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Heart Tolerance Study of Aqueous Extract of *Mitracarpus scaber* in Rabbits

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Abstract: The purpose of this study was to evaluate the cardiac safety of *Mitracarpus scaber* (Rubiaceae) in rabbit. It is a plant traditionally used to treat skin diseases and various ailments in Côte d'Ivoire and elsewhere in West Africa. For this study, we injected different batches of rabbits with increasing doses of aqueous extract of *Mitracarpus scaber* (encoded Misca). Subsequently, changes in the activities of serum glutamic oxaloacetic transaminase (GOT), lactate deshydrogenase (LDH) and creatine phosphokinase (CPK) were measured. The statistical analysis of the serum activities of these enzymes indicate a significant variation ($P<0.05$) of the serum activity of CPK and LDH. But there is no significant change of serum activity of GOT ($P>0.05$). In conclusion, the aqueous extract of Misca at dose of 100 mg/kg body weight for 4 weeks induces no cardiac dysfunction and is therefore well tolerated by the heart.

Keys words: Mitracarpus Scaber · Heart · GOT · LDH · CPK

INTRODUCTION

Traditional medicine has a preponderant place in the treatment of various diseases as well as in Côte d'Ivoire, in Africa and around the world. The pharmacological activity of several medicinal plants have been the subject of several studies[1-5]. However, the therapeutic use of plant is not always without danger to the user populations. The traditional use of plants may cause many therapeutic accidents [6]. Among the causes of these accidents we can mention ignorance of doses of extracts administered empirically as well as their biochemical, pharmacological and toxicological properties [7, 8].

It seems important to make a contribution in the direction of the value of these medicinal plants by studying the toxicity of the extracts administered and their impact at some vital organs such as the heart. This is the case of *Mitracarpus scaber* (Rubiaceae), a plant traditionally used in Côte d'Ivoire and elsewhere in Africa to treat sores, ringworm and various diseases.

The antifungal and antibacterial activities of *Mitracarpus scaber* (encoded Misca) has been highlighted by several studies [9- 13]. It has a marked activity on 12 germs among which we can quote: *Cryptococcus, Aspergillus, Trichophyton, Candida, Staphylococcus, E. coli*, which are opportunistic pathogens of AIDS. Minimum Fungicidal Concentration (MFC) of Misca is 0.20 mg/mL while IC_{50} is 0.10 mg/mL [14-17]. In addition to dermatitis, the cardiodepressive and hypotensive effects has been studied [18].

Given the excellent results of pharmacological tests and the wide use of this plant, a rationalization of its use is required in view of its use in cardiovascular therapeutics. The heart is a very important organ which plays a dominant role in blood circulation. The high cardiac blood flow predisposes heart to toxic drug injury. That is why it is important to investigate biochemical and toxicological activity of the extracts of *Mitracarpus scaber* (Rubiaceae), on this key organ.

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The present study aims to evaluate the cardiac safety of the aqueous extract of Misca following changes of three serum specific parameters in rabbits: glutamic oxaloacetic transaminase (GOT), lactate deshydrogenase (LDH) and creatine phosphokinase (CPK).

Variations in these enzymes can thus assess the impact of this extract on heart function [19- 21].

MATERIAL AND METHODS

Plant Material: The leaves of *Mitracarpus scaber* (Rubiaceae) collected from Abobo-Adjame Campus University (Abidjan) and in some peripheral areas of Abidjan (Côte d'Ivoire) were identified by Professor Ake Assi Laurent of Department of Botany, University of Cocody-Abidjan. A voucher specimen was deposited in the herbarium (N° 13612) of the National Floristic Center of University of Cocody-Abidjan.

Animals: Rabbits, *Oryctolagus cuniculus* (36) of 8-10 weeks old, weighing 1.17± 0,22 kg and bred at the Department of Biosciences, University of Cocody, Ivory Coast, were used for the experiments. They come from a rabbit cattle farm in Bingerville (Abidjan). 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 of Cocody-Abidjan. These guidelines were in accordance with the European Council Legislation 87/607/EEC for the protection of experimental animals [22].

Preparation of Aqueous Extract of *Mitracarpus scaber* (Rubiaceae): Plant harvested were air dried at room temperature (28±1°C) for one month. The dried leaves were ground into fine powder. 100 g of powder were 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 Misca.

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 b.w (which is the Maximum Tolerated Dose (MTD) of the aqueous extract) in a geometric progression of ratio 2 [23]. 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 b.w.

Blood samples were collected in the morning (from 8 to 11 am) 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 (S0), during the five weeks of treatment (S1, S2, S3, S4, S5 and S6). These blood samples were collected in sterile tubes without anticoagulant. They were centrifuged at 3000 rpm for 10 min using a liquidizer Jouan.

Assay for Serum Activities of GOT, LDH and CPK: The principles of the determination of each parameter are described according to the manufacturer's instructions reagents. Heart parameters of the serum were measured with an automatic analyzer, Liasis.

GOT formerly called Aspartate aminotransferase (AST) catalyses the reversible transfer of an amino group from aspartate to α-ketoglutarate forming glutamate and oxaloacetate. The oxaloacetate produced is reduced to malate by malate deshydrogenase (MDH) and NADH. The rate of decrease in concentration of NADH, measured photometrically, is proportional to the catalytic concentration of GOT present in sample.

LDH catalyses the reduction of pyruvate by NADH. The rate of decrease in concentration of NADPH, measured photometrically, is proportional to the catalytic concentration of LDH.

CPK catalyses the reversible transfer of phosphate group from phosphocreatine to ADP. The rate of formation of NADPH + H^+, measured photometrically, is proportional to the catalytic concentration of CPK present.

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 biochemical markers 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 activity of GOT, LDH and CPK expressed in tables (1, 2 and 3) are averages of six assays performed in each group.

The serum activity of GOT was 24±3 UI / L in the untreated lot (lot1). This value varied over time between 24.7±2.6 UI / L (minimum S_1) and 36.8±3.7 UI / L (maximum S_3), representing a change of 3.05 % (S_1) to 53.2 % (S_3) of the initial serum rate activity of GOT (Table 1). In group 2 (12.5 mg / kg), serum activity of GOT was 30.8±1.3 UI / L before treatment. Over the past six weeks, the rate varied of 26.7±2.3 UI/L (minimum S_1) to 36.7±3.5 UI/L (maximum S_3). These values correspond to variations of -13.3 % (S_1) to 18.92 % (S_3).

Percentage changes registered in groups 3, 4, 5 and 6 are respectively-10.5% (S_2) to 12.5% (S_3); -27.32% (S_3) to 2.11% (S_6); -22.63% (S_1) to 2.86% (S_6) and 0.86 % (S_1) to 23.92% (S_6) (Table 2).

The statistical analysis shows no significant change in serum activity of GOT with different doses (P>0.05).

The serum activity of LDH was 853±74.7 UI / L in the untreated lot (lot1). This value varied over time between 787± 63.2 UI / L (minimum S_2) and 1060 ±70. 3 UI / L (maximum S_3), representing a change of -7.73 % (S_2) to 24.26% (S_3) of the initial serum rate activity of LDH (Table 2).

In lot 2 (12.5 mg / kg), serum activity of LDH was 853±74.7 UI / L before treatment. Over the past six weeks, the rate changed of 863 ± 31.8 UI/L (minimum S_2) to 1060 ± 70.3 (maximum S_3). These values ??correspond to variations of 1.17% (S_2) to 24.26% (S_3).

Percentage changes registered in groups 3, 4, 5 and 6 are respectively-10.1% (S_3) to 9.09% (S_6); -20.17% (S_2) to -3.16% (S_5); -10.51% (S_5) to 6.64% (S_1) and -46.75 % (S_2) to 3.83% (S_1) (Table 2). Statistical analysis of the results indicate a significant change in serum activity of LDH (P <0.05), especially with the dose of 200 mg / kg bw (lot 6) in the fifth and sixth week.

The serum activity of CPK was 895±50.6 UI / L in the untreated lot (lot1). This value varied over time between 830±35 UI / L (minimum S_3) and 990 ±10 UI / L (maximum S_6), representing a change of -7.26 % (S_3) to 10.65% (S_6) of the initial serum rate activity ofCPK (Table 2). In lot 2 (12.5 mg / kg), serum activity of CPK was 800±28.9 UI / L before treatment. Over the past six weeks, the rate changed of 847±48.4 UI/L (minimum S_3) to 957±43 (maximum S_2). These values ??correspond to variations of 5.83% (S_3) to 19.58% (S_2).

Percentage changes registered in groups 3, 4, 5 and 6 are respectively -0.23% (S_2) to 29.65% (S_3); -7.78% (S_3) to 13.70% (S_2); -3.45% (S_6) to 4.06% (S_2) and -35.29 % (S_6) to -2. 16% (S_1) (table 2). Statistical analysis of the results indicate a significant change in serum activity of CPK (P <0.05), especially with the dose of 200 mg / kg b.w (lot 6) in the fifth and sixth week.

Table 1: Effect of Misca on the serum activities (UI/L) of GOT over time on rabbits

Serum activities of GOT (UI/L)						
Doses (mg/kg)	0	12,5	25	50	100	200
S_0	24±3	30.8±1.3	31.7±1.6	36.2±2.8	37.3±4.3	34.7±2.6
S_1	24.7±2.6	26.7±2.3	28.7±2.4	32±3	28.8±1.7	35±1.7
S_2	27.8±2.61	28.6±1.3	28.4±2.4	36.8±4.9	30.8±4.9	40±2.9
S_3	36.8±3.7	36.7±3.5	35.7±5.6	26.3±4.1	37.3±10.3	38.3±3.3
S_4	33.7±4.5	35.3±7.4	33±2.3	30.3±3.9	35±2	41.7±3.3
S_5	29.8±3.4	32.3±5	30.5±2.5	30±4	34.5±1.9	42±6.2
S_6	31.3±3	35.3±2	28.5±0.8	37±1.5	38.3±3.3	42.3±1.4
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 S_0 level

S_0: Week preceding the first application of treatment

S1 to S6: Weeks of treatment

Table 2: Effect of Misca on the serum activities (UI/L) of LDH over time on rabbits

Serum activities of LDH (UI/L)						
Doses (mg/kg bw)	0	12,5	25	50	100	200
S_0	853±74.7	853±74.7	990±63.5	1075±118	1060±176	1002±57.8
S_1	1027±112	1027±112	1065±30	1041±138	948±40	963.3±32
S_2	787±63.2	863±31.8	980±160	905±155	1130±101	940±66.5
S_3	1060±70.3	1060±70.3	890±49	1021±92	1097±38	939.3±37.7
S_4	1026±89.3	1026±89.3	1028±36	1040±31	1068±87	800±57.74
S_5	941±109	941±109	973±371	858±264	1095±64	550±28.87*
S_6	920±51.3	920±51.3	1080±60	1037±265	1028±88	533.3±33*
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 S_0 level

S_0: Week preceding the first application of treatment

S_1 to S_6: Weeks of treatment

Table 3: Effect of Misca on the serum activities (UI/L) of CPK over time on rabbits

Serum activities of CPK (UI/L)						
Doses (mg/kg)	0	12,5	25	50	100	200
S_0	895±50.6	800±28.9	860±85	900±57.7	820±45	850±73
S_1	850±29	850±132	933±36	892±51	806±58	832±37
S_2	840±41.6	957±43	858±96	1023±146	853±54	830±64
S_3	830±35	847±48.4	1115±250	830±35	842±68	795±5
S_4	834±42	893±52	947±42	880±15	802±71	788±58
S_5	904±63.4	887±60.5	900±58	872±91	815±57	583±60*
S_6	990±10	862±59.18	897±60.6	933±79.7	792±60	550±76*
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 S_0 level

S_0: Week preceding the first application of treatment

S_1 to S_6: Weeks of treatment

DISCUSSION

Variations in serum activities of enzymes stored in different batches before treatment and those recorded in the control group (lot1) which has not undergone any treatment are in conformity with the usual values obtained in rabbits [24].

Statistical analysis of the results indicate that the aqueous extract of Misca don't lead a significant change in catalytic activity of GOT (P> 0.05), although there was a slight increase in serum GOT activity with the dose of 200 mg/kg b.w (lot 6), especially in last weeks. This observation is corroborated by the fact the variations registered in lot 6 (0.86 to 23.92 %) are lower than those observed in the control group (3.05 to 53.2 %). These disturbances could be related to transient faults heart tissue or other organs such as liver or skeletal muscle where GOT is also present [19-21].

Regarding LDH, statistical analysis show a significant influence of doses in LDH serum activity (P<0.05). The use of aqueous extract of Misca at dose of 200 mg/kg b.w can lead a decrease in serum activity during last weeks. Generally, no particular damage is associated with serum LDH activity decrease. But there is a good correlation between the increase in serum LDH activity and the extent of necrosis of cardiac tissue [25].

As for the CPK, the statistical analysis of the results show a significant effect of reduction in serum CPK activity with the dose of 200 mg/kg b.w during last weeks. In view of these results, we can say this extract doesn't damage the tissue or heart muscle because elevated values of CPK are usually observed in myocardial infarction. This action could even be interpreted as a protective effect of the cardiovascular system by Misca. Among the signs defining coronary infarct one the most constant is the significant increase in CPK MB fraction

above. The determination of CK-MB and that of its isoforms is particularly useful for the myocardial infarction detection because of their stability and good sensitivity [26, 27]. The correlation between increase in serum CPK activity and the onset of myocardial infarction is so narrow that we can easily suppose that substances which stabilize or reduce the activity of CPK, as aqueous extract of Misca could have a possible cardioprotective effect. This observation agrees with the works realized on the aqueous extract of *Phyllanthus amarus* (Euphorbiaceae) by Coulibaly [28] who found that the total extract of this plant have a cardioprotective effect by reducing serum activity of CPK and LDH. Finally we can note that even if the dose of 200 mg/kg bw does not seem to cause any cardiovascular dysfunction, this dose favors increase in serum GOT activity especially during last weeks [29]. Consequently, it would be logical to recommend the use of dose 100 mg/kg bw and reduce processing time to 4 weeks.

CONCLUSION

In conclusion it appears that the use of aqueous extract of Misca at doses ranging from 12.5 to 200 mg/kg bw in rabbits caused a significant decrease activity ($P<0.05$) of CPK, LDH and no significant change in the serum activity of GOT ($P> 0.05$). Decreases in serum activity of CPK and LDH indicate that Misca does not induce specific lesion in the cardiac tissue. Better this action could be considered as a protective action of the heart. Misca is well tolerated by the heart. However, it is necessary to rationalize the traditional use of this plant by reducing the dose (100 mg/kg b.w) and time of treatment (4weeks). We note that with this dose of 100 mg/kg b.w which is much than the therapeutic dose, Misca always keep a safety margin very interesting. Given the interest that could have Misca in therapeutic management of cardiovascular disease, it would be interesting to assess blood electrolytes, to make hematological and histological analyses in order to better understand all aspects of heart tolerance of this plant.

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