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Biosciences

Evaluation of Serum Ionic Profiles in Rabbits Treated with Acetal Extract of *Entandrophragma angolense* (Meliaceae)

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Abstract **Original Research Article**

This study aimed to evaluate the ionic disturbs of acetal extract of *Entandrophragma angolense* (Meliaceae) in rabbits. *E. angolense* is a plant used in the traditional treatment of diabetes and several diseases in the south-east of Coast Ivory. In addition to this antidiabetic activity, this plant rich in polyphenolic compounds has an antioxidant potential that could be beneficial in the management of diseases related to oxidative stress. For this study, different batches of rabbits were injected with increasing doses of acetal extract of E. *angolense*. Then changes in serum calcium, magnesium, chloride, sodium and potassium were evaluated. This study indicated that the acetal extract of *E. angolense* with doses between 312.5 and 5000 mg / kg body weight (bw) in rabbits causes a significant variation ($P < 0.05$) of potassium and calcium serum concentrations. But there is no significant change ($P > 0.05$) of magnesium, chloride, and sodium and serum concentration. Finally, this study suggests that a reduction of the dose (2500 mg / kg) and time of treatment (4 weeks) may help to avoid ionic disturbs other time. This dose of 2500 mg /kg/bw which is much higher than the therapeutic dose, confer on *E. angolense* a safety margin very interesting.
Keywords: *E angolense*, calcium, magnesium, chloride, sodium, potassium.

INTRODUCTION

Today, despite the enormous progress made by modern medicine, plants continue to occupy an increasingly important place in the management of several pathologies. This practice, which concerns all continents, particularly affects Africa. Ivory Coast, like many African countries, is no exception to this reality [1]. However, the misuse of plants is still not safe for the user populations. The inappropriate use of herbal extracts by healers combined with the lack of knowledge of chemical compounds and the necessary doses unfortunately lead to therapeutic accidents that can be tragic.

In order to avoid or minimize these accidents, it is important to evaluate the toxicity, pharmacological and biochemical properties of different plants used by populations [2,3].

Entandrophragma angolense (Meliaceae) is a plant used by people in southeastern Côte d'Ivoire for the treatment of various conditions including diabetes. It has an antioxidant potential that raises real hopes in the management of pathologies related to oxidative stress [4]. Among the many side effects of medications, hydro-mineral disorders occupy a place of choice. Since it is well known that hydro-mineral imbalances are the side effects inherent to many drugs, it has become essential to check whether or not this escapes this reality. The hydromineral imbalances induced by several drugs can have serious consequences, such as a latent metabolic acidosis that directly affects oxygen transport and cell nutrition. Decreased enzymatic activity, degradation of the immune system constituting a reason for the emergence of many diseases such as: the risk of osteoporosis, cardiac, metabolic and thyroid disorders [5-7].

This study aimed to deepen the state of knowledge on bio-tolerance of acetal extract of *Entandrophragma angolense* (AEEA). More specifically, it is to assess the ionic disturbs of AEEA following changes of many specific ions in rabbits: calcium, magnesium, chloride, sodium and potassium. Serum variations in these parameters can thus assess the impact of this extract on ionic disturbs [8, 9].

MATERIALS AND METHODS

Plant material

The barks of *Entandrophragma angolense* (Meliaceae) collected from Agboville (south east of Côte d'Ivoire) were identified by the National Floristic Center of University Felix Houphouet Boigny (Cocody-Abidjan). A voucher specimen of the plant has been deposited in this Center herbarium.

Experimental animals

For these experiments we use adult rabbits, *Oryctolagus cuniculus* (36) of both sexes, 7-9 weeks old, weighing 1.09 ± 0.15 kg and bred at the Department of Biosciences, University Felix Houphouet- Boigny (Abidjan, Ivory Coast), were used for the experiments. The animals were kept in standard cages with good ventilation, free access to food and water. Experimental procedures and protocols used in this study were approved by the Ethical Committee of Health Sciences of University Felix Houphouet-Boigny (Ivory Coast-Abidjan). These guidelines were in accordance with the European Council Legislation 87/607/EEC for the protection of experimental animals [10].

Preparation of acetal extract of *Entandrophragma angolense* (Meliaceae)

Plants harvested were air dried at room temperature (28±1 °C) for one month. The dried leaves were ground into fine powder. The powder (100 g) was soaked in two liters of acetal for 48 hours on a magnetic agitator. The extract was filtered twice through cotton wool, and then through Whatman filter paper (3 MM). The filtrate was evaporated to dryness in a rotary evaporator (BUCHI) at 60 °C. After drying, we get a brown powder used to prepare the acetal extract (AEEA).

Experimental protocol

After randomization into 6 groups of 6 rabbits (3 males and 3 females), and before initiation of experiments, the rabbits were acclimatized for a period of 14 days under standard environmental conditions of temperature, relative humidity, and 12 h dark/light cycle. Animals had free access to food and water *ad libitum*.

Animals in each group were separated according to their sex in cages. Among these 6 groups, 5 experimental groups have received doses ranging from 312.5 to 5000 mg/kg of bw (which is the Maximum Tolerated Dose (MTD) of the aqueous extract) in a geometric progression of ratio two [9]. Twice a week for six weeks, the animals received intraperitoneally 0.2 mL of an injection according to their group. Each rabbit of batch 1 (control) received only 0.2 mL of physiological solution of 0.09% Nacl (B. Braun) used to administrate extracts. Rabbits of batch 2 to batch 6 received respectively 312,5; 625; 1250; 2500 and 5000 mg/kg of bw.

Blood samples were collected in the morning (from 7 to 10 h) via the marginal ear vein of the animals, once a week using sampling needles. Blood sampling was carried out once a week in the one week preceding the first application of treatment (w_0), during the five weeks of treatment (w_1, w_2, w_3, w_4, w_5 and w_6). These blood samples were collected in sterile tubes without anticoagulant. There were centrifuged at 3000 rpm for 10 min using a liquidizer. Serum ions were measured with an automatic analyzer, LIASIS while sodium and potassium have been measured with spectrophotometer flamme SEAC *fp* 20.

Assay for ions (calcium, magnesium, phosphorus, chloride)

The principles of the determination of each parameter are described according to the manufacturer's instructions reagents.

Calcium (Spinreact): The measurement of calcium in the sample is based on formation of color complex between calcium and *o*-cresolphtalein in alkaline medium. The intensity of the color that is proportional to the calcium concentration in the sample is measured in a spectrophotometer at 570 nm wavelength

Magnesium (Spinreact): Magnesium forms a purple colored complex when reacts with calmagite in alkaline solution. The intensity of the color formed that is proportional to the magnesium concentration is measured in a spectrophotometer at 520 nm wavelength.

Chloride (Spinreact): The quantitative displacement of thiocyanate by chloride from mercuric thiocyanate and subsequent formation of a red ferric thiocyanate complex is measured colorimetrically. The intensity of the color formed which is proportional to the chloride ion concentration in the sample is measured in a spectrophotometer at 480 nm wavelength. Sodium and potassium have been measured with spectrophotometer flame SEAC *fp* 20.

Statistical analysis

The data were processed using the software Graph Pad Prism 5.0 (Microsoft, USA). The analysis of variance (ANOVA) was performed according to the multiple comparison test of Tukey for the comparison of mean values of serum ions of different groups but also to relative baseline in each group. Data are presented means ± standard error of mean (S. E.M) for the number of animals in each group (n = 6). The difference is said to be significant if ($P<0.05$) and not significant if ($P>0.05$).

RESULTS

The results of changes in serum, calcium, magnesium, chloride, sodium and potassium expressed

in tables (1, 2, 3, 4 and 5) are averages of six assays performed in each group.

Calcium

The serum calcium (w_0) was 86.6±2.06 mg/L in the untreated lot (lot1). This value varies over time between 86,5±6.9 mg/L (minimum w_2) and 89.66±2.65 mg/L (maximum w_5), representing a change of -0,19 % (w_2) to 3,46 % (w_5) of the initial rate of serum calcium**.** In lot 2 (312.5 mg / kg), serum calcium was 91.33±2.16 mg/L before treatment. Over the past six weeks, the rate changes of 88.63±3.0 mg/L (minimum w_5) to 92.33±4.41 (maximum w_1). These values correspond to variations of -2, 73 % (w_5) to 1,095 % (w_1) (Table 1).

Table-1: Effect of AEEA on the levels of serum calcium (mg/L) over time in rabbits

Doses (mg/kg)	0	312.5	625	1250	2500	5000
w_0	86.6±2.06	91.33±2.16	89.66±1.86	90±1.26	88.83±2.56	88.83±1.47
w_1	87.33±6.8	92.33±4.41	87.33±5.85	89.33±5.2	91.66±2.16	89.66±5.95
w_2	86,5±6.9	91±2.82	88.33±3.44	87.66±3.88	92±3.57	91.83±2.48
w_3	87±5.02	89±3.4	90.16±2.04	91.66±1.97	89.16±3.43	93.5±2.66
w_4	88.16±2.56	90.16±3.71	89.83±5.30	90.66±6.91	90.16±3.6	94.66±1.03
w_5	89.66±2.65	88.63±3.0	90.83±1.83	90.5±3.98	91.33±2.42	96±3.16*
w_6	87.83±0.75	90±6.06	91±2	91.16±1.83	92.83±3.12	96.5±1.97*
Lots	Lot $_1$	Lot $_2$	Lot $_3$	Lot $_4$	Lot $_5$	Lot $_6$

Values are expressed as mean ± S.E.M (n = 6); * P <0.05 compared to control and to w_0 level. w_0: Week preceding the first application of treatment; w_1 to w_6: Weeks of treatment.

In group 3, serum calcium rate was 89.66±1.86 mg/L before treatment. This value varied to 87.33±5.85 (minimum w_1) to 91±2 mg/L (maximum w_6). These evolutions represent variations of -2, 60 % (w_1) to 1, 49% (w_6).

Percentage changes as recorded in lots 4, 5 and 6 are respectively: -2,59 % (w_2) to 1,85% (w_3); 0,37 % (w_3) to 4,50 % (w_6) and 0,93 % (w_1) to 8,63 % (w_6).

Statistical analysis of the results indicates a significant change in serum calcium (P <0.05), especially with the dose of 5000 mg / kg bw (lot 6) in the fifth and sixth week.

Magnesium

The serum magnesium (w_0) was 18.83±1.60 mg/L in the untreated group (group 1). This value which varies over time to 20±0 (maximum w_1), represents 6.19 % (w_1) variation of the initial serum magnesium. In lot 2 (312.5 mg / kg), serum magnesium was 19.5±0.84 mg/L before treatment. Over the past six weeks, the rate changed of 17.83±1.33 (minimum w_5) to 19.5±0.83 mg/L (maximum w_2). These values correspond to variations of 0 % (w_5) to 9, 34% (w_2) (Table 2).

Table-2: Effect of AEEA on the levels of serum magnesium (mg/L) over time in rabbits

Serum concentrations of magnesium (mg/L)						
Doses(mg/kg)	0	312.5	625	1250	2500	5000
w_0	18.83±1.60	17.83±1.5	19.5±0.84	19.16±1.16	19.16±0.98	18.66±0.81
w_1	20±0	18.5±0.84	19.33±0.82	18.66±1.03	18.5±1.51	19±1.26
w_2	19±1.26	19.5±0.83	19.33±1.21	18.3±1.86	18.5±1.37	18±33
w_3	18.66±1.50	19±1.26	17.66±1.36	19.33±1.21	19±1.26	18.33±1.5
w_4	19.16±1.17	18.5±2.34	18.5±1.97	19±1.26	17.83±2.85	19.16±1.6
w_5	19.33±0.81	17.83±1.33	18.66±1.21	18.16±2.04	18.16±2.22	18.16±1.33
w_6	18.83±2.40	19.33±1.21	19.16±1.6	19.5±0.83	19±1.55	19.83±0.41
Lots	Lot $_1$	Lot $_2$	Lot $_3$	Lot $_4$	Lot $_5$	Lot $_6$

Values are expressed as mean ± S.E.M (n = 6); P > 0.05 compared to control and to w_0 level.
w_0: Week preceding the first application of treatment; w_1 to w_6: Weeks of treatment.

Serum magnesium rate in batch 3 was 19.5±0.84 mg/L during the week before treatment (**w_0**). This value changed from 17.66±1.36 (minimum w_3) to19.33±1.21 mg/L (maximum w_2). These variations represent -9, 40 % (w_3) to -0, 85 % (w_2). Percentage changes recorded in batches 4, 5 and 6 are respectively: -5, 21 % (w_5) to 1, 74 % (w_6); -6, 95 % (w_4) to -0, 87 % (w_6) and -2, 67 % (w_5) to 6,25 % (w_6) of the initial serum magnesium. The statistical analysis shows no significant change in serum magnesium with different doses (P > 0.05).

Chloride

In the untreated lot, the serum chloride at w_0 was 99.5±2.16 mEq/L**.** This value which varies over time between 97.83±2.14 mEq/L (minimum w_1) and 102.1±2.31 mEq/L (maximum w_5), represents a

variation of -1.67 % (w_1) to 2.68 % (w_5) of the initial rate of chloride.

In batch 2 (312.5 mg / kg), serum chloride was 97.83±2.56 mEq/L before treatment. Over the past six weeks, the rate changed from 98.5±2.34 mEq/L (minimum w_1) to 102.5±1.37 mEq/L (maximum w_6). These values correspond to variations of 0,681 % (w_1) to 4, 77 % (w_6) of the initial serum chloride (Table 3).

Table-3: Effect of AEEA on the levels of serum chloride (mEq/L) over time in rabbits

Serum concentrations of chloride (mEq/L)						
Doses(mg/kg)	0	312.5	625	1250	2500	5000
w_0	99.5±2.16	97.83±2.56	98.5±2.81	100.5±2.81	99.83±2.63	100.16±2.22
w_1	97.83±2.14	98.5±2.34	100.16±1.6	98.83±1.6	99±1.41	99.5±3.08
w_2	98.5±2.88	98.67±1.86	99.67±1.03	100.6±2.33	100.16±2.9	101.33±2.06
w_3	100.66±0.8	99.16±1.83	99.16±1.6	100.66±2.5	100.66±1.9	100.16±2.63
w_4	102.1±2.3	98.33±1.36	100.5±1.64	99.5±1.64	101±2.53	101.16±1.47
w_5	102.1±2.31	100.5±1.64	100.5±1.22	101.33±1.3	102±2	102±1.79
w_6	101.3±3	102.5±1.37	101.16±1.3	101.3±2.65	102.16±1.7	103.5±1.22
Lots	Lot $_1$	Lot $_2$	Lot $_3$	Lot $_4$	Lot $_5$	Lot $_6$

Values are expressed as mean ± S.E.M (n = 6); P > 0.05 compared to control and to w_0 level.
w_0: Week preceding the first application of treatment; w_1 to w_6: Weeks of treatment.

Serum chloride rate was 98.5±2.81 mEq/L before treatment, in lot 3. This value varied from 99.16±1.6 (minimum w_3) to 101.16±1.3 mEq/L (maximum w_6). These variations correspond to 0, 68 % (w_3) to 2, 71 % (w_6). In group 4, chloride serum rate was 100.5±2.81 mEq/L during w_0. The percentage change during the weeks of treatment is -1, 66 % (w_1) to 0, 83% (w_5).

The percentage changes so recorded in batches 5 and 6 are respectively -0,83 % (w_1) to 2,34 % (w_6) and -0,66 % (w_1) to 3,33 % (w_6). The statistical analysis shows no significant change in serum chloride with different doses (P > 0.05).

Sodium

The serum sodium at w_0 was 137.3±2.25 mEq/L in the untreated lot**.** This value which varies over time between 138.83±2.2 mEq/L (minimum w_1) and 142.3±2.87 mEq/L (maximum w_6), represents a variation of 1, 09 % (w_1) to 3, 64 % (w_6) of the initial rate of sodium.

Before treatment, serum sodium was 139.5±1.97 mEq/L in batch 2 (312.5 mg / kg). Over the past six weeks, the rate changed from 139.5±2.34 mEq/L (minimum w_2) to 142.66±1.0 mEq/L (maximum w_5). These values correspond to variations of 0 % ($_{w2}$) to 2, 27 % (w_5) of the initial serum sodium (Table 4).

Table-4: Effect of AEEA on the levels of serum sodium (mEq/L) over time in rabbits

Serum concentrations of sodium (mEq/L)						
Doses(mg/kg)	0	312.5	625	1250	2500	5000
w_0	137.3±2.25	139.5±1.97	140.33±2.4	139.3±3.26	138.5±2.66	138.83±2.22
w_1	138.83±2.2	140±2.6	141.16±1.6	139.16±1.7	139±1.11	140.6±1.5
w_2	140.2±2.48	139.5±2.34	139.83±2.8	140.33±2.7	142.3±2.65	141.5±2.94
w_3	141.5±3.14	141.3±2.16	139.5±1.51	141.16±3	141.5±4.27	142.16±1.33
w_4	139±2.96	140.8±1.47	140±1.67	141.33±2	141.6±3.94	142.65±2.16
w_5	141.5±2.88	142.66±1.0	141±2.68	141±1.41	142±2.19	142.83±2.13
w_6	142.3±2.87	141.16±1.6	141.16±1.9	142.16±2.4	143.1±1.73	143±1.78
Lots	Lot $_1$	Lot $_2$	Lot $_3$	Lot $_4$	Lot $_5$	Lot $_6$

Values are expressed as mean ± S.E.M (n = 6); P > 0.05 compared to control and to w_0 level.
w_0: Week preceding the first application of treatment; w_1 to w_6: Weeks of treatment.

In lot 3, serum sodium rate was 140.33±2.4 mEq/L before treatment. This value varied from 139.5±1.51 mEq/L (minimum w_3) to 141.16±1.9 mEq/L (maximum w_6). These variations correspond to -0,59 % (w_3) to 0.59 % (w_6). In group 4, serum sodium rate was 139.3±3.26 mEq/L during w_0. The percentage change during the 6 weeks of treatment is -0, 12 % (w_1) to 2, 03 % (w_6) and those recorded in batches 5 and 6 are respectively 0,38 % (w_1) to 3,34 % (w_6) and 1,32 % (w_1) to 3,00 % (w_6). The statistical analysis shows no significant change in serum sodium with different doses (P > 0.05).

Potassium

The serum potassium at w_0 was 3.94±0.46 mEq/L in the untreated lot**.** This value which varies over time between 3.75±0.41 mEq/L (minimum w_4) and 3.91±0.1 mEq/L (maximum w_6), represents a variation of -4,82 % (w_4) to -0,59 % (w_6) of the initial rate of potassium. In batch 2 (312.5 mg / kg), serum potassium

was 3.75±0.34 mEq/L before treatment. Over the past six weeks, the rate changed from 3.73±0.34 mEq/L (minimum w_5) to 4.08±0.19 mEq/L (maximum w_2). These values correspond to variations of -0,44 % (w_5) to 8,89 % (w_2) of the initial serum potassium (Table 5).

Table-5: Effect of AEEA on the levels of serum potassium (mEq/L) over time in rabbits

Serum concentrations of potassium (mEq/L)						
Doses(mg/kg)	0	312.5	625	1250	2500	5000
w_0	3.94±0.46	3.75±0.34	4±0.33	3.85±0.26	4.03±0.22	3.81±0.18
w_1	3.8±0.46	3.95±0.29	3.91±0.13	4±0.26	3.91±0.13	3.98±0.18
w_2	3.86±0.32	4.08±0.19	3.8±0.13	3.96±0.24	3.86±0.16	4.05±0.25
w_3	4±0.41	3.91±0.22	3.98±0.21	3.88±0.13	4.01±0.09	4.28±0.16
w_4	3.75±0.41	3.96±0.23	4.03±0.23	3.96±0.19	4.13±0.22	4.36±0.17
w_5	3.81±0.29	3.73±0.34	3.95±0.12	4.05±0.12	4.21±0.36	4.43±0.23*
w_6	3.91±0.1	3.93±0.19	4.05±0.37	3.91±0.15	4.3±0.16	4.65±0.08*
Lots	Lot $_1$	Lot $_2$	Lot $_3$	Lot $_4$	Lot $_5$	Lot $_6$

Values are expressed as mean ± S.E.M (n = 6); * P < 0.05 compared to control and to w_0 level.
w_0: Week preceding the first application of treatment; w_1 to w_6: Weeks of treatment.

Before treatment, serum potassium rate was 4±0.33 mEq/L in lot 3. This value varied from 3.8±0.13 (minimum w_2) to 4.05±0.37 mEq/L (maximum w_6). These variations represent -5% (w_2) to 1.25 % (w_6).

In group 4, serum potassium rate was 3.85±0.26 mEq/L during w_0. The percentage change during the 6 weeks of treatment is 0, 86% (w_3) to 5.19 % (w_5).

The percentage changes so recorded in batches 5 and 6 are respectively -4.13% (w_2) to 6.61 % (w_6) and -6.11 % (w_1) to 21.83% (w_6).

The statistical analysis shows a significant change in serum sodium with different doses ($P < 0.05$) especially with the dose of 5000 mg / kg bw (lot 6) in the fifth and sixth week.

Discussion

Variations in serum activities of enzymes stored in different batches before treatment and those recorded in the control group (batch 1) which has not undergone any treatment are in conformity with the usual values obtained in rabbits [11].

Statistical analysis of the results indicates that the acetal extract of AEEA with the doses between 0 and 5000 mg / kg body weight for six weeks, don't lead a significant change in serum magnesium, phosphorus, chloride and sodium. But there is a significant change in serum potassium and calcium. These variations are more pronounced with the dose of 5000 mg/kg/body weight especially during fifth and sixth weeks.

Potassium and calcium are substantially removed from the blood by glomerular filtration. The concentrations of these metabolites in urine are regulated by the kidney which has a real role of blood filter. It is also established that the glomerular filtration rate is dependent on the pressure in the glomerular capillaries about 30 mm Hg. The decline in blood pressure can cause a decrease in glomerular pressure about 10 mmHg. Any decrease in blood pressure may decrease plasma volume filtered by the kidney. Thus, ionic concentrations which are not correctly eliminated increase in the blood. That is here the case of potassium and calcium. This is one of the leading causes of kidney failure [12-15].

Many authors highlighted the link between changes in blood pressure and the occurrence of renal failure [16-18]. This phenomenon has been described with other plants such as *Phyllanthus amarus* (Euphorbiaceae) and *Mitracarpus scaber* (Rubiaceae) [19-21]. This could therefore suggest an induction of renal dysfunction with very high doses of acetal extract of *Entadrophragma angolense* (AEEA). These observations confirm to wish that the kidney may play a key role in the elimination of the acetal extract of *E. angolense.*

Conclusion

In conclusion the use of high doses (5000 mg / kg bw) of acetal extract of *E. angolense* could lead ionic disturbs. This study suggests that a reduction of the dose (2500 mg / kg bw) and time of treatment (4 weeks) may help to avoid ionic disturbs in the long term. We note that with this dose of 2500 mg / kg which is much higher than the antioxidant dose (48,704 ± 1.295 mg/kg), *E. angolense* always keep a safety margin very interesting. However, it is necessary that the traditional use of this plant in decoction to relieve various ailments must be rationalized. Moreover, in order to better understand all aspects of bio-tolerance, it would be necessary to carry out further studies including cardiovascular and liver tolerance as well as, urinary metabolites and hematological investigations.

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Conflict of interests

The authors claim that there is no conflict of interest.

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