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Assessment of serum ionic profiles in rabbits treated with aqueous extract of *Mareya micrantha* (Euphorbiaceae)

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Abstract
We investigated the ionic disturbs of *Mareya micrantha* (Euphorbiaceae) in rabbits. It is a plant traditionally used against dermatoid affections and for its laxative, abortive and oxytocic properties in Côte d'Ivoire and elsewhere in West Africa. For this study, different batches of rabbits were injected with increasing doses of aqueous extract of *Mareya micrantha* (MAR). Then changes in serum calcium, magnesium, chloride, sodium and potassium were evaluated. This study showed that the use of the aqueous extract of *Mareya micrantha* with doses between 12.5 and 200 mg / kg body weight (bw) in rabbits causes a significant variation ($P < 0.05$) of calcium serum concentrations. But there is no significant change ($P > 0.05$) of magnesium, chloride, sodium and potassium serum concentration. Finally, this study suggests that a reduction of the dose (100 mg / kg) and time of treatment (4 weeks) may help to avoid ionic disturbs other time. This dose of 100 mg /kg/bw which is much higher than the therapeutic dose, confer on *Mareya micrantha* a safety margin 200 (Tolerate Maximum Dose/ Therapeutic dose) very interesting.

Keywords: *Mareya micrantha*, calcium, magnesium, chloride, sodium, potassium

1. Introduction
In Côte d'Ivoire, as elsewhere in West Africa, traditional medicine occupies a prominent place despite the advances of modern medicine. The survival and intensification of this practice are linked to several factors among which we can cite: economic constraints, socio-cultural data and the high availability of plants. They are everywhere and are part of the living environment of the populations. Today, it is estimated that more than 80% of the African population uses medicinal plants for treatment [1].
However, these intensive uses of medicinal plants expose the user populations to real risks of therapeutic accidents. 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]. This study aims to make a contribution in this direction by studying ionic disturbs induced by the aqueous extract of *Mareya micrantha* (Euphorbiaceae) in the rabbits. *Mareya micrantha* (MAR) is a plant traditionally used against dermatoid affections and for its laxative, abortive and oxytocic properties in Côte d'Ivoire and elsewhere in West Africa. It also has remarkable cradiodepressive and hypotensive properties [4, 5].
The excellent results of pharmacological tests predispose MAR to be an excellent candidate drug in the management of cardiovascular diseases. Insofar as it is well known that hydro-mineral imbalances are the inherent side effects of several medicines, it has become essential to check whether or not MAR is escaping this reality. Hydromineral imbalances that are induced by several drugs can have serious consequences such as latent metabolic acidosis that directly affects the transport of oxygen and cell nutrition. Decreased enzymatic activity, impairment of the immune system constituting a ground conducive to the emergence of many diseases such as: the risks of osteoporosis, cardiac, metabolic and thyroid disorders [6, 7, 8]. Acute and subacute toxicity of MAR in the Swiss mouse have been evaluated. The results made it possible to obtain toxicological parameters such as the lethal dose for 50% (LD_{50}= 540 mg/kg of body weight), the lethal dose for 100% (LD_{100} = 1000 mg/kg bw) while the maximum tolerated dose (MTD) of the aqueous extract of MAR is 200 mg / kg of body weight [9]. In the logical continuation of this work, we wanted to deepen the state of knowledge on bio-tolerance of MAR during this study. More specifically, it is to assess the ionic disturbs of the

aqueous extract of MAR 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 [10, 11].

2. Material and Methods

2.1 Plant material

The leaves of *Mareya micrantha* (Euphorbiaceae) collected from Daloa (South-west, Côte d'Ivoire) were identified by the National Floristic Center of University Felix Houphouet-Boigny (Cocody-Abidjan).

2.2 Experimental animals

Rabbits, *Oryctolagus cuniculus* (36) of 8-10 weeks old, weighing 1.17±0.22 kg and bred at the Department of Biosciences, University Felix Houphouet Boigny (Abidjan, Ivory Coast), were used for the experiments. They come from a rabbit cattle farm in Bingerville (Ivory Coast). 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 [12].

2.3 Preparation of aqueous extract of *Mareya micrantha* (Euphorbiaceae)

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 distilled water for 48 hours on a magnetic agitator (IKAMAG RCT). 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 greenish powder used to prepare the aqueous extract of MAR.

2.4 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, five experimental groups have received doses ranging from 12.5 to 200 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 12.5; 25; 50; 100 and 200 mg/kg of bw.

Blood samples were collected in the morning (from 8 to 11 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 JOUAN. Serum ions were measured with an automatic analyzer, LIASIS while sodium and potassium have been measured with spectrophotometer flamme SEAC *fp* 20.

2.5 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.

2.6 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 ($P>0.05$).

3. 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 88.7±1.03 mg/L in the untreated lot (lot1). This value varies over time between 87.17±7.4 mg/L (minimum w_2) and 89.67±2.3 mg/L (maximum w_5), representing a change of -1.69% (w_2) to 1.13% (w_5) of the initial rate of serum calcium**.** In lot 2 (12.5 mg / kg), serum calcium was 90±0.89 mg/L before treatment. Over the past six weeks, the rate changes of 89.3±4.84 mg/L (minimum w_2) to 91.17±4.8 (maximum w_1). These values correspond to variations of -0.74% (w_2) to 1.29% (w_1) (Table 1).

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

Serum concentrations of calcium (mg/L)						
Doses (mg/kg)	**0**	**12.5**	**25**	**50**	**100**	**200**
w_0	88.7±1.03	90±0.89	90.2±1.72	90.8±1	90.3±0.52	89.33±0.52
w_1	88±7.38	91.17±4.8	86.3±6.59	88.8±5.04	92.5±1.22	90.83±6.43
w_2	87.17±7.4	89.3±4.84	85.3±3.61	88.1±4.12	90.6±5.89	92.67±1.63
w_3	88±4.98	89.3±3.61	86.7±3.83	92±1.83	89.6±4.08	93±3.22
w_4	89.5±2.95	90.67±6.2	87.8±6.47	89.1±7.19	91±4.1	94±2.19
w_5	89.67±2.3	89.67±2.7	91.67±2.1	91.8±2.9	92±2.53	96.8±1.47*
w_6	88.67±2.2	89.5±6.25	90.3±1.4	92±1.72	93.67±2.8	97.67±0.5*
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 90.2±1.72 mg/L before treatment. This value varied to 85.3±3.61 (minimum w_2) to 91.67±2.1 mg/L (maximum w_5). These evolutions represent variations of -5.36% (w_2) to 1.66% (w_5).
Percentage changes as recorded in lots 4, 5 and 6 are respectively: -2.94% (w_1) to 1.47% (w_3, w_6); -0.74% (w_3) to 3.69% (w_6) and 1.68% (w_1) to 9.33% (w_6).
Statistical analysis of the results indicates a significant change in serum calcium (P <0.05), especially with the dose of 200 mg / kg bw (lot 6) in the fifth and sixth week.

Magnesium

The serum magnesium (w_0) was 19.5±0.84 mg/L in the untreated group (group 1). This value which varies over time to 18±1.3 (minimum w_4), represents -7.69% (w_6) variation of the initial serum magnesium. In lot 2 (12.5 mg / kg), serum magnesium was 18.33±1.5 mg/L before treatment. Over the past six weeks, the rate changed of 18.17±0.9 (minimum w_5) to 19±1.26 mg/L (maximum w_2 w_6). These values correspond to variations of -0.91% (w_5) to 3.96% (w_2, w_6) (Table 2).

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

Serum concentrations of magnesium (mg/L)						
Doses (mg/kg)	**0**	**12.5**	**25**	**50**	**100**	**200**
w_0	19,5±0.84	18.33±1.5	19.1±0.98	18.6±1.37	18.83±0.9	19±0.89
w_1	19.5±0.55	18.5±0.84	19±0.89	19.1±0.75	17.67±1	18.17±1.17
w_2	18.33±1.3	19±1.26	18.8±1.47	18.3±1.86	18.5±1.38	19±0.89
w_3	19±0.89	18.3±0.82	18.6±0.51	18±1.26	17.3±1.37	17.5±0.84
w_4	18.67±1.3	18±2.28	19.6±0.51	18±1.41	16.67±2.3	17±2
w_5	18±0.63	18.17±0.9	18±0.89	19±1.55	17.33±1.7	19±0.89
w_6	18.5±2.76	19±1.26	18.33±1.6	19±0.89	18.67±1.5	19.33±1.03
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 19.1±0.98 mg/L during the week before treatment (**w_0**). This value changed from 18±0.89 (minimum w_5) to 19.6±0.51 mg/L (maximum w_4). These variations represent -6.09% (w_5) to 2.61% (w_4).
Percentage changes as recorded in batches 4, 5 and 6 are respectively: -3.57% (w_3, w_4) to 2.68% (w_1); -7.96% (w_3 w_5) to -0.88% (w_6) and -10.53% (w_4) to 1.75% (w_6) of the initial serum magnesium.
The statistical analysis shows no significant change in serum magnesium with different doses ($P > 0.05$).

Chloride

The serum chloride at w_0 was 98.67±1.97 mEq/L in the untreated lot**.** This value which varies over time between 98.5±1.64 mEq/L (minimum w_1) and 102±3.1 mEq/L (maximum w_6), represents a variation of -0.17% (w_1) to 3.38% (w_6) of the initial rate of chloride.
In batch 2 (12.5 mg / kg), serum chloride was 98.67±1.97 mEq/L before treatment. Over the past six weeks, the rate changed from 97.83±1.6 mEq/L (minimum w_1) to 103±0.63 mEq/L (maximum w_6). These values correspond to variations of -0.84% (w_1) to 4.39% (w_6) of the initial serum chloride (Table 3).

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

Serum concentrations of chloride (mEq/L)						
Doses (mg/kg)	**0**	**12.5**	**25**	**50**	**100**	**200**
w_0	98.67±1.97	98.67±1.97	100±1.41	101±2.53	101±1.9	100.16±2.22
w_1	98.5±1.64	97.83±1.6	98.83±0.98	100.8±1.16	99±1.41	98.8±2.22
w_2	99.33±1.86	98.67±1.86	99.67±1.03	100.6±2.33	99±1.78	100±1.26
w_3	99.33±1.51	98.5±1.22	98±0.89	101.5±2.50	100±1.67	99.3±1.86
w_4	100.2±0.75	99±2	99.33±1.36	99.5±1.64	101±2.53	101.16±1.47
w_5	101.3±1.37	100.5±1.64	100.5±1.22	100.6±1.86	102±2	102±1.79
w_6	102±3.1	103±0.63	100.16±1.6	101.3±2.65	100.8±2.13	102±2.28
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 chloride rate was 100±1.41 mEq/L in lot 3. This value varied from 98±0.89 (minimum w_3) to 100.5±1.22 mEq/L (maximum w_5). These variations correspond to -2% (w_3) to 0.5% (w_5). In group 4, chloride serum rate was 101±2.53 mEq/L during w_0. The percentage change during the weeks of treatment is -1.49% (w_4) to 0. 5% (w_3).

The percentage changes so recorded in batches 5 and 6 are respectively -1.98% (w_1 w_2) to 0.99% (w_5) and -1.33% (w_1) to 1.83% (w_5, 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 138.3±2.34 mEq/L in the untreated lot**.** This value which varies over time between 138±2.76 mEq/L (minimum w_4) and 141.5±3.14 mEq/L (maximum w_3), represents a variation of -0.24% (w_4) to 2.29% (w_3) of the initial rate of sodium.

In batch 2 (12.5 mg / kg), serum sodium was 140.8±1.83 mEq/L before treatment. Over the past six weeks, the rate changed from 138.6±2.16 mEq/L (minimum w_3) to 142±1.41 mEq/L (maximum w_1). These values correspond to variations of -1.54% (w_3) to 0.82% (w_1) of the initial serum sodium (Table 4).

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

Serum concentrations of sodium (mEq/L)						
Doses (mg/kg)	**0**	**12.5**	**25**	**50**	**100**	**200**
w_0	138.3±2.34	140.8±1.83	141±1.26	139.6±1.36	138.5±2.66	139.6±1.86
w_1	140.3±1.5	142±1.41	140.5±0.83	138.6±1.03	139±1.11	140.6±1.5
w_2	140.2±2.48	139.8±0.75	140.8±2.23	142.1±0.75	141.83±2.5	138.8±1.33
w_3	141.5±3.14	138.6±2.16	139.5±1.51	138.6±1.75	142.1±3.4	142.16±1.33
w_4	138±2.76	140.8±1.47	140±1.67	139.8±1.8	142.8±2.79	139.5±2.07
w_5	139.8±1.72	140.8±1.83	139.1±1.47	141.7±1.41	143.3±1.63	141.3±1.37
w_6	139.3±1.63	140.5±0.84	142±1.26	139.3±1.21	142.1±2.63	142±2.1
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 sodium rate was 141±1.26 mEq/L in lot 3. This value varied from 139.1±1.47 mEq/L (minimum w_5) to 142±1.26 (maximum w_6) mEq/L. These variations correspond to -1.3% (w_5) to 0.71% (w_6). In group 4, serum sodium rate was 139.6±1.36 mEq/L during w_0.The percentage change during the 6 weeks of treatment is -0.72% (w_1, w_3) to 1.79% (w_2) and those recorded in batches 5 and 6 are respectively 0.38% (w_1) to 3.49% (w_5) and -0.6% (w_2) to 1.79% (w_3).

The statistical analysis shows no significant change in serum sodium with different doses ($P > 0.05$).

Potassium

The serum potassium at w_0 was 4±0.49 mEq/L in the untreated lot**.** This value which varies over time between3.88±0.33 mEq/L (minimum w_2) and 4.01±0.41 mEq/L (maximum w_3), represents a variation of -2.92% (w_2) to 0.42% (w_3) of the initial rate of potassium.

In batch 2 (12.5 mg / kg), serum potassium was 3.96±0.32 mEq/L before treatment. Over the past six weeks, the rate changed from 3.85±0.18 mEq/L (minimum w_3) to 4.01±0.35 mEq/L (maximum w_1). These values correspond to variations of -1.7% (w_3) to 2.55% (w_1) of the initial serum potassium (Table 5).

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

Serum concentrations of potassium (mEq/L)						
Doses (mg/kg)	**0**	**12.5**	**25**	**50**	**100**	**200**
w_0	4±0.49	3.96±0.32	4.06±0.36	3.8±0.2	4±0.25	3.96±0.27
w_1	3.92±0.29	4.01±0.35	3.86±0.12	3,86±0.37	3.97±0.18	3.9±0.15
w_2	3.88±0.33	3.98±0.15	3.91±0.19	4.08±0.28	3.95±0.2	4.33±0.2
w_3	4.01±0.41	3.85±0.18	4.08±0.28	3.85±0.16	3.93±0.08	4.05±0.16
w_4	3.98±0.23	3.93±0.24	3.95±0.25	3.93±0.21	4.18±0.24	4.06±0.13
w_5	3.96±0.2	3.98±0.27	4.01±0.13	4±0.19	4.21±0.36	4.26±0.23
w_6	3.96±0.18	3.85±0.16	3.96±0.39	3.96±0.22	4.13±0.26	4.21±0.17
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 4.06±0.36 mEq/L in lot 3. This value varied from 3.86±0.12 (minimum $w_{1)}$ to 4.08±0.28 mEq/L (maximum w_3). These variations represent -4.92% (w_1) to 0.41% (w_3).

In group 4, serum potassium rate was 3.8±0.2 mEq/L during w_0. The percentage change during the 6 weeks of treatment is 1.32% (w_3) to 7.47% (w_2).

The percentage changes so recorded in batches 5 and 6 are respectively -1.67% (w_3) to 5.42% (w_5) and -1.68% (w_1) to 9.24% (w_2).

The statistical analysis shows no significant change in serum sodium with different doses ($P > 0.05$).

4. 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 [13].

Statistical analysis of the results indicate that the aqueous extract of MAR with the doses between 0 and 200 mg / kg body weight for six weeks, don't lead a significant change in serum magnesium, phosphorus, chloride, sodium and

potassium. But there is a significant change in serum calcium. These variations are more pronounced with the dose of 200 mg/kg/body weight especially during the fifth and sixth week. Calcium is 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 calcium. This is one of the leading causes of kidney failure [14-16].

In fact, the link between changes in blood pressure and the occurrence of renal failure have been revealed by many authors [17-19]. This phenomenon has been described with other plants such as *Phyllanthus amarus* (Euphorbiaceae) and *Mitracarpus scaber* (Rubiaceae) [20, 21]. This could therefore suggest an induction of renal dysfunction with very high doses of the aqueous extract of MAR. Indeed, MAR would have a cardiodepressant activity on isolated rat heart coupled with an hypotensive effect on blood pressure at 4.5 mg / L.

In addition, the metabolism of several well-known calcium antagonists such as nifedipine and verapamil indicate that the kidney plays an important role in eliminating them. For example, 70-80% of nifedipine is excreted by the kidneys, more than 90% of this amount is recovered in the urine after 24 hours, while the metabolites of verapamil, are excreted exclusively via the kidney for 70% [22, 23]. These data confirm to wish that the kidney may play a key role in the elimination of the aqueous extract of *Mareya micrantha* like that of some calcium antagonists.

5. Conclusion

At the end of this work, it appears that the use of high doses of aqueous extract of *Mareya micrantha* (more than 100 mg / kg bw) could lead ionic disturbs. This study suggests that a reduction of the dose (100 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 100 mg / kg which is much higher than the therapeutic dose (0, 5 mg/kg), *Mareya micrantha* always keep a safety margin of 200 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. Finally, the impact on parathyroid hormone which regulates phosphocalcic metabolism deserves to be evaluated carefully.

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7. Conflict of interests

The authors claim that there is no conflict of interest.

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