

# Hypoglycaemic Risk and Antihyperglycaemic activity of “Diabète free” and “Pancréas free”, an Anti-diabetic Combination from an Ivorian Traditional Practitioner

**Keywords:** Diabetes; Diabète Free; Pancréa Free; Hypoglycaemic; Antihyperglycaemic

## Abstract

Diabetes remains a public health issue for which traditional medicine offers a therapeutic response. The aim of this study was to assess the hypoglycaemic risk and antihyperglycaemic activity of ‘Diabète Free’ and ‘Pancréa Free’, remedies used by an Ivorian traditional practitioner to treat diabetes.

For the hypoglycaemic risk, 4 groups of 6 rats per group were successively given ‘Diabète Free’ and ‘Pancréa Free’ by oral route at respective doses of 7mg/kg and 4.5mg/kg, 14mg/kg and 9mg/kg, 28mg/kg and 18mg/kg, or NaCl. To evaluate the antihyperglycaemic activity, 5 groups of 6 rats per group were successively treated with ‘Diabète Free’ and ‘Pancréa Free’ by oral route at respective doses of 7mg/kg and 4.5mg/kg, or 14mg/kg and 9mg/kg, or 28mg/kg and 18mg/kg, or NaCl, or glibenclamide at 10mg/kg. An oral glucose overload at a dose of 10g/kg was administered 30 min later. In each case, blood glucose levels were monitored every hour for 4 hours using blood from rats’ tailvein.

The ‘Diabète Free’ and ‘Pancréa Free’ combination showed no hypoglycaemic risk. The combination at doses of 14mg/kg and 9mg/kg, as well as 28mg/kg and 18mg/kg, showed a significant reduction in orally induced hyperglycaemia from the 1st hour without causing hypoglycaemia.

The combination of ‘Diabète Free’ and ‘Pancréa Free’ is thought to have antihyperglycaemic activity without any risk of hypoglycaemia. This remedy combination could be an alternative to conventional anti-diabetic treatments.

## Introduction

Diabetes is a major challenge for healthcare systems worldwide. In 2021, approximately 537 million adults had diabetes, and this figure is expected to rise up to 783 million by 2045 if appropriate measures are not taken [1]. Type 1 diabetes and type 2 diabetes are the most common forms of the disease [2].

In Côte d’Ivoire, the prevalence of diabetes in 2017 was around 6.2% in the adult population [3]. This is due to a number of factors, such as rapid urbanisation, changes in lifestyle, diet and an aging population [4]. Diabetes-related complications, such as cardiovascular disease, neuropathy and nephropathy, represent a significant burden for Ivorian healthcare systems [5-7]. Therefore, effective diabetes management requires an integrated approach including lifestyle modifications, medication and, in some cases, alternative therapies. Among the alternative approaches, herbal remedies and natural products have increased in popularity. Around



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Etienne EK, Josué YK, Adebo AY, Awa S, Genevièvelrié NG and Gisèle KS\*

Department of Pharmacology, Faculty of biological and pharmaceutical sciences, University of Félix Houphouët-Boigny, Abidjan - Côte d’Ivoire

### Address for Correspondence

EFFO Kouakou Etienne, Department of Pharmacology, Faculty of biological and pharmaceutical sciences, University of Félix Houphouët-Boigny, Abidjan - Côte d’Ivoire, E-mail Id: effoet@yahoo.fr

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80% of the population of Côte d’Ivoire rely on traditional medicine for their healthcare, including the treatment of diabetes [8].

Studies have shown that several plants possess anti-hyperglycaemic properties, making them potential candidates for diabetes management [9, 10]. These traditional remedies are often chosen because of their accessibility, affordability and cultural confidence [11]. However, the safety and efficacy of these plants are yet to be scientifically demonstrated to ensure their safe use in modern treatment protocols [12].

In this context, a combination of herbal remedies from an Ivorian traditional practitioner called ‘Diabète Free’ and ‘Pancréa Free’ was the subject of an observational study on Ivorian diabetics, and exhibited promising results [13]. However, no preclinical studies were conducted on the efficacy and safety of this remedy combination. The objective of this study was to evaluate the efficacy and safety of this anti-diabetic combination ‘Diabète Free’ and ‘Pancréa Free’.

## Materials and methods

### ‘Diabète free’ and ‘Pancréa free’ remedies

The remedies were directly collected from the traditional practitioner in April 2024. They are in the form of white tablets. The partial composition given by the traditional practitioner was as follows:

‘Diabète free’: 160 mg garlic clove (*Allium sativum*), 180 mg cinnamon bark (*Cinnamomum verum*)

‘Pancréa free’: 100 mg ginseng root bark (*Panax ginseng*), 150 mg gurma leaves (*Gymnemasylvestre*)

### Experimental animals

Wistar rats (*Rattus norvegicus*) with an approximate 3 months of age and weighing between 129 and 243 g were used in this study. They were kept in plexiglass cages with stainless steel lids and feeding

bottle. Temperature and humidity within the laboratory met the standards of experimental premises ( $T = 22^{\circ}\text{C} \pm 3^{\circ}\text{C}$  and 50-60% humidity), with a 12 h of and 12 h of dark cycle. Animals were given food pellets and had free access to water.

### Solvents and reagents

Powders, solutions, solvents and standard substances used in this study were as follows: Glucose powder (D glucose), Sodium chloride solution (NaCl) 0.9%, Distilled water, Glibenclamide 5 mg (Daonil®) (Laboratoire Sanofi (as standard substance).

### Equipment

Several laboratory devices and equipment were used to carry out this study, including scales, a glucometer, test strips, scalpel blades, beakers, a mortar and pestle, a spatula, a watch glass, and syringes.

## Methods

### Determination of equivalent dose in animals

According to the owner of 'Diabète Free' and 'Pancréa Free' remedies, the recommended dose for treating diabetes in a 70 kg adult is 1 tablet (160 mg of garlic) corresponding to 2.29 mg/kg/d for 'Diabète Free' and 1 tablet (100 mg of ginseng) corresponding to 1.43 mg/kg/d for 'Pancréa Free'.

The animal equivalent dose was estimated using the method of Nair and Jacob [14].

#### For 'Diabète free'

The dose in experimental rats was obtained by multiplying the human dose by a conversion factor, i.e.  $2.29 \times 6.2$ , giving a dose of 14mg/kg/d. Two other doses were used to bracket this equivalent dose in animals, namely at 7mg/kg and 28mg/kg.

A tablet containing 160mg of garlic extract from the « Diabète Free » remedy was homogenised in 57ml of physiological water to obtain a 2.8mg/ml solution and a volume of 10ml/kg was administered to rats, corresponding to a dose of 28mg/kg. From this 2.8 mg/ml stock solution, a dilution to one-half ( $\frac{1}{2}$ ) was carried out to obtain two solutions at 1.4 mg/ml and 0.7 mg/ml corresponding to doses of 14mg/kg and 7mg/kg respectively.

#### For 'Pancréa free'

The dose in experimental rats was obtained by multiplying the human dose by the conversion factor, i.e.  $1.43 \times 6.2$ , giving a dose of 9mg/kg/d. Two other doses were used to bracket this equivalent dose in animals, namely at 4.5mg/kg and 18mg/kg.

A tablet containing 100mg of garlic extract from the 'Pancréa Free' remedy was homogenised in 55ml of physiological water to obtain a 1.9mg/ml solution and a volume of 10ml/kg, was given to rats, corresponding to a dose of 19mg/kg. From this 1.9 mg/ml stock solution, a dilution to one-half ( $\frac{1}{2}$ ) was carried out to obtain two solutions at 0.95 mg/ml and 0.475 mg/ml corresponding to doses of 9 mg/kg and 4.5 mg/kg respectively.

### Glibenclamide 1mg/ml

Four (4) tablets of glibenclamide 5 mg (Daonil®) were dissolved in 20 ml of physiological water for the preparation of the glibenclamide 1mg/ml solution. Corresponding to a dose of 10 mg/kg.

### Glucose solution 1000 mg/ml

One hundred (100) grams of glucose in an hydrous powder form were dissolved in 100 ml of physiological water to obtain the 1000 mg/ml glucose solution corresponding to a dose of 10 g/kg.

### Assessment of hypoglycaemic risk

#### ✓ Principle:

The test is used to measure the effect of the 'Diabetes Free + Pancrea Free' combination on basal blood glucose, i.e. in the absence of hypoglycaemia, with in order to predict its safety of use.

#### ✓ Procedure:

Four (4) groups of homogeneous weight of 6 rats per group were kept fasting 8 hours prior to experiment. The baseline blood glucose levels of 24 rats were measured by collecting blood from the tail vein and read with a glucometer 'Hummas'.

Animals were then given the different solutions by oral route, at a rate of 10 ml/kg, as follows: Group 1: rats received NaCl; Groups 2, 3 and 4: rats were successively given 'Diabète Free' and 'Pancréa Free' at doses of 7 mg/kg and 4.5mg/kg; 14 mg/kg and 9mg/kg; and 28 mg/kg and 18mg/kg respectively.

After administration of substances, blood glucose levels were also measured after 1h, 2h, 3h and 4h.

### Assessment of antihyperglycaemic activity

#### ✓ Principle:

The test is designed to measure the effect of 'Diabète Free + Pancréa Free' combination on oral hyperglycaemia caused by glucose overload.

An antihyperglycaemic substance prevents hyperglycaemia in rats. In the opposite case, hyperglycaemia is observed in rats.

#### ✓ Procedure :

Five (5) groups of homogeneous weight of 6 rats per group were kept fasting 8 hours before experiment. Their baseline blood glucose levels were measured by collecting blood samples from the tail vein and then read with a glucometer 'Hummas'.

Animals were given the various solutions by oral route at a rate of 10ml/kg, as follows: Group 1: Rats received NaCl; Group 2: Rats were administered glibenclamide at a dose of 10mg/kg; Groups 3, 4 and 5: Rats successively received 'Diabète Free' and 'Pancréa Free' at doses of 7 mg/kg and 4.5mg/kg; 14 mg/kg and 9mg/kg; and 28 mg/kg and 18mg/kg, respectively.

After 30 minutes, they were all given a glucose overload of 10g/kg and blood glucose levels were measured every hour for 4 hours, after 1, 2, 3 and 4 hours.

### Data processing and analysis

The results were expressed as the mean  $\pm$  standard deviation. Graphs were produced using Graph Pad Prism version 8.0.2 software. Means were compared by analysis of variance using the ANOVA test at a risk of  $\alpha = 5\%$ .

## Results

### Hypoglycaemic risk

Figure 1 shows the effect of the ‘Diabète Free et Pancréa Free’ combination at different doses on the baseline of blood glucose levels.

During the 4 hours of observation, the combination of ‘Diabète Free’ at a dose of 7mg/kg and ‘Pancréa Free’ at a dose of 4.5mg/kg did not cause hypoglycaemia compared to NaCl ( $p=0.59$ ). This combination led to a marked hypoglycaemia after 1 hour at doses of 14mg/kg and 9mg/kg respectively ( $p=0.04$ ); and 28mg/kg and 18mg/kg ( $p=0.01$ ) compared to NaCl. This hypoglycaemia was corrected from the second (2<sup>nd</sup>) hour ( $P=0.30$ ).

### Antihyperglycaemic activity

Figure 2 shows the effect of combination of “Diabète Free et Pancréa Free” at different doses on the prevention of oral hyperglycemia.

Glucose overload resulted in hyperglycaemia observed at the first (1<sup>st</sup>) hour in rats from the control group (NaCl). This hyperglycaemia remained practically stable until the third (3<sup>rd</sup>) hour. However, it began to decrease after the second (2<sup>nd</sup>) hour in rats given ‘Diabète Free’ at a dose of 7mg/kg and ‘Pancréa Free’ at a dose of 4.5mg/kg. This decrease was more observed at the third (3<sup>rd</sup>) hour ( $p=0.006$ ) and fourth (4<sup>th</sup>) hour ( $p=0.0003$ ).

No increase in blood glucose levels was observed in rats given ‘Diabetes Free’ at a dose of 14mg/kg and ‘Pancrea Free’ at a dose of 9mg/kg despite oral glucose overload. The p values were 0.01, 0.01, 0.0007 and 0.00001 after 1h, 2h, 3h and 4h respectively.

A reduction in blood glucose despite glucose overload was observed from the first hour in rats given ‘Diabète Free’ at a dose of

28mg/kg and ‘Pancréa Free’ at a dose of 18mg/kg. The p values were 0.004, 0.004, 0.002 and 0.001 after 1h, 2h, 3h and 4h respectively.

Basically, the ‘Diabète Free and Pancréa Free’ combination tended to maintain blood glucose levels close to baseline, whereas with glibenclamide, the antihyperglycaemic effect was followed by hypoglycaemia compared to the control group ( $p<0.05$ ).

### Discussion

The aim of this study was to evaluate the hypoglycaemic risk and antihyperglycaemic activity of the combination ‘Diabète free and Pancréas free’, remedies from an Ivorian traditional practitioner.

‘Diabète free’ is said to contain garlic (*Allium sativum*) and cinnamon (*Cinnamomum verum*), while ‘Pancréa free’ contains ginseng (*Panax ginseng*) and gurmar (*Gymnema sylvestre*).

Generally, the ‘Diabète free et Pancréa free’ combination did not cause hypoglycaemia during 4 hours of follow-up. However, the combination at doses of 14mg/kg and 9mg/kg and 25mg/kg and 18mg/kg respectively showed a significant drop in baseline blood glucose levels during the first hour after administration. This hypoglycaemia was immediately corrected at the second (2<sup>nd</sup>) hour. According to the owner of these remedies, ‘Diabète Free’ has a hypoglycaemic effect and ‘Pancréa Free’ has a regenerative effect on the pancreas, enabling it to fulfil its blood sugar regulation functions.

In addition, the work of Wang et al. on the assessment and selection of the hypoglycaemic risk of ginseng showed results similar to our own. Wang et al. demonstrated that ginseng could significantly reduce fasting glucose levels in diabetic rats without inducing a risk of hypoglycaemia [15].

Similarly, the work of Sotaniemi et al. on ginseng [16] also showed similar results, confirming its role in regulating blood sugar levels. Other studies, particularly on *Gymnema sylvestre* (gurmar), have shown that gurmar improves glucose balance and is involved in the repair and regeneration of pancreatic cells [17, 18].

The effects of ‘Diabète free et Pancréa free’ combination could be explained by the presence of ginseng and gurmar.

As for the antihyperglycaemic activity, the oral administration of a concentrated glucose solution (10 g/kg) to fasting animals produced hyperglycaemia from the 1st hour to the 3rd hour of follow-up. In response to this hyperglycaemia, the  $\beta$  cells of the islets of Langerhans are stimulated, leading to the secretion of insulin [19]. This hormone promotes glucose uptake by muscle cells, adipocytes and hepatocytes, causing the normalcy of blood glucose levels, as observed in control rats at the fourth hour. These results are similar to those obtained by Irié-N’Guessan et al. [20], who studied the antihyperglycaemic activity and hypoglycaemic risk of Sarenta, a medicinal plant remedy from the Ivorian pharmacopoeia. Irié-N’Guessan et al. [20] showed that oral administration of glucose at a dose of 5 g/kg in rats caused a peak in hyperglycaemia the first hour, followed by a decrease from the second (2<sup>nd</sup>) hour. This finding was also exhibited by Rasolofoson et al. [21]. However, difference in doses could justify the persistence of hyperglycaemia in this study.

Pre-treatment with the combination of ‘Diabète Free et Pancréa Free’ at doses of 14mg/kg and 9mg/kg, and 28mg/kg and 18mg/kg

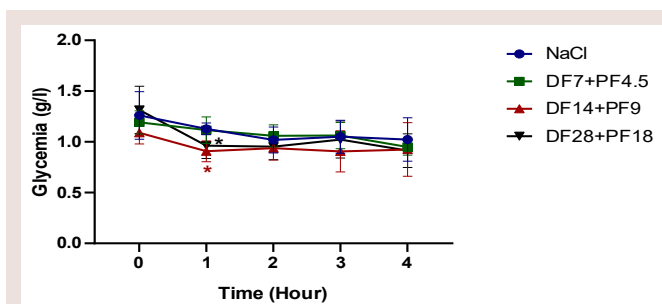


Figure 1: Effect of ‘Diabète Free + Pancréa Free’ on blood glucose levels.

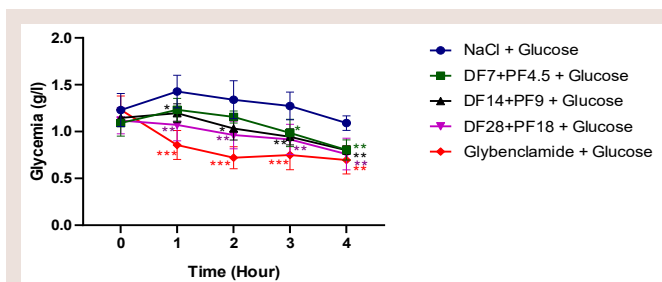


Figure 2: Anti-hyperglycaemic effect of the combination of ‘Diabète Free and Pancréa Free’, DF: Diabète Free; PF: Pancréa Free.

respectively in rats, demonstrated a significant effect on reducing the hyperglycaemic peak observed during glucose overload. The combination of ‘Diabète Free et Pancréa Free’ therefore has an effective preventive effect against orally-induced hyperglycaemia in experimental rats. According to the traditional practitioner who designed these remedies, ‘Diabète Free’ has antihyperglycaemic properties and ‘Pancréa Free’ regenerates the pancreas, by stimulating its blood sugar regulation functions. The combination of these remedies might therefore has a synergistic effect against induced hyperglycaemia.

These results are similar to those of Eidi et al.[22], who showed that the oral administration of garlic extract significantly reduced glycaemia while increasing serum insulin in rats, thus demonstrating its antihyperglycaemic effects.

These results are also in line with studies conducted on *cinnamomum verum*(cinnamon), where its antihyperglycaemic activity has been demonstrated [23].

Since garlic and cinnam on are components of the ‘Diabète Free’ and ‘Pancréa Free’ remedies, the antihyperglycaemic activity of the combination could be justified by the presence of these plants.

The hypothesis of the mechanism of action of these remedies could be explained by the ability to improve ATP production and consequently increase insulin production following the upgrading of pancreatic  $\beta$ -function and also the reduction in insulin resistance as demonstrated with ginseng [24]. This mechanism might justify the absence of hypoglycaemic risk in the ‘Diabète Free and Pancréas Free’ combination, which can be observed in contrast with glibenclamide, which is a purely insulin-secreting agent.

The combination of ‘Diabète Free et Pancréa Free’ could therefore be of good interest in both type 1 and type 2 diabetes, with good safety of use.

## Conclusion

The objective of this study was to evaluate the efficacy and safety of ‘Diabète Free’ and ‘Pancréas Free’, two remedies combined by an Ivorian traditional practitioner for the treatment of diabetes, in experimental animals.

The animal equivalent dose was 14 mg/kg for ‘Diabète Free’ and 9 mg/kg for ‘Pancréa Free’. Two other doses were used to bracket this animal equivalent dose, namely at 7mg/kg and 28mg/kg for ‘Diabète Free’ and 4.5mg/kg and 18mg/kg for ‘Pancréa Free’. We found that the combination of ‘Diabète Free’ and ‘Pancréa Free’ did not show any hypoglycaemic risk apart from hyperglycaemia. As for the antihyperglycaemic activity, this combination demonstrated antihyperglycaemic activity in experimental rats.

This finding highlights the therapeutic potential of this remedy in the management of diabetes mellitus and suggests that it could represent an effective medication to conventional treatments.

**Conflict of Interest:** We declare no conflicts of interest.

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