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Original Research Paper

Stem Bark Aqueous Extract of *Citrus Sinensis* Reduces Postprandial Glycaemia Better Than Glibenclamide, An Anti-Diabetic Drug

ABSTRACT:

Aims: Diabetes Mellitus remains amongst the highest cause of mortality in the world. This study was carried out to determine the phytochemical composition of stem bark extracts of *Citrus sinensis*, to study its anti-hyperglycaemic activity as well as its modulatory effects on starch and sucrose digestion on normal Wistar rats.

Methodology: Stem barkAqueous (AqE), Ethanolic (EtE), Hydroethanolic (HEE) extracts of*C. sinensis*were prepared.The content of polyphenols, flavonoids, alkaloidswasdetermined. Anti-hyperglycaemic activity was evaluated *in vivo* by oral glucose tolerance test (OGTT) for 120 minutes. Wistar male rats of 180-200g were used. After an overnight fast, their glycaemia were measured (T0). Rats were then distributed intofive groups of six each: Control (water), Tests (400mg/kg of each extracts), Reference (4mg/kg B. W., glibenclamide). Thirty minutes later, an overload of 2g/kg B. W. of glucose was administered to all the groups. Glycaemia was measured by tail pricks: 30, 60, 90, 120 minutes after glucose administration. Sucrose (2g/kg bw) and starch (1g/kg b. w) and acarbose in co-administrationwere used as substrates for digestion in a protocol similar to OGTT.

Results: EtE was very rich in polyphenols (435.56 ± 3.85 µg of eq catechin/mg).

Area under the Curves, AUC (mg.min.dL^{-1}, P=.05) were: 4015, 786.6, 1163 for PC, AqE group, Reference respectively and confirmed that AqE was more efficient than glibenclamide. AqE also showed moderate efficacy with sucrose (841.2 vs 1172 mg.min/dL, P=.05) and starchdigestion (892.8 vs 1148; P=.05) compared to positive controls.

Conclusion: Therefore, stem bark aqueous extract of*C. sinensis* is able to reduce postprandial glycaemia by slowing down the absorption of glucose, challenging the efficacy of glibenclamide,an anti-diabetic drug. Also,AqE has moderate efficacy on starch and sucrose digestion. AqE could thus be further explored for its potency in the treatment of diabetes mellitus.

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Key words: Antihyperglycemia, Postprandial Glycaemia, stem bark, C*itrus sinensis*, digestion

1. INTRODUCTION

The incidence of metabolic syndrome (MS) all over the world including Africa is increasing, due to a rise in obesity rates among adults [1-2]. National Heart and Lung Institute [3]reported that in future years, metabolic syndrome may overtake smoking as the leading risk factor for heart disease. Lifestyle, eating habits, sedentarity and urbanization are amongst the factors that contribute to its morbi–mortality[4-5-6]. MS is defined as a cluster of cardiovascular risk factors: dyslipidemia, hypertension, abdominal obesity and impaired glucose tolerance or diabetes [7]. The common manifestation of diabetes include hyperglycemia associated or not to insulin resistance. In fact,postprandial hyperglycemia is a predisposing factor for vascular dysfunction and organ damage[8].It is also associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vesselsand also an independent risk factor for CVD in patients with or without diagnosed diabetes [9]. Hyperglycemia or PPHG also induces an increase in stiffness of intermediate-sized arteries [10-11-12]. PPHG produces ROS in oxidative stress involved in tissue alteration and disease complications associated with the development of diabetic nephropathy and retinopathy [13-14].

Hyperglycaemia or PPHG also arises from food digestion. In fact, food is the main and natural source of energy with carbohydrates, lipids and proteins being the basic nutritive substances. Digestion and absorptionof food lead tohyperglycemia [8-15]followed by a resorption period 2–3 hours later in healthy individuals or longer in disease condition [16-17],

Amongst the anti-diabetic medications glucagon-like peptide 1 [GLP-1] receptor agonists, dipeptidylpeptidase -4 [DPP-4] inhibitors have significant benefits in reducing post meal plasma glucose excursions and lowering HbA1c in people with diabetesthrough inhibition of digestive enzymes[11-15-18].Unfortunately, there are many side effects related to these medications, amongst which hyperglycemia associated to glucocorticoid and corticosteroid therapies [19-20-21]. Diabetes treatment and its complications represent a significant financial burden for the budget of every developed country [17]. Despite awareness and prevention measures taken by governments to control and reduce mortality, management of diabetes and adequate treatment remain a challenge. The current clinicaltrend is the utilization of naturally active compounds asreplacement therapies and World Health Organization has substantiated their utilization for the management of diabetes [22-23],

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due to easy availability, economic reasons and lesser side effects [24].Their use has been reported in Guinea [25], in Morocco [26] and many other countries.

Citrus sinensis(L.)Osbeck(Sweet Orange) is one of the most important and widely grown fruit crop. Itaccounts for approximately 60% of citrus production for both fresh fruit and processed juice consumption.Oranges are an important nutritional source for human health and have immense economic value[27] for its tasty juice and medicinal value [28].Orange peel extracts have been used to treat colic, upset stomach, cancer, diuretic andto fight diverse viral and bacterial infections [29-30-31], In addition, only orange peel oil extracts and leave oil extracts of C*itrus sinensis* was listed amongst over a hundred plants with hypoglycemic and antidiabetic effects reported by UdoamakaetPrieto[32]. To date, few or no data on the effect of stem bark extracts on acute treatment of hyperglycaemia and digestion of carbohydrates' key substrates have been reported. Therefore, this study was conducted to determine the phytochemical composition of stem bark extracts of *Citrus sinensis*, to study its anti-hyperglycaemic activity and the effect on sucrose and starch digestion on normal Wistar rats.

2. MATERIALS AND METHODS

2.1 Chemicals

All the chemicals used were of analytical grade and were purchased from Sigma Co., Louis, MO, USA. These include; Folin- ciocalteu reagent, catechin, ethanol, potassium acetate, Quercetin, $FeCl_3$; 1, 10-phenanthroline, acarbose, glibenclamide.

2.2 Plant materials

Citrus sinensis(L.)Osbeckwas harvested in February 2016 in Yaoundé, city capital of Cameroon. It was identifiedat national herbarium with botanical characteristics as described by Letouzey et al., [33] as belonging to Rutaceae family. Stem bark wereisolated, cut into small pieces and then shade dried in open air for one month. The dried materials were ground to obtain powder, from which the different extracts were prepared.

2.2.1 Preparation of Ethanolic,Aqueous, hyroethanolic Extracts

One hundred grams (100g) of stem bark were placed in 800mL of ethanol (95%) for maceration for 48 hours. After filtration, the filtrate was then evaporated at 50°C to obtain the ethanolic extracts (EtE). The same procedure was followed to prepare aqueous extract (AqE) and hydroethanolic extracts

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(HEtE); ethanol been replaced by distilled water and mixture water/ethanol (95 %) in a ratio of 1:1 (v/v) respectively.

2.3 Quantitative determination of bioactive compounds

The quantitative analysis of some bioactive compounds includingpolyphenols, flavonoids, alkaloidswas done.

2.3.1 Determination of polyphenolic content

The polyphenol content was evaluated using the method described by Singleton and Rossi [34]. Briefly, to 30 µL of the extract, 1 mL of the Folin- ciocalteu reagent was added. Thirty minutes after the incubation at 25°C, the absorbance was read at 750 nm using a spectrophotometer. Catechin was used as standard. The total polyphenol was expressed in microgramequivalent of catechin/mg of extract.

2.3.2 Determination of total flavonoids content

The total flavonoids' content was evaluated using the method described by Aiyegoro and Okoh [35]. For each extract, 1mL (1 mg/mL) prepared in ethanol solution, 1mL of aluminium chloride, 1mL of potassium acetate and 5.6 mL of distilled water. The mixture was allowed to stand at 25 °C for 30 minutes. The absorbance of the reaction mixture was read at 420 nm with a spectrophotometer. Quercetin was used as the standard. The flavonoids content was expressed in mg equivalence of quercetin/mg of extract.

2.3.3 Determination of alkaloids' content

Alkaloid content was evaluated following the method reported by Singh *et al*. [36].One hundred (100) mg sample powder was mixedwith10ml of ethanol (80%). The supernatant was used for the estimation of total alkaloid content. The reaction mixture contained 1ml extract, 1ml of 0.025M $FeCl_3$ in 0.5M HCl and 1ml of 0.05M of 1, 10-phenanthroline in ethanol. The mixture was incubated for 30 minutes using a water bath at the temperature of 70 ± 2°C. Absorbance of red coloured complex developed was read at 510nm against reagent blank. Alkaloid content was expressed as microgram equivalenceof quinine /mg of extract.

2.4 Animals and treatments

Sixty sixmale albinos' rats weighing 180–200 g wereobtained from the Laboratory of Animal physiology, University of Yaoundé 1, Cameroon. Animals were treated according to the ethical

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guidelines outlined in the Guide for Care and Use committee of the Institutional ethic committee. All protocols were approved by the UniversityofYaounde 1 Animal Ethics Committee. Animals were housed under standardconditions in cages; 25°C, 50-60% relative humidity,with12h light - 12h dark cycle. They were fed with a standard diet and received waterad-libitum. All the animals were acclimatized for 10days prior to the start of the experiment.

2.4.1 Study of anti-hyperglycaemic activity: OGTT

Oral Glucose Tolerance Test (OGTT);an*in vivo* acute test was conducted as described by Al-malki et *al.*[8], to evaluate the capacity of extracts to prevent the absorption and the rise of glycaemia. Briefly, thirty (30) ratswere randomly divided into five groups of sixeach. After 12 hours overnight fasting, blood glucose at baseline (T0) was measured from vein tails of all rats using a glucometer and test strips (One touch Gluco-plus). Simultaneously, Group 1 serving as control group or Positive Control (PC) wasgiven water orally. Group 2 received Ethanolic Extract (400mg/kg body weight), Group 3 received Aqueous Extract (400 mg/kg body weight); Group 4 receivedHydroethanolic extract(400 mg/kg body weight); Group 5 received Glibenclamide (4mg/kg b. w). Thirty (30) minutes afteradministration of extracts, animals in all the groups were given overload glucose solution (2g/kg body weight). Blood glucose levels were measured using glucometer through tail pricks at 30, 60, 90 and 120 minutes after glucose loading. Administration of extracts and glucose was done orally with water 5mL/kg b. w.

2.4.2 *In vivo* study of the effects of Aqueous Extract on sucrose and starch digestion

The protocol used was similar to OGTT with some modifications. Briefly, animals were randomly divided into three groups of six animals each. After 12 hours overnight fasting, blood glucose at baseline (T0) was measured from vein tails of all rats using a glucometer and test strips (One touch Gluco-plus). Simultaneously, Group 1 or Positive Control (PC) was given water + 2g/kg sucrose orally. Group 2 received Aqueous Extract (400 mg/kg body weight + 2g/kg sucrose);Group 3 received Acarbose 3mg/kg b.w. + 2g/kg b.wsucrose). Blood glucose levels were measured using a glucometer through tail pricks at 30, 60, and 120 minutes after sucrose loading. A similar design was implemented to study starch digestion as described above, except that starch 1g/kg b. w replaced sucrose and the follow up was done at 60, 90, 120, 180 minutes. Administration of extracts and substrates (sucrose, starch) was done at the same time to allow the interactions between extracts,

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substrates and enzymes in the gastrointestinal track. Blood glucose was measured as end products from starch and sucrose digestion and absorption.

2.5 Data processing and analysis

Results were expressed as incremental change and as Mean± Standard Deviation. Graphpad prism software, version 6.0 (GraphPad Prism INC., CA, USA) was used to determine the area under the curve (AUC) as an expression of efficacy of extracts. Statistical Package for Social Science (SPSS 20.0 Illinois, Chicago) was used to analyze results. Paired sample Student-*t*-test was used to analyze blood glucose levels for each extract at each time. One-way analysis of variance ANOVA test followed by Waller-Dunkan as post-hoc was used to compare variables between groups under 95% confidence interval.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Phytochemical content

The phytochemical analysis of *Citrus sinensis* stem bark extracts obtained using different soft solvent systems; water, ethanol and Water-ethanol mixture (1:1 v/v) revealed larger quantities of polyphenolic compounds in all the extracts, the ethanolic extracts being richer than the aqueous andhyroethanolic extracts. However, hydroethanolic and ethanolic extracts possess a higher content of alkaloids. Flavonoidswere higher in ethanolic extracts (Table 1).

Table 1: Phytochemical content of *C. sinensis*stem bark extracts

Extracts / Compounds	Aqueous	HydroEthanolic	Ethanolic
Alkaloids(µg EqQuinine/mg)	4.34 ± 0.6[a]	13.13 ± 1.6[b]	13.18 ± 1.6[b]
Polyphenols(µg Gallic acid/mg)	208.89 ± 25.24[a]	406.67 ± 57.74[b]	435.56 ± 3.85[b]
Flavonoids(µg EqQuercetin/mg)	0.85 ± 0.05[a]	1.16 ± 0.15[b]	9.40 ± 0.70[b]

Results expressed as Mean ± SD, Tests were done in triplicates, eq: equivalent; variables with different letters a,b, c associated are significantly different P=.05

3.1.2 Anti-hyperglycaemic effects of *C. sinensis* stem bark extracts

Administration of glucose to rats receiving no extracts resulted in highest peak at 30 min and thereafter a gradual reduction of glycaemic levels with time. All other groups showed a peak at 30 min lower than PC. Values gradually decreased during the experiment. It clearly appears that aqueous extracts of *C.Sinensis* was able to prevent the increase of blood glucose. The values were lower

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compared to positive control, and interestingly, lower compared to glibenclamide,antidiabetic drug of reference (Figure 1).

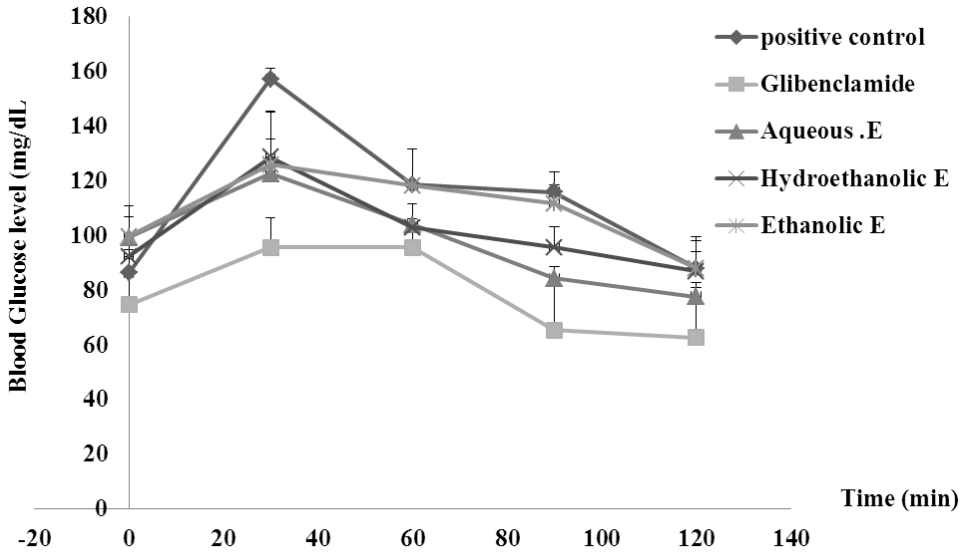

Figure 1: Effect of stem bark extracts on blood glucose level

Results are expressed Mean +/- SD, n= 5 rats/ group

3.1.3 <u>Variation of blood glucose in each group within two hours experiments</u>

With paired-sample Student*t* test, it is observed that acute administration of each extract during thirty minutes revealed significant increaseof 82.24% in PC compared to 23.49% in AqE group 1 in all the groups except the group receiving glibenclamide. The decrease in groups treated with glibenclamide (-16.07%) and AqE (-21.81%) was significant after two hours compared to baseline Glycaemia (Table 2).

Table 2: Percentage variation within time intervals

Groups	Variation T0 - T30		Variation T30 - T120		Variation (T0-T120)	
	%variation	***P* value**	**%variation**	***P* value**	**%variation**	***P* value**
PositifControl	82.24	<.001	-44.07	.001	1.93	.778
Glibenclamide	28.13	.093	-34.49	.026	-16.07	.05
EtE	26.42	.002	-30.16	.008	-11.71	.06
HEE	39.35	.001	-32.38	.001	-5.78	.286
AqE	23.49	.006	-36.68	.004	-21.81	.004

Stem bark Aqueous (AqE), Ethanolic (EtE), Hydroethanolic (HEE) extracts of C. sinensis

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3.1.3 Comparison inter groups at each time intervals

An adjustment from glycemic levels at baselineshowed the trends of each extract in comparison with positive control group and with glibenclamide, anti-diabetic drug (Figure 2).

Statistical analysis with ANOVA and Waller-Duncan post hoc test revealed that at each time interval, there was a significant difference between blood glucose increment of PCgroup and all the treated groups and with Glibenclamide, reference group. At 60 minutes the group receiving AqE significantly decreased blood glucose (*P*=.05) than the group treated with glibenclamide (Figure 2).

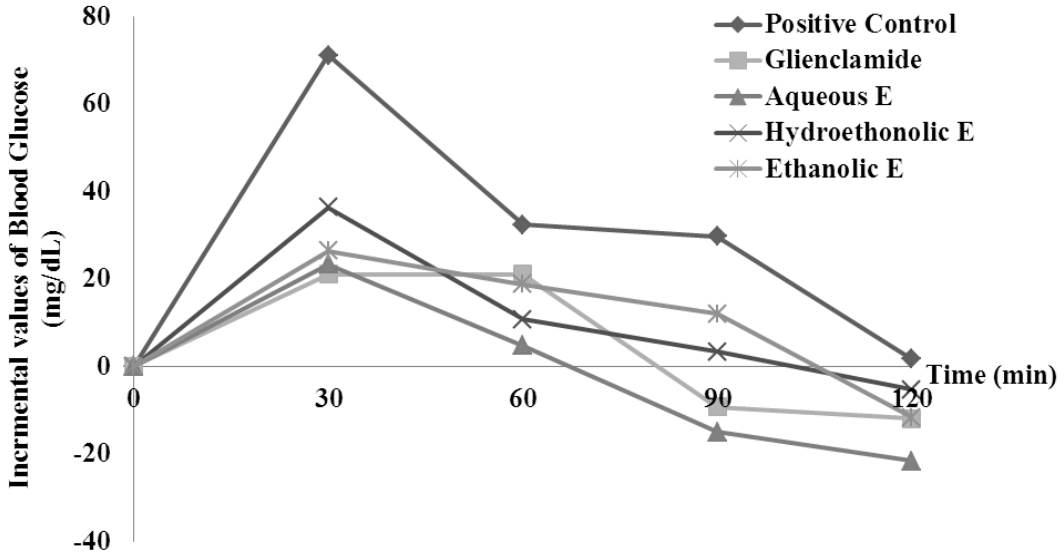

Figure 2: **Effects of *C. sinensis*stem back extracts on regulation of overload glucose adjusted from baseline**

Results expressed as Mean ± Standard deviation; n=6 rats/group

3.1.4 *Efficacy of Citrus sinensisExtracts*

The efficacy of each extractmeasured as AUC confirmed that stem bark Aqueous Extract has the lowest AUC compared to PC and more interestingly to glibenclamide. All other extracts showed an AUC lower than Positive Control (Figure 3).

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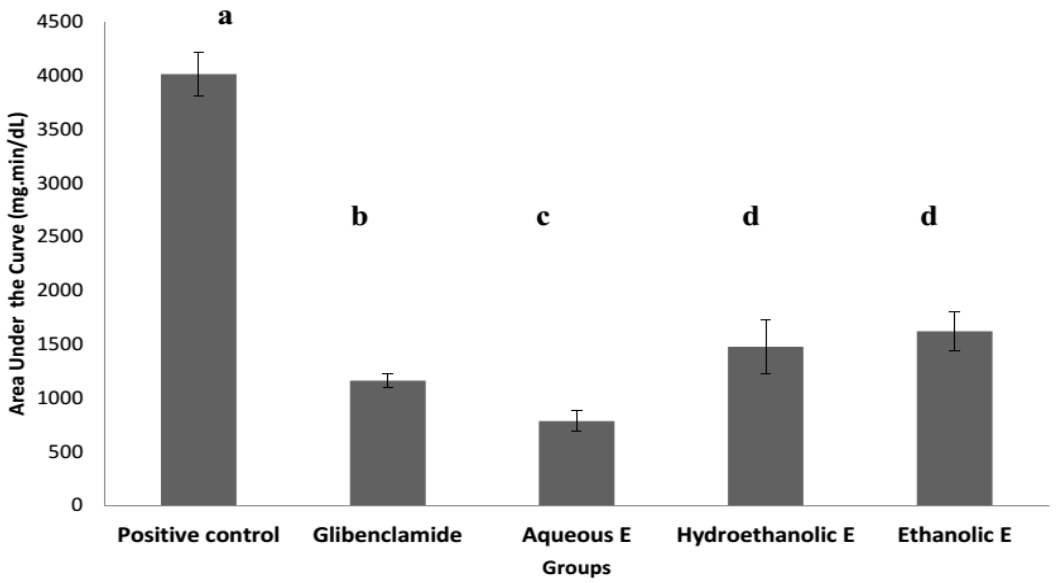

Figure 3: Efficacy of stem bark extracts of *C. sinensis* on overload glucose

Results expressed as Mean± Standard deviation; n=6 rats/group; histograms different letters a, b, c, d associated are significantly different P=0.5

3.1.4Effectsof extract on sucrose digestion

Based on results above, Aqueous Extract (AqE) being the best antihyperglyceamicextract, was selected for digestion studies. Administration of sucrose (only), to rats increased blood glucose within 30min (variation of 13.66 mg/dL). After an hour,sucrose was completely digested and glucose released,absorbed in PC group. Inthe presence of AqE, there was a delay of 90 minutes in the digestion/release of glucose from sucrosebefore glucose started subsequently appearing in the blood, to reach a peak after 2 hours (15.33 mg/dL). AqEdemonstrated its ability to inhibit digestion of sucrose and promoted the shift of peak appearance from 30min with sucrose only (PC) to 120 min in presence of AqE(Figure 4).

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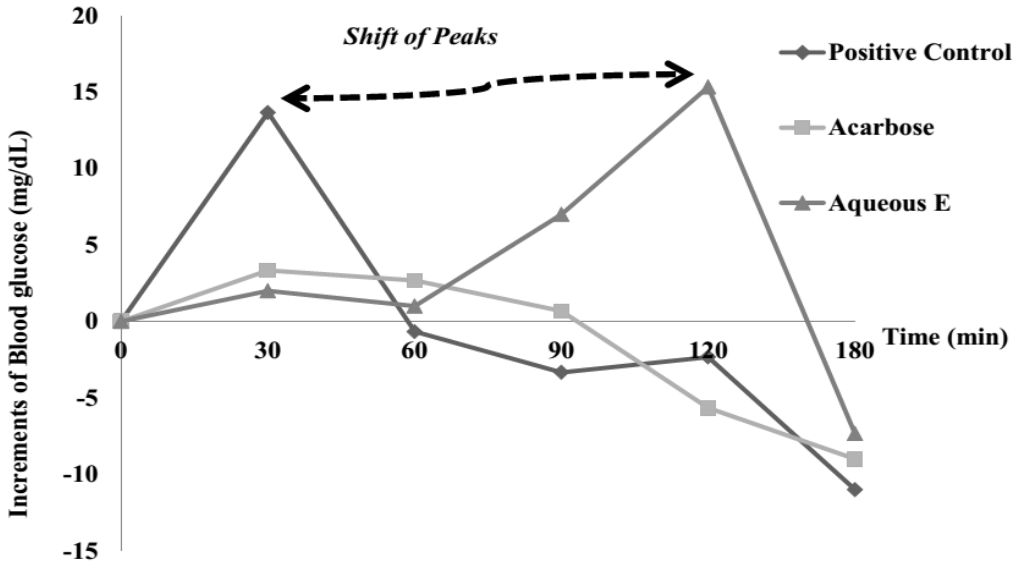

Figure 4: Effects of aqueous extract on sucrose digestion *in vivo*

Results were expressed as incremental difference (mg/dL). n=6 rats

3.1.5<u>Efficacy of aqueous extract on sucrose digestion</u>

After two hours experiment, the efficacy of AqE was lower than positive control as confirmed by AUC values. However,acarbose showed highest efficacy (Figure 5).

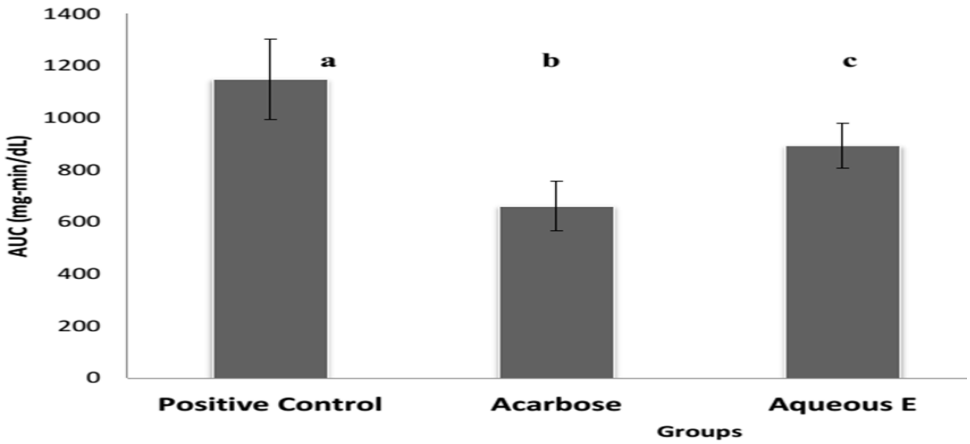

Figure 5: Efficacy of Aqueous extract on sucrose digestion

Results expressed as Mean ± Standard deviation; n=6 rats/group; histograms different letters a, b, c associated are significantly different P=0.5

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3.1.6Effects of aqueous extracts on starch digestion

In Figure 6, It has been observed that in the absence of AqE or reference drug, starch is digested into its monomers of glucose leading to blood glucose rise within an hour to 22.66 mg/dL (PC) followed by a consistent digestion and absorption all through the experiment

With co-administration of AqE, digestion within the first hour is similar to PC **(P>.05).** But, between 60 to90 min, digestion of starch is slowed down at a rate greater than PC group to become constant 90 min.

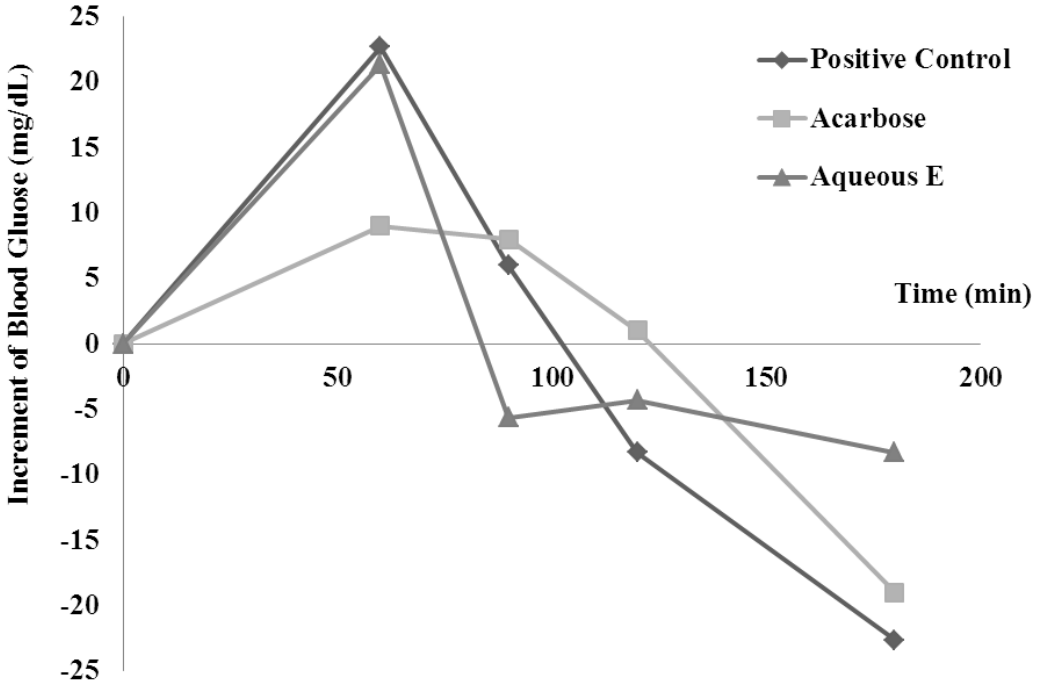

Figure 6: Effects of Aqueous extracts on starch digestion

Results were expressed as incremental difference (mg/dL). n=6 rats/ groups

3.1.7Efficacy of Aqueous Extract on starch digestion

The efficacyofacarbose (*P*=.05)was greater than the efficacy of the group treated with AqE which had moderate activity compared to Positive Control (PC, *P*=.05). The efficacy of AqEwas -35% compared to acarbose(Figure 7).

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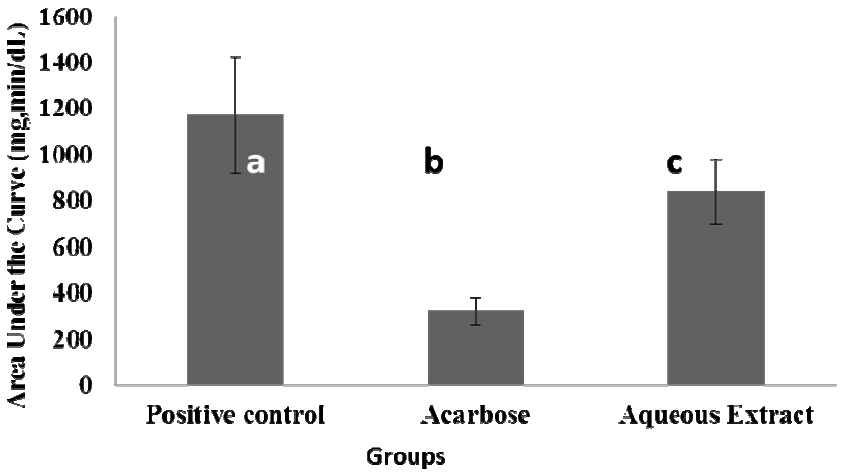

Figure7: Efficacy of Aqueous Extract on starch digestion*in vivo*

Results were expressed as mean ± SD. n=6 rats/group; AUC: Area under the Curve, Different histograms different letters a,b,c associated are significantly different P=0.5

3.2 Discussion

Metabolic syndrome including obesity and diabetes as individual components is the most prevailing health concern worldwide and its incidence is increasing at a high rate, resulting in enormous social costs [2-37]. Control of glycaemic excursions is an approached to manage MS.This study demonstrated the ability of AqueousEthanolic and Hydroethanolicstem bark extracts of *C sinensis* to gradually and effectively reduce post prandial glycaemia compared to a Positive Control(Figures 1, 3). It can be speculated that the efficacy of the extracts can be helpful in the prevention and management of diabetes and its complications. In fact, *Citrus sinensis* extracts revealed their high content in polyphenols, flavonoidsand alkaloids (Table 1); molecules that could justify the efficacy of extracts in reducing blood glucose or preventing its increase (Figures 1, 2,3). Numerous *in vitro* cell and *in vivo* animal studies support the beneficial effects of dietary flavonoids on glucose homeostasis for the prevention and treatment of obesity and diabetes [38] by regulation of carbohydrate digestion, adipose deposition,insulin release and glucose uptake in insulin-responsive tissues through numerous cell-signaling pathways[37]. Flavonoids and polyphenols could alleviate chronic hyperglycaemiaand by so doing preventinsulinresistance and oxidative stress found in the complex and heterogeneous condition of diabetes [39].Aqueous Extract was the most efficacious amongst the extracts (Table 2) though its polyphenols, alkaloids, flavonoids content was smaller than in EtEand HEE(Table 1). Its efficacy was highercompared toglibenclamide, an antidiabetic drug used as reference (Figures 2, 3).

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AqE may be rich in quality molecules acting via mechanism similar to glibenclamide with better effectiveness. In fact,glibenclamide, a5-chloro-N-(2-{4-[(cyclohexylamino)carbonyl] aminosulfonyl} phenyl)ethyl)-2-methoxybenzamide is a second-generation sulfonylurea that reduces blood glucose by binding to the specific receptor for sulfonylureas on β-pancreatic cells, blocking the inflow of potassium (K^+) through the ATP-dependent channel. The resulting increased flow of calcium into β-cells causes the contraction of the filaments of actomyosin and prompt secretion ofinsulin in large amounts [40-41-42]. Although the aqueous extract is just a crude extract, it can be speculated thatflavanonessuch as naringenin and hesperidin abundant in citrus fruits such as grape, tomatoes and oranges are reported to possess antioxidant, anti-diabetic properties [43]could be also found in their stem bark.In addition, AqE may also reduce glucose absorption through interaction with, GLUT2, the predominant glucose transporter in the intestine [44].

An indirect appreciation of theaqueous extract oninvertase an alpha amylase was evaluated on the basis of the correlation existing between *in vitro*and*in vivo*studies on glucose response and portal glucose appearance up to 8 h post meal [45].This study revealed that stem bark AqE of *C. sinensis*wasable to moderately slow down the digestion-absorption process of starch (Figures 6 and 7) and sucrose (Figures 4 and 5) compared to PCs. This is result is in accordance with drugs used to treat metabolic disease such as obesity / diabetes. They act in gastrointestinal tract (GIT) to inhibit key enzymes of the digestive system including alpha glucosidase, invertase and alpha amylase [46-47]. The moderate effects AqE is important because in humans, between 40% and 80% of total caloric intake is accounted for by carbohydrates in their various forms making them the most important energy source [46]. Starch is digested primarily to maltose and other short chain carbohydrates by salivary and pancreatic amylase [43-46] and postprandial glycaemia occurs as a result of absorption of monosaccharide mainly glucose.Interference of AqE with those enzymes reduces postprandial glycaemia.

Sucrose concentration of approximately 1.11 M administered in this experiment probably led to glucose and fructose appearing in the serosal compartment of rats at similar rates of serosal transfer as proven *ex vivo* by Ruth andLeese[48].AqE interfering withsucrose digestion-absorption was proven to slow down digestion and delayed absorption (Figure 4). Such delay can be helpful for the acute treatment of diabetes /or of glucose excursions in patients; mainly in condition of diabetes where consumption of diet with high glycemic index can lead to coma in very short period. The delay may

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also give time to hormones and enzymes to be secreted in amount higher enough to stimulate the uptake of glucose and better promote its plasma clearance in normal or diabetic rats,given that the status normal or diabetesdoesnot alter the GIT functions[49].

Although theefficacy of AqE was lesser (-35%) compared to reference drug acarbose (Figure 5). it can be speculated that aqueous extract of stem bark of *C.sinensis* in its constituents can act through inhibition of invertase and alpha amylase. In fact,polyphenolic compounds present (Table 1) have been shown to possess antioxidant actions and to be able to inhibit digestive enzymes. Naturally occurring polyphenols, in particular catechins and condensed tannins isolated from various plant sources have been shown to inhibit digestive enzymes including lipase and α-amylase *in vitro*[50].Also, Aq extract may possess molecules which could act with mechanisms similar to acarbose given thatacarbose,C25H43NO18 is a pseudo-tetrasaccharide that inhibits intestinal α-glucosidasereversibly at the brush border of intestinal mucosa. As a consequence, the digestion of disaccharides to monosaccharides is prevented, the uptake of monosaccharides is retarded and thus postprandial insulin and glucose levels are reduced[50].The inhibition of the enzymes delays the degradation of oligosaccharides to glucose, and therefore controls postprandial hyperglycemia[47].Such action mechanism may explain the shift of peaks from 30 min to 1h30 minutes observed on sucrose digestion (Figure 4). Moreover, the faster digestion (Figure 5) of substrate by extracts followed by their rapid absorption in acute test (Figure 2, Table 2) may avoid the gastrointestinal side-effects which unfortunately hampered the usage of acarbose, despite its good safety record [47].

Flavonoids, polyphenols, alkaloid found in Aqueous Extract probably contributed to its moderate efficacy on starch digestion and inhibition. In fact, black tea polyphenols exert a positive effect on inhibiting obesity through two major mechanisms: inhibiting lipid and saccharide digestion, absorption and intake; thus reducing calorie intake[51]. Lochocka et al. [52] reported that a single dose of green tea extract taken with a test meal decreases starch digestion and absorption. Also,Haibo et al. [51] and Hara et al. [53] in another study reported that theaflavins showed stronger inhibitory effect on GIT enzymes than catechins. Such flavonoidsmainly inhibit only GLUT2 but not SGLT1 [54].

Many other studies have reported onthe use of herbs/medicinal plants that interfere with carbohydrate digestion and absorption[37-43]. These include another Rutaceae, a Vietnamese Citrus Peels of“Buddha’s hand”, whose essential oil strongly inhibited α-glucosidase activity in a dose dependent

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manner [47]. Also include is an extract from black, green, and mulberry teas; in which acute administration of 1.5 g of phaseolamine to healthy participants blocked the absorption of 66% of carbohydrates present in a standard meal[55].

4. CONCLUSION

Aqueous (AqE), Ethanolic (EtE), Hydroethanolic (HEE) stem bark extracts of *C. sinensis*with their rich phytoconstituents, reduce postprandial glycaemia by slowing down absorption of glucose.Anti hyperglycemic efficacy of aqueous extract challengesglibenclamide, anti-diabetic drug. AqEmoderatelyinterferes on starch and sucrose digestion. Stem bark AqE of *Citrus sinensis* could thus be further explored for its potency in the treatment of diabetes mellitus and other metabolic disorders.

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