicating no reaction and a score of 5 indicating an abnormal bizarre behaviour. The mean scores obtained in this function ranged from 2.2 to 3.0. This is the score that was entered in the analysis. An uncorrected F-test was used. The difference between the groups and between the first and the last observations within groups were statistical insignificant (p-value = 0.71). This is depicted in the next Table IIIc.

TABLE IIIc. ANOVA RESULTS OF THE CLICK RESPONSE SCORES (HP-2)

<i>SOURCE</i>	<i>SS</i>	<i>df</i>	<i>MS</i>	<i>V.R.</i>	<i>p-Value</i>
Among groups	0.0953	2	0.0477	0.5005	0.071
Within groups	1.7142	18	0.0952		
TOTAL	1.8095	20	0.1429		

df = degrees of freedom, SS = sum of squares, MS = mean squares and V.R. = variance ratio.

4.3.1.2.4 Histopathology Results

The microscopic examination performed on the tissues and organ samples submitted from this experiment revealed no abnormal lesions. (see Appendix II)

4.3.2. DIABETIC CLINICAL TRIAL

Diabetes was induced by a single dose, intraperitoneal administration, of 65 mg/kg body weight of Streptozotocin solution to normal healthy Wistar Albino rats. The STZ was dissolved in 10ml of normal saline and adjusted to pH 4 with citric acid buffer of 0.25mol/l.

4.3.2.1. Herbal Preparation -1

The three groups of rats, labelled group X, Y, and Z were given 2ml Glibenclamide suspension, 2ml Distilled water and 2ml HP-1 respectively and monitored for 26 days with blood glucose tests done on alternative days.

On the first test date, five readings of glucose levels were done at intervals of two hours. TABLE IV (overleaf) depicts the average glucose level per group and the trend observed on the first day is illustrated in Figure 3.

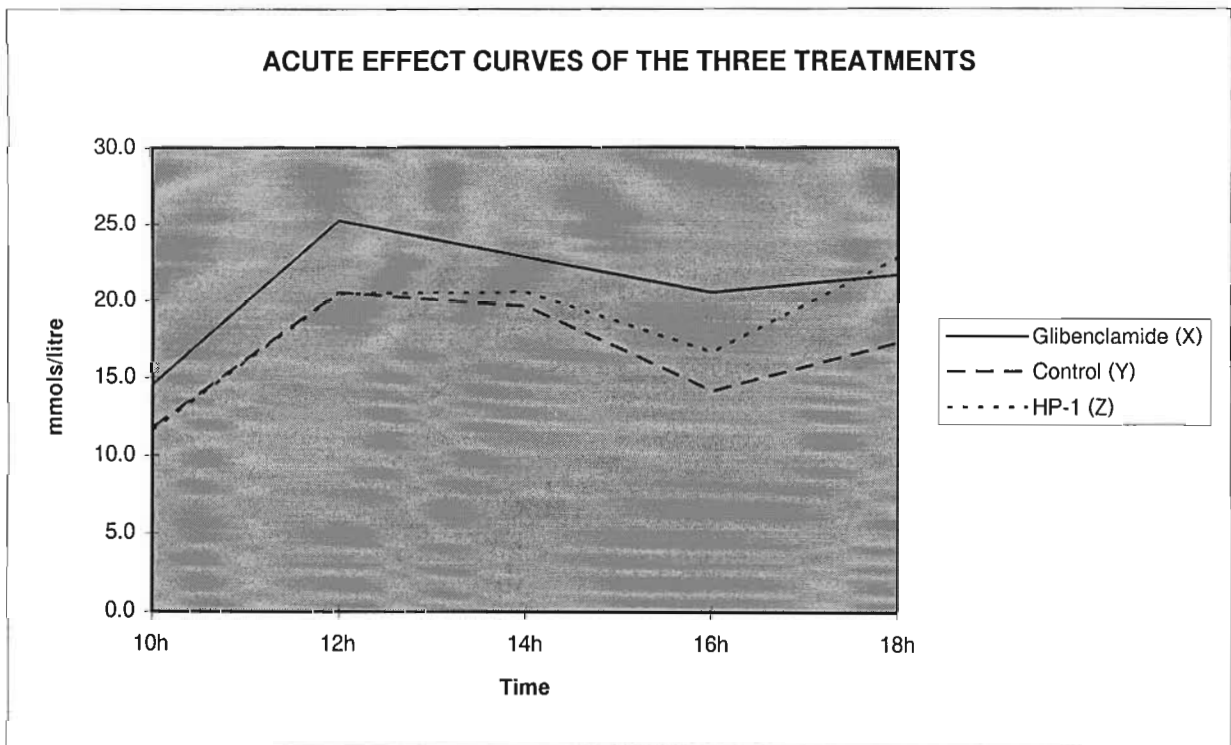
No difference in blood glucose levels were observed at 2, 4, 6, 8 and 10 hours after the administration of the treatment dose in all groups. A slight increase was observed with the second reading in all cases, and this tapered slightly towards the end of the day.

TABLE IV**ACUTE EFFECT OF HP-1, GLIBENCLAMIDE AND CONTROL ON DIABETIC RATS****(MEAN GLUCOSE LEVELS IN mmol//L +/- S.E.M.*)**

Treatment	Average Pre-Treatment Levels				
	1st Reading 0hrs	2nd Reading 2hrs	3rd Reading 4hrs	4th Reading 6hrs	5th Reading 8hrs
Glibenclamide (X)	14.3 +/- 2.4	25.2 +/- 2.4	22.9 +/- 2.4	20.5 +/- 2.4	21.6 +/- 2.41
Control (Y)	11.2 +/- 2.4	20.3 +/- 2.4	19.6 +/- 2.4	14.5 +/- 2.4	17.1 +/- 2.41
HP-1 (Z)	1.65 +/- 2.4	20.8 +/- 2.4	20.7 +/- 2.4	16.8 +/- 2.4	22.8 +/- 2.41

*S.E.M. is the Standard Error of the Mean

FIGURE 3



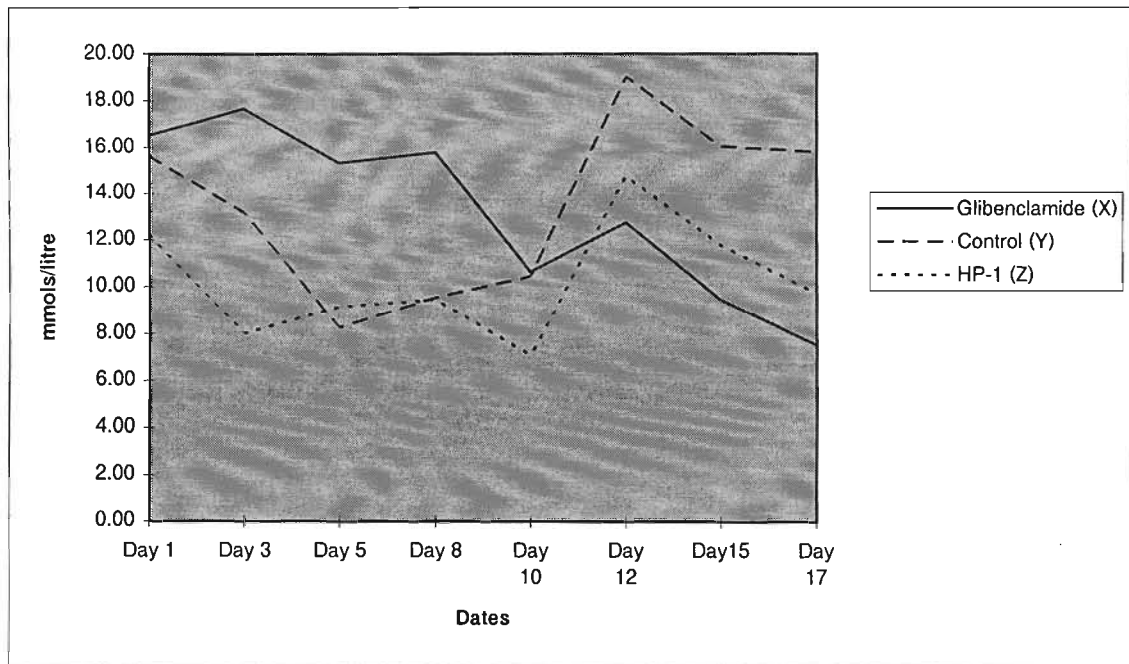
Using Scheffe's F test in the analysis of variance, the 3 groups of data were not significantly different from one another at p value of $p=0.28$ with respect to average decrease (or lack of it) in level of blood glucose in the test samples.

The experiment was then continued for an additional seventeen days with blood glucose levels done every second day. Table V relates the blood glucose levels over this period and Figure 4 demonstrates the trend observed. The blood glucose levels that demonstrated normoglycaemia of the rats, were excluded to avoid introduction of a confounding factor in the analysis. The test groups failed to exhibit hypoglycaemic activity for both HP-1 and Control except for the Glibenclamide group which demonstrated an average of 54% decrease in blood glucose levels. The HP-1 demonstrated a 11% decrease and the Control 0% decrease in glucose levels.

TABLE V								
CHRONIC EFFECT OF HP-1, GLIBENCLAMIDE AND CONTROL ON DIABETIC RATS								
(MEAN GLUCOSE LEVELS - mmol/L +/- S.E.M*)								
Treatment Groups	Average Pre-Treatment Levels							
	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12	Day 15	Day 17
Glibenclamide (X)	16.5 +/-1.9	17.7 +/-1.9	15.3 +/-1.9	15.8 +/-1.9	10.6 +/-1.9	12.7 +/-1.9	9.44 +/-1.9	7.49 +/-1.9
Control (Y)	5.65 +/-2.7	13.18 +/-2.	8.25 +/-2.7	9.55 +/-2.8	10.45 +/-2.	19.03 +/-2.	16.05 +/-2.	15.8 +/-2.8
HP-1 (Z)	12.23 +/-3.	8.0 +/-3.18	9.17 +/-3.1	9.47 +/-3.1	7.07 +/-3.1	14.7 +/-3.1	11.8 +/-3.1	9.7 +/-3.18
*S.E.M. is the Standard Error of the Mean								
Average % decrease in blood glucose levels								
HP1	-	11%						
Control	-	0%						
Glibenclamide	-	54%						

FIGURE 4

CHRONIC EFFECT OF HP-1, GLIBENCLAMIDE AND CONTROL ON DIABETIC RATS (CURVES)



The variance between the two groups (HP-1 and the Control) was not significantly different from each other (p= 0.57). This is illustrated in the following table (Table VI).

TABLE VI. ANOVA RESULT AT THE END OF HP-1 TREATMENT

<i>SOURCE</i>	<i>df</i>	<i>SS</i>	<i>MS</i>	<i>F ratio</i>	<i>p-Value</i>
Among groups	2	68.014	34.007	0.566	0.575
Within groups	22	1321.720	60.078		
TOTAL	24	1389.734	94.085		

*df = degrees of freedom, SS = sum of squares, MS = mean squares

4.3.2.1.1.Histopathological Results

The results are presented in Appendix III whereby xx1 to xx9 represents specimens (pancreas, liver and kidney) from the group treated with Glibenclamide; yy1 to yy9 represents the Control group and zz1 to zz9 the HP-1 group.

The histological reports indicated very mild to moderate pancreatic and hepatocellular atrophy, steatitis in the mesenteric fat and multifocal cortical

tubular dilatation. Most changes were found in the kidney and the liver specimen. These changes are reported to be mild to moderate and to a degree, similar in all three groups. Similarly, STZ has been found to be cytotoxic and the lesions reported are consistent with the pre-neoplastic lesions caused by cytotoxic and degenerative action of streptozotocin [Prof Kriek, pers comm]. This is consistent with other studies whereby the isolated zona glomerulosa cells of the STZ-induced diabetic rats, showed a marked atrophy [Andreis et al, 1990].

The hypothesis is advanced that the chronic lack of insulin may also directly impair the growth and steroidogenic capacity of the organs in the rat.

4.3.2.2. Herbal Preparation -2

Similarly, the tests on the first day were performed five times (five blood glucose readings) at two-hour intervals. The results are illustrated in Table VII and Figure 5 respectively.

A noticeable elevation in blood glucose levels was observed on the first day and this was not significantly different among the groups ($p= 0.23$). The results of the three weeks of experiments, demonstrate a gradual decrease in blood glucose levels with each treated group average differing from each other by 10% and that

of the control group remaining almost unchanged. The difference in that group (control) of glucose levels from day one to the last day of the experiment was 10% whereas that of HP-2 and Glibenclamide was 59% and 49% respectively. These results are illustrated in Table VIII and Figure 6.

TABLE VII

ACUTE EFFECT OF HP-2, GLIBENCLAMIDE AND CONTROL ON DIABETIC RATS (MEAN GLUCOSE LEVELS mmol/L +/- S.E.M*)					
Treatment	Average Pre-Treatment Levels 1st Reading 0hr	2nd Reading 2hrs	3rd Reading 4hrs	4th Reading 6hrs	5th Reading 8hrs
HP-2 (A)	12.6 +/- 2.3	16.3 +/- 2.3	15.5 +/- 2.3	19.1 +/- 2.31	19.1 +/- 2.31
Glibenclamide (B)	16.9 +/- 2.3	17.4 +/- 2.3	11.7 +/- 2.3	22.8 +/- 2.57	23.5 +/- 2.46
Control (C)	18.4 +/- 2.3	11.1 +/- 2.3	17.95 +/- 2.5	18.9 +/- 2.3	19.7 +/- 2.3
*S.E.M. = Standard Error of the Mean					

FIGURE 5

ACUTE EFFECT OF THE THREE TREATMENTS ON DIABETIC RATS (CURVES)

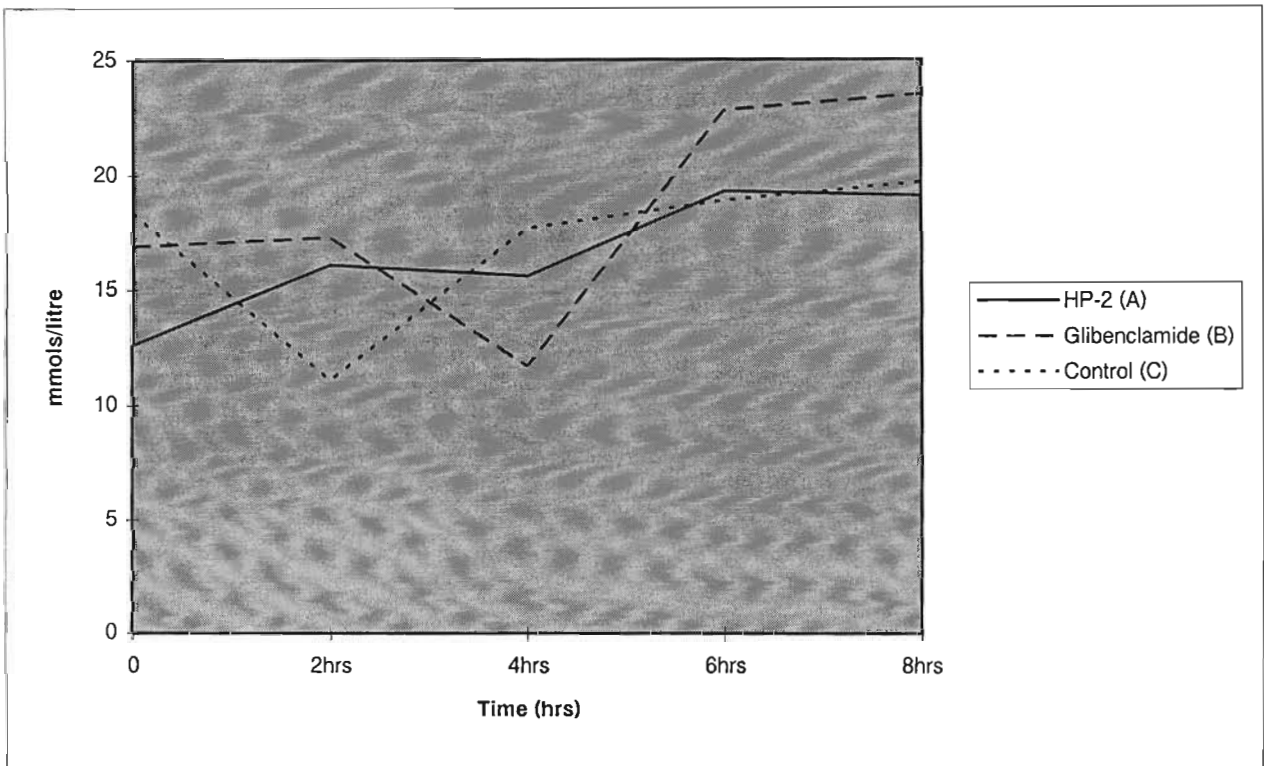


TABLE VIII

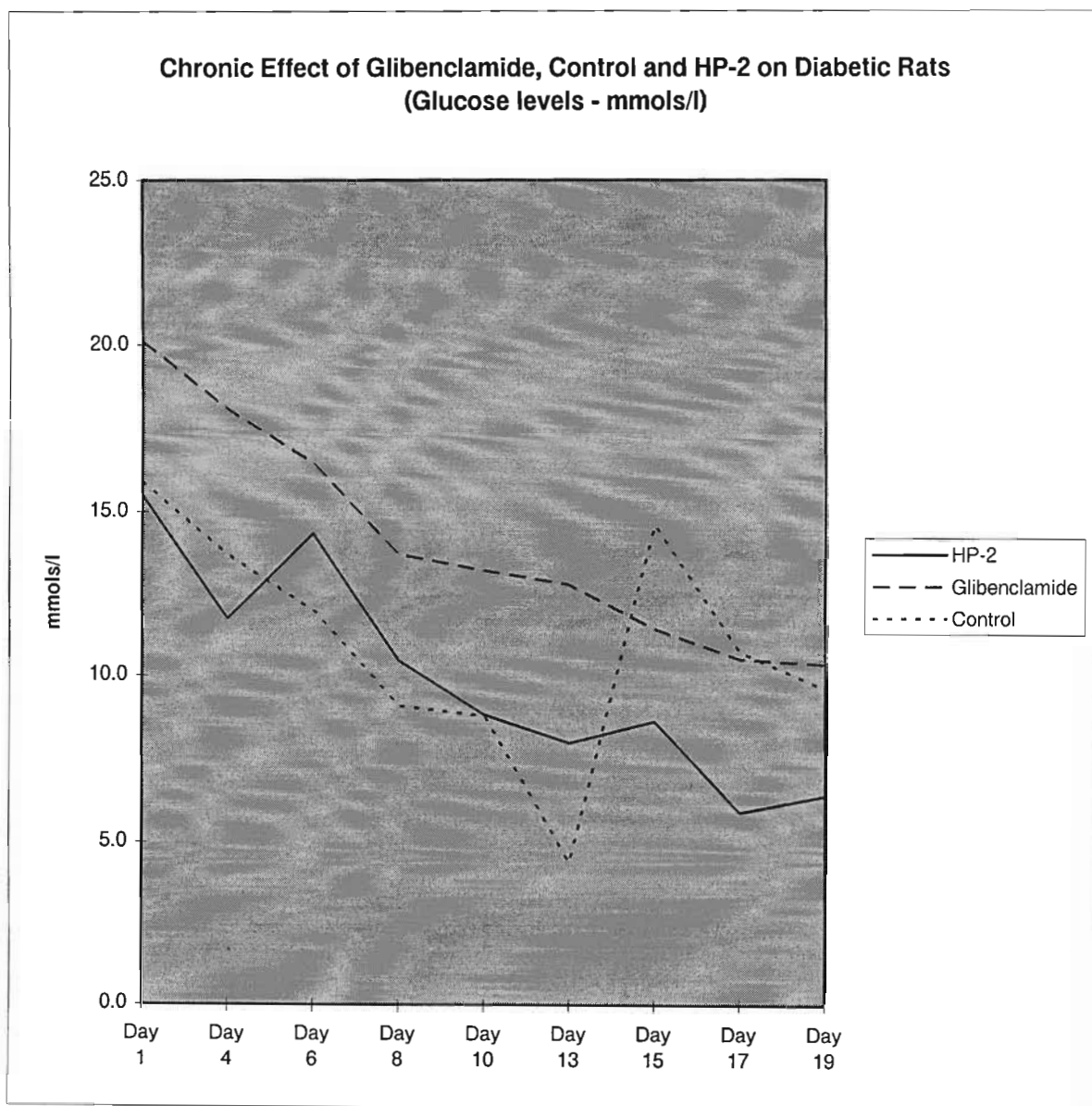
**CHRONIC EFFECT OF HP-2, GLIBENCLAMIDE AND CONTROL ON DIABETIC RATS
MEAN GLUCOSE LEVELS mmol/L +/- S.E.M.***

Treatment Groups	Average Pre Treatment Levels Day 1	Day4	Day 6	Day 8	Day 10	Day 13	Day 15	Day 17
HP-2 (A)	15.5 +/-1.5	11.7 +/-1.52	14.33 +/-1.52	10.45 +/-1.52	8.83 +/-1.52	7.98 +/-1.52	8.63 +/-1.52	5.9 +/-1.52
Gliben- clamide (B)	20.11 +/-2.3	18.1 +/-2.32	16.47 +/-2.32	13.7 +/-2.32	13.21 +/-2.32	12.77 +/-2.3	11.41 +/-2.32	10.49 +/-2.3
Control (C)	15.9 +/-2.01	13.7 +/-2.01	12.0 +/-2.01	9.1 +/-2.01	8.8 +/-2.01	4.4 +/-2.01	14.6 +/-2.01	10.7 +/-2.01

*S.E.M. is the Standard Error of the Mean
Average % change in blood glucose concentration

HP-2	-	59%
Control	-	1%
libenclamid	-	49%

FIGURE 6



The HP-2 group demonstrated a 59% decrease with Glibenclamide demonstrating a 49% decrease in blood glucose levels. The control group demonstrated a 1% decrease in glucose levels. At the end of this experiment the blood glucose levels under various treatments were significantly different at the 99% confidence level. This is depicted in the following table.

TABLE IX. ANOVA RESULTS AT THE END OF HP-2 EXPERIMENT.

<i><u>SOURCE</u></i>	<i><u>df</u></i>	<i><u>SS</u></i>	<i><u>MS</u></i>	<i><u>F-ratio</u></i>	<i><u>p-Value</u></i>
Between groups	2	153.198	76.599	7.227	0.006
Within groups	16	169.589	10.599		
TOTAL	18	322.787	87.198		

*df = degrees of freedom

4.3.2.2.1. Histopathological Results

These results are also presented in detail in Appendix III whereby A1 to A9 represents the specimen (pancreas, liver and kidney) from the HP-2 group, B3 to B9 the Glibenclamide group and C2 to C9 the Control group respectively. There was mild sporadic hepatocellular atrophy reported (see Appendix III) in some cells, which were consistent with the endocrinological disturbances caused by

STZ. In addition to STZ disturbances, the specimen from the two groups treated with HP-2 and Glibenclamide exhibited steatitis in mesenteric fat tissue and some hepatocellular fatty changes. Bearing in mind that both Glibenclamide and HP-2 demonstrated a similar hypoglycaemic effect, it is not surprising that lesions seen on the histopathological examination from the two groups, also exhibit similar trends in atrophy, hyperplasia and changes in the fatty tissue compared with the control group. Glibenclamide is reported to have mild lipolytic properties on adipocytes [Koda-Kimble & Rotblatt, 1995].

Similar lesions on the tissues taken from the liver and kidneys were reported. These were reported to be of significance and suggested that these may progress to neoplasia in experiments of longer duration. This is consistent with other findings and the oncogenic properties of STZ.

4.3.3. ORAL GLUCOSE TOLERANCE TEST RESULTS

It was the intention of this study to do an OGTT at the end of the 26 days, in order to determine whether there was an improvement in glucose utilization after the treatment with HPs. According to the OGTT methodology, the glucose bolus is administered four hours after the various treatments (HP or Glibenclamide) have been given. In this case, as it was customary, the various treatments were given first thing in the morning, mixed with a portion of daily ration of food, four hours

before the administration of glucose. This form of administration of the treatment doses inadvertently broke the fast, and invalidated the results.

4.3.4. WEIGHT STUDIES RESULTS

A noticeable weight loss was observed in the group treated with HP-1 and this was comparable to the weight loss in the Glibenclamide group whereas the control group treated with Distilled water demonstrated a weight gain consistent with the normal growth process (see Table X and Figure 7).

HP-2 group demonstrated a slight gain in weight compared with both Glibenclamide and the control groups. Goodman & Gillman (1995) reported that marijuana smokers frequently reported increased hunger and this could have lead to overeating and resultant gain in weight over the three weeks of the experiment. (Table XI and Figure 8).

TABLE X

**WEIGHT STUDIES
AVERAGE WEIGHT IN GRAMS**

Treatment Groups	Day 1	Day 10	Day 17
Glibenclamide (X)	206	184	176
Control (Y)	199	194	206
HP-1 (Z)	193	185	175

FIGURE 7

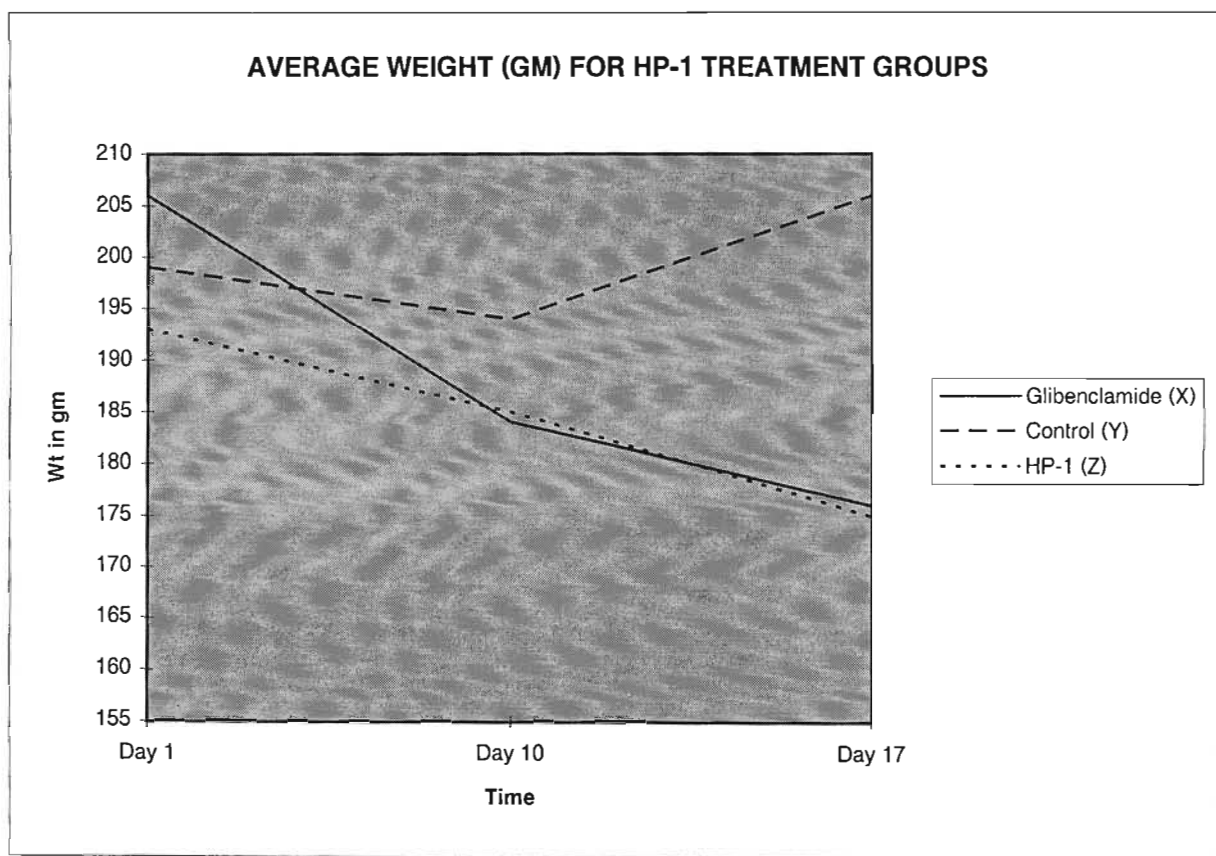
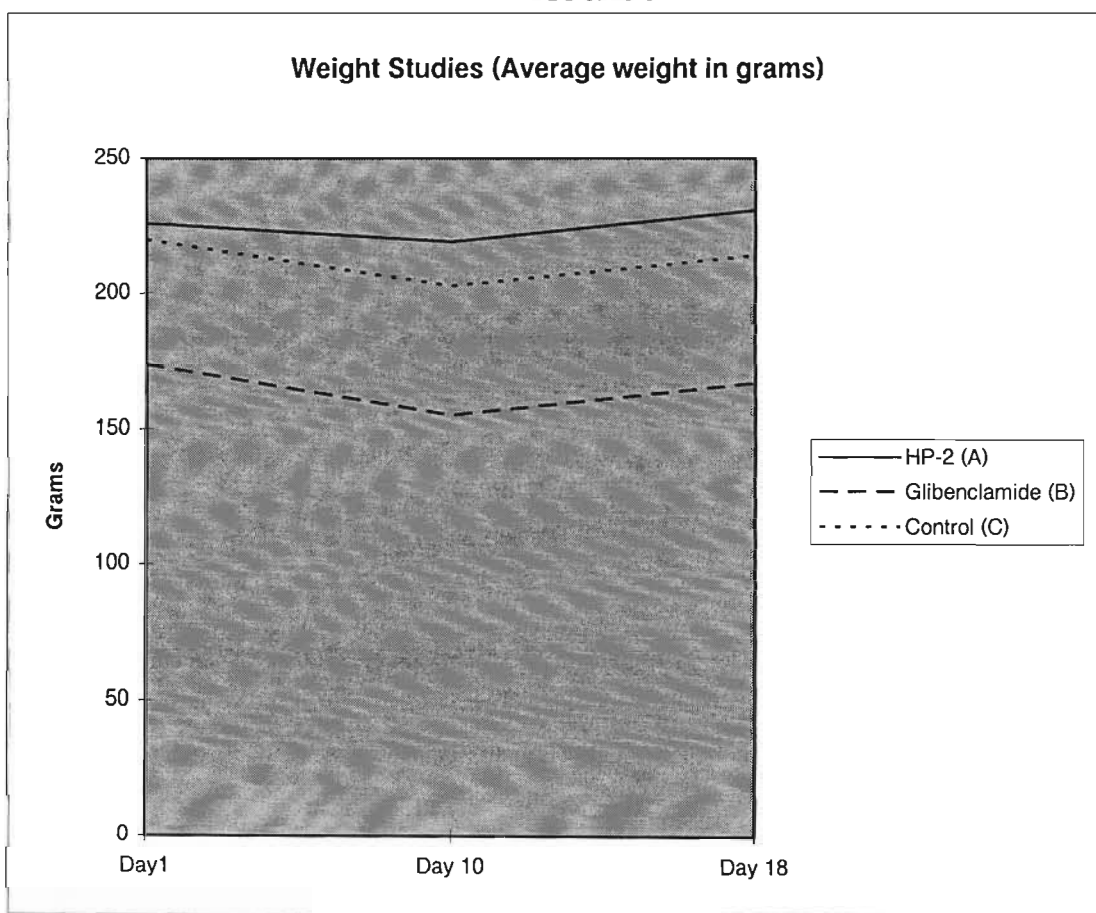


TABLE XI

**WEIGHT STUDIES
AVERAGE WEIGHT IN GRAMS**

Treatment Groups	Day 1	Day 10	Day 17
HP-2 (A)	225.7	218.9	230.4
Glibenclamide (B)	173.3	154.9	166.6
Control (C)	219.7	202.7	214

FIGURE 8



4.4. GENERAL DISCUSSION OF THE HERBAL PREPARATIONS

The results of this study suggest that acute treatment (first day) with both HPs failed to exert any hypoglycaemic effect. The HP-1 as tested here also failed to demonstrate any significant hypoglycaemic activity over a period of three weeks. There could be several explanations for this; the dose used might have been insufficient (although it was calculated based on body weight and the dose given to humans) or the added excipients might have had an attenuating effect on the hypoglycaemic activity of the main ingredients or the HP might have been devoid of hypoglycaemic activity. What pharmacological effects the individual plants in the mixture would exert, if and when used alone, was beyond the premise of this study.

Although no hypoglycaemic effect was demonstrated with HP-1, the individual constituents have been associated with therapeutic activity in previous research. The traditional healers believe that if *Catharanthus roseus* is in combination, with other medicinal plants, the hypoglycaemic effect is enhanced whereas the toxic effect is toned down or minimised. Ilabatheka (*Hypoxis oligotricha*) for an example, has been found to have anti-emetic properties and used to quell nausea and vomiting immediately if taken as tea [Pujol, 1990]. Most Zulus and Xhosas use it to calm the heart and anxiety [Hutchings, 1991]. In what context it was used here, could not be determined; but aloes are known to be bitter and could induce vomiting and purgation.

Several studies on the activities of medicinal plants have documented the hypoglycaemic effect of some Aloe species [Mossa, 1985; Ghannan et al, 1986]. The dried sap of the Aloe plant is one of several traditional remedies used in the treatment of diabetes in the Arabian peninsula since time immemorial [Ajabnoor, 1990]. Ghannan and his co-workers (1986), speculated that the mechanism of action of aloes is mediated through stimulation of residual insulin secretion from the β -cells of Langerhans. Aloe has been found to contain anthraquinone glycosides, barbaloins and beta-barbaloins, resins and saponins. None of these individual constituents have shown any antidiabetic effect in the past studies. The effect that the aloe species (as used in HP-1) would have had, if used alone or in higher doses, was beyond the scope of this research project. Similarly, the leaf infusions and decoctions of *Catharanthus roseus* (*periwinkle*) have been reported in a study conducted by Neame and Pillay (1964) to have mild hypoglycaemic effect in healthy rats. Several alkaloids have been isolated; viz: leurosine, vindoline and catharanthine. However, the neurologic and cytotoxic effect of these alkaloids did not encourage further investigation [Bailey et al, 1985; Day and Bailey, 1988].

Treatment of streptozotocin-diabetic rats with HP-2 for twenty six days resulted in a noticeable hypoglycaemic effect, and weight gain, and in some cases these

results were comparable to Glibenclamide treated group. Again, the antidiabetic properties of HP-2 could be dose-dependent.

Similarly, previous studies have documented the hypoglycaemic effect of *Momordica foetida* (found mostly in Africa) and *M. charantia* (found mostly in Asia, Australasia and Central America) used alone or extractions thereof. These studies suggest that *Momordica* species have a significant hypoglycaemic activity and has been widely used to treat diabetes world wide. The glycoside charantin (which is a mixture of β -sitosterol-D-glucoside and stigmadinine glucoside), found in these species, was found to inhibit hepatic gluconeogenesis while improving glycogenesis in healthy and alloxan-induced diabetic rabbits, but found to be ineffective in pancreatectomized animals [Vad, 1960; Meir et al, 1985; Keder et al, 1982; Leatherdale et al, 1981; Day and Bailey, 1988; Bailey et al, 1985].

Other studies cite a polypeptide designated as P-insulin to be responsible for the antidiabetic action [Iwu, 1993; Bailey & Flatt, 1986]. This insulin-like peptide has been found to inhibit hepatic gluconeogenesis as well as decreasing intestinal glucose uptake in the laboratory experiments [Day & Bailey, 1988]. If injected subcutaneously into Type I diabetic patients, it has been found to lower blood glucose levels [Murray & Pizzorno, 1990].

The young shoots of *Musa paradisica* and *sapientum* have been used for blisters and wounds in New Guinea from time immemorial. In India it is popularly used for snakebite wounds [Wheelwright, 1974]. The reason for inclusion of this species in the herbal preparation could not be determined in this study.

On the contrary, *Cannabis sativa* which was used in this herbal preparation (HP-2) has been found to be devoid of antidiabetic activity. Instead, it has been associated with hyperglycaemia [Goodman & Gillman, 1995]. An infusion of leaves and stem is said to be used for cough and is also very effective in averting an acute asthmatic attack [Gumede, 1990]. However, several studies demonstrated its anti-emetic properties (as tetrahydro-cannabinol isolated from *Cannabis* is used for nausea in cancerous patients) and it could have been used in that context in the HP-2. The bitter gourd or melon (*Momordica*) is known for its strong emetic and spasmodic properties sometimes resulting in death [Vad, 1960; Leatherdale et al, 1981].

The results of the Acute Oral toxicity tests indicates that no toxic reactions or untowards effects could be attributed to the herbal preparations investigated in this study. Mild to moderately mild lesions as reported in the results and also in Appendix II and III, were found by histopathologist. No mortality was observed in these experiments for both HP-1 and HP-2.

The mortality rate in Diabetic clinical experiment was very low; three rats died prior to the beginning of HP-1 experiment with one rat dying four days after the treatment was initiated. Five died prior to the beginning of the experiment (HP-2 group) resulting in an overall mortality rate of 15% for the whole study. The death of these animals could be attributed to advanced stage of diabetes and the degenerative properties of streptozotocin. In the absence of insulin, metabolic alterations which affect glucose metabolism and homeostasis in the cells, results in atrophy. The oncogenic properties of STZ also contributed to the formation of the lesions reported by histopathologists and these (at an advanced stage) could have contributed to the death of these animals.

In the case of the rat that died after the experiment (HP-1) had begun, the same reason as above could be the cause or it could be that HP-1 could have possible toxic effects. The combination of the two could have had a synergistic toxic effect and resulted in death of this rat.

According to the protocol of the study, the OGTT was to be conducted in order to test the effectiveness of the various antidiabetic treatments after the Diabetic Clinical Trial. However, the protocol did not stipulate the method of administration of the treatment doses for this particular experiment. Following

the method used for the preceding 26 days for the diabetic experiment, the same method of administration of the treatment doses was used for the OGTT, thus creating a serious error that invalidated the results. The study could not be repeated due to lack of funds.

Herbal remedies have been reported to have untowards effects and precautionary measures need to be taken in dosing. Several studies have documented the toxic and adverse effects of traditional medicines [Bye and Dutton, 1991; McVann et al, 1992; Dunn et al, 1991; Victor et al, 1988; Koff, 1995; Macgregor et al, 1989; Maurice and Cream, 1989]. It is on this basis that recommendations are made for more research into medicinal plants and the compilation of herbal remedies pharmacopoeia [Murray, 1990; Arnold and Gulumian, 1984].

Although animal models are used for the testing of safety and efficacy of medical substances, it should also be borne in mind that substances tested on animals do not necessarily produce the same effects on humans. As human responses to medicines are also known to vary from one individual to another, they may vary from animal to animal [Grundy, 1990] as well. Also, the absence of an effect in one type of diabetes does not exclude the possibility of an effect on glycaemia in other types of diabetes or a beneficial effect other than glycaemic control. Thus, caution should be exercised when extrapolating these results to human beings.

4.5 Limitations of the Study

Funding was the most crippling and yet an essential part of the study. It was the intention of the investigator to conduct a number of tests to monitor the progress and to determine the effectiveness of the various treatments administered to the animals; tests such as the insulin content at the end of AOTT. However, due to limited funds, these tests could not be done.

The study design had a flaw as far as randomisation of rats is concerned. The rats were randomised prior to diabetes induction which created a confounding factor in the experiment.

Another lesson learned is that the protocol should be explicit in outlining the methodology to be followed in the experiment and that technicians assisting in the study should be closely monitored in order to avoid errors such as the one committed in the OGTT.

4.6 CONCLUSION

Both the herbal preparations (HP-1 and HP-2) were found to be non-toxic to the animals and therefore it is possible that they could be non-toxic and non-hazardous to human subjects at the concentrations used. HP-2 was found to

have a sustainable lowering effect on glucose levels over the period of experimentation. As a result, a reversal of diabetic state or in the least, control of blood glucose level is a possibility.

The findings of this study however, encourages further research of more similar studies. Based on these findings the foundation is laid to initiate more research into medicinal plants used in treating diabetes countrywide and other indigenous plants used in order to evaluate the safety or toxicity of the medicinal herbal preparations.

CHAPTER 5

THE EPIDEMIOLOGICAL STUDY

5.1 METHODOLOGY

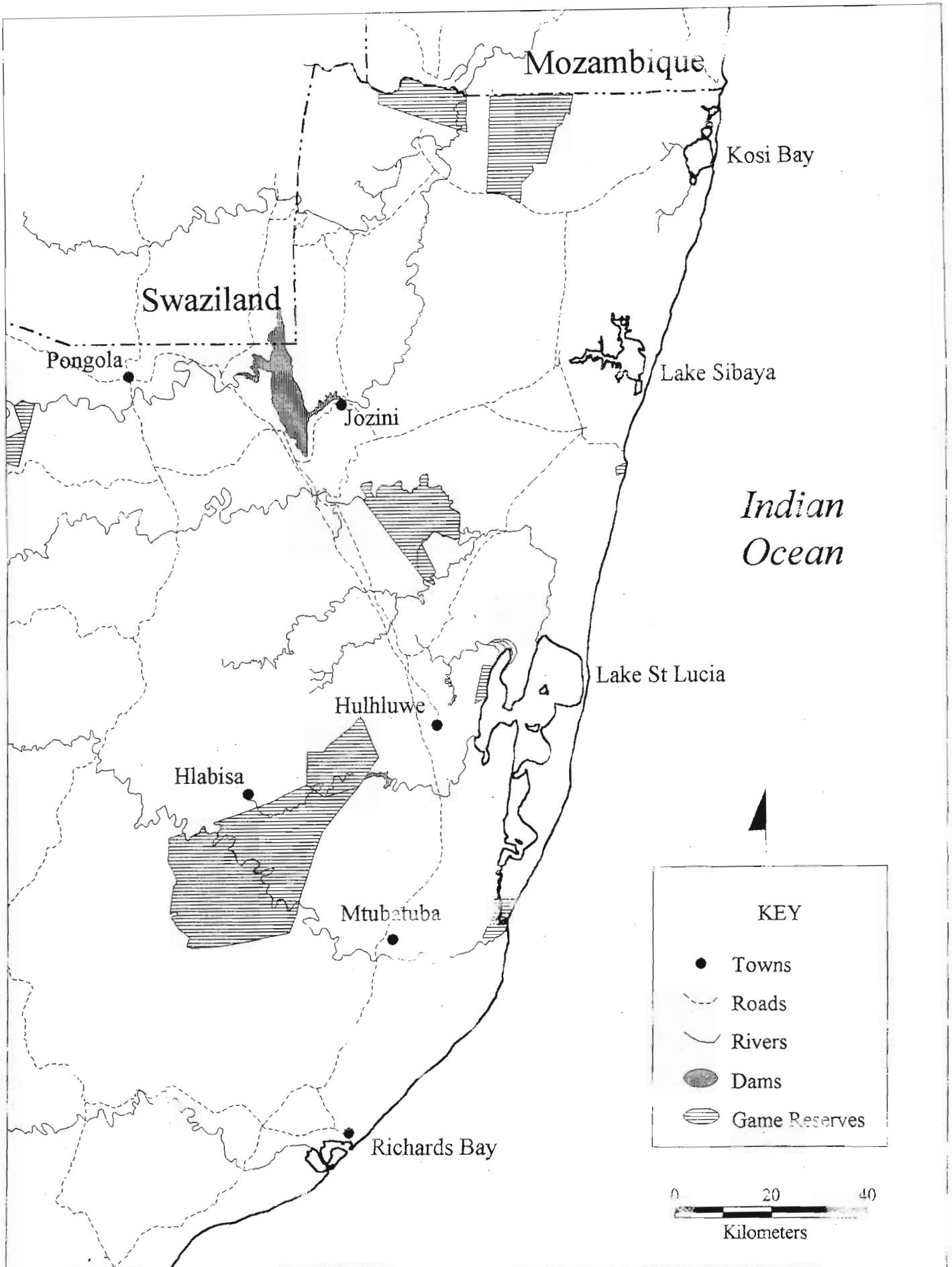
The proposal for the study was reviewed and approved by the Medical Research Council (MRC) Protocol/Editorial Committee as well as the ethical clearance given by the Ethics Committee of the University of Durban-Westville. (see Annexure I & III respectively)

5.1.1. Study Site:

The research was conducted in a rural area in Northern KwaZulu-Natal where the majority of the population use herbal remedies (self prescription) or patronise traditional healers in great numbers. The principal investigator (TZ-P) was familiar and had good rapport with the traditional healers in the area. The specific localities targeted were Hlabisa, Jozini, Pongola and Hluhluwe as reflected in Figure 9. These areas were chosen partly because they have easily accessible hospitals and clinics (for verification of diagnosis as well as the presence of diabetic clinics) and also the fact that MRC has substations in those areas which facilitated the gathering of medicinal plants pertinent to the study as well as the collection of data.

FIGURE 9

STUDY SITE AREAS



Study Population

The study involved interviewing traditional healers (Appendix IV) and their patients (Appendix V), taking traditional remedies and/or allopathic medicine for the treatment of diabetes. The target population was therefore the traditional healers in the areas mentioned; the people who use traditional medicine for this ailment; as well as people who had diabetes and did not use traditional medicines to form a control group.

5.1.3. Ethical Considerations.

Because of the sensitive nature of the information required from both patients and the traditional practitioners, the research study presented a number of methodological and practical challenges. It was therefore decided, at an early stage to use both qualitative and quantitative techniques. Qualitative methods were considered to be appropriate measuring tool to determine the attitudes and practices in this case. Where necessary, homogeneous groups were selected for focus group discussions.

It is a well known fact that traditional practitioners keep most of their knowledge to themselves and those who patronise them do not volunteer information easily; all because of the stigma and negativism that has been associated with traditional healing. Hence, a consent form (Appendix VII) was designed as an agreement

between the researcher and the respondents that their confidentiality would be maintained, as well as the intellectual property rights would be protected. The non-disclosure of “other” excipients in the herbal preparations, was part of this agreement.

5.1.4. Study Design

5.1.4.1. Respondents:

An observational study - unobtrusive observations with a twelve month's follow-up (case series) was used. Patients (age range of 20-65 yrs) were stratified into three groups; those who used traditional medicine only, those who used the herbal remedies concurrently with allopathic medicine, and those who used allopathic medicine only. These groups were monitored for a period of 12 months from the date of enrolment to the study. Interviews with clinical examinations (blood glucose tests and BP measures) upon enrolment and during the course of the study were done.

In order to identify users of traditional medicines, a list of healers in the area was obtained from the National Inyangas Association and the Health Inspectorate in the four geographic areas. The healers that specialised in treating diabetes, and gave their consent to participate in the study, were further interviewed. A list of

the diabetic patients they had treated or were still under their treatment was requested.

Those patients who agreed to participate in the study and whose diagnoses of diabetes was confirmed clinically (see Appendix VI) were enrolled.

In order to identify users of allopathic medicine, patients were randomly selected and interviewed as they attended the diabetic clinics in the study area. If they gave their consent, they were enrolled and monitored like the other groups.

The inclusion criteria for the three groups were basically, the patient's consent (Appendix VII), a clinically confirmed diagnosis - Appendix VI - at the clinic, hospital or doctor's office prior to this interview as well as spot checks of glucose levels at the site. Those with gestational diabetes were excluded. Initially, it was envisaged to enrol 120 patients in each group, but due to the logistics and other problems encountered in searching for patients, this number was reduced, (see the results) and design adjustments made with the help of the statistician.

The following table (Table XII) show the number of hospitals and clinics involved in the study.

TABLE XII
FACILITIES ENGAGED IN THE TREATMENT OF
DIABETIC PATIENTS (IN THE STUDY)

GROUP ONE (HOSPITALS)

<u>Name</u>	<u>Bed Capacity</u>
Itshelejuba	185
Hlabisa	350
Bethesda	320

GROUP TWO (CLINICS)

<u>Name</u>	<u>Approx Number of Patients seen/ month</u>
Mpukunyoni	670
KwaMsane	650
Macabuzela	300

Source: 1994 Hospital & Nursing Yearbook

5.1.4.2. Traditional Healers:

Forty two traditional healers were interviewed. Thirteen were excluded because they did not or had not treated diabetic patients. Therefore, twenty nine out of this forty two were enrolled and further interviewed concerning their treatment for Diabetes mellitus and traditional practice in general.

5.1.4.3. Data Collection Procedure;

It was crucial to the study that the ethnographers were well trained, fluent in the language, and familiar with traditions and culture of the people in order to build rapport with the interviewees. These ethnographers had to undergo a day of training in Zulu customs and traditions as well as sensitised to the rural way of life by role playing. At the end of the day, they were tested on the knowledge of this and the manner of approach applicable to different possible scenarios. For instance, they were instructed not to come with clipboards and a high-handed attitude but to humble themselves to the extent of joining the activities of the villagers if possible, and re-schedule their visit for another time. They were also given an instruction manual of how to fill in the questionnaires, conducting interviews in Zulu and interpretation to English.

Semi-structured questionnaires (see Appendices IV and V) and one-on-one

interviews were used as study instruments to compile a detailed medical history from the time of diabetic diagnosis. Examples of items abstracted from both hospital/clinic records and interview sessions included date of birth, date of diabetes diagnosis, sex, age, diabetic treatment, family history and reasons for clinic encounters or hospital visits and problems encountered that hindered clinic attendance. The questionnaires used were piloted, pre-tested and adjustments made before the actual data collection.

5.1.4.4. Interpretation of data

All information was edited for accuracy and consistency before computer entry. Reliability of the data entered was assessed by re-entering data from a random five percent sample of respondents, and was found to be highly satisfactory within error rate of 1.6% (95% confidence interval, 0.8%- 2.7%).

5.2. Follow-up and Outcome Measures

5.2.1. The Dependent Variable:

The progress of the respondents was evaluated after three, six, nine and twelve months. Both subjective and objective outcome measures were examined. At each follow up interview, respondents were asked about their perceived health, generally; any changes and consultations or hospitalisations, symptoms of complications and the respondents' assessment of the treatment received.

During analysis where possible, the responses were dichotomised into “positive results” and “negative results” (1= +ve, 0= -ve) in creating variables. For the rest of the information, content analysis was performed.

5.2.2. The Independent Variables

A health care services use model was developed to examine the relationship between the dependent and independent variables [model adapted from the one used by Andersen et al, 1974]. Independent variables were grouped into two domains; the demographic and/or predisposing characteristic; and access to health care and other issues that may enable or hinder conventional or biomedical services thus influencing the choice between traditional or conventional medicine.

The demographic characteristics were represented by dichotomous variables for gender, age, education and employment status.

Characteristics that may hinder access to health care were represented by variables that included distance, amount of time spent travelling to and from health facilities, time spent waiting in clinics, the fees payable as well as the treatment received.

5.2.3. Statistical Analysis

Descriptive analyses were used for the main results, the Mantel-Haenszel χ^2 test, McNemar test to analyse the outcome measures and multivariate analysis for association where applicable. The missing data as a result of those lost to follow-up or incomplete intermittent checks, was analysed by a regression method whereby an analytic expression matrix of estimated effect was obtained. The results are given as means with 95% confidence interval and significance was accepted at the 5% level.

Multivariate models were constructed using forward linear regression, introducing predisposing, need and enabling variables successively as predictors for traditional medicine use. To determine the impact of excluding partial respondents from the models, all but the final stage of each series was run with their data included; parameter estimates remained virtually unchanged. The exclusion of partial respondents from analysis appeared to have little impact on the findings

5.3. RESULTS AND DISCUSSION

5.3.1 Traditional Practitioners and their Healing Systems

The twenty nine traditional healers interviewed treated various ailments including diabetes though fourteen (48%) of the healers interviewed were specialists and tutors or had had initiates and apprentices. The average years in practice was 14.7 (ranging from 3-41yrs).

They used various medicinal plants (from roots, bark, leaves, flowers and fruits) including intshungu (*Mormodica* spp), umgwenya (*Harpephyllum* spp), nhliziyonkulu (*Dombeya* spp), banana (thyrses from *Musa* spp), inhlaba (*Aloe* spp), insangu (*Cannabis* spp), and tobacco leaves. These were concocted in different formulations with different excipients added (depending on individual traditional healer) which included, blue stone, yellow or sour stone (alum), vinegar etc etc. The medicinal plants were collected at any time as needed but most of the healers preferred summer season. The reason for that could not be determined. All the healers interviewed willingly shared their recipes for the formulation except for nine (31%) who demanded money for them to disclose what their ancestors has "alloted" to them - their life line.

The ingredients were chopped or sometimes dried before use, and boiled for a few minutes or just brought to boiling point then cooled. The dose varied with

individuals, from a spoonful to a cupful, three times a day and the duration would be two weeks to three months, before the results are noticeable. According to the traditional healers most patients needed two or three repeat visits and never came back. Though this was a subjective assessment, they strongly believed that their patients were cured, especially because they referred other people with similar ailments to them (traditional healers).

Upon being asked whether collaboration between ethnomedicine and biomedicine was a feasible venture most of them (22 {76 %}) agreed that both sectors had something to offer the patient. There are certain diseases and ailments that they believe can only be appropriately treated by traditional medicine, and similarly, certain ailments can only be treated by western doctors. Given that, they expressed a need for additional training of traditional practitioners in some aspects of health such as hygiene. They also believed that they need certification or licences to be recognised as equals to western doctors. Five (17 %) felt that there is a need for government support in building traditional medicine hospitals and clinics where they can treat patients and then their performance judged on equal basis to that of western practitioners. In order to be able to offer a “holistic” treatment to patients, they believe collaborative efforts between providers of both sectors should be pursued. They take pride in the fact that people came from hospitals to seek their treatment and that there were referrals from various parts of

the country (mostly by other patients previously treated). There were some cases where referrals were made by doctors and nurses.

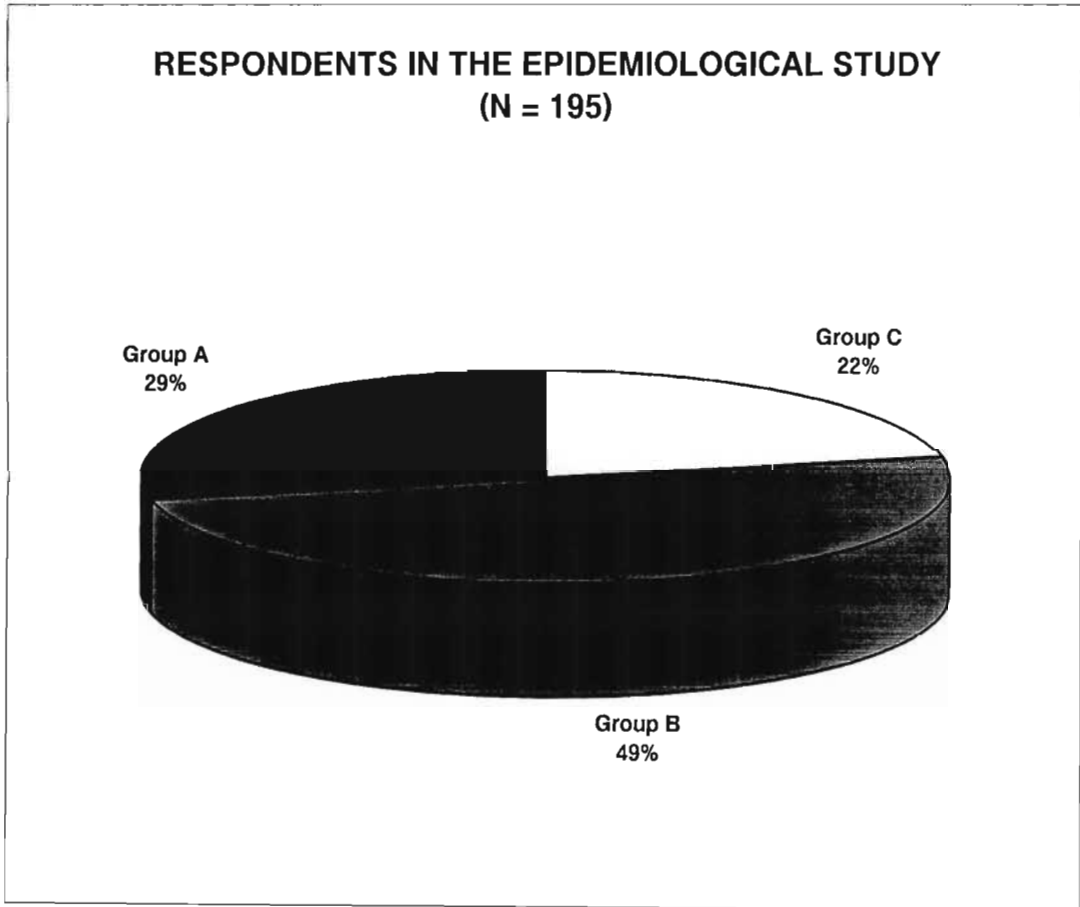
They felt there would be no competition between the two sectors, because western medicine has its place and they respect that. They cited oxygen and other hi-tech equipment that is used in hospitals but equally demand respect for their own form of treatment and healing systems.

Seven (24%) adamantly opposed any form of collaboration, the reason being that the doctors looked down upon traditional healers. Unless that attitude is addressed and enough mutual trust developed between the two sectors and doctors started referring patients to them, they did not see any collaboration at all with the conventional medical practitioners. Some of them believe that all the western practitioners wanted to do was to steal their secretive knowledge of medicinal plants without them (traditional healers), getting acknowledgement or remuneration as originators of the treatment. Three out of this seven, felt strongly that traditional medicine is potent and should not be used with conventional medicine.

5.3.2. Observational Study of the Diabetic Cohort

A total of 222 patients (respondents with confirmed clinical diagnosis of Diabetes mellitus) were interviewed, gave their consent and were enrolled for the study. Nine were insulin dependent and four did not have a confirmed diagnosis and were all excluded. Thirteen (6.9%) were lost to follow-up. One hundred and ninety five - 195 i.e. { 56 (28.7%) using traditional medicine only, 97 (49.7%) taking conventional medicine and 42 (21.5%) using both} were monitored for twelve months with intermittent checks every three months. Figure 10 - **THE PIE CHART**) overleaf is an illustration of responders. The mean age was 51.1 +/- 12.9 years (range 20- 62) years. The median duration of the disease was 5.9 (0 - 51) years.

FIGURE 10



Group A = Traditional Medicine Users
Group B = Allopathic Medicine Users
Group C = Users of both types of Medicine

TABLE XIII

**DISTRIBUTION OF SAMPLE DEMOGRAPHIC CHARACTERISTICS
BY GROUPS**

		Group A	Group B	Group C
Characteristics		n = 56 (28.7%)	n = 97 (49.7%)	n = 42(21.5%)
Age	20-29	0	4	3
	30-39	5	12	2
	30-49	17	19	6
	50-59	26	43	21
	> 60	8	19	10
Sex	Males	7	36	13
	Females	49	61	29
Employment Status				
	Pensioners	17	27	12
	Homemakers	26	43	16
	Employed	5	11	7
	Not-employed	6	8	5
	Other	2	8	2
Total		195 = 100%		
Male / Female ratio		2 : 5		

* A= Traditional Medicine Users, B= Allopathic Medicine Users, C= Both Medicine users.

5.3.2.1 The Characteristics of the users of Herbal Remedies (Group A)

The average age was 49.4 yrs (range 27-62) with seven male and forty nine female. They were mostly pensioners and homemakers which makes them an indigent group as far as income is concerned. Only 5 (12%) were employed and money was a problem for most (money for clinic fees when they had to pay and transport). Few lived at a distance that was over 40 km from the nearest clinic or hospital. Most of them lived within 20km and yet, transportation cost was commonly cited as the reason for poor clinic attendance. The commonly prescribed antidiabetic drug on their record cards (when they attended a diabetic clinic) was noted to be glibenclamide though sometimes metformin was added.

The majority of traditional medicine users 52 (93%) believed that the herbal preparations they used was effective and none of them had been admitted for ailments that suggested herbal poisoning and two in this group actually thought that the tablets they get at the clinic makes them feel worse. Neame and partner in 1964, reported fatal hypoglycaemia after consumption of unspecified herbal medicine in a study conducted in South Africa and this was associated with hepatic and renal necrosis. Du et al, 1995, reported several episodes of adverse events associated with the use of Chinese herbal medicines. No reports of

complications or mortalities were associated with the herbal remedies used in this study. Only 2% of this group, complained of diarrhoea and had to stop using the herbal preparation though they found it useful in controlling blood sugar.

Out of the whole group (n=56), 3 (5%) were hesitant as far as the effectiveness of the herbal remedies were concerned, and only one was definitely convinced that traditional medicine does not work.

5.3.2.2. Characteristics of the users of Allopathic Medicine (Group B)

Unlike the above group that comprised seven times more females than males, the gender distribution in this group was in the ratio of 1:2. Their ages ranged between 28 and 64 yrs, with an average of 51years. Similar employment status to the first group was reported by these respondents with largely pensioners and homemakers making up the majority. Fifty five (57%) lived within 5 km of a health centre and only 11 (11%) lived at a distance over forty kilometres. The clinic fees and waiting times were the most reasons for not attending diabetic clinics regularly. They only went to the clinic when there was no medication left, when they were sick or need to check on their sugar levels or blood pressure. More often, where and when possible, they simply sent their relatives to collect medication for them.

5.3.2.3.The Characteristics of the users of Herbal Remedies and Allopathic Medicine

(Group C)

The average age of this group was 49.6 (range 36-65) years with a similar ratio (1: 2) male to female to the allopathic medicine users group. Most of them were again homemakers and pensioners comprising 79% of the group. Only 17% was employed (including self-employed). They mostly lived within 20km of hospital or health centre and this (distance and transport cost) was cited as the most common hindrance to clinic attendance. Few (9.5%) lived at a distance above 40km.

Distance meant different things to different people; some to private doctors or traditional healers (by-passing nearby clinics and hospitals).

The most intriguing aspect of this group was that most of them were using traditional medicine that was self-prescribed. Either they got it (herbal preparation) from the “bus stop”, or pick up intshungu from the veld themselves, used garlic or followed “chemist’s advise” on alternative medicine to conventional sulfonylureas prescribed. The ‘alternative medicine’ (self-medication) they bought mostly from pharmacy shops was “ isibiba samaNdiya” and garlic tablets. Upon investigation this turned out to be dried aloe sap that is

sold in brown crystal form. Few (33%) got their herbal remedies from traditional healers.

There was this perception that if one had to take medication for a chronic disease, it was necessary to periodically substitute this with herbal remedy in order to give the body a rest from medication and its blood impurities.

Glibenclamide (Daonil ® or Glycomin ®), sometimes with metformin (Dextin ® or Glucophage ®) added, were the most commonly prescribed conventional medicine used. Tolbutamide (Rastinon ®) and Gliclazide (Diamicron ®) were rarely used.

Similar to the above two groups (Group A & B) financial problems and distance were the major causes for defaults in clinic attendance. The reasons that made them go to health facilities were illness, collecting medication and checking glucose levels or blood pressure. Only one member of this group belonged to a medical aid scheme.

The majority, twenty nine respondents (69%) from this group were convinced that their glucose levels were controlled because of the use of herbal medicines. Three (7%) was borderline and one (2.4%) emphatically said it had no effect.

The following table (Table XIV) depicts some of the common reasons that were hindrances or facilitated clinic attendance and the percentage times they were quoted.

TABLE XIV

FACTORS INFLUENCING DIABETIC CLINIC ATTENDANCE

FEATURES HINDERING REGULAR CLINIC ATTENDANCE (n=195)

- Distance and transportation (29.7%)
- Costs and clinic fees (32.3%)
- Waiting times at the clinic (11.3%)
- Lack of appropriate care, critical tests and procedures, drugs (8.2%)
- Getting time off work (1.5%)

REASONS FOR ATTENDING HEALTH FACILITIES (n=195)

- Sickness (mostly not diabetic related) (33.8%)
- Replenishing medication (51.8%)
- Need to check blood glucose levels and blood pressure (35%)

5.3.2.4. Concomitants of Diabetic Clinic Attendance

A very small percentage, 2% of the respondents (n=195) had medical insurance.

In the absence of medical aid, they were relying on the state health for their health care needs. According to the Andersen and Aday model (1974), health services utilisation is influenced by predisposing, need and enabling factors.

5.3.2.4.1. Need Characteristics

Need characteristics relate to perceived or self-rated health status and they could be subjective or objective if a medical status scale is constructed and used as a measure. How one perceives his or her physical health and functional ability determines when they should pay a visit to a health centre or a doctor.

Once the need has been established, other factors; enabling and predisposing factors are considered. In this study, the need comprised of medication, to check on blood glucose levels or simply sickness (other conditions unrelated to diabetes).

5.3.2.4.2. Enabling Characteristics

These are measures of use of health services and their affordability - those factors that hinder or facilitate use of a service once a need has been recognised. The hindrance mostly frequently mentioned was the respondents financial status. Most of them were pensioners or homemakers (which means they depended on husbands or relatives who were migrant workers somewhere far away, for income). As a result, the distance to the nearest clinic, though most of them lived within 20km, and the transport cost was a big issue. They also, at some stage in the study (though this was later changed to free, early in 1995) had to pay R3 - R4 clinic fees. That, coupled with transport costs and waiting times at the health centres, contributed towards the poor clinic attendance.

Distance and transport costs meant different things to different people. Those who favoured the use of traditional medicine for their illness, complained that the healer who could or had helped them in the past was located far away and they could not go there as regularly as they wanted. Some did not seem to mind paying the traditional healer's fee (R60-R120) compared to the low clinic fees. On the other hand, they may have been desperate to be cured, if they thought that the biomedicine was not of any help.

5.3.2.4.3. Predisposing Characteristics

These are exogenous characteristics of individuals that may affect need or recognition of need for health care services including physical functionality of the individual. The perceived state of physical health or impaired functional status coupled with depression and anxiety, influenced the respondents willingness to attend regular clinics. The level of education of respondents and their understanding of the disease state played a major role in the regularity or irregularity of their attendance. The study site being in a rural area, most of the respondents had very little understanding of the disease and what they should do to control it or prevent complications.

Another contributory factor was the shortage of drugs or lack of testing equipment related to their disease; blood glucose tests or even urine strips were often not available.

These factors explained 21% of variation in diabetic clinics attendance.

5.3.2.5. Comparative Overview of the need, enabling and predisposing factors

The predisposing characteristics contributed minimally to the amount of variance - only 0.8% in the use of traditional medicine. Need characteristics explained 6% of variance; self-assessed health was statistically significant with self-rated health being more important than other characteristics. Those who were objectively or subjectively in poorer health or had poor control of their blood glucose, were more likely to be taking both traditional remedies and allopathic medication. Hence, the reports of monilial infection and blurred vision were more commonly reported by this group (Group C).

It therefore comes as no surprise that poor control of glucose levels (symptomatic) and the presence of a chronic condition, seems to be the major determinant of traditional medicine use. The factors influencing the choice of traditional medicine use being better explained by multiple factors rather than by a single characteristic.

5.3.3. Disease Outcome Measures.

Adherence to treatment was very erratic across the board. The respondents adherence to a treatment schedule, whether conventional or traditional, indicated desperation and lack of knowledge of the disease process and management. Very

few 23 (12%) took their medication regularly, followed the recommended diet strictly or exercised regularly as recommended. Only four (2.1%) did self-monitoring procedures such as checking their own urine or blood glucose levels, mostly because they could not afford to buy the necessary equipment such as glucometers and dipsticks. More often than not, they would try several treatment regimes, or go without treatment for weeks (as long as there were no severe symptoms of hyperglycaemia) when they could not go to clinics or healers. Transport, money or medicine being out of stock at the clinics were cited as the general reasons.

Logistic regression analysis was performed to assess the independent nature of the risk factors for Diabetes mellitus (elevated Blood Pressure {BP}, gender and age). A significant correlation was observed between the levels of diabetes and hypertension demonstrating a highly significant trend with age ($p < 0.5$).

Variables known to be associated with hypertension risk in the general population [Sprafka et al, 1988; Sharma et al, 1989; Chahal et al, 1985] were also associated with hypertension among diabetic individuals, i.e. older age (Odds ratio (OR) = 4.1), being female (OR = 3.9) and hypertensive (OR = 3.8) were significant independent risk factors for diabetes.

The summary of this analysis is presented in Table XV overleaf.

TABLE XV

**MULTIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH
DIABETES MELLITUS IN THE SAMPLE**

Interval		Odds Ratio (OR)	95% Confidence
Age	20-29	0.9	0.4-1.7
	30-39	1.4	0.9-2.1
	40-49	2.8 *	1.8-4.4
	>50	4.1 *	1.03-19.8
Sex	Male	2.5	1.3-4.9
	Female	3.9 *	1.8-13.3
Hypertensive	Yes	3.8 *	2.1-7.4
	No	1.6	1.2-2.0

*Statistically significant, $p < 0.05$.

Diabetic foot ulceration, was the most common complication of diabetes found to occur in all three groups. Because of poor care, and lack of advice on nail care and hygiene by health care workers, this was common in 63% (123 out of 195) of the respondents. The presence of callus (a known predictor of ulceration) was reported by 47% of respondents and this was evidently the greatest cause for concern among the respondents. Three amputations were recorded during the study period of which two were sample members. This variable was a highly significant predictor of poor control and poor monitoring of blood sugar levels.

Regular measurement of haemoglobin A1c values enables the prescriber to adjust the treatment regime according to levels thus improving the metabolic and blood glucose control with a subsequent improved diabetic control as a whole in a clinical setting [Nathan et al, 1984; Schwartz & Clancy, 1984; Gabbay et al, 1977; Sharma et al, 1989; Goldstein et al, 1982; Anon, 1980; Stickland et al, 1984; Larsen et al, 1990]. It was the intention of this study project to measure the HbA1c levels, at least at three-months intervals and compare the trends. However, due to financial constraints and other related resources, these tests were not completed.

Consequently, the initial HbA1c levels recorded when the respondents were

enrolled could not be compared with anything. The initial levels recorded were markedly elevated in all three groups (12.37 +/-0.46 g/dl) and were found to be highly significant ($p < 0.001$). The normal range is 5.5 - 8.5 g/dl. Out of 211 diabetic patients that were admitted at Hlabisa Hospital during the twelve months of the study period, 29 (14%) had blood glucose levels that were erratic. In the current study, 3.1% (6 out of 195 respondents) had three or four follow-up interviews with complete blood glucose levels. Consequently, this parameter could not provide meaningful comparison of the groups.

Depression in diabetes resulting from, or leading to family dysfunction and eventual floundering in the diabetic control, was not uncommon. Winocour et al, 1990; in their study, found abnormal depression ratings more in women than men, although a notably low feeling of anxiety and insecurity was observed more frequently in men. It was beyond the premise of this study project to measure that quantitatively, but a subjective assessment (from patients themselves) indicated a similar pattern of insecurities and depression. This was due to several factors; the lack of control of their ailment and the complications thus resulting, the attention given to them by health workers, the procedures (or lack of them) performed such as blood glucose tests or BP measurements. It was observed that in most diabetic clinics, patients were only given their monthly supply (which sometimes was out of stock - more often than not) and sent home.

No proper education and counselling was given to them at the diabetic clinics about foot care, diet, importance of proper sugar control, exercise etc. Several studies [Wensing et al, 1994; Cleary et al, 1988; Bestvater et al, 1988; & Cymbalist et al, 1988; Skyler, 1978] that dealt with patient satisfaction as an indicator of quality care, showed that patient involvement in their own care contributes to the quality of that care. They discovered that this can be improved when a patient contributes towards his/her own care, by being made to feel they are part of the team.

Firstly, if patients are well informed by providers about their disease state and the prognosis, and secondly, being given responsibility to monitor certain aspects of care, such as diet, self-monitoring (BP or glucose measures) etc, they are made to feel responsible and learn to manage their disease state much better [Balant, 1981; Skyler, 1978; Koda-Kimble et al, 1995; Jackson et al, 1981]. This was partly one of the reasons why patients resorted to traditional medicine when their blood sugar levels were uncontrolled and also the reason that led to depression and anxiety. This was found to be more common in the groups using traditional medicine either alone or together with the conventional medicine ($p = 0.019$) than the group using allopathic medicine only.

Edeling et al in their study conducted in the Free State in 1990 reported that 12% of Black diabetic patients were referred for routine eye care. Most of them were referred with visual acuity of 6/18 or worse. Many were seen very late with an advanced sight-threatening retinopathy. In this study, very few +/- 5% reported to have been referred for ophthalmological care though complaints about blurred vision were common across the board in all three groups - 138 (71%). The exact extent of this and any other changes of the retina that usually occur with poor control could not be determined .

Second to complaints of blurred vision, were complaints of monilial infection (indicated by respondents reporting itching and skin rash in the groin areas) which were recorded in 76% of cases in their follow-up interviews. This was more common in the group using both traditional and conventional medicine - Group C (p-value=0.021).

None the less, 29% of those who said they preferred modern medicine, used a combination of modern and traditional medicines. Culturally based myths and beliefs play a large role in the perceptions and attitudes towards diabetes treatment in black communities.

Those who preferred traditional medicine cited the following reasons for patronising it; cost, closer and accessible, no intimidation, and better attention, and the fact that traditional medicine can find social causes of the illness (e.g. witchcraft and supernatural) and other manifestation of a disturbed equilibrium of life.

Overall, responses of the patients to the survey concerning their attitude towards health care especially diabetes care, reflected that the respondents' attitudes were consistent with the findings of other studies [Anderson et al, 1990]. These studies, conducted in Michigan, came up with factors representing patient's attitude towards the need for special training for those who provide diabetic care, patient autonomy, patient compliance and team involvement of both patients and providers. In this study, patients felt alone and were not satisfied with the kind of treatment they received. Consequently, they had to do what they thought was best for them in order to survive.

5.4. Limitation of the Study

Some of the important limitations of the study must be recognised. First, non-randomized clinical trials are susceptible to numerous types of bias, including selection bias; and this trial was no exception.

5.4.1. Sampling:

Convenience sampling may be an easy way out, especially in studies like this that are conducted in a rural area with no street addresses, or telephones to conduct meaningful follow-up interviews and transportation problems abound, but they might not give reliable information. With better planning and availability of funds, the trial could improve greatly and we hope to do that at a later stage. For this particular case it was sufficient to monitor the disease outcome in addition to HbA1c; the incidence of vision deterioration, kidney complications, gangrene or other skin disorders associated with Diabetes mellitus.

5.4.2 Confounders:

The second limitation involved the difficulty in analysing the confounding effect of past drug use (be it traditional or conventional) in evaluating the present pattern. This could not be ruled out and it might have affected the present results somewhat.

5.4.3. Beliefs and Religion:

A third limitation relates to fear of religious and social disapproval (especially from modern medical practitioners and “christians”) that is connected to the stigma attached to the use of traditional medicine, may well have made some respondents reluctant to admit that they used any traditional remedies and thus biased the data in favour of modern medicine and self-medication.

5.4.4. Sample Size:

The fourth limitation is related to the size of the sample. As explained earlier, due to the difficulty encountered in tracing the patients in a rural setting, the originally calculated sample size was not attained. In addition, not all the respondents who were enrolled could be followed throughout the period of the study. Due to attrition, 16% were lost to follow up. Though this was taken into consideration in the final analysis of covariance, the effect it had on the diminishing sample size cannot be overlooked. Thus, the number of patients studied and followed up represents a relatively small “slice” of diabetic patients in the study areas.

5.4.5. Monitoring Tests:

It was the intention of this study to monitor blood glucose levels of the patients on regular basis as well as the glycosylated haemoglobin levels in order to establish

the effectiveness of the medication the subjects were taking (be it herbal remedy, allopathic medication or both). The blood glucose levels collected could not yield meaningful results because of the attendance of the respondents at the diabetic clinics. This was very erratic and riddled with gaps of non-attendance for any trends and patterns (of the blood glucose levels) to be established. With regard to HbA1c, the tests were too costly and the limited funding of the project could not accommodate the cost. In addition, there were serious logistic issues regarding transportation of these samples to the laboratory from clinics (approx 600km away) in a timely fashion, that could not be overcome.

5.4.6. Quality of data in Medical Records:

Although an attempt was made to use reliable and valid methods to collect data, the measurement work was restricted to information available from medical records (which were often incomplete) and inherent limitations of self-reported information.

5.4.7. Analytical Bias:

Last but not least, even though statistical methods were used in “adjusting” results when making comparisons, inferences based on any observational studies must be accepted with caution.

5. 5. CONCLUSION

The findings of these studies in human subjects, although observational, and uncontrolled demonstrate patient satisfaction with the results they obtained in using alternative or traditional medicine. The sustainability of prolonged glucose-lowering effect of these herbal preparations were not confirmed. No untoward effects or reaction was attributed to the use of the herbal remedies.

These results have important implications for health policy planning as well as other care services and there is indeed a need to implement appropriate therapeutic strategies. This study should serve as a springboard for more studies, with better control and more generalisability available which is lacking in this study.

Chapter 6

6.1. FUTURE CONSIDERATIONS AND SUMMING UP

This study was successful in achieving its initial objective; that of preliminary evaluating the safety and efficacy of the herbal remedies used in Northern KwaZulu-Natal in the treatment of Diabetes mellitus. HP-2 demonstrated hypoglycaemic effect that was comparable to that of Glibenclamide. Although HP-1 failed to exhibit noticeable antidiabetic effect, under different conditions it could have some therapeutic value. The results of the epidemiological study were even more intriguing than anticipated in the sense that in addition to positive results, the study also managed to glean and uncover much more in depth insight of the reasons, the attitudes and acceptability of traditional medicine, the problems encountered in attending diabetic clinics by rural communities and the quality of care given in these areas.

Traditional Medicine has many advantages as well as disadvantages that need to be carefully considered, for the benefit of health care delivery to all people [Abdool Karim et al, 1994; Gumede, 1990]. The advantages of traditional medicines include the fact that they are accessible, and sometimes more acceptable to a larger population [Anyinam, 1987; Green & Makhubu, 1984; Upvall, 1992]. The disadvantages include imprecise and sometimes doubtful

efficacy, could be unhygienic and may sometimes have a witchcraft aspect to it.

However, if these are addressed, traditional medicine can become an integral part of health care delivery.

On the other hand, synthetic products used, do not cure diabetes and they do not necessarily correct the fundamental biochemical lesions or reinstate a normal pattern of glucose homeostasis in diabetic patient. Scientists therefore have a great responsibility and challenge to redress the neglect which many of their colleagues of the past accorded traditional medicine and should continue seeking a cure for this crippling disease.

Self-monitoring - a key to management and control of sugar levels in Diabetes mellitus, was not encouraged. The majority of respondents have never checked their own urine sugar levels, let alone blood glucose tests. They only rely on clinic nurses, once a month, or even less than that if relatives are sent to collect medication for them or when the tests materials are temporarily unavailable at the clinic. Findings of this study showed great need for education for those providers who tend to diabetic patients and health promotion, for the disease to be appropriately managed.

6.2. RECOMMENDATIONS

6.2.1. The doses for traditional medicines needs to be refined and standardised.

This is only possible with more research of herbal medicines.

6.2.2. Only 5-15% of the world's plants have been scientifically investigated [Abebe, 1990]. The government should channel more funds into traditional medicines research such as TRAMED, various universities that conduct research in indigenous medicinal plants, conservation strategies and formal institutes of traditional practitioners and traditional healing systems. This would serve to encourage researchers to conduct more controlled studies of microvascular, macrovascular or neuropathic complications that are usually associated with traditional therapies.

6.2.3. Collection and dissemination of information pertaining to traditional medicine. A kind of a database coupled with a clearing house for this information that could be accessible to both traditional and medical practitioners.

6.2.4. Educational programmes with the aim to educate the community and the traditional healers as well as to change the attitudes of biomedical sector members

and allied professions on proper diabetic care education. Failure to counsel patients appropriately and adequately can mask serious underlying problems which otherwise could be identified at an early stage before complications set in.

6.2.5. Set up a multidisciplinary research programme including various aspects of medicinal plant research, validation of popular traditional medicine therapies and promotion of research activities on the integration of various systems of medicine.

6.2.6. A creation of a national drug formulary or pharmacopoeia of traditional medicines would very useful.

6.3. FINAL COMMENTS

As a final conclusion, one can say that the importance of Traditional medicine cannot be underestimated, it will have to play a significant role in South Africa in delivery of health care. Since the two forms of medical care continue to coexist and complement each other to a certain extent, they should find ways to collaborate actively. In the interest of the patient, who is the first priority, community health programmes must take cognizance of the cultural realities of the population. These results have important implications for health policy and

other care services in an attempt to provide and maintain quality and higher levels of health care for the rural masses.

Validation studies on locally used plant remedies for the treatment of diabetes, could lead to the adoption of some safe and affordable remedies that are acceptable to both patients, medical and traditional practitioners. For South Africa the primary health care potential is enormous, if its medicinal plant resources are fully exploited. It seems more appropriate to give serious consideration to indigenous medicinal plants where the majority of the population's medical health care is largely served by medicinal flora.

This work should be viewed as early, path-finding research in this direction to encourage more structured and controlled studies in evaluation of traditional medicine.

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ANNEXURE I



University of
Durban-Westville

PRIVATE BAG X54001 DURBAN
4000 SOUTH AFRICA
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TELEX: 6-23228 SA
FAX: (031)820-2383
☎ (031)820-9111

C3/6
RESEARCH ADMINISTRATION

12 December 1994

Ms TTZ Page
Department of Pharmacy

Dear Ms Page

ETHICAL CLEARANCE: NUMBER 94150

I wish to confirm that ethical clearance has been granted in respect of the following project:

"An investigation of the Antidiabetic Herbal Remedies used by Traditional Healers in Northern Natal and their Effect on Serum Glucose Level"

Thank you

Yours faithfully

.....
R NAIDOO
(for) HEAD: RESEARCH ADMINISTRATION

PS: The following general condition is applicable to all projects that have been granted ethical clearance:

THE RELEVANT AUTHORITIES SHOULD BE CONTACTED IN ORDER TO OBTAIN THE NECESSARY APPROVAL SHOULD THE RESEARCH INVOLVE UTILIZATION OF SPACE AND/OR FACILITIES AT OTHER INSTITUTIONS/ORGANISATIONS

CC: THE HEAD: PHARMACY

ANNEXURE II

UNIVERSITY OF DURBAN-WESTVILLE
BIOMEDICAL RESOURCE CENTRE
BRC/A003/94-001

PHYSICAL EXAMINATION FORM

ANIMAL I.D. NO.: _____ CAGE NO.: _____
DATE : _____ TIME : _____
BODY MASS : _____

GENERAL OBSERVATION

HABITUS : _____
BODY POSTURE : _____
PHYSICAL CONDITION : _____
RESPIRATORY : _____
OBVIOUS ABNORMALITIES: _____

SUPERFICIAL PALPATION

SKIN : _____ EARS : _____
COMMENT : _____ COMMENT : _____
LYMPH NODES: _____ GENITALIA : _____
COMMENT : _____

HEAD AND NECK

MUCOUS MEMBRANES : _____ EYES : _____
NOSTRILS : _____ COMMENT : _____
BUCCAL CAVITY : _____
COMMENT : _____

ABDOMEN

ABDOMINAL PALPATION: _____

OTHER : _____

SIGNATURES:

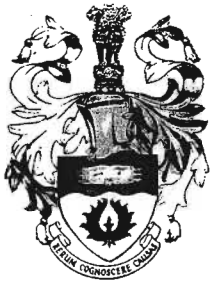
EXAMINED BY : _____

RECORDED BY : _____

SCORE

	<u>HABITUS</u>		<u>SKIN</u>
0	Dead/Moribund	1	Normal
1	Inactive/Sluggish	2	Abnormal (comment)
2	Depressed		
3	Active/Alert		<u>EARS</u>
4	Hyperactive	1	Normal
	<u>BODY POSTURE</u>	2	Abnormal (comment)
1	Hunched		
2	Recumbent		<u>GENITALIA</u>
3	Standing	1	Normal
4	Rears	2	Abnormal (comment)
	<u>PHYSICAL CONDITION</u>		
1	Emaciated	1	Generalised
2	Thin	2	Localised
3	Normal	3	Mild enlargement
4	Obese	4	Moderate enlargement
		5	Severe enlargement
	<u>RESPIRATION</u>		
1	Normal		<u>MUCOUS MEMBRANES</u>
2	Shallow and fast	1	Normal
3	Shallow and slow	2	Anaemia
4	Deep and slow	3	Mild inflammation
5	Deep and fast	4	Moderate inflammation
6	Coughing/Wheezing	5	Severe inflammation
	<u>EYES</u>		
1	Normal	1	Normal
2	Abnormal (comment)	2	Discharge
	<u>BUCCAL CAVITY</u>		
1	Normal		<u>ABDOMINAL PALPATION</u>
2	Abnormal (comment)	1	Normal
		2	Pain
		3	Distention
		4	Pain and distention

ANNEXURE III



University of Durban-Westville

PRIVATE BAG X54001 DURBAN
4000 SOUTH AFRICA
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TELEX 6-23228 SA
ACADEMIC FAX (031) 820-2383
ADMINISTRATION FAX (031) 822192
☎ (031) 820-9111

9409225 Student Affairs

3 January 1995

Ms T.T. Ziqubu-Page
72 Bowen Avenue
GLENMORE
4001

Dear Ms Ziqubu-Page

TITLE AND SCHEME OF WORK : PHD. DEGREE

I wish to inform you that the University Senate has approved the title and scheme of work submitted by you for the PhD. degree.

Title : " An investigation of the Antidiabetic Herbal Remedies used by Traditional Healers in Northern Natal and their effect on Serum Glucose level.

Promoter : Prof C.M. Dangor

Joint Promoters : Dr E.L. Makubalo
Dr M. Chetty

Yours faithfully

A handwritten signature in black ink, appearing to read 'Sempersad', written over a dotted line.

(FOR) REGISTRAR (ACADEMIC)
P. SEWPERSAD - CHIEF ADMISSION OFFICER



University of
Durban ~ Westville

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940925 STUDENT ACADEMIC ADMINISTRATION

19 February 1997

MS T.T. ZIBQUBU-PAGE
3 WOUTER STREET
RIDGEWAY EXTENSION 3
P.O. BERTSHAM
2091

Dear Ms Ziqubu- Page

CHANGE OF TITLE

I have pleasure in informing you that your request for a change of title has been approved by the University Senex. Your title now reads as follows:

"AN INVESTIGATION OF THE HERBAL REMEDIES USED BY TRADITIONAL HEALERS IN IN NORTHERN NATAL AND THEIR EFFECT ON BLOOD GLUCOSE LEVEL".

Kindly use this approved title when submitting your dissertation for examination.

Yours faithfully

(for) REGISTRAR (ACADEMIC)

P.K. RAMLACHAN
PRINCIPAL OFFICER
GRADUATE AND INTERNATIONAL STUDIES UNIT

c.c. Prof M A Seedat
Prof C M Dangor

APPENDIX I



- 7 - Other (describe)
- 4. Vocalization
 - 1 - None
 - 2 - Yes
- 5. Palpebral Closure
 - 1 - Eyes wide open
 - 2 - Eyelids slightly drooping
 - 3 - Ptosis (eyelids drooping approximately halfway)
 - 4 - Eyelids completely shut
 - 5 - Cannot observe eyes without disturbing the animal

Observations while Handling - Response/s

- 1. Ease of removing from cage
 - 1 - Very easy (body limp, no resistance, unresponsive)
 - 2 - Easy (little resistance to being picked up, maybe vocalization)
 - 3 - Moderately difficult (rodent rears and shies away)
 - 4 - Difficult (runs around cage, hard to grab)
 - 5 - Very difficult (tail and throat rattles, attempts to bite)
 - 6 - Other (describe)
- 2. Ease of handling rodent in hand
 - 1 - Very easy (does not resist handling, completely unresponsive)
 - 2 - Easy (does not resist handling but is alert, some movement)
 - 3 - Moderately difficult (rigid, tense)
 - 4 - Difficult (squirming, twisting)
 - 5 - Very difficult (squirming, twisting, and attempts to bite)
 - 6 - Other (describe)
- 3. Lacrimation
 - 1 - None
 - 2 - Slight
 - 3 - Moderate
 - 4 - Severe
- 4. Palpebral closure
 - 1 - Eyes wide open
 - 2 - Eyelids slightly drooping
 - 3 - Ptosis (eyelids drooping approximately halfway)
 - 4 - Eyelids completely shut

5. Piloerection

- 1 - No
- 2 - Yes

6. Salivation

- 1 - No
- 2 - Yes

7. Vocalization

- 1 - No
- 2 - Yes

Observation in the Open Field

1. Rears- defined as each time the animal raises up and the front legs come completely off the horizontal surface. This includes when the animal uses the side or lip of a cart top as support.

2. Defecation (at end of 3 min)

- # - specify number of fecal boluses on paper
- D - Diarrhea

3. Urination (at end of 3 min)

- # - Specify number of pools of urine on paper
- X - Overlapping pools of urine (count number of overlapping pools)

4. Clonic Convulsions

- 1 - None
- 2 - Chewing (clonus of jaw)
- 3 - Quivers of limbs, ears, head, skin
- 4 - Mild tremors, jerking
- 5 - Whole body tremors

5. Tonic Convulsions

- 1 - None
- 2 - Tonic (constant contraction and extension of limbs)
- 3 - Opisthotonus (head, body and limbs rigidly arched backwards)
- 4 - Emprosthotonus (head, body and limbs extended forwards)
- 5 - Popcorn (animal repeatedly pops in air)
- 6 - Asphyxial (bout of severe clonic-tonic convulsions resulting in difficult respiration, postictal depression or death)

6. Gait Type

- N - Normal
- A - Ataxic, excessive swaying, rocking or lurching
- H - Hindlimbs splayed or dragging
- FO - Feet markedly pointing outwards from body
- F - Front limbs dragging, unable to support body
- HU - Hunched body
- T - Walks on tiptoe
- F - Body drags or is flattened against surface
- M - Insufficient Spontaneous Movement to assess gait

7. Gait Score - ranking of gait abnormalities

- 1 - Normal
- 2 - Slightly abnormal
- 3 - Moderately abnormal
- 4 - Totally abnormal
- 5 - Insufficient Spontaneous Movement to score gait

8. Mobility Score

- 1 - Normal
- 2 - Slightly impaired
- 3 - Moderately impaired
- 4 - Totally impaired (ataxic)
- 5 - Insufficient Spontaneous Movement to score mobility

9. Level of Arousal

- 1 - Very low (comatose, stupor)
- 2 - Low (somewhat stuporous but with some head and/or body movement, exploratory movement virtually absent)
- 3 - Slightly low (slight stupor, some exploratory movements with periods of immobility longer than approximately 30 seconds)
- 4 - Normal (alert, exploratory movements)
- 5 - Slightly high (excited, tense, sudden darting or freezing)
- 6 - High (hyperalert, very excited, sudden bouts of body running movements)

10. Vocalization

- 1 - None
- 2 - Yes

11. Stereotypy - record any behaviors that are excessive or repetitive such as circling, stereotypic grooming, pacing, repetitive sniffing, or head weaving.

- 1 - None
- 2 - Yes (describe)

12. Bizarre Behavior

- 1 - None
- 2 - Yes (describe)

Observation of Reflexes

1. Object Approach Response (approach rodent with a blunt object, e.g. pen).

- 1 - No reaction
- 2 - Rodent freezes
- 3 - Normal rat slowly approaches and sniffs or turns away
- 4 - More energetic response than 3, includes vocalizations
- 5 - Bizarre reaction (jumps, bites, attacks)

2. Touch Response (touch rump gently with blunt object).

- 1 - No reaction
- 2 - Slight reaction, some evidence that touch was felt
- 3 - Normal (may slowly turn or walk away)
- 4 - More energetic than 3, may vocalize
- 5 - Bizarre reaction (jumps, bites, attacks)

3. Click Response (use a metal ~~clicker~~^{clicker} to make one sharp sudden noise).

- 1 - No reaction
- 2 - Slight reaction, some evidence that noise was heard
- 3 - Normal (startles, alerts and freezes)
- 4 - Increased Reaction
- 5 - Bizarre reaction (jumps, bites, attacks)

4. Tail Pinch Response (metal ~~pincers~~^{thumb forceps} are used to squeeze the tail approximately 2 cm from tip).

- 1 - No reaction
- 2 - Slight reaction, some evidence that pinch was felt
- 3 - Normal (may turn or walk away)
- 4 - Increased reaction (more energetic than 3, may vocalize)
- 5 - Bizarre reaction (jumps, bites, attacks)

5. Pupil Response - The beam of a penlight flashlight is brought in from the side of the rodent's head and constriction of pupil is noted

- 1 - Pupil constricts (normal)
- 2 - Pupil does not constrict
- 3 - Pupil highly constricted

-
6. Air Righting Reflex (rodent is held in a supine position, dropped from a height of approximately 30 cm onto a padded surface and ease of landing is scored).
 - 1 - Lands with all feet on the ground
 - 2 - Uncoordinated landing
 - 3 - Lands on back
 - 4 - Does not move for 20 seconds
 7. Landing Foot Splay - refer to ~~the current revision of~~ TOX/003.
 8. Forelimb Grip Strength - refer to ~~the current revision of~~ TOX/004.
 9. Hindlimb Grip Strength - refer to ~~the current revision of~~ TOX/003.
 10. Body Temperature - record rectal temperature. Refer to ~~the current revision of~~ TOX/006.
 11. Other (includes torn toenails, broken teeth, and any other findings which may confound data).

APPENDIX II

Ref: s1995 - 2024.95

Mr M P Kruger
University of Durban-Westville
Private Bag X54001
Durban
4000



University of Pretoria

Private Bag X04 Onderstepoort 0110 Republic of South Africa
Tel (012) 529-8000 Fax (012) 546-3102

Faculty of Veterinary Science

Department of Pathology

Fax no. (012) 529 8303

29 August 1995

HISTOPATHOLOGY REPORT: BIOLOGICAL ASSESSMENT - MRS ZIQUBE-PAGE

Your reference: MPK/am; Our reference: S1995/95 - S2024/95; Date submitted: 23 August 1995

Species: Rat; Breed: (Sprague Dawley)

Specimen(s): Pancreas, liver and kidney in formalin for histopathology

RESULTS:

Three groups of rats (X,Y and Z, each containing ten rats) were submitted for histopathology. Specimens of the liver, kidney, spleen and pancreas were examined for each of the rats. Sections were processed routinely for histopathology and stained with haematoxylin and eosin, and examined with a standard light microscope

No specific lesions were detected in any of the groups. In all the groups a number of animals manifested scant to moderate accumulations of protein droplets (hyaline droplets) in the epithelial cells of the proximal convoluted tubules. These changes were not associated with specific lesions in the glomeruli

COMMENT: No lesions were detected in the three groups. The hyaline droplets reflect some glomerular damage, which appears to reflect the onset of chronic progressive nephropathy that is known to be a characteristic of Sprague-Dawley rats (Alden & Frith, 1991)

It thus appears that the compounds tested had no morphological effects at the levels administered, or that the time period of exposure was too short to detect toxic effects

If you need to further discuss the findings, feel free to contact me at any time

Yours sincerely

N P J KRIEK

PROF AND HEAD: DEPARTMENT OF PATHOLOGY

Ref: Alden, C. L. & Frith, C. H., 1991. Urinary system *In*: Haschek, W. M. & Rousseau, C. G., *Handbook of Toxicologic Pathology*, p. 365

22 November 1995:

Ref. No.	Histo no.	Remarks
A1	s2889.95	No lesions seen
A2	s2890.95	No lesions seen
A3	s2891.95	Mild to moderate multifocal tubular necrosis and cell swelling. Numerous hyaline droplets in the proximal tubular cells. No other lesions seen
A4	s2892.95	No lesions seen
A5	s2893.95	No lesions seen
A6	s2894.95	No lesions seen
A7	s2895.95	No lesions seen
A8	S2919.95	No lesions seen
A9	s2896.95	No lesions seen
A10	s2897.95	No lesions seen
B1	s2898.95	Few single necrotic hepatocytes; No other lesions seen
B2	s2899.95	Few foci of very mild hyaline droplet accumulation in the proximal convoluted tubules; no other lesions seen
B3	s2900.95	Mild scattered fatty changes in the liver (without specific distribution); No other lesions seen
B4	s2901.95	No lesions seen
B5	s2902.95	Very mild multifocal hyaline droplet accumulation in proximal convoluted tubular cells. Odd single necrotic cells were also present; No other lesions seen
B6	s2903.95	No lesions seen
B7	s2904.95	No lesions seen
B8	s2905.95	No lesions seen
B9	s2906.95	No lesions seen
B10	s2907.95	No lesions seen
C1	s2908.95	Mild multifocal steatitis of the mesenteric fat; No other lesions seen
C2	s2909.95	No lesions seen
C3	s2910.95	No lesions seen
C4	s2911.95	No lesions seen
C5	s2912.95	No lesions seen
C6	s2913.95	No lesions seen
C7	s2914.95	Mild diffuse tubular epithelial haemosiderosis; liver contains scattered Kupffer cells containing large aggregates of lipofuscin. The lesions in the kidney reflect prior systemic haemolysis; No other lesions seen
C8	s2915.95	No lesions seen
C9	s2916.95	No lesions seen
C10	s2917.95	Mild hepatocellular atrophy; No other lesions seen

The lesions seen in the individual animals are considered to be very mild and are likely to be non-specific; there was no pattern seen in the various groups nor were there consistent changes within groups

APPENDIX III

Ref.: UDW EC No. 94150



Universiteit van Pretoria

Privaatsak X04 Onderstepoort 0110 Republiek van Suid-Afrika
Tel (012) 529-8000 Faks (012) 546-3102

Fakulteit Veeartsenykunde
Department of Pathology

24 September 1996

Ms TT Ziqube-Page
Biomedical Resources Centre
Private Bag X54001
DURBAN

Dear Ms Page

HISTOLOGICAL ASSESSMENT OF TISSUE SAMPLES

The following are the results of rat organ samples (liver, kidney and pancreas) of 21 September 1995, ref. 94150 (22 November 1995) and 94150 (14 February 1996). The organs were examined blind (not having knowledge of treatment, not which were control or treatment groups). The results are for interpretation by the investigator

Should you require photomicrographs of the lesions seen in the various animals, I shall be happy to produce them for you

I will be happy to discuss these findings as they cannot be interpreted further without other relevant information

I trust that you will find these results to be of some value

Yours sincerely

A handwritten signature in black ink, appearing to read 'N P J KRIEK', is written over a light blue horizontal line.

N P J KRIEK
PROF AND HEAD: DEPARTMENT OF PATHOLOGY

21 September 1995:

Ref no.	Histo no.	Remarks
xx1	s2610.95	Mild multifocal pancreatic atrophy and fibrosis; No other lesions seen
yy1	s2611.95	Moderate multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
zz1	s2612.95	Mild multifocal exocrine pancreatic hypertrophy; No other lesions seen
xx2	s2613.95	Moderate multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
zz2	s2614.95	No lesions seen
xx3	s2615.95	Mild anisonucleosis in the hepatocytes; mild diffuse nephrosis characterized mostly by mild to moderate cell swelling; mild renal tubular dilatation; No other lesions seen
yy3	s2616.95	Mild to moderate anisonucleosis and mild hepatocellular atrophy; Moderate multifocal granulomatous steatitis in mesenteric fat; mild renal tubular dilatation; No other lesions seen
xx4	s2617.95	No lesions seen
yy4	s2618.95	Lesions masked by advanced autolysis; severe congestion of all the tissues; mild anisonucleosis of the hepatocytes
zz4	s2619.95	Mild multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
xx5	s2620.95	No lesions seen
yy5	s2621.95	Mild focal pancreatic atrophy and fibrosis (single focus); No other lesions seen
zz5	s2622.95	No lesions seen
xx6	s2623.95	No lesions seen
yy6	s2624.95	No lesions seen
zz6	s2625.95	Mild hepatocellular atrophy; Mild multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
xx7	s2626.95	Moderate hepatocellular atrophy; moderate multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
yy7	s2627.95	Mild multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
zz7	s2628.95	Mild multifocal granulomatous steatitis in mesenteric fat; No other lesions seen
xx8	s2629.95	No lesions seen
yy8	s2630.95	No lesions seen
zz8	s2631.95	Mild renal cortical tubular dilatation; mild hepatocellular atrophy; No other lesions seen
xx9	s2632.95	Mild multifocal cortical tubular dilatation; No other lesions seen
yy9	s2633.95	Mild multifocal cortical tubular dilatation; No other lesions seen
zz9	s2634.95	Mild multifocal cortical tubular dilatation; No other lesions seen

The lesions seen in these animals are very mild and mostly related to changes in the kidneys and the liver. The changes in the liver are limited to atrophy. The affected kidneys manifested varying degrees of tubular dilatation on the cortex; in all instances there was no accumulated material in the tubules but the epithelium manifested mild to severe atrophy of the epithelial cells. One would need access to the details of the experimental design to fully interpret the significance of the changes

14 February 1996 (The organs were examined blind (not having knowledge of treatment, not which were control or treatment groups. The results are for interpretation by the investigator)

Ref no.	Histo no.	Remarks Mild multifocal granulomatous steatitis in mesenteric fat;
A1	s500.96	Mild hepatocellular atrophy; No other lesions seen
A2	s501.96	Moderate hepatocellular atrophy; scant variation in hepatocellular nuclear size (anisonucleosis); scant hepatocellular fatty changes; moderate autolytic changes in the kidney and pancreas
A3	s502.96	No lesions seen
A4	s503.96	Moderate multifocal granulomatous steatitis of mesenteric fat (amorphous particulate matter present in some of the foci; No other lesions seen
A5	s504.96	Moderate multifocal granulomatous steatitis of mesenteric fat (amorphous particulate matter present in some of the foci; mild hepatocellular atrophy and cell swelling;
A6	s505.96	Moderate multifocal granulomatous steatitis of mesenteric fat (amorphous particulate matter present in some of the foci; mild hepatocellular atrophy and cell swelling;
A9	s506.96	Mild focal nodular pancreatic hyperplasia (exocrine); moderate multifocal renal cortical scarring with multifocal tubular atrophy and marked focal increase in nuclear size, clustering of nuclear and pronounced nuclear atypia; scattered small aggregates of haemosiderin and lipofuscin occur in these areas; mild hepatocellular anisonucleosis; No other lesions seen
B3	s507.96	Mild hepatocellular atrophy; No other lesions seen
B4	s508.96	Mild hepatocellular atrophy; No other lesions seen
B5	s509.96	Severe renal lesions characterized by hyaline casts, multifocal severe renal tubular atrophy and mild dilatation. In all these areas there is severe nuclear atypia characterized by increased nuclear size, irregular outline, large single nucleoli and piling-up of nuclei in certain of the areas. Aggregates of lipofuscin occur in macrophages in these areas in addition to a scant multifocal lymphocytic infiltrate. In the remaining normal renal tubules few cells are necrotic and being cast off into the lumen
B7	s510.96	Mild hepatocellular atrophy; mild diffuse renal haemosiderosis; No other lesions seen
B8	s511.96	Moderate hepatocellular atrophy; lesions in the kidney cortex as for B5, though the cellular atypia is not as advanced
B9	s512.96	Mild hepatocellular atrophy; mild multifocal exocrine pancreatic hyperplasia; mild diffuse renal haemosiderosis; No other lesions seen
B10	s513.96	Moderate hepatocellular atrophy; No other lesions seen
C2	s514.96	No lesions seen
C3	s515.96	No lesions seen
C4	s516.96	Mild hepatocellular atrophy; No other lesions seen
C5	s517.96	No lesions seen
C8	s518.96	Moderate multifocal pancreatic exocrine hyperplasia; mild focal steatitis; no other lesions seen
C9	s519.96	No lesions seen

The lesions seen in a number of these animals, particularly those in the kidney, and to a lesser extent in the liver, are considered to be of significance. The lesions reflect chronic changes induced most likely by some or other toxin that also has a marked effect on nuclear growth and development. The changes seen in the renal nuclei reflect those seen in pre-neoplastic lesions. It is suggested that these lesions may progress (to neoplasia?) in experiments of longer duration

It may be that some of the mild lesions seen in the kidneys in the animals in the earlier groups, may have evolved into the pronounced chronic changes seen in these animals

APPENDIX IV

TRADITIONAL HEALERS QUESTIONNAIRE

INTRODUCTION

Name of the interviewer _____

Briefly what the study is all about

1. Name: _____

2. Name of the place: _____

3. Yrs in Practice: _____

4. Previous address: _____

5. Any referrals from other places? : _____

6. List the diseases which you treat _____

7. Do you specialise in treating any disease? If yes, specify _____

8. Have you ever treated sugar diabetes before? _____

9. How do you diagnose it? _____

10. May I talk to some of the patients that you have treated? _____

11. How do you treat it _____
12. Do you mind telling us what goes into the preparation: the plants used, whether it's a root, bark, leaves, flowers or seeds
13. Are there particular times during the day or season that these are collected and why?
14. Are there any other additional ingredients added?
15. How is this (mixture) prepared?
16. How is this (medication) taken (dose);
- b) how often and
 - c) for how long?
17. How frequent (in the last month) do you encounter patients who have been to the hospital or doctor and feel they did not get the help they needed and they want YOU to treat them? _____
18. What is your opinion regarding allopathic medicine as opposed to traditional healing?

19. If you have problems treating certain ailments or cannot diagnose what is wrong with the patient, do you refer them to a) other Traditional Healer or

b) biomedical practitioners?

20. Is collaboration between ethnomedicine and biomedicine a feasible venture?

21. Do you have any suggestions how can this be achieved?

22. Do you foresee any conflicts and/or competition between ATHs and western practitioners over patients?

APPENDIX V

Interviewer:..

PATIENTS QUESTIONNAIRE

Date:

--	--	--	--	--	--

D D M M Y Y

1. Name.....Address & Phone:.....
.....

2. Hosp/Clinic No.

--	--	--	--	--	--

D D M M Y Y

3. D.O.B.....

--	--	--	--	--	--

4. Sex (M = 1; F = 2).....

5. Do you work for money or goods at all?
Yes = 1; No = 2.....

a. If yes, work address and phone #.....
.....

- b. If no,
- Would you describe yourself as:
- Homemaker
 - Student
 - Disabled
 - Unemployed (fit for work)
 -

On an old age pension

Other, specify.....

6. How far is the nearest clinic/hospital < 5km
 6-20km
 21-40k
 > 40km

7. How do you usually travel to clinic?
- | | |
|-------------------|----------------------|
| 1. Walk | 4. Bus or Taxi |
| 2. Taxi | 5. Train |
| 3. Bus | 6. Private Transport |
| 7. Other, specify | |
-

8. What is your average transport cost of visiting the clinic?
- | | |
|---------------|-----------------|
| 1. R0 | 4. R5 - R9.99 |
| 2. <R2 | 5. R10 - R19.99 |
| 3. R2 - R4.99 | 6. R20 - R30 |

9. How long does it usually take to get to the clinic?
- | | |
|-------------|---------------|
| 1. < 1 hr | 3. > 2 - 3 hr |
| 2. 1 - 2 hr | 4. > 3 hr |

10. About how much do you usually pay at the clinic?
- R

11. From when you arrive at the clinic grounds, how long do you usually wait before you are seen?
- | | |
|---------------|---------------|
| 1. < ½ hr | 4. > 2 - 3 hr |
| 2. ½ - < 1 hr | 5. > 3 - 4 hr |
| 3. 1 - 2 hr | 6. > 4 hr |

12. a. How long have you attended the diabetes clinic?
- M M Y Y
- b. When were you told you have diabetes?

c. Where else have you been treated for diabetes?

Specify

13. Have you ever been treated by a traditional healer? Yes

No

14. What is the name of the traditional healer you see/saw
.....

15. Have you ever used traditional medicine for treatment of this
ailment - diabetes? Yes

No

16. If yes: Did you prepare this yourself or did you go to the
traditional ealer? Self

Traditional Healer

17. Do you know what went into the preparation of this remedy?

Plant(s):.....

- 1 = Root;
- 3 = Leaves;
- 5 = Seeds;

- 2 = Bark;
- 4 = flowers;
- 6 = Other

specify.....

7 = Don't know

18. How often did you/are you taking this muti?

.....
.....

19. For how long have you been taking this muti?

.....

20. Did/Does it help? Did/Does your sugar goes down after taking it?

.....

21. Does/Did it make you feel better?

.....
.....

22. Do/Did you take this together with the medication you got from the hospital/doctor/clinic?
1 = yes; 2 = no

23. Do you think your sugar is controlled because of this traditional muti?

.....
.....

24. a. What usually makes you go to the diabetic clinic?

.....
.....

b. You might have other reasons for going to the clinic. Do you go to the clinic when?

1. You are ill

2. You have an appointment

3. You have no medication left

4. When you have the time

5. Other specify

25. What makes it difficult for you to attend the clinic?

.....

26. Is it difficult to attend because of:

Transport cost/distance

Clinic fees

Waiting times at clinic

Getting time off work

Other specify

27. Does your health make it difficult for you to do any work, chores around the house or walk for a distance?

.....
.....

28. Who told you you have diabetes?

- Doctor
- Nurse
- Traditional Healer
- Other, specify

29. What is diabetes?

(1 = correct; 2 = incorrect; 3 = don't know)

30. Do you know when your sugar is too low?

(1 = yes; 2 = no; 3 = don't know)

31. If yes, how can you tell?

.....

32. What do you do when your sugar is low?.....

.....

.....

33. a. What are you using or doing to help your diabetes?

- b. Are you using
- 1. Diet
 - 2. Injection
 - 3. Tablets
 - 4. Tradition
al Med

34. How do you know if your sugar is alright?.....

.....
.....

35. a. Do you ever check your own sugar? 1 = yes; 2 = no

b. If yes, how do you test it?

Urine

Blood

Other

36. Do you mind if we check your BP and blood sugar? 1 = yes; 2 = no

BP:
Blood Glucose:

Pulse:

APPENDIX VI

Questionnaire #
(Same as on patient's)

HOSPITAL/CLINIC RECORDS - DATA COLLECTION SHEET

Interviewer's ID: _____

Hospital : _____

Date : _____

1. Patient Name: _____ 2. ID: _____
3. Age : _____ 4. Approx DOB: _____
5. Sex : _____ 6. Weight : _____
7. Height : _____

8. Date of 1st Admission/Diagnosis: _____

9. Date of Discharge : _____

10. Diagnosis : 10.1 Initial : _____

10.2 Final Type I: _____

Type II: _____

11. Blood Glucose at

11.1 Admission : _____

11.2 Discharge : _____

12. G.T.T. : _____

13. Record of Risk Factors:

13.1 Family History

13.2 Alcohol Consumption

13.3 HBP

13.4 Pregnancy

13.5 Drug Induced

13.6 Other/Specify

15. TTO Treatment:

15.1: Medication (type & dosage): _____

15.2: Insulin (type & dosage): _____

15.3: Test Equipment: Urine

Blood

15.4: Councelling: Dietician
Nurse
Doctor
Pharmacist
Other

APPENDIX VII

CONSENT TO PARTICIPATE IN THE RESEARCH PROJECT

I, hereby give my consent to participate in the research study

Mina, nginika imvume yokungenela lolucwaningo

where traditional remedies used in treating diabetes mellitus are investigated. I therefore promise that all the lapho imithi yendalo esetshenziselwa ukwelapha isifo sikashukela izobe icwaningiswa khona. Ngakhoke

the information that is given here is true and to my best knowledge is all that I know about this subject. ngiyaqinisa ukuthi ngigeqe amagula olwazi lwami ngalesisifo nokwelashwa kwaso kusetshenziswa eyoMdabu.

I do this with understanding that this information will be kept secret and only be made available to the Ngikwenza lokhu nginesiqiniseko sokuthi konke engikushoyo lapha kuzogcinwa esilulwini esaziwa

authorized research personnel and under no circumstances will it be divulged to pharmaceutical companies abacwaningi abakhethiwe futhi alusobe (lolulwazi) ludluliselwe ezinkampanini ezakha imithi namaphilisi

or any other researchers without prior agreement or permission from me. ngaphandle kokuba sisayine isivumelwano esisha nalabacwaningi.

I, the undersigned,.....have agreed to participate voluntarily in this research
Mina, engisayine lapha, ngiyafakaza futhi ukuthi ngivumile ukujoyina lolucwaningo
ngaphandle kwempoqo.

Witness 1.

2.

Date/Usuku.....

STUDY SITE AREAS

