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Effects of Aqueous Extracts of *Xylopia aethiopica* (Annonaceae), *Aframomum melegueta* (Zingiberaceae), *Picralima nitida* (Apocynaceae) and *Irvingia gabonensis* (Irvingiaceae) on Glycaemia in Mice

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Abstract: The aim of this study was to evaluate the effects of aqueous extracts of *Xylopia aethiopica* (Annonaceae), *Aframomum melegueta* (Zingiberaceae), *Picralima nitida* (Apocynaceae) and *Irvingia gabonensis* (Irvingiaceae), designated AEXa; AEAm; AEPn and AEIg, respectively, on glycaemia in mice in order to contribute to the valorisation of their use in traditional medicine. In acute toxicity study: a total of 36 male mice (20-30g) were divided into 12 batches of 3 mice each, with three batches per extract. The animals in the control batch (batch 1) received distilled water, while those in batches 2 and 3 received 2000 and 5000 mg/kg body weight of all the four extracts via oral gavage for 14 days. In glucose tolerance test, 18 male mice (20-30g) were divided into 6 batches of 3 mice namely control and tested group which received an oral dose of aqueous extracts and glibenclamide at doses of 1 ml/100 g body weight (bw) and 2.5mg/100g body weight (bw) respectively for 125 minutes. Phytochemical screening was performed using chemical reactivity. Qualitative phytochemical tests carried out on all the aqueous extracts revealed the presence of numerous secondary metabolites, including polyterpenes, polyphenols, alkaloids, quinone compounds and saponins. Acute toxicity studies showed that these extracts were not toxic at doses of 2000 mg/kg and 5000 mg/kg body weight, nor did they cause any significant variation in the weight of the treated animals. AEPn and AEAm extracts significantly reduced the hyperglycaemia induced by the glucose solution, with an effect comparable to that of the standard antidiabetic drug glibenclamide. However, AEXa and AEIg had no significant effect on blood glucose levels in mice. The Results showed that *A. melegueta* and *P. nitida* had a great therapeutic potential and justify the use of these two plants in traditional medicine, particularly in the treatment of diabetes.

Keywords: *Aqueous extracts, antihyperglycemic effect, medicinal plants, diabetes, toxicity study*

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1. Introduction

For centuries, natural resources have been a major source of new and original therapeutic remedies [1]. According to the World Health Organisation (WHO), 80% of the African population uses traditional medicine for their health needs. In addition, research conducted in several regions of Côte d'Ivoire has shown that more than 90% of the population uses traditional medicine for primary health care [2]. In the current health context, non-communicable diseases (NCDs) have become one of the major challenges and are a leading cause of death, especially in low- and middle-income countries. Diabetes is one of the four major NCDs, along with cardiovascular disease, cancer and chronic respiratory disease [3]. The main feature of this disease is chronic hyperglycaemia resulting from a defect in the secretion and/or action of insulin [4]. This silent epidemic is reaching alarming proportions around the world. In Côte d'Ivoire, where the prevalence of diabetes is estimated at 9.6% [5], several species of medicinal plants have been identified for the traditional treatment of this disease [6]. However, scientific data on the efficacy and safety of most of these plants are lacking [7]. This study investigated the effects of aqueous extracts of *Xylopia aethiopica* (Annonaceae), *Aframomum melegueta* (Zingiberaceae), *Picralima nitida* (Apocynaceae) and *Irvingia gabonensis* (Irvingiaceae), four plants from the Ivorian pharmacopoeia, on blood

glucose levels in glucose induced diabetic mice.

2. Material and Methods

2.1. Preparation of Plant Extracts

Fresh seeds of A*framomum melegueta, Irvingia gabonensis, Picralima nitida* and fresh fruits of *Xylopia aethiopica* were purchased in the markets of Abidjan (Yopougon), in Côte d'Ivoire. They were identified and authenticated at the National Floristic Center at Félix HOUPHOUËT-BOIGNY University (Côte d'Ivoire).

2.2. Preparation of Plant Extracts

Swiss strain *Mus musculus* (Muridae) mice, aged 3-4 months and weighing between 20g and 30g were used in this study. They were obtained and bred in the department of animal physiology of the Félix HOUPHOUËT-BOIGNY University (Abidjan, Côte d'Ivoire). The room had natural lighting and an average temperature of 20 ± 2°C. The animals were fed ad libitum with a diet manufactured by the company Ivograin in Abidjan (Côte Ivory Coast) and had free access to tap water.

2.3. Equipment and Instruments

The technical equipment consisted of a feeding cannula, an electronic scale, an On-Call Extra glucometer, test strips and glassware.

2.4. Chemicals and Reagents

All chemicals and reagents used in this study were of analytical grade: glibenclamide (5mg), a reference anti-diabetic substance and anhydrous glucose, a hyperglycaemic substance.

2.5. Preparation of Aqueous Extracts from Fruits and Seeds

The different samples were dried and then ground. Then 50 g of powder was homogenised in 100 mL of distilled water and shaken vigorously with a blender. The homogenate obtained was filtered through a percale cloth. The liquid obtained was filtered three times on cotton wool. The collected filtrates were then lyophilized for 72 hours. After drying in the freeze-dryer, the total extracts in powder form were stored in clean, dry boxes.

2.6. Procedure for Phytochemical Screening

The respective fruits and seeds were separately screened for the following phytochemicals: sterols and polyterpenes, polyphenols, flavonoids, gallic and catechic tannins, anthraquinones, alkaloids and saponins using standard phytochemical reagents and procedures. The procedures used in the phytochemical screening were described by [8]. For these assays, a solution of the aqueous extract was prepared by dissolving 5 g of the extract in 50 mL of distilled water.

2.7. Toxicity Study

The acute toxicity study was performed with aqueous extracts of *X. aethiopica, A. melegueta, I. gabonensis* and *P. nitida* by gavage to mice in accordance with the OECD Guideline 425 [9] and consisted of test doses of 2000 and 5000 mg/kg body weight of the extracts. 12 batches of 3 mice each were tested, with three batches per extract. The animals in the control batch (batch 1) received distilled water by gavage, while those in batches 2 and 3 received 2000 and 5000 mg/kg. The following signs of toxicity were investigated: changes in coat colour, respiration, sensitivity to noise and body weight, tremors weight, tremors and grooming. These phenomena were observed for 4 h after administration of the product. The product was administered and weights were measured every 2 days for 14 days. Food and water were given ad libitum daily for the duration of the experiment. The number of dead mice was counted 24 hours after administration of the substance.

2.8. Study of the Effect of Aqueous Extracts of *X. Aethiopica, A. Melegueta, I. Gabonensis* and *P. Nitida* on Glycaemia (Oral Glucose Tolerance Test)

This study was performed on 18 male mice with a body weight between 20 and 30 g, divided into 6 batches of 3 mice each: Batch 1: control mice given distilled water by gavage ; Batch 2: mice treated with the reference solution (glibenclamide) ; Batch 3: mice treated with aqueous extract of *Xylopia aethiopica*; Batch 4: mice treated with aqueous extract of *Aframomum melegueta*; Batch 5: Mice treated with aqueous extract of *Picralima nitida*; Batch 6: Mice treated with aqueous extract of I*rvingia gabonensis.*

After a 24-hour fast, a drop of blood is taken from each animal and collected on a strip. The blood glucose level is read on the glucometer screen as the baseline blood glucose (T0). Each animal is then given 1 ml of extract solution per 100 g body weight by gavage (1 ml/100 g body weight) at a dose of 2 mg/100g body weight. The second glibenclamide-treated group received glibenclamide solution at 2.5mg/100g body weight. Thirty minutes later, each animal received glucose solution by gavage at a rate of 1mL per 100g of body weight. 5 minutes later, a drop of blood was collected from the tail of the mouse was collected directly onto a strip and the result was read on the screen of the Glucometer to obtain the blood glucose level at T35. Further samples are then taken every 30 minutes, 65 minutes, 95 minutes and 125 minutes to obtain blood glucose levels at T35, T65, T95 and T125.

2.9. Statistical Analysis

Statistical analysis of values and graphing of data were performed using Graph PadPrism 8 (San Diego, California, USA). The statistical difference between means was performed using analysis of variance (ANOVA), followed by the Tukey-Kramer multiple comparison test, with a significance level of P=.05. All values are presented as

mean ± SEM (Standard Error on the Mean). The values with the same letter are not significantly different.

3. Results

3.1. Phytochemical Screening

In order to determine the chemical composition of aqueous extracts of *X. aethiopica* (AEXa), *A. melegueta* (AEAm), *P. nitida* (AEPn) and *I. gabonensis* (AEIg), a qualitative phytochemical analysis was carried out. The phytochemical screening of the four extracts revealed the presence of numerous secondary metabolites (Table 1). Sterols, polyphenols and alkaloids are present in all the extracts. The extract AEXa is richer in secondary metabolites while AEPn contains fewer phytochemicals. All our extracts contain polyphenols.

3.2. Acute Toxicity

We administered the substances orally. The aim of this scientific approach is not only to anticipate the risks associated with the administration of these products, but also to determine a safety interval and a range of concentrations for subsequent pharmacological studies. Gavage of a dose of 2000 mg/kg bw did not result in any behavioural changes in the mice tested. However, administration of 5000 mg/kg bw of AEXa, AEPn and AEAm caused the mice in the cage to stand upright and become restless. This dose-dependent phenomenon began 5 min after gavage and lasted 10 min. Despite this brief adverse effect at 5000 mg/kg, doses of 2000 mg/kg and 5000 mg/kg bw of all extracts did not cause death in mice (Table 2).

Table 1. Phytochemical composition of the aqueous extracts

	AEXa	AEAm	AEPn	AEIg
Polyterpens And Sterols	+	+	+	+
Flavonoids	+	+	+	-
Tannins Cat	+	+	-	+
Tannins Gal	-	+	-	+
Anthraquinones	+	+	-	-
Alkaloids	+	+	+	+
Saponins	+	-	+	+

*Cat= cathechic; Gal= gallic; + = presence of compound; - = absence of compound

Table 2. General appearance and behavioral observations of acute toxicity study for control and treated groups

	Batch	Doses ingested (mg/kg)	Number of mice tested	Behaviour	Number of dead mice	Death rate %
AEXa	1	Distilled water	3	Normal	0	0
	2	2000	3	Normal	0	0
	3	5000	3	Shaken for the first 15 minutes, then returns to normal	0	0
AEAm	1	Distilled water	3	Normal	0	0
	2	2000	3	Normal	0	0
	3	5000	3	Shaken for the first 15 minutes, then returns to normal	0	0
AEPn	1	Distilled water	3	Normal	0	0
	2	2000	3	Normal	0	0
	3	5000	3	Shaken for the first 15 minutes, then returns to normal	0	0
AEIg	1	Distilled water	3	Normal	0	0
	2	2000	3	Normal	0	0
	3	5000	3	Normal	0	0

3.3. Pharmacological Effects of Different Extracts on Blood Sugar Levels

- At T0 (time 0 min), there was no significant difference between the blood glucose levels of the different batches of mice; the mean blood glucose level was 90±15 mg/dL;

- At T35 (time 35 min), the control batch had a blood glucose level of 224±24.66 mg/dL, while batches 4 and 2 had a mean blood glucose level of 140±15 mg/dL, a significant reduction of 62.50%.

The other batches, with a mean blood glucose of 173.55±33 mg/dL, showed no difference from the control batch;

- At T65 (time 65 min), the control batch had a blood glucose level of 231.66±16.44 mg/dL, while batches 4 and 2 had a mean blood glucose level of 99±7.22 mg/dL, giving a significant reduction of 42.74%.

The other batches, with mean blood glucose levels of 187.11±23.85 mg/dL, showed no difference from the control batch;

- At T95 (time 95 min), the control batch had a blood glucose level of 176±16.66 mg/dL, while batches 4 and 2 had a mean blood glucose level of 92.67±7.09 mg/dL,

giving a significant reduction of 52.65%.

The other batches, with a mean blood glucose level of 146.22±24.55 mg/dL, showed no difference from the control batch;

- At T125 (time 135 min), the control batch had a blood glucose level of 157±10.66 mg/dL, while batches 2, 4 and 5 had a mean blood glucose level of 85.66±9.33 mg/dL, giving a significant reduction of 54.56%.

The other batches, with a mean blood glucose level of 173.55±33 mg /dL, showed no difference from the control batch (Table 3). The blood glucose levels of the control batch and the *Xylopia* and *Irvingia* extracts increased after the administration of glucose (T35) and then slowly decreased (from T65 to T125). However, for *Aframomum* and *Picralima* extracts, blood glucose levels increased after administration of glucose (T35) and then fell rapidly after 30 min to reach the initial value at the start of the experiment at T125. The variation of blood glucose levels over time has been recorded (Figure 1).

Table 3. Effect of extracts of 4 medicinal plants on blood glucose levels

Substance administered	Blood glucose values measured (mg/dL)				
	T0	T35	T65	T95	T125
Distilled water	94,33±8,22^{a}	224±24,66^{a}	231,66±16,44^{a}	176±16,66^{a}	157±10,66^{a}
Giclinbamide	84,66±10,88^{ba}	135±16^{b}	102,66±2,22^{b}	88,33±8,88^{b}	83,33±12,44^{b}
AEXa	100±14,66^{ca}	164,66±30,88^{c}	183,66±29,77^{c}	137,66±11,77^{c}	126,66±23,55^{c}
AEAm	100±6da	140±21,33^{db}	95,33±12,22^{db}	97±5,3^{db}	88,33±3,77^{db}
AEPn	84,33±7,77^{ea}	189,66±50,44^{ea}	151,66±13,77^{e}	117±20,66^{e}	85,33±11,77^{ebd}
AEIg	95±9,33^{fa}	166,33±19,11^{f}	226±28^{a}	184±41,33^{fa}	138±20,66^{fc}

* $^{a\text{-}f}$ within a row means without a common superscript differ (p=.05)

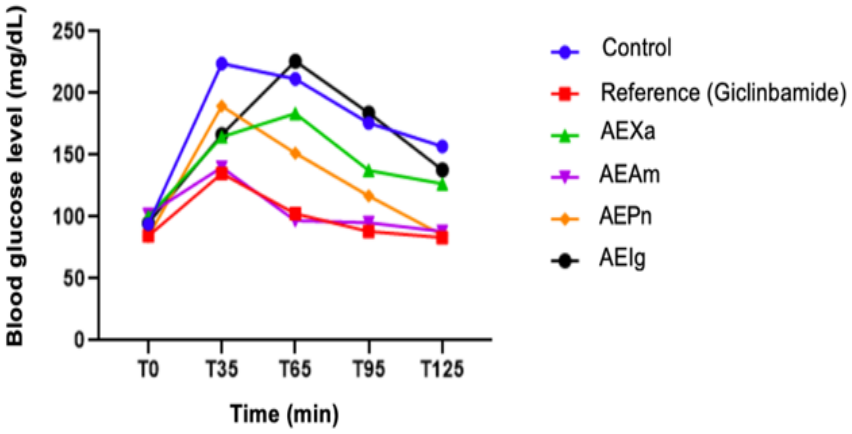

Figure 1. Effect of aqueous extracts (AEXa, AEAm, AEPn and AEIg) on blood glucose levels at different time intervals in normal mice

4. Discussion

Aqueous extracts of seeds of *Aframomum melegueta*, *Irvingia gabonensis*, *Picralima nitida* and fruits of *Xylopia aethiopica* were subjected to qualitative phytochemical analysis to detect the presence of different groups of chemical molecules involved in their secondary metabolism. Plant secondary metabolism is also known as specialised metabolism. It is involved in the protection, communication and adaptation of the plant to its environment. They are structurally very diverse. This chemodiversity gives them their bioactivity [10]. They are sometimes species-specific and are synthesised in small quantities. The most important groups are alkaloids, polyphenols and terpenoids, which have been shown to have potent anti-hyperglycaemic effects by stimulating insulin release from pancreatic ß-cells, increasing glucose utilisation in the body or inhibiting glucose absorption.

Phytochemical screening of the four extracts revealed the presence of numerous secondary metabolites including polyterpenes, polyphenols, alkaloids, quinones and saponins. *Xylopia aethiopica* seems to lack only gallic tannins while *Aframomum melegueta* and *Picralima nitida* seem to have only sterols, alkaloids and flavonoids. These chemical results are in agreement with the work of [11] and [12], who also reported the presence of sterols, alkaloids and flavonoids in extracts of *Aframomum melegueta* and *Picralima nitida*. In our study, *Irvingia gabonensis* was the poorest in secondary metabolite of interest.

Toxicological studies on aqueous extracts of these plants showed that these extracts were not toxic at doses of 2000 mg/kg and 5000 mg/kg bw in accordance with the OECD Guideline 425. This justifies their use in food as a flavouring or in traditional medicine. In the case of chronic diseases such as diabetes, where multiple and prolonged doses can be administered, it is important to avoid the serious side effects of an eventual subacute toxicity.

During the study of the effects of these plants on glycaemia, the observation period was 125 minutes, sufficient time to assess a potential anti-hyperglycaemic activity of the plant. The protocol consisted of first administering the various extracts (T0), then administering a glucose solution 30 minutes later and monitoring the variations in blood glucose levels from 5 minutes after glucose up to 125 minutes. This protocol, called Oral

Glucose Tolerance Test (OGTT), measures the body's ability to use glucose and reflects the extent of intestinal glucose absorption and hepatic glucose metabolism.

At T0, all blood glucose levels measured showed no significant difference (P=.05). Fasting blood glucose levels were statistically identical in controls and all other groups. Oral administration of glucose resulted in hyperglycaemia in the mice, followed by a gradual return to baseline blood glucose levels over time. This phenomenon has been observed in other similar studies [13]. Glibenclamide (the reference substance) significantly reduces blood glucose levels. The suppression of the peak by the aqueous extracts suggests that they may contain principles comparable to those of glibenclamide. Similar results have been reported by several authors [14]. Glibenclamide is an antidiabetic drug prescribed to patients with type 2 diabetes. It stimulates insulin production via the β-cells of the pancreatic islets [15]. It is therefore an insulin secretor that binds to its receptors on the surface of the pancreatic β-cell membrane, causing depolarisation of this membrane followed by the opening of calcium-dependent calcium channels leading to calcium entry into the cell. This calcium entry results in the release of insulin, which can lower blood glucose levels in non-diabetic and diabetic subjects that are non-insulin dependent [16].

Aqueous extracts of *Xylopia aethiopica* (AEXa), *Picralima nitida* (AEPn), *Aframomum melegueta* (AEAm) and *Irvingia gabonensis* (AEIg) had an effect on glucose-induced hyperglycaemia, and the fall in blood glucose levels was much faster for AEAm and AEPn than for the control. Like glibenclamide, AEAm and AEPn significantly reduced blood glucose levels, which tended to return to baseline. However, AEXa and AEIg had lower effects, comparable to the control. As a result, *Aframomum melegueta* and *Picralima nitida* have significant glucose lowering activity comparable to that of the reference compound. Moreover, *A. melegueta* has an activity that mimics that of glibenclamide.

Indeed, mice treated with aqueous extracts of *Aframomum melegueta* and *Picralima nitida* have a better glucose utilisation capacity. This glucose-lowering ability may be due to the inhibition of glucose absorption, stimulation of peripheral glucose utilisation, reduction of glycogenolysis and gluconeogenesis, suggesting that the aqueous extracts of these two plants are able to obtain better regulatory mechanisms, indicating a potential advantage of the extract in minimising hyperglycaemia-related complications of diabetes.

The reduction in hyperglycaemia observed in mice could also be explained by a stimulation of pancreatic insulin secretion [17] and/or, probably, by an increase in peripheral glucose utilisation in the presence of the aqueous extracts [18]. Therefore, the phytochemical composition of the aqueous extracts of these plants may explain the results. Polyphenolic compounds, particularly flavonoids, have been shown to activate the phosphoinositide 3-kinase (PI3K) signalling pathway. This activation is thought to have an insulin-mimetic effect, stimulating glucose uptake and glycogen synthesis and inhibiting gluconeogenesis in target tissues. All these synergistic reactions would have the effect of reducing the installed hyperglycaemia, giving the extracts under study an anti-diabetic potential [19]. The therapeutic effect of these extracts could also be due to their antioxidant activity [20]. The improvement in oxidative status would normalise damaged endothelial function and improve insulin secretion by reducing free radical damage to pancreatic beta cells [21].

5. Conclusion

This study suggests that aqueous extracts of *Aframomum melegueta* and *Picralima nitida* seeds contain principles that may have multiple actions involving different mechanisms contributing to glucose-lowering effects in exerting hypoglycaemic or antihyperglycaemic effects, whereas seeds of *Irvingia gabonensis* and fruits of *Xylopia aethiopica* had no significant effect on glycaemia. Since acute toxicity tests on the extracts showed that they are not toxic when administered orally, this route is recommended for their pharmacological use. This study confirms that A. *melegueta* and *P. nitida* have therapeutic potential and justifies the use of these two plants in traditional medicine, particularly in the treatment of diabetes.

Conflict of Interest

Authors declared that no competing interests exist.

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