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Effect of the aqueous extract of *Catharanthus roseus* leaves against hypertention induced by fructose in rats

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Abstract
Catharanthus roseus is a plant native to Madagascar. It is used for both ornamental and medicinal purposes. In traditional medicine, the leaves and roots of this plant are used in the treatment of many diseases. Studies on wistar rats showed that 60 % fructose consumption significantly induced (p<0, 0001) diabetes and high blood pressure (HTA) in these animals after 30 days. Treatment of these animals with the aqueous extract (EA) of *Catharanthus roseus* leaves showed a very significant decrease in blood glucose and cardiovascular parameters after seven days (p<0, 001). This decrease was observed at doses ranging from 200 to 1000 mg/kg. Compared with metformin, the aqueous extract has been shown to be effective. But compared to nifedipin NIFE 20 mg/kg dose gave satisfactory but not significant results compared to that of the EA 1000 mg/kg dose. The aqueous extract makes it possible to restore the homeostatic balance of the glycemic and cardiovascular parameters by reducing the values obtained after induction to values that are sensitive to those observed in the control.

Keywords: Effect, aqueous extract, *Catharanthus roseus*, hypertension-induced, fructose, rats

Introduction
It is characterized by an abnormal rise in blood pressure in the arteries. One of the main risk factors associated with heart, kidney disease, etc. It can also have various origins including age, overweight, stress, eating habits etc. (Anonym, 2020) [26]. In 2012, one in three adults worldwide had hypertension. Out of fifty-six (56) million deaths worldwide, cardiovascular disease accounts for 68% of these hyperthyroidism death (WHO, 2015), and 40% of those who died were 70 years old. In Africa, complications linked to this pathology are frequent and precocious, especially with late treatment. In 2000, approximately eighty (80) million subjects in sub-Saharan Africa were hypertensive and this rate could reach 150 million people in 2025. This disease does not affect only the elderly, children and newborns are also the target. Indeed, today, five thousand (5000) newborns are born from a heart defect and 80% of children generally from modest families suffering from heart disease do not have access to health care. (WUA, 2016). The statistics are alarming, so high blood pressure is a real public health problem that needs to be addressed. The treatment of this disease can be done, either for a short duration, or for a long duration or even for the whole life. In developing and low-income countries, the expensive cost of treating this disease means that a large part of the population has to turn to traditional medicine. Several studies have shown that all plant species are rich in secondary metabolites (tannins, flavonoids, polyphenols and saponosides) which are chemical compounds with therapeutic efficacy (Dongmo *et al.*, 2007; N'Guessan *et al.*, 2009; Kuete and Efferth, 2010; Zerbo *et al*., 2010). Many herbal remedies have been shown to be effective in treating hypertension and myocardial dysfunction by increasing endogenous antioxidant enzymes or even suppressing the formation of free radicals. Among these botanical families are the Apocynaceae. Several species of this family are used for ornamental purposes and as medicinal plants. One species of Apocynaceae is *Catharanthus roseus*. The leaves and roots of this plant have been found to be effective in the treatment of these diseases. The objective of this study is to assess the effect of the aqueous extract of the leaves of this plant on blood sugar and cardiovascular parameters in hypertensive fructose-induced rats.

2- Material and Methods
2.1- Plant material
The leaves of *Catharanthus roseus* were collected in Cocody (Abidjan). The plant species was later identified and authenticated at the National Floristic Center (CNF) under herbarium

number UCJ001986. These leaves were collected, washed and dried at room temperature two weeks.

2.2 Animals
The animals used for the manipulations are adult rats, of wistar strain, aged from eight (8) to twelve (12) weeks and weighing on average between 140 and 180 g. The rats were bred in the animal facility of Higher Normal School of Abidjan (ENS) in Abidjan.

2.3- Extract preparation
After drying, they were pulverized using an IKA-MAG type grinder. The powder obtained was used to prepare the aqueous extract. Eighty grams (80g) of this powder was dissolved in 2L of distilled water. The whole is brought to the boil for 20 minutes. After the mixture obtained had cooled, three successive filtrations were carried out respectively on cotton wool and whattman paper. The filtrate obtained is dried in an oven at a temperature of 50 ° C. The dark brown raw aqueous extract constitutes the aqueous extract (Guédé, 1993) [9].

2.4 Induction of hypertension by fructose
To assess the effect of fructose in the induction of hypertension, we used rats (21 males and 21 females) were used. The males are separated from the females to avoid reproduction. Two batches of 42 rats were made up, including the control batch (6 rats) and the test batch (36 rats). The animals in the control lot received unlimited running water while the animals in the test lot received 60 % fructose solution for 30 days. During the experimental period, glycemia, insulinemia, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were determined every five days until the end of the experiment. Blood glucose was determined by the enzymatic method Mellouk Zoheir, (2013) [13, 16] and insulinemia by radioimmunoassay (RIA) Bray and coll. (2004a) [14]. The invasive method made it possible to determine the cardiovascular parameters (SBP, DBP and HR).

2.5 Statistical analysis
The results were compared using the GRAPHPAD Prism 7 software. The values obtained are expressed as Mean ± standard error from 6 animals. The statistical analysis was carried out using one-way analysis of variance (ANOVA) followed by Turkey Test. The differences were considered meaningless compared to the control at $p<0.05$; $P<0.01$ = significant difference compared to the control; $P<0.001$ = very significant difference compared to the control; $P<0.0001$ = highly significant difference compared to the control.

3. Results
3.1. Effect of fructose on glycemia and insulinemia
Figure 1 shows that on D15 the amount of glycemia becomes significant compared to D0. It started to 0.82 ± 0.01g/ L and reached 1.51 ± 0.03g/L on D15. This result is therefore very significant compared to D0. Glycemia is highly significant increase ($P<0.0001$) on D30 related to D0 (3.27 ± 0.045 g/L). From D5 the rate of insulin increased gradually until becoming significant to days D15 compared to D0. It went from 0.2 ± 0.10 mUI/mL to 0.45 ± 0.14 mUI/mL This increased, compared to D0, becomes highly significant on D30 ($P<0.0001$) because it reached the value of 1.04 ± 0.14 on D30.

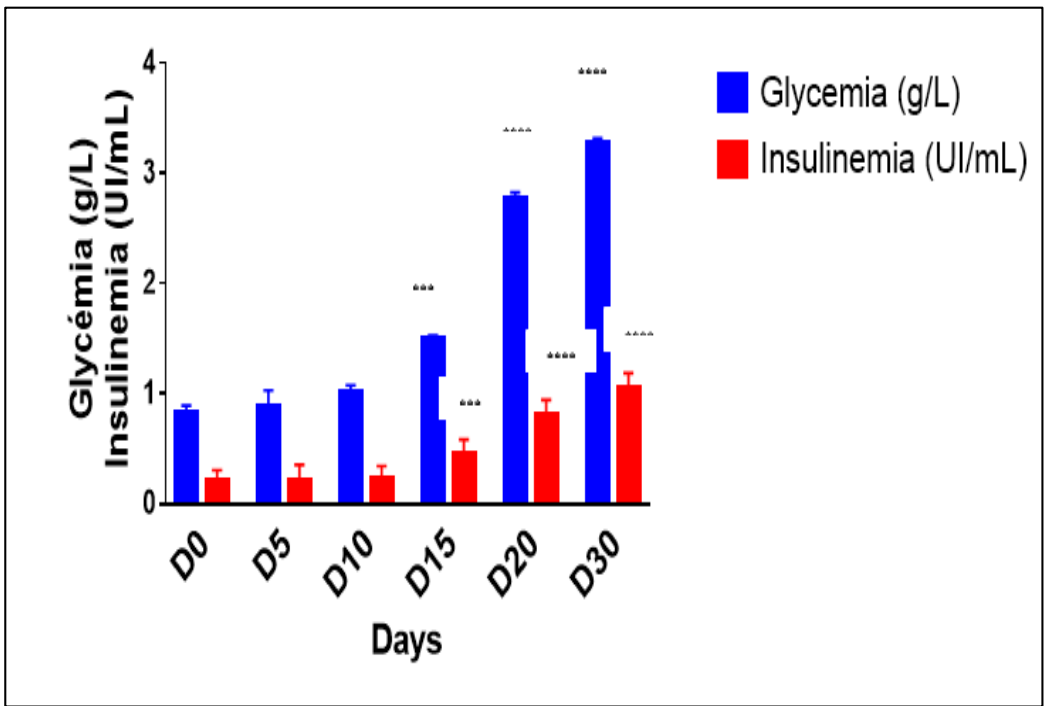

Fig 1: Effect of fructose on glycemia and insulinemia ****: $P<0.0001$ = highly significant difference compared to the control; ***: $P<0.001$ = very significant difference compared to the control. The means are in the form ± SEM (n = 6); D= Days

3.2 Effect of fructose on cardiovascular parameters
3.2.1 Effect of fructose on systolic blood pressure (SBP)
Figure 2 shows an increase of systolic blood pressure (SBP) of normal holy rats during induction of hypertension arterial by fructose 60%. The normal control value of this parameter recorded on D0 of the induction of hypertension is 120.4 ± 0.65 mmHg. This value increase significantly from D0 to D15 (135.5 ± 1.93) and then very significantly ($P<0.0001$) from D15 to D30 (164.7 ± 1.95 mmHg).

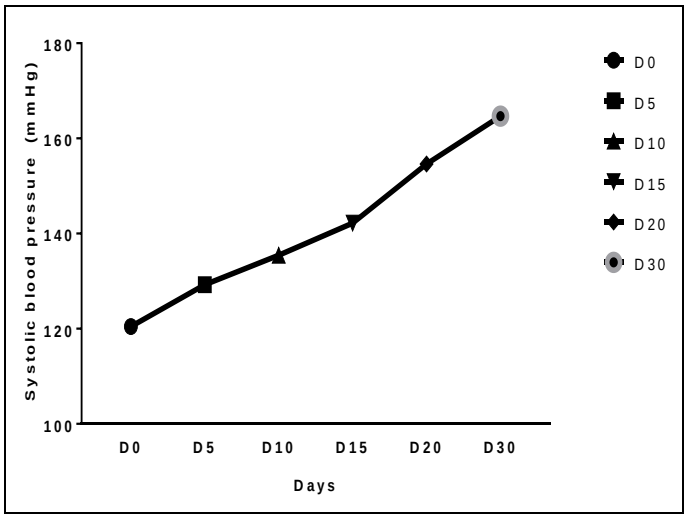

Fig 2: Effect of fructose on systolic blood pressure

3.2.2 Effect of fructose on diastolic blood pressure (DBP)
Figure 3 shows also an increase of diastolic blood pressure (DBP) normal holy rats during induction of hypertension arterial by fructose 60%. The normal control value on D0 is 103.3 ± 1.05 mmHg. This value increase significantly from D0 to D10 (116.5± 0.06), during the induction of hypertension. It becomes very significantly (P<0.0001) from D10 to D30 (139.3 ± 6.15 mmHg).

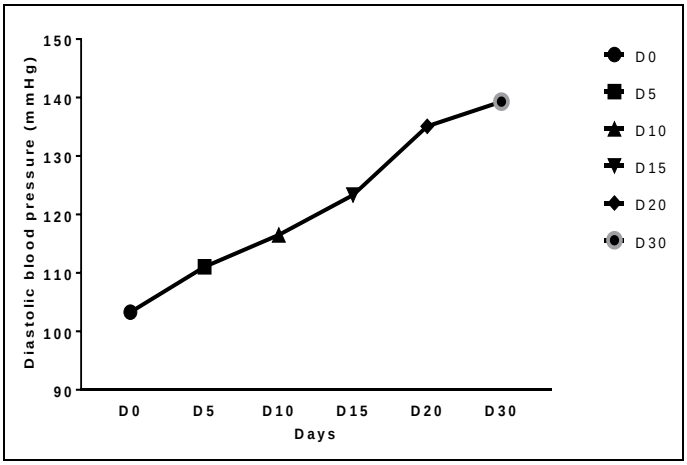

Fig 3: Effect of fructose on diastolic blood pressure

3.2.3 Effect of fructose on heart rate (HR)
Figure 4 shows that heart rate were normal to normal control rats during induction of hypertension by fructose 60%. The normal value was 250.3 ± 3.38 bpm. The heart rate (HR) drops significantly from D0 to D5 with the induction of hypertension by fructose 60% and then increases significantly from D5 to D30. The HR values go from 250.3 ± 3.38 bpm at D0 to150 ±3.78 bpm at D5 then from 150 ± 3.78 bpm to351.7 ± 3.75 bpm at D30

3.3- Effect of the aqueous extract and metformin on glycemia and insulinemia
Figure 5 shows that after 7 days of treatment the aqueous extract the glycemia at the doses of EA 500 mg / kg bw (0.87 ± 0.11) and EA 1000 mg / kg bw (0.83 ± 0.03) does not show any significant difference compared to the control batch (0.82 ± 0.01). But still presents a highly significant decrease compared to the control patient batch (3.46 ± 0.02).
The treatment, of diabetic rats, with the aqueous extract of the leaves of *Catharanthus roseus* at doses ranging from EA 200 to EA 500 mg /kg bw compared to the treatment with Metformin has reduced glycemia to values almost equal to those of rats in the control group.

After seven days of treatment, rats treated with 1000 mg/kg of aqueous extract significantly decreased insulinemia (0.28 ± 0.14) compared to treated patient (0.97±0.22) but does not present any significant difference compared to the witness batch (0.2 ± 0.1).

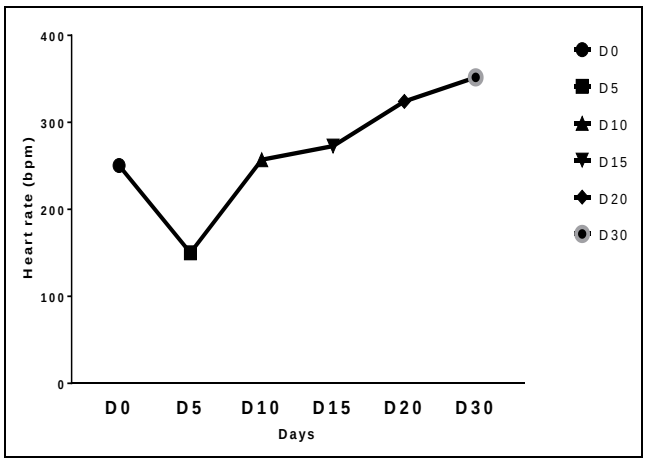

Fig 4: Effect of fructose on heart rate

The treatment, of diabetic rats, with the aqueous extract of the leaves of *Catharanthus roseus* at the dose of EA 1000 mg /kg bw compared to the treatment with Metformin 20 mg /kg bw (0.56 ± 0.14) has reduced insulinemia to values almost equal to those of rats in the witness group.

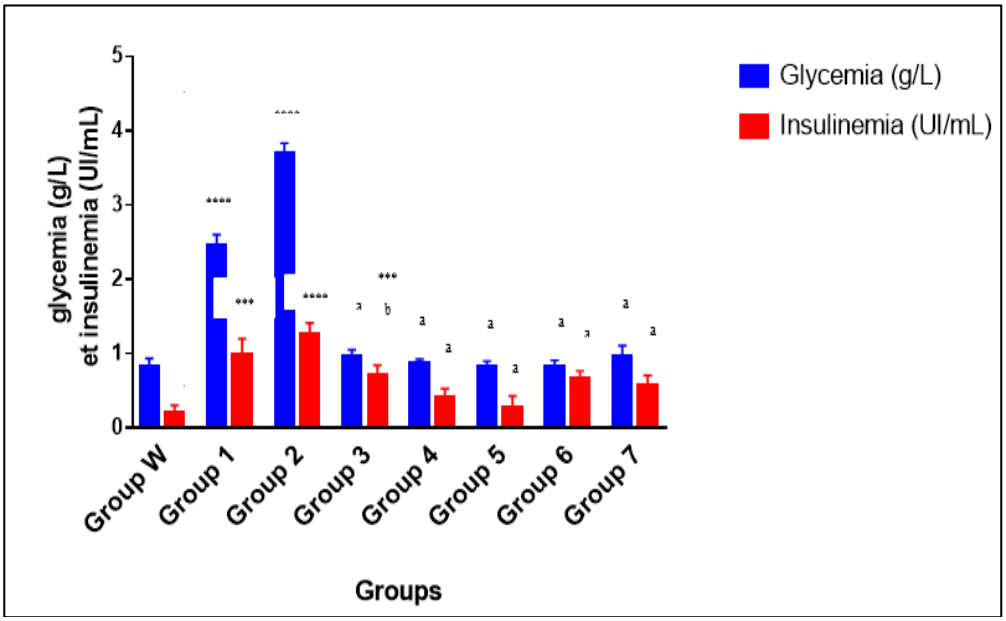

Fig 5: Effect of the aqueous extract and metformin on glycemia and insulinemia ****: *P*<0.0001 = highly significant difference compared to the control; ***: *P*<0.001 = very significant difference compared to the control. a: *P*<0.0001 = highly significant difference compared to the patient treated; . b: *P*<0.001 = very significant difference compared to the patient treated. The means are in the form ± SEM (n = 6).Group W: Witness; Group 1 = Patient treated; Group 2 = Untreated Patient; Group 3= E.A 200 mg/kg bw; Group 4 = E.A 500 mg/kg bw; Group 5= E.A 1000 mg/kg bw; Group 6 = Metformin 10 mg/kg bw ; Group 7 = Metformin 20 mg/kg bw EA = aqueous extract.

3.4 Effect of the aqueous extract and nifedipin on hypertensive rats

Figure A shows a decrease in SBP. It goes from 164.7 ± 1.95 (PT) to 124.5 ± 1.43 (EA 1000mg /kg) and 122.8 ± 4.04 (NIFE 20). This significant decrease at baseline at EA 200 (*P*<0.01) becomes highly significant compared to patients treated with EA 1000 mg /kg and NIFE 20 (*P*<0.0001) but shows no significant difference compared to the control (W).

Figure B also shows a decrease in DBP. This decrease becomes highly significant at the dose of EA 1000 mg / kg and with NIFE 10 and NIFE 20 compared to the treated patients (*P*<0.0001). At these same doses, no significant difference was observed compared to the control. On the other hand, at the doses of 200 and 500 mg /kg, a very significant and significant decrease was observed respectively compared to the control (W).

The heart rate (HR) in Figure C decreases with administration of the extract ranging from 200 to 1000 mg /kg and with NIFE at different concentrations. This highly significant decrease in the dose of EA 1000 mg/kg and NIFE 20 compared to the PT shows no significant difference compared to the control (W).

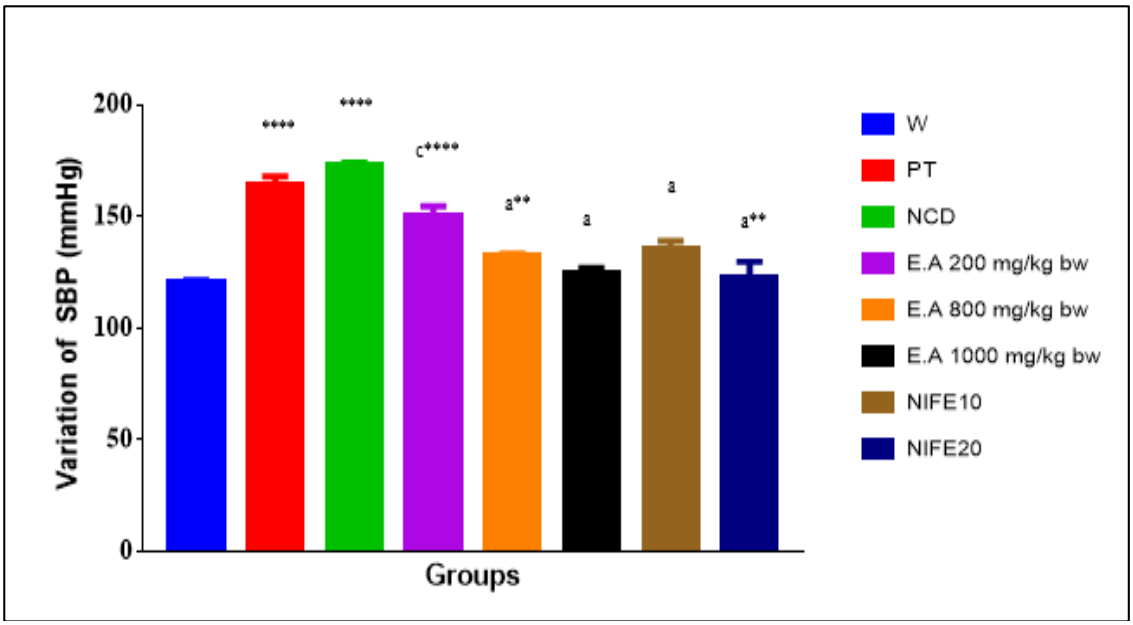

Fig A: Effect of aqueous extract and nifedipin on systolic blood pressure (SBP)

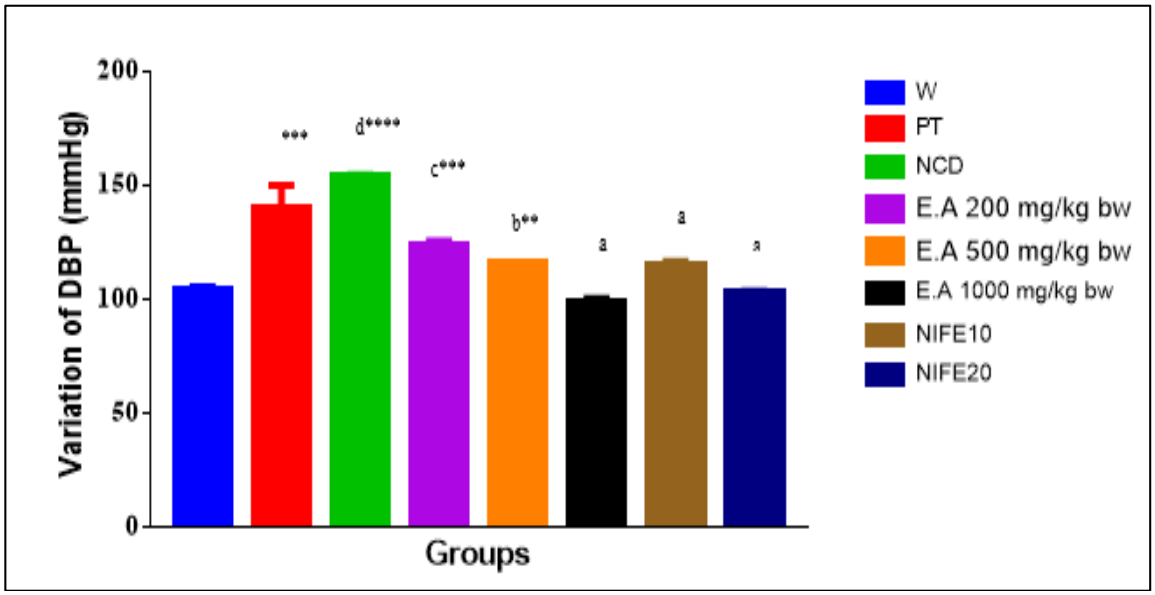

Fig B: Effect of aqueous extract and nifedipin on diastolic blood pressure (DBP)

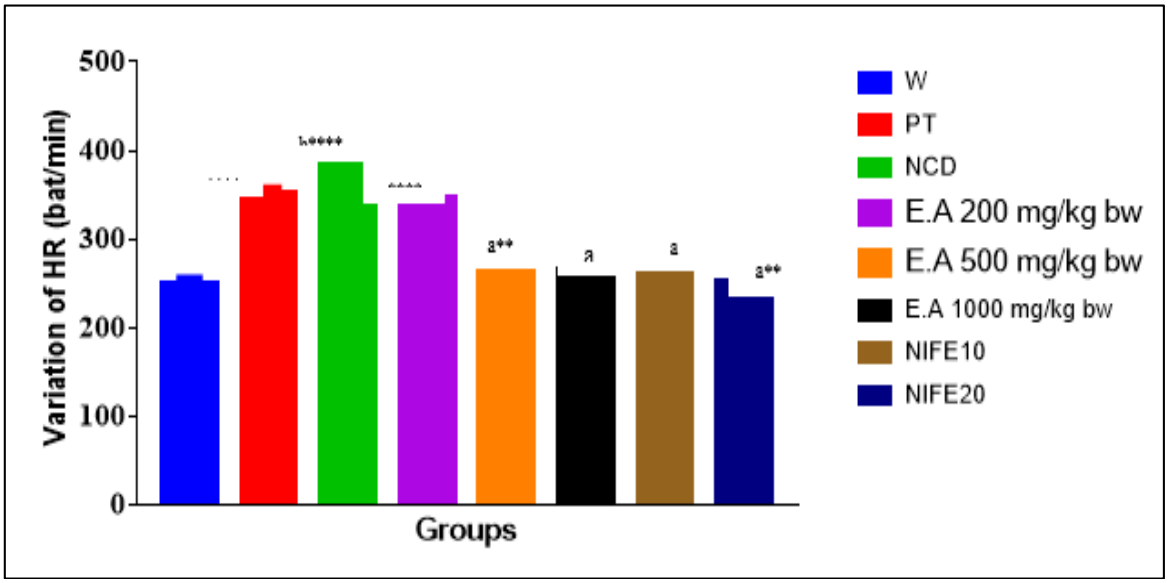

Fig C: Effect of aqueous extract and nifedipin on heart rate (HR) ****: $P<0.0001$ = highly significant difference compared to the control; ***: $P<0.001$ = very significant difference compared to the control. **: $P<0.01$ = significant difference compared to the control. a: $P<0.0001$ = highly significant difference compared to the patient treated; b: $P<0.001$ = very significant difference compared to the patient treated. c: $P<0.01$ = significant difference compared to the patient treated. d: $P<0.05$ = insignificant difference compared to the patient treated. The means are in the form ± SEM (n = 3). W: Witness; P.T = Patient treated; NCD = Untreated Patient. E.A = aqueous extract; NIFE = Nifedipin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate

4. Discussion

The consumption of fructose 60% significantly increases blood sugar and insulin levels. The results are similar with those of Bantle and coll. (2000) [15]; Mellouk Zoheir (2013) [13, 16] who have shown that consumption of fructose is responsible for hyperglycemia and hyperinsulinemia. The hyperglycemia and hyperinsulinemia observed may be due to the inhibition of insulin secretion of Langherans islets by chronic consumption of fructose. This inhibition can be due to an absence of be due to an absence of GLUT 5 receptors in the β cells of the pancreatic islets according Sathishsekar and Subramanian (2005) [17]; Fernandes (2007) [18]. These receptors are said to transport fructose to target cells.

Rats treated with fructose showed a significant increase in systolic blood pressure, diastolic blood pressure and heart rate. This increase in cardiovascular parameters could be due to an increase in blood sugar and insulinemia. This result is in accordance to those of recent studies of Bray (2004a) [14]; Bantle and coll. (2000) [15]; Mellouk Zoheir (2013) [13, 16] and Abdollahi (2010) [19]. They have shown that the consumption of fructose is responsible for hyperglycemia, hyperinsulinemia and an increase in cardiovascular parameters throughout the duration of the experiment. It has also been shown that a decrease in the nitric oxide concentration would influence cardiovascular parameters. The variation of values observed at the cardiovascular parameters level could be one of the Consequences of the decrease of nitric oxide concentrations in tissue causing attenuation of their production or their inactivation by the superoxide anion according Mellouk Zoheir (2013) [13, 16].

The treatment of glycemia and insulinemia of hypertensive rats induced by fructose with different doses of the aqueous extract and metformin, significantly decreases. The results obtained are similar to those of Dawei and coll. (2010) [20]; Pari and Latha (2005) [21]; Tomiyama (2000) [22]. These authors have shown the hypoglycaemic activity of certain

extracts of medicinal plants in rats. They reported in their work that plant extracts improve insulin secretion by pancreatic beta cells. This would explain the decrease in glycemia. The treatment of cardiovascular parameters of hypertensive rats with different doses of the aqueous extract and nifedipin, significantly decreases rates of systolic blood pressure, diastolic blood pressure and heart rate. The results obtened are similar to that of Bahi, (2015) [23, 25] and Majiminiyi *et al*., (2007) who have shown the hypotensive effect of the respective extracts of *Morinda morindoides on rabbits* and *Hibiscus sabdariffa* on rats.

These decreases observed may be due to endothelial dysfunction. Mojiminiyi and coll. (2007) [24] shown that hypertension associated with glucose intolerance is closely linked to endothelial dysfunction**.** Also according Madani and coll. (2012) [12] certain active compounds such as the alkaloids contained in the aqueous extract of *Catharanthus roseus* having a hypotensive activity would have decreased the values of the cardiovascular parameters**.**

5. Conclusion

The present study revealed that the aqueous extract of the leaves of *Catharanthus roseus* at dose dependent, stabilizes blood sugar, considerably reduces insulinemia, systolic blood pressure, diastolic blood pressure and heart rate. This extract would therefore have anti-diabetic and antihypertensive properties and could help in the treatment of these diseases.

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