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***Research article***

# EFFECT OF DICHLOROMETHANE-ETHANOL EXTRACT OF *MORINDA MORINDOIDES* (BACKER) MILNE-REDHEAD (RUBIACEAE) (ETDE) ON RABBIT CAROTID BLOOD PRESSURE

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**ABSTRACT:** *Morinda morindoides* (Backer) Milne-Redhead (Rubiaceae) is used by the people of west and central Africa for the treatment of diarrhea. The dichloromethane/ethanol extract of *M. morindoides* (Back) (ETDE) known to be used orally, will be in direct contact with the nobles organs. This study is conduced to see if this extract has effects on the body more precisely on blood pressure. ETDE injected intravenously (10.40 mg/kg b.w to 31.19 mg/kg b.w) provoked a decrease in the arterial blood pressure (hypotension) in a dose-dependent manner ($ED_{50}$ = 7.08 mg/kg b.w). ETDE at 41.58 mg/kg b.w induce a maximum and irreversible hypotension which leads to the death of the animal. The effects induced by ETDE were inhibited in the presence of atropine at a concentration of 4.46 $\times 10^{-4}$ mg/kg b.w. Our observations, regarding the effects of ETDE on the high blood pressure initiated by adrenaline, showed that the hypertensive effects induced by adrenalin were totally inhibited by ETDE. ETDE induced a dose-dependent hypotension and reversible and his antihypertensive effect could militate for its use in the treatment of hypertension.

**Keywords:** *Morinda morindoides* (Baker) Milne-Redhead, hypotensive, hypertensive, antihypertensive.

## INTRODUCTION

The importance of the African traditional medicine in the management of diseases has long been established (Sofowora, 1982). In Côte d'Ivoire, traditional medicines are increasingly sought from tradipractitioners and herbalists for the treatment of various diseases. Among the remedies used, plant drugs constitute an important part. A number of scientific investigations have highlighted the importance and the contribution of many medicinal plants (Grayer *et al*., 1994). *Morinda morindoides* (Backer) Milne-redhead (Rubiaceae) is a plant widely used in Democratic Republic of Congo for the treatment of various diseases including malaria, diabetes, microbial infections and dermatitis (Mankélé et al., 2006). It constitutes a remedy for the treatment of intestinal worms, rheumatic pains and amoebic abscess (Cimanga et al., 2006). The plant popularly called "Zêlékélé" in 'Bété' (local language in central part of Côte d'Ivoire) is found widely in the borders of tropical forests (Méité et al., 2009). In Côte d'Ivoire, *M. morindoides* (Back) is used by the people of west for the treatment of diarrhea (Bahi; 2000). Previous studies have indicated that the aqueous, ethanolic and acetatic extracts of *M. morindoides* (Back) induced, on the rabbit arterial blood pressure, a reversible hypotension at low doses and an irreversible hypotension at high doses (N'guessan, 2001). On the isolated heart of rat, these extracts induced a cardio inhibition (Moroh et al., 2008) and inhibited the *in vitro* increasing of *E. coli* (Bagré et al., 2006), Cryptococcus neoformans (Bagré et al., 2007), *Candida albicans* and *Aspergillus fumigatus* (Guégé-Guina et al., 1993). In this paper, we studied the hypotensive activity or not of the dichloromethane/ethanol crude extract prepared with leaves of *M. morindoides*. In an effort to elucidate the action of ETDE, we studied the interaction between ETDE and atropine. Furthermore, the effect of ETDE has been tested against the high arterial blood pressure induced by adrenaline.

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## MATERIALS AND METHODS

### Plant material

The leaves of *Morinda morindoides* were collected in Lakota in the west region of Côte d'Ivoire, in March and April 2008. This plant was identified by the herbarium of Centre National de Florestique, Abidjan, where a voucher specimen was conserved with reference number 17710.

### Animals

Rabbit of both sexes 3-4 months old weighing 1.5 -2.5 kg and bred at animal house in Abidjan (Côte d'Ivoire), were used experimentations. All the animals were acclimated at the experimental conditions one week before the experiment. The animals were treated according to the principles for the care and use of laboratory animals, and approval for the studies was given by the Ethical Committee of the University of Cocody-Abidjan.

### Chemicals

Previous chemicals were used for our study: Ethyl-urethane obtained from SIGMA (Switzerland), Sodium chloride obtained from MERCK (Germany), Heparin from PROLABO (France) and Dichloromethane from SANOFI-SYNTHLABO (France).

### Preparation of the dichloromethane/ethanol extract

The freshly collected leaves of the plant were air-dried at room temperature (25 – 37°C) for three weeks and powdered. The extract was prepared according to the method described by GUEDE-GUINA *et al* (1993). According this method, 150 g of leaves powder was dissolved in 800 ml of a mixture of dichloromethane/ ethanol (made up of 200 ml dichloromethane and 600 ml of ethanol) (1/3 v/v). The obtained mixture was homogenized for 24 hours at room temperature (25-3O°C) using a magnetic stirrer IKAMAG-RCT. The homogenate obtained was filtered twice through cotton wool, then through Whatman filter paper (n°1). The filtrate was evaporated at 48°C to dryness using a rotary evaporator (BÜCHI). The resulting dry powder was taken as the dichloromethane /ethanol extracts of *M. morindoides*. Solutions of the extracts were prepared freshly for each study.

### Recording of the rabbit arterial blood pressure

The rabbit was anesthetized with ethyl-urethane (40 %) at a dose of 2.5 ml/ kg b.w. Then, the a sleep animal was put in dorsal *decubitus* on grid placed in a vat for dissection. The dissection of the thigh and the neck were made in order to expose the saphenous vein and the carotid. Thereafter we carried out the intubation of the vessel and artery. Intubations permitted possible placement of blood carotid and the mercury contained in the 'U' tube the pressure gauge of Ludwig in close contact. The mercury was surmounted by a float connected by a wire to a stylet inscriptor. Thus, the variations of the carotid blood pressure witch were transmitted to the mercury were collected by the float and were registered by the stylet inscriptor on paper.

### Statistical analysis

Data were analysed by one-way ANOVA followed by Dennett's t-test using Instat (Graph Pad Software, U.S.A). At 95 % confidence interval $P < 0.05$ was considered statistically significant.

## RESULTS

The recordings relate to changes in the level of arterial blood pressure, determined from reference blood pressure. This reference pressure is measured from the downward of the stylet insciptor. The increasing doses of the same pharmacodynamic substance were injected at intervals of 35 to 40 minutes.

### Dose-response effects of dichloromethane/ethanol extract of Morinda morindoides (Backer) (ETDE) on the rabbit arterial blood pressure

The figure 1 presents the dose-response effect of ETDE on the rabbit arterial blood pressure. The administration of NaCl 9 ‰ intravenously did not induce any modification of the arterial pressure. The injection of ETDE to anesthetized rabbit induced a decrease in the arterial blood pressure. ETDE applied in a range of doses from 10.40 mg/kg b.w. to 31.19 mg/kg b.w. caused a reversible dose-response decrease of the blood pressure level from 17.32 % to 43.14 % in comparison with the normal arterial blood pressure (102 ± 4 mmHg). At 41.58 mg/kg b.w., ETDE induced a maximum and irreversible hypotension witch leads to the death of the animal. The action of ETDE was graphically represented in fig. 2 (percentage of arterial pressure). The dose at witch the half-effect of ETDE was obtained (efficacy dose at 50%, $ED_{50}$) was 7.08 mg/kg b.w.

### Effects of the interaction between atropine and dichloromethane/ethanol extract of Morinda morindoides (Backer) (ETDE) on the rabbit arterial blood pressure

The effect of ETDE at 17.86 mg/kg b.w. in presence of increasing doses of atropine at doses from $4.46 \times 10^{-10}$ to $4.46 \times 10^{-4}$ mg/kg b.w. on the rabbit blood pressure was represented in figure 3.

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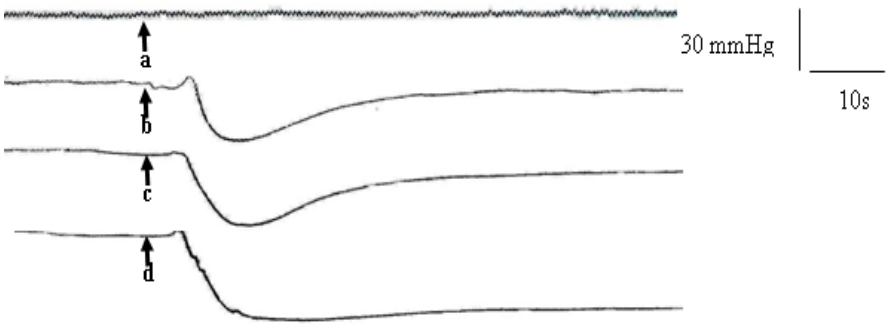


**Figure 1: Effects of the dichloromethane/ ethanol extract of *Morinda morondoides* (Backer) (ETDE) on the rabbit arterial blood pressure.**

The arrows indicate administration of ETDE. The different doses applied are: **a**: NaCl (0.009 mg/ml); **b**: ETDE at 10.40 mg/kg b.w; **c**: ETDE at 20.80 mg/kg b.w; **d**: 41.58 mg/kg b.w.

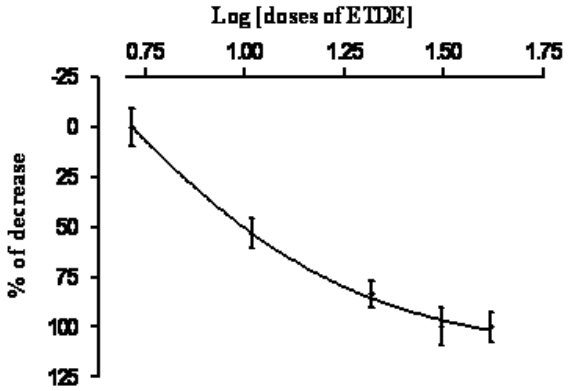


**Figure 2: Dose-response curve for the dichloromethane/ ethanol extract of *Morinda morindoides* (Backer) (ETDE) on the rabbit arterial blood pressure.**

Values are expressed as percentage decrease of control (mean ± sem, n = 3, p< 0, 05). Horizontal scale: ETDE Log [mg/kg b.w.]. Vertical scale: decrease of arterial blood pressure [%].

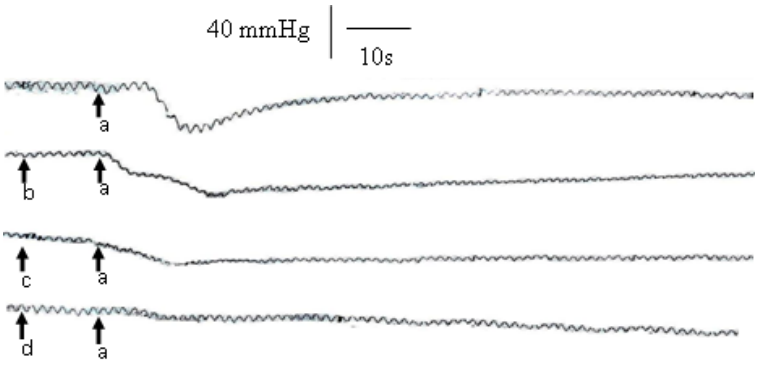


**Figure 3: Effects of the dichloromethane/ethanol extract of *M. morindoides* (Back) (ETDE) in presence of atropine on the rabbit arterial blood pressure.**

The arrows indicate respectively the administration of ETDE and atropine. The different doses applied are: **a**: ETDE at 17.86 mg/kg b.w.; **b**: atropine at $4.46 \times 10^{-10}$ mg/kg b.w; **c**: atropine at $4.46 \times 10^{-7}$mg/kg b.w; **d**: atropine at $4.46 \times 10^{-4}$ mg/kg b.w.

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The hypotension induced by ETDE at dose of 17. 86 mg/kg b.w (32 ± 2 mmHg: a reference blood pressure), was gradually reduced by atropine at doses from 4.46 × $10^{-10}$ to 4.46 × $10^{-4}$ mg/kg b.w. The pretreatment of the rabbit with increasing doses of atropine inhibits the hypotension induced by ETDE from 26 mmHg to 0 mmHg. This corresponds to a percentage reduction from 19.75 % to 100 %, in comparison with the reference arterial blood pressure. At high doses, the atropine reduces totally the hypotensive effect of ETDE. These results are similar to those observed in the interaction atropine-acetylcholine.

**Effects of the interaction between ETDE and adrenaline on the rabbit carotid blood pressure**

Figure 5 represents the recording of the effects of the adrenaline on the rabbit blood pressure in presence of various increasing doses of ETDE.

The reference high blood pressure (54 ± 3 mmHg) induced by the adrenaline at dose of 1.46×$10^{-3}$ mg/kg b.w., was gradually reduced until it is totally inhibited by the various increasing doses of ETDE (11.14 mg/kg b.w. to 46.34 mg/kg b.w.). Indeed, this hypertension was reduced from 18.52 % to 99.45 % in comparison with the reference pressure. The hypertension induced by the adrenaline at 48.78 mg/kg b.w., was completely inhibited and only the slight hypotension was observed. Then, the injection of increasing doses of ETDE (11.14 mg/kg b.w. to 46.34 mg/kg b.w.) provoked the reduction of the hypertension induced by the adrenaline in more than 100 %. This signified that ETDE have an antihypertensive action.

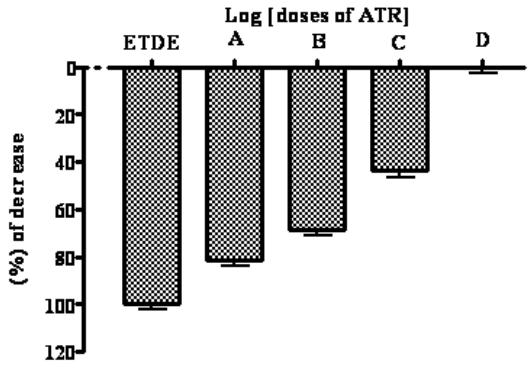


**Figure 4: Effect of the dichloromethane/ ethanol extract of *Morinda morindoides* (Baker) (ETDE) at 17, 86 mg/kg b.w. on rabbit blood pressure in presence of various doses of atropine.**

A = 4. 46 × $10^{-10}$ mg/kg b.w.; B = 4.46 1× $0^{-9}$ mg/kg b.w.; C = 4.46 × $10^{-7}$ mg/kg b.w.; D = 4.46 × $10^{-4}$ mg/kg b.w. Values are expressed as percentage decrease of control (mean ± sem, n = 3, p< 0, 05)

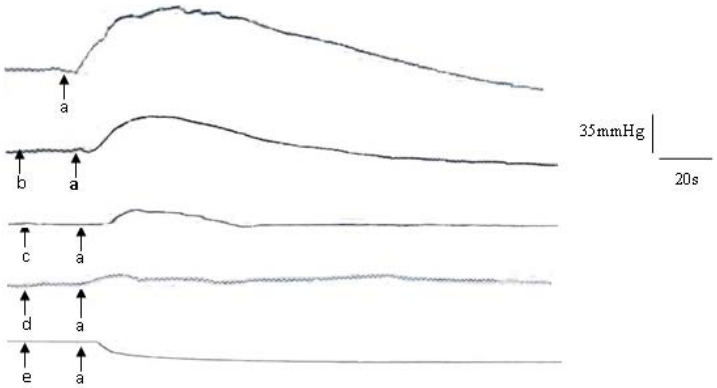


**Figure 5: Recording of the effect of the interaction between adrenaline at 1.46×$10^{-3}$ mg/kg b.w. and the dichloromethane/ ethanol extract of *Morinda morindoides* (Baker) (ETDE) at increasing doses on rabbit blood pressure.**

a = adrenaline at 1.46×$10^{-3}$ mg/kg b.w.; b = ETDE at 29.27 mg/kg b.w.; c = 43.90 mg/kg b.w.; d = 46.34 mg/kg b.w.; e = 48.78 mg/kg b.w. The arrows indicate respectively the administration of adrenaline and adrenaline.

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**Effects of the interaction between Diltiazem and adrenaline on the rabbit carotid blood pressure**

The effect of adrenaline at $3\times10^{-2}$ mg/ml in presence of various increasing concentrations of diltiazem ($3\times10^{-5}$ mg/ml to $3\times10^{-2}$ mg/ml) was presented in figure 7.

The adrenaline at $3\times10^{-2}$ mg/ml induced a hypertension. In presence of increasing concentrations of diltiazem ($3\times10^{-5}$ mg/ml to $3\times10^{-2}$ mg/ml), the reference high blood pressure (62 ± 2 mmHg) induced by the adrenaline at dose of $3\times10^{-2}$ mg/ml, was greatly reduced but not totally inhibited. The results showed that the adrenaline administrated at concentration of $3\times10^{-2}$ mg/ml caused a maximum hypertension of 62 ± 2 mmHg. The injection of increasing concentrations of diltiazem at $3\times10^{-5}$ mg/ml to $3\times10^{-2}$ mg/ml reduced the hypertension induced by the adrenaline from 12.52 % to 69.36 % in comparison with the reference pressure. The figure 8 illustrates the reduction of the hypertension induced by the adrenaline in presence of diltiazem.

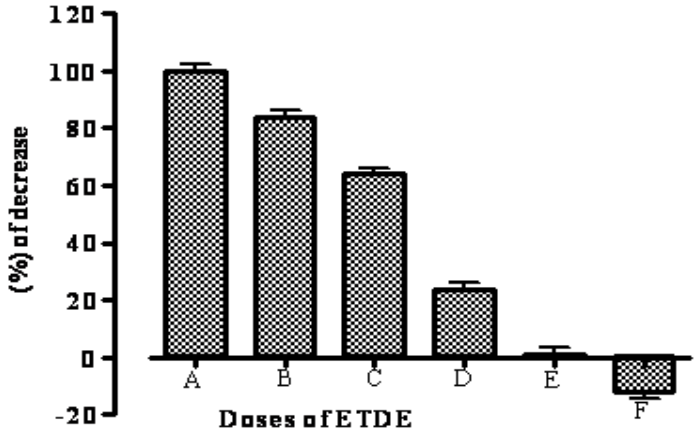


**Figure 6: Effect of the adrenaline at $1.46\times10^{-3}$ mg/kg b.w. on rabbit blood pressure in presence of various doses of dichloromethane/ ethanol extract of *Morinda morindoides* (Baker) (ETDE).**

A = adrenaline at $1.46\times10^{-3}$ mg/kg b.w.; B = ETDE at 11.14 mg/kg b.w.; C = ETDE at 29.27 mg/kg b.w.; D = ETDE at 43.90 mg/kg b.w.; E = ETDE at 46.34 mg/kg b.w.; F = ETDE at 48.78 mg/kg b.w. Values are expressed as percentage decrease of control (mean ± sem, n = 3, p< 0, 05)

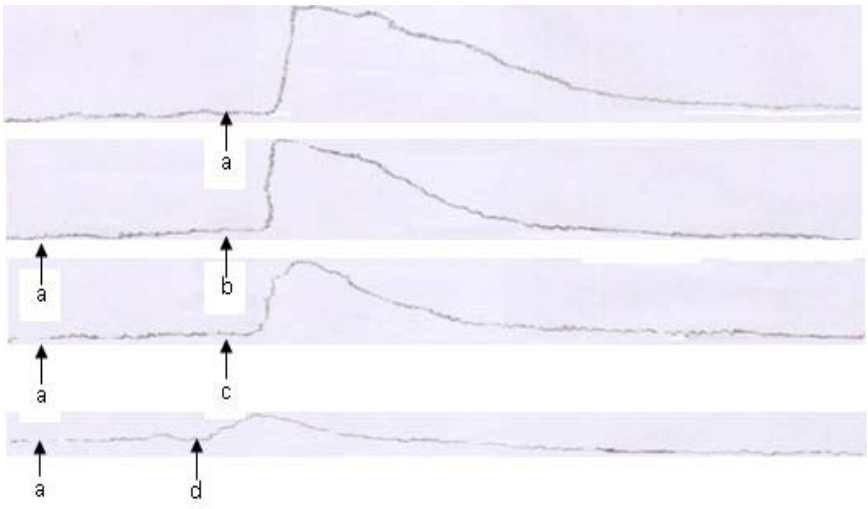


**Figure 7: Recording of the effect of the interaction between adrenaline at $3\times10^{-2}$ mg/ml and the diltiazem at increasing concentrations on rabbit blood pressure**

a = adrenaline at $3\times10^{-2}$ mg/ml; b = Dil at $3x10^{-4}$ mg/ml; c = Dil at $3x10^{-3}$ mg/ml d = Dil at $3x10^{-2}$ mg/ml. The arrows indicate respectively the administration of adrenaline and adrenaline.

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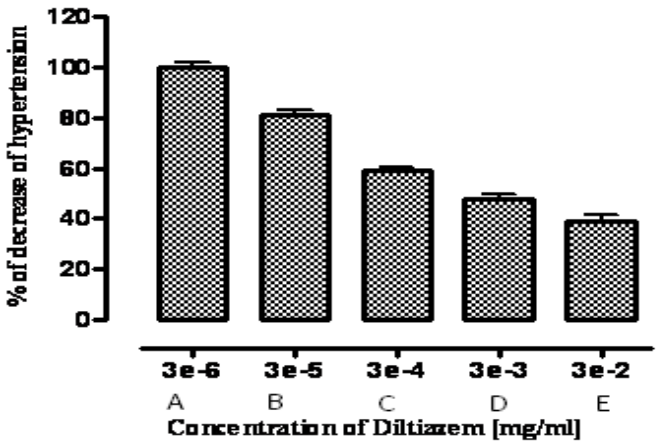


**Figure 8: Effect of the adrenaline at $3\times10^{-2}$ mg/ml on rabbit blood pressure in presence of various concentrations of diltiazem**

A = adrenaline at $3\times10^{-2}$ mg/ml; B = Dil at $3\times10^{-5}$ mg/ml; C = Dil at $3\times10^{-4}$ mg/m; D = Dil at $3\times10^{-3}$ mg/ml; E = Dil at $3\times10^{-2}$ mg/ml. Values are expressed as percentage decrease of control (mean ± sem, n = 3, p< 0, 05).

## DISCUSSION

The dichloromethane/ethanol crude extract of *M. morindoides* (Back) (ETDE) induces a dose-dependent hypotension and reversible. These results are comparable with that observed by N'GUESSAN with the fraction 5 of *M. morindoides* (N'guessan, 2001). This author showed that the fraction 5 of *M. morindoides* provokes a reversible dose-dependent hypotension at low doses and irreversible at high doses. The effect of ETDE is also similar to that observed with *Caesalpinia bonduc* (Datté et al., 1997), an uterotonic plant used traditionally to facilitate deliveries of parturient women and with *Mareya micrantha* (Benth) Mill. Arg (Euphorbiaceae) (Abo et al., 2000). The hypotension caused by ETDE is similar to that exerted by acetylcholine. This suggests that ETDE could be cholinomimetic. According to Datte (1997) and Zlingg (2001), the pharmacodynamic substances witch have a hypotensive action are often cholinomimetic. Furthermore, analysis of our results showed that pre-treatment of animals with atropine (ATR), a specific ACh-muscarinic receptor antagonist, removes the hypotension induced by ACh and ETDE. This suggests that ETDE could contain muscarinic cholinergic compounds. These compounds have the same mechanism of action of ACh. Acetylcholine (ACh), in effect, exerts its hypotensive effect via two routes. In the heart, ACh binds to muscarinic cholinergic receptors and causes cardiac slowing it. This slowing of the heart causes cell hyperpolarisation following the opening of potassium channels that are directly related to G protein (Noda *et al*., 1983; Hammond and Trisch, 1990). This hyperpolarisation causes the reduction of the entry of calcium due to inhibition of adenylyl cyclase and olso reduced the release of calcium from the sarcoplasmic reticulum. Then the decrease in the strength of heart contractions and subsequently hypotension (Dupouy, 1993; Hanf et al., 1993). In terms of vessels, ACh causes secondary peripheral vasodilatation to stimulation of M2 receptors coupled to protein G This coupling leads to the production of inositol triphosphate (IP3) and diacylglycerol (DAG) It finally leads to the release of a vasodilator substance called Endothelium Derived Realxing factor or EDRF or nitric oxide (NO) (Takano et al., 2004; Jiang et al., 2005)**.** Our work also showed that the ETDE at doses of 11.14 mg / kg b.w to 48.78 mg / kg b.w caused a total reduction of hypertension induced by adrenaline at a dose of $1{,}46.10^{-3}$ mg / kg bw This suggests that the ETDE contain compounds which have antihypertensive effectsThese antihypertensive effects resemble those of extracts of *Tetranda stephania* (Menispermaceae) (YU et *al*., 2004)**,** *Berberis vulgaris* (Berberidaceae) (Fatehi-Hassanabab et al., 2005) and BGG, F5 a fraction of *M. morindoides* (Back) (Rubiaceae) (N'guessan *et al*., 2004)These authors have shown that these extracts reduced the hypertension induced by adrenaline. Adrenaline causes constriction of blood vessels and accelerated heartbeat, increasing blood pressure (Campbell, 1993). This hypertensive action is due to the binding of ADR on the $\beta_2$ adrenergic receptors. The inhibition of the hypertensive effects of adrenaline by ETDE, suggesting the existence in the ETDE of $\beta_2$-receptor blockers compounds. The β blockers reduce cardiac output as opposed to induced hypertension by adrenaline (Watanabe et al., 1978)**.**

The effect of ETDE is similar to that exerted by diltiazem, an antihypertensive calcic inhibitor. This would mean that more of the cholinomimetic compounds, ETDE also contains calcium compounds inhibitors. Indeed, calcium channels blockers reduce the tonus of the arteries by reducing the vasoconstrictive capabilities (calcium-dependent) of arterial smooth muscle by inhibiting the transmembrane transfer of calcium. The diltiazem affects blood vessels and heart muscle (by decreasing its contractibility). This antihypertensive effect of ETDE could militate for its use in the treatment of hypertension.

## CONCLUSION

The pharmacologic studies of dichloromethane/ethanol extract of *Morinda morindoides* (ETDE) on the rabbit blood pressure revealed that ETDE exerts a reversible dose-dependent hypotension at low doses and an irreversible dose-dependent hypotension at high doses. This extract could contain muscarinic cholinergic compounds and could use the same action mechanism like the acetylcholine. Studies showed again that ETDE could contain antihypertensive substances that could militate for its use in the treatment of hypertension.

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