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Remedies for glucose intolerance – are traditional herbal concoctions for diabetes effective?

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background:Preventing or delaying the onset of diabetes in prediabetes has the potential to reduce the disease prevalence.
Objective:The effectiveness of traditional herbal concoctions for diabetes in ameliorating glucose intolerance was investigated.
Material and Methods:Oral glucose tolerance test (OGTT) was carried out by giving 500 mg/kg and 1000 mg/kg of individual plant extract and their aqueous herbal concoctions made from *Musa sapientum + Allium sativum + Tetracarpidium conophorum; Gongronema latifolia + Bauhinia monandra*; and *Alstonia boonei + Mangifera indica* to groups of rats, 30 and 60 minutes respectively prior to 3 g/kg of glucose load. Blood glucose levels were determined at 0, 10, 20, 30, 45, 60, 90, and 120 minutes post administration. Area under the curve (AUC) for OGTT and glycemic index were calculated and compared with the vehicle control and metformin (100 mg/kg). Level of significance was set at P<0.05.
Results:Oral glucose tolerance test AUCs of individual plants were significantly lower than that of the vehicle control (P<0.05) but comparable with that of metformin (P>0.05) when given 30 minutes prior to glucose load. The OGTT curve AUCs of the three herbal concoctions were significantly higher than the two controls (P>0.05). Glycemic index of the concoctions were significantly higher than that of metformin (P>0.05)
Conclusion:The herbal concoctions were not effective in ameliorating glucose intolerance. Individual plants were more effective when administered 30 minutes prior to glucose load. The individual herbs showed potentials to delay the onset of diabetes. Further investigations should be conducted on the numerous herbal concoctions used for diabetes**.**

Keywords: Diabetes, Herbs, Oral glucose tolerance test

INTRODUCTION

The prevalence of diabetes is increasing worldwide and as at 2013, the global estimate for the prevalence of diabetes was 382 million people.This figure has been projected to increase to 592 million by the year 2035 (Guariguata et al., 2014). This projected increase are largely going to be due to urbanization, life style changes, population growth, and ageing of the population (Shaw et al., 2010). Diabetes mellitus is one of the leading cause of deaths globally. It is ranked the 5th cause of death in the US after cardiovascular disease (Roglic et al., 2005). The high mortality and morbidity of diabetes is as a result of its microvascular and macrovascular complications (Roglic et al., 2005). In the developed world, most people with diabetes are above the age of 60 years while in the developing countries, they are from 40-60 years (Shaw et al., 2010).
Type 2 diabetes is more prevalent than type 1 diabetes. The latter is more of an autoimmnune defect while the former is as a result of partial lack of insulin secretion or sensitivity. Many drugs are available for the management of the disease including insulin and oral hypoglycemic agents. However, these drugs are not without attendant side effects which sometimes make adherence to therapy and the achievement of therapeutic goals difficult.

Table 1: Traditional herbal concoctions for diabetes, the plant part used, and their local names.

S/N	Herbal concoction	Plant part	Local name	Common name
1	*Musa sapientum* Linn (Musaceae)	Unripe fruits	Ogede	Banana
	Allium sativum Linn (Liliaceae)	Bulbs	Ayu	Garlic
	Tetracarpidium conophorum (Mull.-Arg.) Hutch. & Dalz. (Euphorbiaceae)	Seeds	Asala	Walnut
2	*Gongronema latifolium* Benth. (Asclepiadaceae)	Leaves	Madunmaro, Utazi	Amaranth globe.
	Bauhinia monandra Kurz (Fabaceae)	Leaves	Abefe	Pink orchid Napoleon's plume
3	*Mangifera indica* Linn (Anacardiaceae)	Stem bark	Mangoro	Mango
	Alstonia boonei De Wild (Apocynaceae)	Stem bark	Ahun	Stoolwood

Complications arising from diabetes are usually as a result of sustained uncontrolled plasma glucose. With the increasing challenge of managing diabetes, prevention or delay in the manifestation of the disease becomes paramount. A study showed that 60% of people who develop diabetes previously had impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) for more than 5 years (Unwin et al., 2002). People with IFG and/or IGT slowly progress to overt diabetes, which may explain the 50-85% prevalence of asymptomatic or undiagnosed diabetes depending on the country, the highest being in Africa (Oputa and Chinenye 2012). The prevalence of prediabetes (IGT) differs from one population to another and the prevalence of IGT in Nigeria is about 7.1% (Unwin et al., 2002; Ojewale and Adejumo, 2012).

As stated by Edelman and coworker, preventing a disease is to completely avoid its development and to employ intervention that slows down the progression of the disease (Edelman et al., 1997). Globally the trend in identifying people with prediabetes (IGT and/or IFG) is with the aim of preventing or delaying the manifestation of diabetes through lifestyle modifications and sometimes the use of oral hypoglycemic agents like metformin (Ojewale and Adejumo 2012). Studies have shown that type 2 diabetes can be prevented or delayed by a considerable life style modification. There was a decrease of about 58% in the incidence of diabetes in these studies (Pan et al., 1997; Eriksson et al., 1999; Tuomilehto et al., 2001).

Many randomized controlled trials have shown that oral hypoglycemic agents may reduce the development of diabetes in comparison with placebo (Padwal et al., 2005). Herbs are available for the management of diabetes mellitus and many of these herbs have also been shown to be effective in IGT. Often times in African setting, single herb is rarely used in the treatment of an ailment, rather a combination of herbs is commonly employed. These are referred to in southwest Nigeria as agbo (herbal concoction) (Oreagba et al., 2011; Akande et al., 2012). The individual plants in the traditional herbal concoctions used for diabetes have been shown to be effective in the management of diabetes (Ezuruike and Prieto 2014) but their effectiveness when combined togeteher to treat the same ailment has not been ascertained. This is an age-long practice in traditional medicine in sub-saharan Africa and since it is difficult to get pharmacological agents to effectively prevent or delay diabetes onset we, investigated if some of these traditional herbal concoctions are effective in preventing diabetes mellitus.

Plant parts used

Table 1 shows the list of different individual plants in the three traditional herbal concoctions used in this study. The parts of the plants used and their local name are also given.

Collection of plants

Plant parts were collected in Ibadan and its suburbs. These plants were obtained from various sources. *Gongronema latifolium* leaves was bought from Moniya market in Ibadan, *Bauhinia monandra* leaves was plucked in front of pharmacognosy laboratory, University of Ibadan, *Mangifera indica* and *Alstonia boonei* barks were obtained from the back of department of maintenance, University of Ibadan. Other plants purchased from traditional herbal vendors in Oje market were *Musa sapientum* fruits; *Allium sativum* bulbs; and *Tetracarpidium conophorum* seeds.

Identification and authentication of plant parts.

Some of the plants were identified and authenticated at the Department of Pharmacognosy, Faculty of Pharmacy, University of Ibadan, Nigeria. The plants were deposited in the herbarium and the voucher numbers are: *Alstonia boonei* (DPHUI 1385), *Mangiferan indica* (DPHUI 1386), *Musa sapientum* (DPHUI 1387), *Bauhinia monandra* (DPHUI 1388). Other plants were identified at the department of Botany, Faculty of Science, University of Ibadan.

Processing of the plant parts

The leaves of *Gongronema latifolium* and *Bauhinia monandra* were plucked, seeds of *Tetracarpidium conophorum* were unshelled, the stem-barks of *Mangifera indica* and *Alstonia boonei* were chopped into smaller pieces with a cutlass, the unripe fruits of *Musa sapientum* were peeled and sliced into bits while the outer dried leaves of *Allium sativum* were removed. These plant parts were dried in the oven (Gallenhamp oven, Cat number GVH 500.010 G. Germany) at 40^{o}C for 24 to 48 hours.

Extraction procedure

The dried plant parts were powdered, and 300 g of each plant powder was macerated in 1.5 L of distilled water for 24 hours. Each mixture was filtered, concentrated with rotary evaporator and freeze dried. The extracts were individually weighed.

Aqueous extract of the herbal concoctions were prepared by weighing 300 g of each powdered plant component of each herbal concoction and macerated in 4.5 L of distilled water for 24 hours. Each herbal concoction mixture was filtered, concentrated with a rotary evaporator and freeze dried. The resultant weight of each herbal concoction aqueous extract was recorded.

Animals

Seventy-eight albino rats (120-241g) were obtained from the animal house, University of Ibadan. The rats were housed in polyethylene cages and allowed to acclimatize for a period of one week prior to the commencement of the experiment. They were allowed to feeds and water *ad libitum*.

Acute toxicity test

Eighteen rats were divided into three groups of six rats each consisting of 3 males and 3 females per group for the acute toxicity test for the three herbal concoctions using previously described method (Yamanaka et al., 1990). Briefly, 2000 mg/kg body weight of reconstituted aqueous extract of each concoction was administered once orally to the rats. The rats were fasted overnight for 14 hours prior to the administration of the herbal concoction extracts. They were denied access to food for a further 4 hours post-administration of the extracts. The animals were watched daily for 14 days for behavioral changes and number of mortality was recorded.

Determination of dose

For the individual plant extracts, 500 mg/kg and 1000 mg/kg body weight representing 1/10th and 1/5th of reported literature LD_{50} values were the doses used except for *Allium sativum* where 420 mg/kg and 840 mg/kg were used. For the herbal concoctions 500 mg/kg and 1000 mg/kg body weight were used for the OGTT. These also represented the 1/5th and 1/10th of the LD_{50} determined during the acute toxicity test for each of the three herbal concoctions. These two doses for the individual plant extracts and herbal concoction extracts were considered as the low and high doses.

Oral glucose tolerance test (OGTT)

Sixty rats were used for the OGTT. The rats were labeled and randomly divided into 12 groups of five rats. Seven groups for the individual plants that make up the herbal concoctions, three groups for the three herbal concoctions, a group for vehicle control and another group for positive control (metformin). The animals were weighed to determine the appropriate dose of the extract, drug, and/or glucose to be administered. Prior to the administration of the extracts, metformin, and/or glucose, the animals were fasted overnight for 14 hours and the appropriate dose of the extracts/metformin were administered either 30 minutes or 60 minutes before 3 g/kg of glucose was administered (Nyunaï et al., 2009). Low dose of the extracts or drug (metformin – 100 mg/kg) was administered 30 minutes before the oral glucose load while high dose of the extracts or drug (metformin – 200 mg/kg) was administered 60 minutes prior to oral glucose load. Blood glucose level (BGL) was measured with the aid of Accuchek® glucometer from the cut-tail-tip at 0, 10, 20, 30, 45, 60, 90 and 120 minutes post administration of oral glucose (Nyunaï et al., 2009).

Ethical consideration

The study was approved by the joint University of Ibadan/University College Hospitals Ethics Committee. The ethical approval number is UI/EC/14/0335

Data analysis

Data are expressed as mean ± standard deviation. For the comparison of the effectiveness of the herbal concoctions and their individual plant components in ameliorating glucose intolerance; OGTT curve AUCs and GI ($AUC_{extract}/AUC_{control}$) were determined and analysis of variance (ANOVA) was used to compare the differences of these parameters between the treatment groups. Paired sample t-test was used to compare differences in the OGTTcurve AUCs and GI of each extract when administered 30 and 60 minutes prior to glucose load. Bonferroni and Games-Howell post hoc tests were used when equal variances were assumed and not assumed respectively. Statistically significant differences were considered at $p<0.05$. GraphPad Prism 5.4 and SPSS version 20 (Statistical Package for Social Sciences) were used for the analysis.

RESULTS

Percentage yield

The percentage yield for the herbal concoctions were 13.80% for *Gongronema latifolium* + *Bauhinia monandra*, 9.39% for *Mangifera indica* + *Alstonia boonei*, 8.85% for *Allium sativum* + *Tetracarpidium conophorum* + *Musa sapientum*, while the percentage yield for the individual plants were 19.75% for *Allium sativum*, 35.10% for *Bauhinia monandra*, 11.90% for *Gongronema latifolium*, 7.30% for *Tetracarpidium conophorum*, 27.40% for *Mangifera indica*, 5.55% for *Musa sapientum* and 10.99% for *Alstonia boonei.*

Acute toxicity study

For the herbal concoctions, no abnormal behavior was noticed and no mortality was recorded at a dose of 2000 mg/kg. Thus, the LD_{50} for the herbal concoctions was between 2000 mg/kg and 5000 mg/kg (2 to 2.5 of the dose administered in the acute toxicity study) (Yamanaka et al., 1990). We used $1/10^{th}$ and $1/5^{th}$ of this upper limit of the LD_{50} in the OGTT test as the low and high dose respectively.

Oral glucose tolerance test

Figure 1, shows BGL against time curve when the extracts and metformin were given at low dose and 30 minutes prior to oral glucose load. The peak BGL was reached at

about 20 minutes during the OGTT for the controls, individual herbal extracts and for one of the herbal concoctions, *A. sativum* + *T. conophorum* + *M. sapientum*. Peak BGL was reached at 30 minutes and 45 minutes for the herbal concoctions made up of *A. boonei* + *M. indica* and *B. monandra* + *G. latifolium* respectively. However, few of the individual plants were able to return the BGL back to normal in 90 minutes. These plants included *M. indica*, *A. boonei* and *M. sapientum* while *A. sativum* was able to normalize the BGL at 60 minutes (Figure 1). The drug metformin and the vehicle control were unable to normalize the BGL within 120 minutes.
But when the extracts were given at a higher dose and 60 minutes prior to the OGTT test, the time to reached peak BGL were mostly 20 minutes for the extracts except *M. indica*, and *M. sapientum* where the peak BGL was attained at 45 and 90 minutes respectively (Figure 2). Despite attaining a late peak BGL, *M. sapientum* was able to normalize the blood glucose at 120 minute like metformin, *A. sativum*, *G. latifolium* and the herbal concoction made up of *A. boonei* + *M. indica* (Figure 2)

The OGTT curve AUC for *M. indica* (12886.00 mgmin/dL), *A. sativum* (13036.00 mgmin/dL), *A. boonei* (12963.00 mgmin/dL), and *M. sapientum* (12582.67 mgmin/dL) when given at low dose and 30 minutes prior to glucose load were statistically significantly lower than the vehicle control (15192.20 mgmin/dL). But the OGTT curve AUC for *Bauhinia monandra* (17130.33 mgmin/dL), *B. monandra* + *G. latifolium* (16698.40 mgmin/dL) and *A. boonei* + *M. indica* (15873.60 mgmin/dL) were higher than the vehicle control but not significant different. However, these values were statistically significantly higher than the OGTT curve AUC of metformin (14101.50 mgmin/dL) (Figure 3).

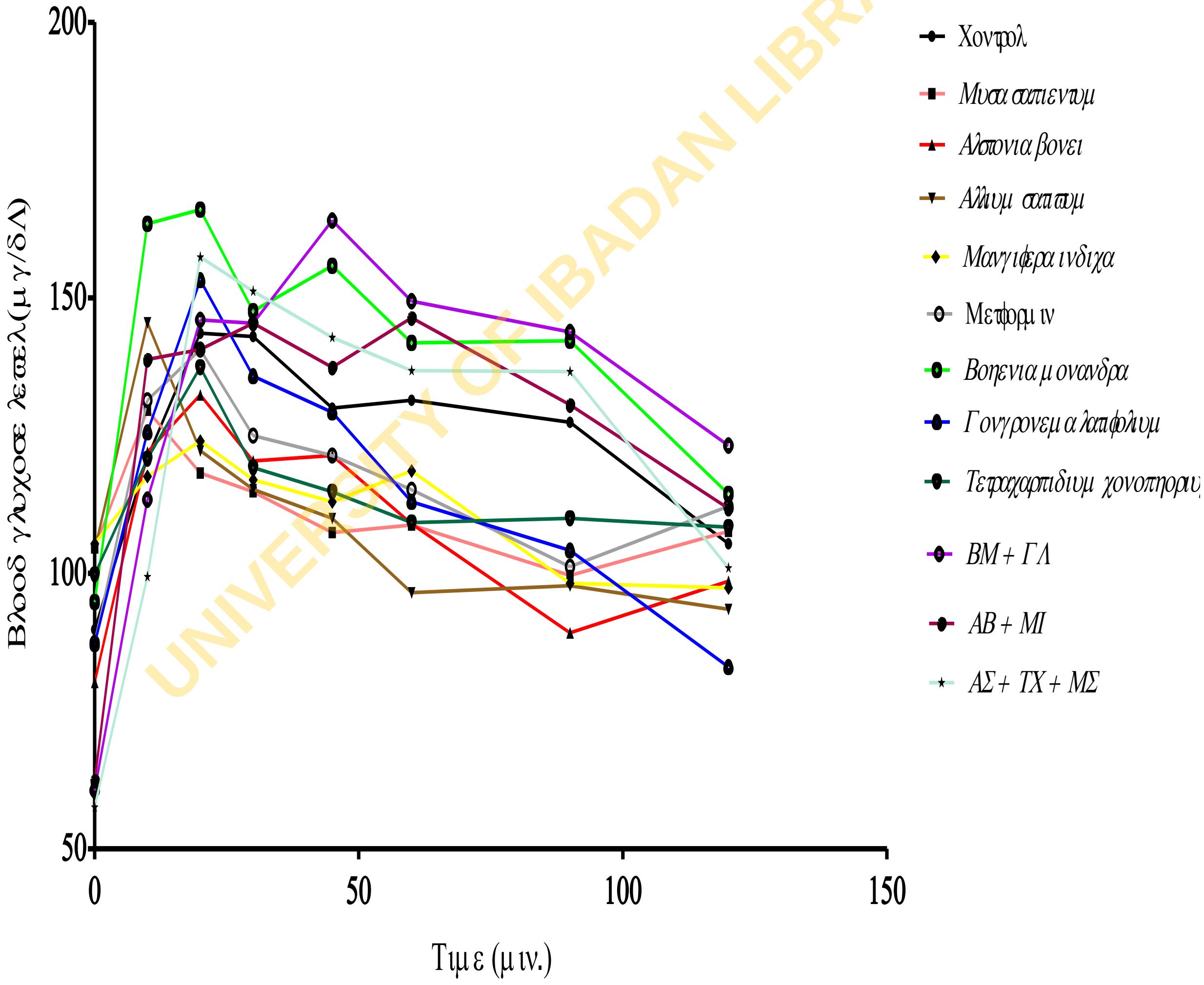

Figure 1: Oral glucose tolerance test showing BGL at each time point, when glucose load was given 30 minutes after the administration of drug or extracts. Each point represents an average of five readings.

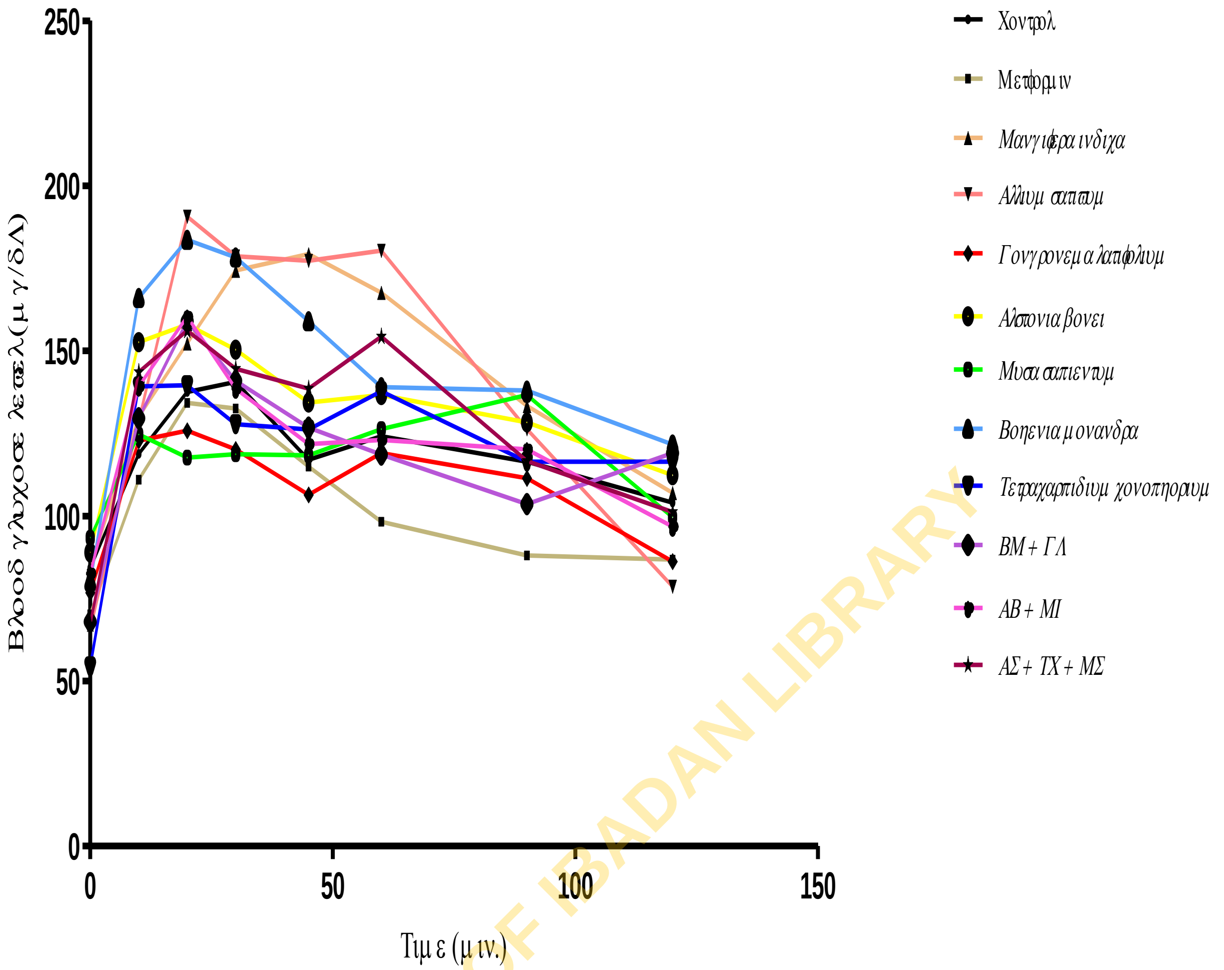

Figure 2: Oral glucose tolerance test showing BGL at each time point, when glucose load was given 60 minutes after the administration of drug or extracts. Each point represents an average of five readings.

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When administered at a high dose, 60 minutes prior to glucose load, the OGTT curve AUCs of the extracts were higher than that of the vehicle control but not statistically significantly different. The OGTT curve AUC of metformin was 12337.00 mgmin/dL, this was significantly lower than the OGTT curve AUCs of *M. indica* (17492.00 mgmin/dL), *A. sativum* (17442.67 mgmin/dL), *A. boonei* (16056.00 mgmin/dL), *B. monandra* (17603.67 mgmin/dL) and *A. sativum* + *T. conophorum* + *M. sapientum* (15710.80 mgmin/dL).

Tetracarpidium conophorum showed a significant difference (P=0.047) between the OGTT curve AUCs 30 minutes before glucose load (13676.20 mgmin/dL) and 60 minutes before glucose load (14889.20 mgmin/dL). The only herbal concoction that showed significant difference (P=0.011) in the OGTT curve AUC 30 minutes before glucose load (15873.60 mgmin/dL) and 60 minutes before glucose load (14452. 40 mgmin/dL) was *B. monandra* + *G. latifolium* (Figure 3).

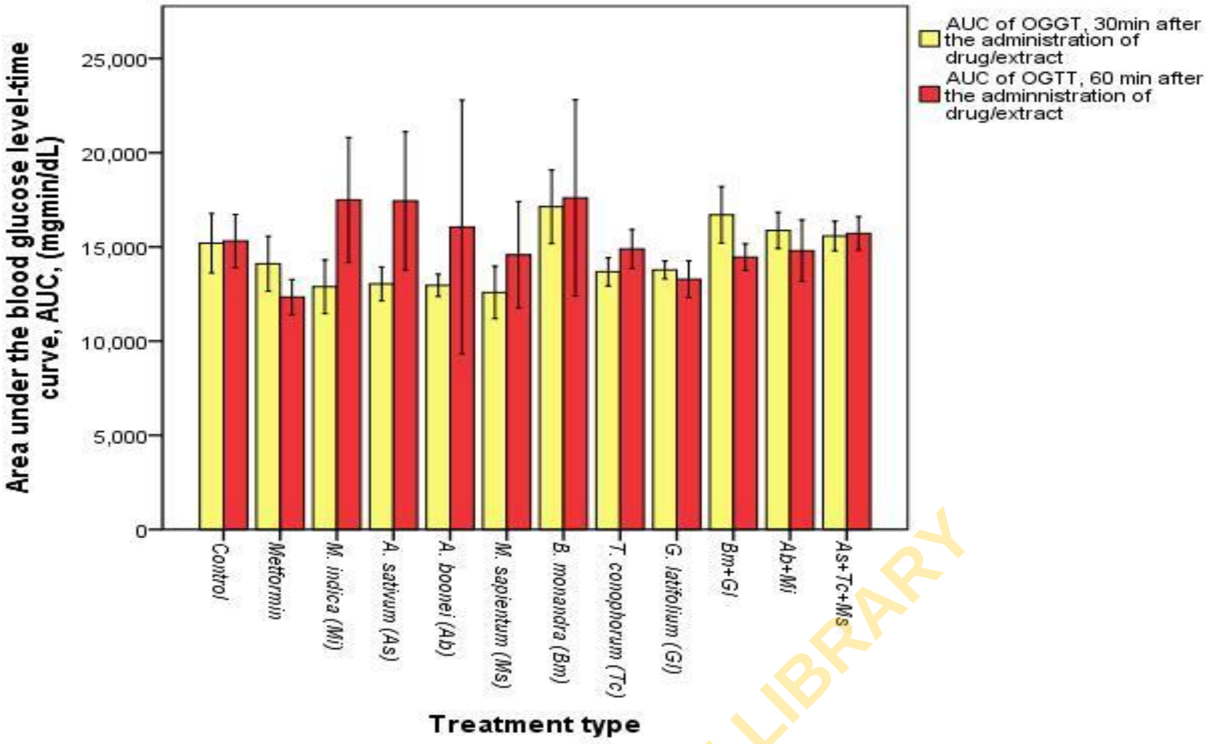

Figure 3: Area under the curve for oral glucose tolerance test, 30 and 60 minutes after the administration of the plant extracts and metformin.

Table 1 shows that the glycemic index of *A sativum* (56.22%) is significantly lower than the GI for metformin (92.82%) when the extract was administered 30 minutes prior to oral glucose load but the GI for *B. monandra* (112.76%) and *B. monandra* + *G. latifolium* (109.91%) were significantly higher (P>0.05) (Table 1)

DISCUSIONS

The increasing prevalence and burden of diabetes calls for multifactorial intervention to prevent or delay the onset of the disease in people with prediabetes. Lifestyle modification such as diet, exercise, weight loss and pharmacological interventions have shown moderate beneficial effects (Pan et al., 1997; Eriksson et al., 1999; Tuomilehto et al., 2001; Ojewale and Adejumo 2012). People with chronic diseases have been reported to use herbal medicine either alone or concurrently with conventional medicines with the believe that a synergistic effect will be obtained (Hasan et al., 2009). In Africa many of these herbal medicines come in the form of herbal concoctions that are polyherbal formulations (Olowokudejo et al., 2008; Soladoye et al. 2012). The belief, is that, if several individual herbs work for the same condition, combining them together would give a more beneficial effect. Our aim was to determine the effectiveness of traditional herbal concoctions for diabetes and their individual herbal componenets in delaying the onset of the disease. We approached the study by combining equal proportions of the individual plants to make the herbal concoctions.

The LD_{50} for each of the herbal concoction was found to be above 2000 mg/kg, hence each of the herbal concoction could be regarded as safe and of low toxicity since the LD_{50} was higher than 1000 mg/kg (Clarke and Clarke 1967). The safety of these herbal concoctions at this dose justified their age-long use without any serious reported side effects.

Oral glucose tolerance test measures insulin action, beta cell function and the rate of post prandial appearance of glucose in the blood (Breda et al., 2001). The extent of blood glucose level in the blood over a two hour period is determined by calculating the OGTT curve AUC. Our study revealed that the three traditional herbal concoctions (*Musa sapientum + Allium sativum + Tetracarpidium conophorum; Gongronema latifolia + Bauhinia monandra; and Alstonia boonei + Mangifera indica*) had significantly higher OGTT curve AUC values than the conventional drug (metformin) when administered at low and high doses, 30 and 60 minutes prior to glucose load respectively. But some of the individual components of the herbal concoctions; *M. indica*, *A, sativum*, *A. boonei* and *M. sapientum* had comparable OGTT curve AUCs with metformin. However, these individual herbs were able to return the blood glucose level to normal before 120 minutes which was better than metformin.

Table 1: Glycemic index (GI) of traditional diabetes herbal concoctions and the individual plant components

Herbs	Glycemic Index, 30 minutes before oral glucose load (mean percent ± S.D)	Glycemic Index, 60 minutes before oral glucose load (mean percent ± S.D)
Metformin	92.82 ± 9.63	86.01± 6.50
M. indica	84.82 ± 8.13	121.9 ± 20.05*
A. sativum	56.22 ± 48.89*	121.60 ± 22.14*
A. boonei	85.33 ± 3.36	111.94 ± 40.68
M. sapientum	82.83 ± 7.94	101.69 ± 17.04
B. monandra	112.76 ± 11.12*	122.72 ± 31.46*
T. conophorum	90.02 ± 5.48	103.80 ± 8.09
G. latifolium	90.66 ± 3.50	92.56 ± 7.60
B.monandra + G. latifolium	109.91 ± 11.09*	100.75 ± 5.50
A.boonei + M. indica	104.49 ± 7.07	103.14 ± 12.75
A. sativum + T. conophorum + M. sapientum	102.55 ± 5.76	109.53 ± 6.93*

*P<0.05 when compared with metformin.

During OGTT two mechanisms comes into play; one is the suppression of hepatic glucose output and the other is increased uptake of glucose into the muscle and liver cells. These are mediated by increase secretion of insulin and increase sentivity of the liver and muscle cells to insulin (Unwin et al., 2002). All the individual herbs in the concoction when used alone were able to increase the clearance of glucose from the blood into the liver and muscle cells better similar to metformin with the exception of *B. monandra*. These results agrees with several other studies showing the effectiveness of these individual herbs in ameliorating glucose intolerance (Pari and Maheswari, 1999; Abo and Jimoh, 2005; Hossain et al., 2010; Adebajo et al., 2013; Moradabadi et al., 2013; Nkono et al., 2014; Onwuli et al., 2014).

The ineffectiveness of the herbal concoctions in curbing glucose intolerance could be due to interaction between the various phytochemicals of the herbs, causing decreased ability of the concoctions to increase glucose uptake by the muscle and liver cells. Aside from the possible interaction of the phytochemicals, the preparation of the herbal concoctions from equal proportions of the individual plant component might also be responsible for its ineffectiveness in improving glucose intolerance perhaps because the right proportion of the individual plant components was not used though ethnobotanical surveys and other studies have reported the use of these herbal concoctions in diabetes (Oreagba et al., 2011; Akande et al., 2012; Ezuruike and Prieto, 2014). Ethnobotanical survey only revealed the individual herbal components of the concoctions not the proportion in which they are prepared (Soladoye et al., 2012). One of the challenges of traditional medicines in sub-saharan Africa is the problem of standardization of herbal products. Traditional healers belief that this should be their secret mostly for personal gain (Soladoye et al., 2012). The unavailability of the right proportion makes standardization difficult and introduces inconsistency in the preparation of herbal concoctions for various ailments among traditional healers. The search for a pharmacological agent like metformin that could prevent or delay the onset of diabetes may be nearing its end if these individual herbs are considered as leads for the development of drugs for IGT and/or IFG. Though these herbs have been used for decades in the management of diabetes, there are no reports of clinical trials examining their use in the prevention of the disease or in prediabetes.

Glycemic index indicate the extent to which a food substance, drug, or herbal medicine provide glucose to the blood and invariably the release of insulin. Substances with low glycemic index are thus useful in the management of diabetes (Brand-Miller et al., 2003). All the herbal concoctions studied had high glycemic indexes while their individual plant component had lower glycemic indexes. Substances with low GI have been reported to have a clinically important marginal usefulness in short term glycemic control in type 2 diabetes (Brand-Miller et al., 2003). Thus the individual plants in the herbal concoctions because of their low glycemic indexes may be more beneficial than the concoctions in short term management of impaired glucose tolerance.

CONCLUSION

The three traditional herbal concoctions used in the management of diabetes were not effective in improving glucose intolerance but the individual herbs in these concoctions were more effective when administered 30 minutes prior to oral glucose load. These individual herbs are potential candidates for impared glucose tolerance to prevent or delay the onset of diabetes. Further investigations should be conducted on the numerous traditional herbal concoctions used for diabetes.

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