Re-Evaluation of Diabetes Mellitus Management in Nigeria Using Mechanized Herbal Extraction Technology: A Case Study

[1]E. Rove-Steiner and[2]E. E. Jumbo

[1]Dept. of Microbiology, College of Science and Technology, Poma Int'l Business University, Republic of Benin.
[2]Dept. of Mechanical Engineering, Faculty of Engineering, Niger Delta University, Bayelsa State, Nigeria.

Abstract: *Diabetes mellitus (DM) is a chronic, metabolic disease considered as one of the five leading causes of death in the world. It affects more than 422 million people worldwide and in the next 10 years, may affect five times more people than it does now. Medical authorities such as World Health Organization encourage research works on herbal medicines to actualize alternatives for its treatment, since oral anti-diabetic agents have side effects in the long term. To date, a vast number of plants have been evaluated for their anti-diabetic potencies. Although, Nigeria has a rich flora and an approximately 4.9% prevalence of diabetes mellitus, onlyfew ethno-botanical studies have been conducted on the possibilities of herbal treatment of diabetes. The aim of this study is to re-evaluate the modern approach to the management of diabetes in Nigeria. Thus, a case study of selected, approved health centers in Ipokia LGA of Ogun State, Nigeria was embarked on as to proffer herbal alternative to treatment for diabetes mellitus.In order to achieve this, a survey was conducted between December of 2018 to February of 2019 with 98 diabetic patients who consented to participate in the study through the assistance of some medical personnelof government approved health centers. Patients who used herbal therapies as well as orthodox therapies were documented. These patients used a variety of plants combinations alongside their conventional anti-diabetic medicines to control their blood glucose levels. The results show remarkable improvement in the condition of health of those that applied the ethno-botanical treatment over the period of assessment; however, further investigations show that the deployment mechanical juice extractors increased the potency and efficacy of the herbal recipes.*
Key words*: diabetesmellitus, patients, hyperglycemic agents, herbal medicine.*

I. Introduction

Diabetes is a disease characterized by excretion of excessive urine (polyuria). It is divided into two classes: *diabetes insipidus and diabetes* mellitus.Diabetes insipidusisa condition marked with polyuria and polydipsia due to a deficiency of anti-diuretic hormone (ADH). It affects the kidney and has nothing to do with insulin, but shares the symptom of increased urine production with diabetes, which is why it has diabetes in its name. This kind of diabetes is less common among Nigerians and treatment involves the use of anti-diuretic hormones and diet (Anselm, 2012).

Further, diabetes mellitus (DM) is a chronic, metabolic disease of the endocrine system characterized by hyperglycemia. High blood glucose level may be a result of several factors such as insufficient insulin production of pancreas, or resistance of the body to the action of insulin. Uncontrolled blood glucose levels may result in micro-vascular complications such as retinopathy, nephropathy, and neuropathy. It may also lead to vascular complications such as coronary artery disease resulting in strokes and myocardial infarcts (Ghosh and Collier, 2012).

It is estimated that the number of people with diabetes globally has risen from 108 million in 1980 to 422 million in 2014. While global prevalence among adults over 18 years has risen from 4.7% in 1980 to 8.5% in 2014 (WHO, 2014). This number keeps increasing as a result of insulin resistance triggered by unhealthy eating habits and sedentary lifestyles (Aslan and Orhan, 2010). In modern medicine, insulin and/or oral agents such as sulfonylureas, biguanides, meglitinides, alpha-glycosidase inhibitors, and thiazolidinedionesare used for the treatment of diabetes. On the other hand, traditional herbal medicines are used all over the world by diabetic patients. It is estimated that more than 1000 plant species are used against diabetes as folk medicine (Marles and Farnsworth, 1995).

Researchers on herbal medicines are encouraged to come up with alternatives for treatment of diabetes since oral anti-diabetic agents have side effects in the long run (Samad et al., 2009). To date, a vast number of plants have been evaluated for their anti-diabetic activity. Plants are considered to be the basis for deriving natural or semi-synthetic constituents that can be used against diabetes (Aslan and Orhan, 2010). The anti-diabetic activity of some herbal medicines is attributed to the presence of compounds such as flavonoids,

terpenoids, coumarins, and phenolic compounds, among others (Jarald et al., 2008; Rao et al., 2010). Investigations must be carried out to identify the chemical constituent(s) responsible for the anti-diabetic activities of the medicinal plants, and to elucidate their mechanism of action. It is in view of the above that this study in reviewing the anti-diabetic medicinal treatment practices by use of plants in Nigeria, considered the deployment of mechanical juice extractors in the processes of materials handling with respect to the quality of medicinal active ingredients that are derivable from the plants as opposed to the traditional method of hand squeezing in water. The result shows remarkable difference in the quality of the product and the allowable treatment time.In the view of this study, this is a better alternative with the promise of enhanced performance of increased medicinal value.

1.1 Classification of Diabetes Mellitus

The contemporary classification of diabetes and other categories of glucose intolerance, based on research on this heterogeneous syndrome, were developed in 1979 by the National Diabetes Data Group. Two major forms of diabetes are recognized globally; insulin dependent diabetes mellitus (IDDM, type I diabetes) and non-insulin dependent diabetes (NIDDM, type II diabetes) (Harris and Zimmet, 1997).

1.2 Insulin Dependent Diabetes Mellitus (IDDM)

The subclass of diabetes, type I diabetes, is an autoimmune disorder in which the immune system attacks the cells which normally generate insulin, a compound necessary for the digesting of glucose (Amodu, 2011). It is generally characterized by the abrupt onset of severe symptoms, dependence on exogenous insulin to sustain life and proneness to ketosis even in the basal state, all of which is caused by absolute insulin deficiency. IDDM is the most prevalent type of diabetes among children and young adults in developing countries, and was formally termed juvenile diabetes (Harris and Zimmet, 1997). It is a catabolic disorder in which circulating insulin is virtually absent, plasma glucagon is elevated, and the pancreatic B cells fail to respond to all insulinogenic stimuli (Nolte and Karam, 2001).

1.3 Non-Insulin Dependant Diabetes Mellitus (NIDDM)

Type II diabetes greatly out numbers all other forms of diabetes. Patients with NIDDM are not dependant on exogenous insulin for prevention of ketonuria and are not prone to ketosis. However, they may require insulin for the correction of fasting hyperglycaemia if this cannot be achieved with the use of diet or oral agents, and they may develop ketosis under special circumstances such as severe stress precipitated by infections or trauma (Harris and Zimmet, 1997).

II. Research Method

Although, the research design for this project work can best be described as a descriptive survey, for which Cambell(2006) opined that descriptive design is that plan or pattern of events which tends to explain what a situation is at a given period of time. Suffice to say that the study is also innovative in nature in the sense that it replaced the traditional hand or manual squeezing of leafs with mechanical juice extractors which showed higher production efficacy and efficiency.

2.1 Research Population

This research was based on a survey conducted between December, 2018 to February, 2019 with 98 diabetic patients who consented to participate in the study. Type I and type II diabetic patients who visited Idiroko General Hospital, MayowaHospital, Idiroko, Olutunu Medical Centre, Agosasa, and KIA Medical Diagnostics were asked to respond to a face to face questionnaire. The purpose of the study was explained and each diabetic patient was questioned on socio-demographical characteristics, disease condition and medicines used, and whether or not they use plants or plant parts to lower their blood glucose levels. If so, more information was obtained on the plants that were used, such as the name, used part, preparation method, frequency of administration, and their general opinions on the use of herbs. The survey consists of 2 different sections and a total of 22 questions.

2.2 Sample Collection

It was requested that the patients bring samples of the used medicinal plants. The specimens were indentified using 'Nature power' (Anselm, 2012) and the International Plant Names Index (IPNI, 2012). The data collected indicates the use of 13 plants and 1 animal product for the treatment of diabetes; most of which are available locally (Table 1).

Table 1. Plants used in combination for the treatment of diabetes in Nigeria

S/N	Herbal plant (biological names)	Common names
1.	Allium cepa	Onion
2.	Allium sativum	Garlic
3.	Capsicum frutescens	African red pepper
4.	Xylopiaaethiopica	Negro pepper
5.	Carica papaya	Green Pawpaw leaves
6.	Vernoniaamygladina	Bitter leaf
7.	Viscum album	Mistletoe
8.	Momordicacharantia	Balsam pear
9.	Basil ocinum	Scent leaf
10.	Zingiberofficinale	Ginger
11.	Anacardiumoccidentale	Cashew
12.	Morindalucida	Brimstone tree
13.	Alstoniaboonei	Stool wood
14.*	Apismillifera (Honey bee)	Honey

Source: Field Survey (2019)

2.3 Sample Analysis
1.   Allium cepa: English – Onion. Igbo – Yabase, Yoruba – Alubosa, Hausa –Alubasa
Parts Used: Leaves, bulb
Biochemical composition: Riboflavin
Medicinal values: Diabetes, Insomnia, Hypertension, Headache, Loss of memory and Cough/cold (Anselm, 2012).

2.   Allium sativum: English – Garlic, Igbo – Ayo, Yoruba – Ayu, Hausa – Tafamuwa.
Part Used: Bulb
Biochemical composition: Saponins, Tanins
Medicinal values: Allergy, Anti-tumor, Hypertension, Arthritis, Asthma, Cough, Worms and Epilepsy(Anselm, 2012).

3.   Capsicum frutescens: English: African red pepper, Igbo – Oseolibo, Yoruba- Ata eiye, Hausa – Barkono. Part Used: Fruit
Biochemical composition: Capsaicin, Trace elements, Vitamins, Flavonoids, Alkaloids and Tannins.
Medicinal value: Diabetes, stomach ache, back pains, muscle spasms, headaches, skin aging, peptic ulcer, monopausal problems and cardiovascular disease.
(www.organicfacts.net/vegetables, 2019).

4.   Xylopiaaethiopica: English - Negro pepper, Igbo – Uda, Yoruba-Erunje, Hausa – Kimba.Part used: Fruit
Biochemical composition: Flavonoids, Glucosides, Tannins, Alkaloids and Steroids.
Medicinal value: Diabetes, bronchitis, dysentery, toothache, asthma and rheumatism.
(www.researchgate.net/publication,2015).

5.   Carica papaya: English – Pawpaw. Part used: leaves
Biochemical composition: Papain, chemopapain, cystatin, tocopherol, ascorbic acid,
flavonoids and cyanogenic glucoside.
Medicinal value: Diabetes, stomach ulcer, external ulcer, malaria fever, impotence, convulsion,asthma and piles.(www.researchgate.net/publication,2015).

6.   Vernoniaamygladina: English - Bitter leaf, Igbo – Onugbo, Yoruba – Ewuro, Hausa – Shuwaka. Part used: Leaves.
Biochemical composition: Vernodalin, venomygdin and saponin.
Medicinal value: Diabetes, stomach ache, prostate cancer, stroke, skin infection, loss of memory, arthritis and pneumonia. (Anselm,2012).

7.   Viscum album: English – Mistletoe. Part used: Leaves
Biochemical composition: Alkaloids, tannins, choline and acetylcoholie.
Medicinal value: Diabetes, cancer, hypertension, liver and kidney problems, nervous breakdown and gynecological problems (Anselm, 2012).

8. ***Momordicacharantia:***English - Balsam pear, Igbo – Alo-ose, Yoruba – Ejirin.
 Part used: Leaves
Biochemical composition: Alkaloids, mimordicine, saponins, charantin and oleic acid.
Medicinal value: Diabetes, constipation and convulsion (Anselm,2012).

9. ***Basil ocinum:*** English - Scent leaf, Igbo – Nchanwu,Yoruba – Efirin.
 Part used: Leaves
Biochemical composition: Essential oils, eugenol, flavonoids, anthocyanins and E-beta-caryophyllene.
Medicinal value: Anti-ageing, anti-inflammatory, anti-bacterial, anti-cancer.
(www.medicalnewstoday.com, 2018).

10. ***Zingiberofficinale:*** English – Ginger. Part used: Rhizome.
Biochemical composition: Essential oils, phenols, resin, borneol, camphere, citral,eucalyptol, linaol and zingiberol.
Medicinal value: General health (Anselm,2012).

11. ***Anacardiumoccidentale:*** English – Cashew. Part used: Stem bark
Biochemical composition:Anacardic acid, phenols and tannins.
Medicinal value: Diabetes, malaria and dysentery (Anselm,2012).

12. ***Morindalucida:*** English – Brimstone tree, Igbo – Eze-ogu, Yoruba – Oruwo
Part used: Leaves
Biochemical composition: Athraquinones and glucosides
Medical value: Diabetes, jaundice and fever (Anselm, 2012).

13. ***Alstoniaboonei:*** English – Stool wood, Igbo – Egbu, Yoruba – Ahun.
Part used: Leaves
Biochemical composition: Alkaloids, echitamine, tannins and saponins.
Medical value: Diabetes, arthritis, fever and convulsion (Anselm,2012).

14. *Apismillifera* **(Honey bee):** English – Honey
Biochemical composition: Fructose, glucose, maltose, sucrose, flavonoids, vitamins and minerals.
Medical value: High blood pressure, cholesterol, lowers triglycerides, wound healing and cough.

2.4 Sample Preparation
Materials:
A.   Cashew stem-bark (half small bucket)
B.   7 green pawpaw leaves
C.   1 medium size pot of bitter leaves
D.   10 bulbs of garlic
E.   10 finger pieces of ginger
F.   5 bulbs of onions
G.   10 pods of *Capsicum frutescens*
H.   15 pieces of *Xylopiaaethiopica*
I.   15 liters of water
J.   2 bottles of honey

2.5 Procedure 1:
        Boil A to H together in (I) under a laboratory controlled temperature for 40 minutes. Allow to stand for 24 hours before adding J. Stir well, sieve and store in a container. However, an alternative approach for better result could be carried out by pressurized mechanical blending of A to H into powder or viscous paste after which the mixture is poured into 15 liters of boiling water and allowed to boil for between 20 to 30 minutes after which it is cooled for 24 hours to settle and structurally combine before sieving and adding of J, mix well and store in a hygienic container.

Dosage:
One glass, 3 times daily, for two months. (Anselm, 2012)

Formula II

Materials:
A. Leaves of Mormodicacharantia (English- Balsam pear, Yoruba - Ejirin)
B. Leaves of Basil ocinum (Scent leaves, Yoruba - Efirin)
C. 10 liters of water

2.6 Procedure 2:
This procedure involves the use of a well designed mechanical juice extractor to blend and squeeze an equal amount or weight of the leaves of A and B under laboratory controlled running water of not more than 10 liters (as in C above). The precise quantity of leaves is not the major concern as the basic requirement is to blend and squeeze equal weight of both leaves and to make the preparation as thick and concentrated as possible.

Dosage:
1 glass 3 times daily for 2 months (Anselm, 2012)

III. Results and Analysis
It should be noted that of the 120 patients contacted, 98 patients agreed to participate in the survey (response rate 89%). From the 98 respondents who participated in the study, 96 (98%) had Type II Diabetes while 02 (2.0%) had Type I. 54 (55.1%) of them declared that they used herbal medicine. The socio-demographical data of diabetic patients as captured by the researcher is shown in Table 1. Information about the use of medicinal plants is given in Table 2.While Table 3 gives a vivid description of the common herbal plants used within the Local Government Council for the treatment of diabetes. Figure 1 shows how patients provide medicinal herbs they use against diabetes. Figure 2 illustrates the sources from which patients obtain information on the use of medicinal herbs. Figure 3 shows the general opinions of patients about plants. Figure 4 illustrates the percentage of patients who experienced any other chronic disease. The outcome shows that the age of patients varied between 36 (6.1%) and 56(77. 6%) years of age.

Table 1. The socio-demographical data of diabetic patients (N=98)

Parameter	Range	%
	18-25	0
Age	26-35	0
	36-45	2
	46-55	26
	56+	70
	Males	43
Sex	Females	55
	Primary sch.	48
	Secondary sch.	32
Education	High sch.	13
	University	05
	Self employed	38
Occupation	Retired	20
	House wife	30
	Others	10
Diabetes	Type 1	02
	Type 2	96

Source: Field Survey (2019)

**Table 2.** Information on the use of medicinal plants (N = 54).

| Parameter	No. of Patients	%
Herbal Medicine Used:		
Alone	08	14.8
Mixed with other herbs	46	85.2
Preparation Method:		
Directly	06	11.1
Infusion	20	37.0
Decoction	26	48.2
Others	02	3.7
Time Of Use:		
Pre-prandial	22	40.7
Post-prandial	32	59.3
Duration of Use:		
Few weeks	06	11.1
Continuous	48	88.9

Source: Field Survey (2019)

Table 4 Statement of patients about how they purchase the herbal medicine they use against Diabetes (N=54)

Area of drug purchase	No. of Respondents	%
I buy it from the supermarket	04	7.4
I buy it from the pharmacy	0	0
I buy it from herbal shops in the form of medicine	05	9.3
I buy it from herbal shops in the form of raw herbs	15	27.7
I pick it from nature	25	46.3
I grow the herbs my self	05	9.3

Source: Field Survey (2019
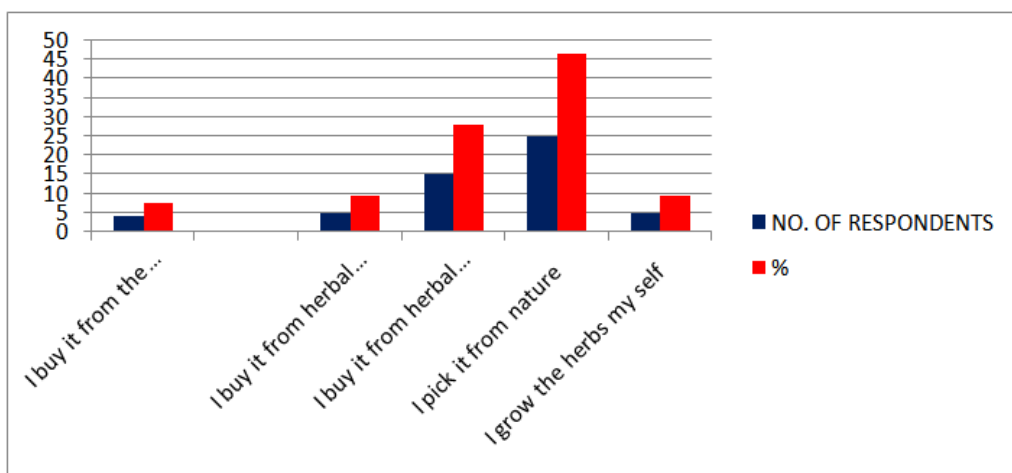
Fig 1 Chart/Graph Showing How Diabetic Medicines Are Bought
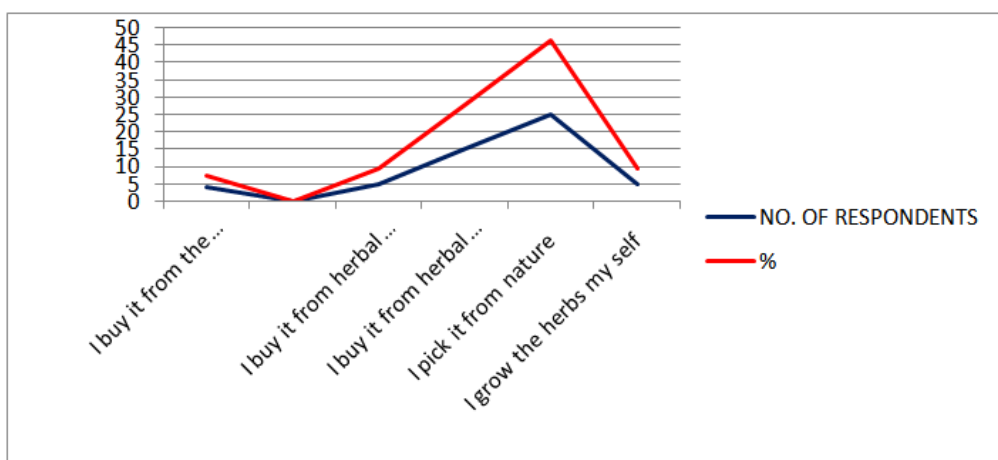
Figure 2. Bar Chart/Graph Showing Information on Herbal Medicine

Table 5 Areas Patients Obtain Information on Herbal Medicine (N=54)Source: Field Survey (2019

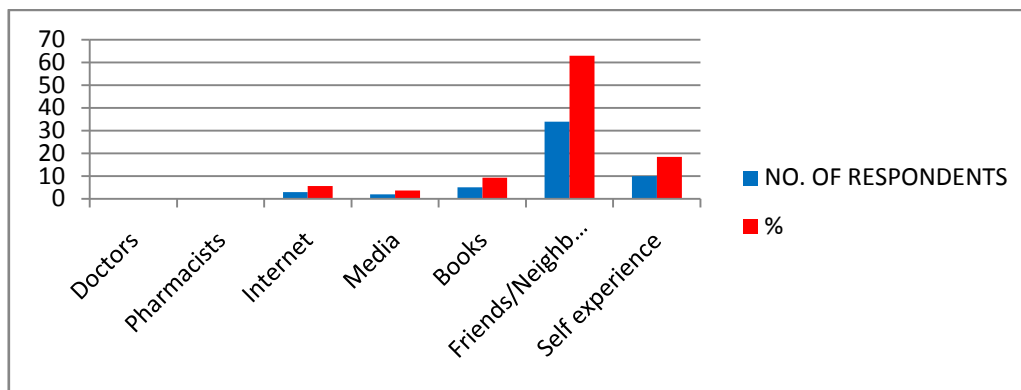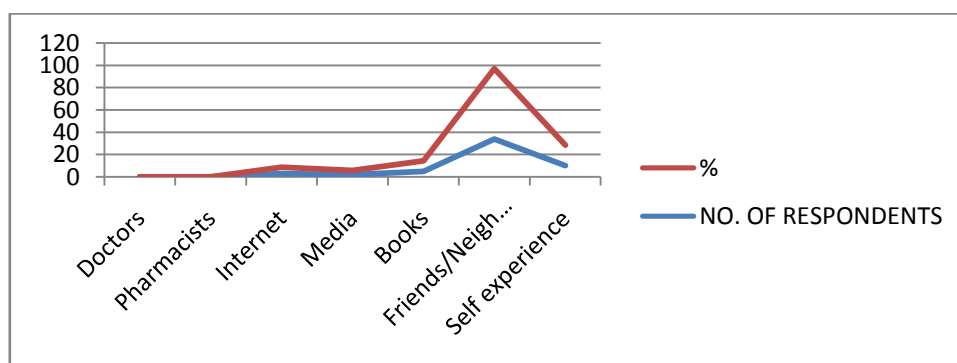| Information centres	No. of Respondents	%
Doctors	0	0
Pharmacists	0	0
Internet	03	5.6
Media	02	3.7
Books	05	9.3
Friends/Neighbors	34	62.9
Self-experience	10	18.5

Fig 3 Chart of Study Respondents and Sources

Fig 4 Chart of sources of herbal information

Table 6 Opinions of Patients About Herbal Medicine (N=54)

Opinion	No. of Respondents	%
Doctors should be informed about herbal medicine	02	3.7
Pharmacists should be informed about herbal medicine	01	1.9
Herbal medicine interact well with other conventional medicine	05	9.3
Adverse effects of herbal drugs are less compared with conventional drugs.	10	18.5
They have no adverse effects	36	66.6

Source: Field Survey (2019)
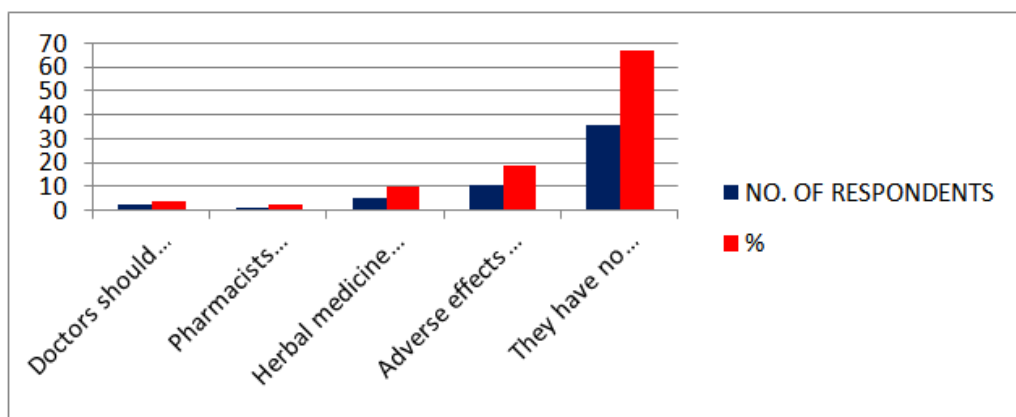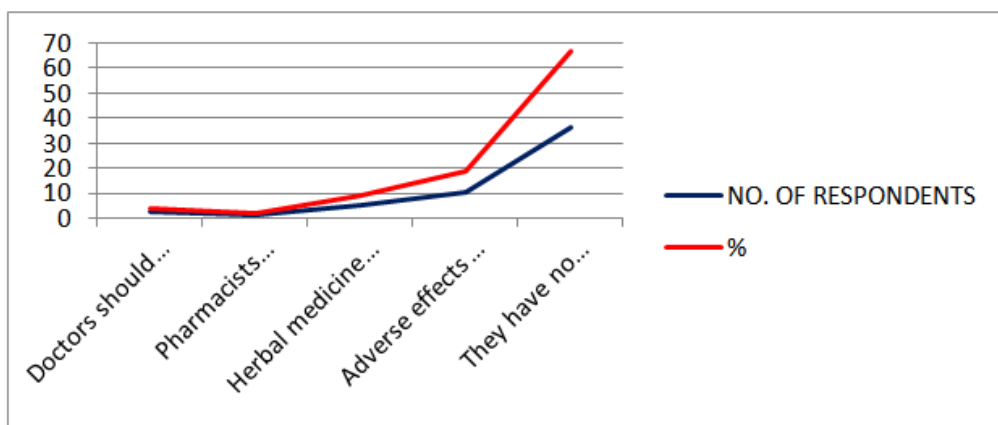

Fig 5 Bar Chart of Responses

Fig 6 Graph of Respondents to questionnaires

Table 7. No. of Respondents on Injection/Oral Drugs/
Herbs showing drug reaction/no reaction

Respondents	No.	%
On Injection only	58	59.2
On Injection only showing reaction	14	14.3
On Oral drugs only	40	40.8
On Oral drugs only showing reaction	30	30.6
On Herbs $_+$ Injection or Oral drugs showing no reaction	54	55.1

Source: Field Survey (2019

IV. Discussions

From the research data available, and the figures of various charts/ graphs above, majority of the patients (96%) had Type II DM whereas only 2% of them had Type I DM. Further, out of 54 patients who use herbal medicines against diabetes, approximately 14.8% of the patients use a single medicinal plant, while 85.2% prefer to prepare a mixture from the medicinal plants. 37% of the medicinal plants are prepared as Infusion, while 48.2% are prepared as Decoction. Though majority of the patients (59.3%) took the medicinal plants after food, the difference was not marked as some of the patients (40.7%) proffered before meal. These finding is in agreement with the work of Anselm, 2012 who opined that medicinal preparations (infusions, decoction etc) can be taken one hour before or after meal.

Further, all of the patients (N = 54) claim to experience positive effects as a result of herbal medicine they used. None of the patients claim to experience any adverse effects due to these herbal medicines. In this study, the use of 13 plants and 1 animal product by 54 diabetic patients was documented. This is indicative of the fact that most patients rely on herbal remedies to bring down their blood glucose levels. These diabetic patients use a variety of plants along with their conventional anti-diabetic medicines to control their blood glucose levels. A recently conducted ethno-botanical study in Nigeria indicates the use of plants or plant parts, either alone, or in combination with other plants for the treatment of diabetes (Anselm, 2012).

It should be stated however that the respondents on herbs, taking insulin injection/oral drugs 54 (55.1%) showed no visible drug reaction or had mild reaction with respect to those on Oral drugs. This finding is in agreement with the work of Amodu, 2011 who observed that herbs stimulate B-Cells of *Islet of Langerhans* in the pancreas to release insulin naturally thereby preventing reaction.

V. Conclusion

This research paper has been able to assert that insulin dosing as well as insulin hypoglycemic agents used currently in the management of diabetes mellitus builds adverse drug reaction. That the management of Type I and Type II Diabetes with herbs have been researched and found to stimulate the B-cells of Islet of Langerhans in the pancreas to release insulin naturally thereby preventing drug reaction.

Consequently, the study showed clearly that the respondents who used herbs to control their blood sugar levels showed little or no sign of adverse drug reaction.That ethno-botanical study is crucial in terms of revealing the traditional use of medicinal plants and guiding research on new drugs. However, attempts will be made to complete the ethno-botany of other areas in Nigeria in order to develop evidenced –based complementary medicine to cure diabetes. Further, age, sex, and education can be influencing factors in herbal medicine use. However, we could not evaluate the relation due to the small number of patients that participated in the study. Further, investigations would be carried out with a larger population to identify and elucidate the mechanism of action of these medicinal plants.

Further, although the study did not establish an empirical difference in terms of the potential benefits and efficacy of the added medicinal value of deployment of pressurized mechanical juice extractors in the processing of the leaf recipes (instead of manual squeezing), suffice to say that such innovation is crucial in the hygienic standardization of the production of herbal medicines. Thus, while such innovation produces finer particles of the leafs and other added materials,this study is of the opinion that extraction of the medicinal active ingredients of such leafs are better achieved by high pressure mechanical blending than manual squeezing.This is based on the fact that significant material loss is occasioned by manual squeezing due to the large particulate sizes of the leafs,resulting from manual squeezing, which are later discarded as waste material.

VI. Research Recommendation

The popularity of herbal medicine has lead to increasing concerns over their safety, quality and efficacy. In many countries just like Nigeria, the herbal medicine market is poorly regulated and products are neither registered nor controlled. This study however found relevance on the calls that relevant Government regulatory bodies, such as the Nigeria Natural Medicine Development Agency, the National Institute for Pharmaceutical Research and Development as well as NAFDAC should commence, without delay, herbal therapy regulations and control as well as genuine product registration.

There is a lack of detailed documentation on the use of medicinal plants in Nigeria. This study is of the opinion that documentation of traditional knowledge is of grave priority because the rapid pace of urbanization and acculturation in the country could easily lead to the permanent loss of these knowledge.

Further, Nigeria tropical rain forest abounds with medicinal plants with promising medicinal activities that need to be researched. Grants from government to researchers and research institutes will open this new field. For Nigeria to meet WHO *Health For All By 2020*, the Traditional Medicine Bill and other health related legislature need to be passed into law so that traditional medicine is fully integrated into Nigeria healthcare system.

Acknowledgement:

References

[1]. Albright, A.L. (1997), Diabetes In: Exercise Management for persons with chronic diseases anddisabilities,USA: Human Kinetics (Braun-Brumfield). pp 94-100.
[2]. Amodu, B. (2011),Diabetes: Between Curing and Healing. PAX Herbal Clinic &Research Laboratory Publication. Pp 12-14
[3]. Anselm A, (2012), Nature Power, pp 78-90.
[4]. Anselm, A., (2005), New Frontiers in African Medicine, pp 68-73
[5]. Aslan, M, Orhan, N. (2010),Diyabettedavisindekullanılanbitkiselürünlervegıdadestekleri, MISED 23-24:27-38.
[6]. Dune Foods, 2005, Manna: Blood Sugar Support Leaflet.
[7]. Gerich. J.E. 2001. Matching Treatment to Pathophysiology in type 2 Diabetes, Clinical Therapeutics. Vol.23, No 5. pp. 646-659.
[8]. Grover, J. K., Yadav, S and Vats, V., 2002 Medicinal plants of India with Anti-diabeticPotential, Journal of Ethnopharmacology 81(1) 81-100.
[9]. Harris, M.I. and Zimmet, P. (1997), Classification of Diabetes Mellitus and Other Categories ofGlucose Intolerance. In: International Textbook of Diabetes
[10]. Mellitus, Second Edition.Ed. K.G.M.M.,Alberti, P. Zimmet, R.A. DeFronzo andH.Keen. John Wiley and Sons Ltd, New York, pp. 9 -23.
[11]. Heart Foundation, 2019. [www.heartfoundation.co.za] (2019/06/16).
[12]. Roussel, M., (1998), Handbook on How toControl Diabetes, South Africa, Hoechst Marion Roussel.
[13]. Society of Endocrinology, Metabolism and Diabetes in South Africa, 2003. Prevalence Data [www.semda.org.za/ prevamencedata.htm]
[14]. U.S. Census Bureau, (2019), [www.census.gov] (2019/05/20)
[15]. World Health Organization Study Group on Diabetes Mellitus, (2014), Technical Report Series No.844, World Health Organization, Geneva, p3, 78 – 79.
[16]. Yajnik, C.S. (1990), Diabetes in Tropical Developing Countries In: Diabetes Annual 5, K.G.G.M. Alberti, Krall L.P (eds) Elsevier, Amsterdam. pp. 72-87.