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Mechanism of action of *Cola cordifolia* barks on the reproductive system of Wistar strain rats (*Rattus norvegicus*).

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Abstract:
Background*:*
This study aims to determine the mechanism of action of the aqueous extract of Cola cordifolia bark on the reproductive system of female rats
Methods.
In this study, 48 young ovariectomized rats were selected after weighing. The selected rats were divided into eight batches of six animals. Each batch was treated for seven days with different doses of extract. Batch 1 received distilled water (controls). The animals in lot 2 received olive oil. Batch 3, batch 4 and batch 5 received the doses of 50, 100 and 200 mg/Kg mc of aqueous extract of C. Cordifolia. Lot 6, lot 7 and lot 8 received respectively the doses 50, 100 and 200 mg/kg of mc of aqueous extract C. cordifolia associated with each, the dose of 2.10^{-2} mg/kg of bw of 17β-estradiol. At the end of the seven days of treatment, the animals were sacrificed. Fresh and dry masses of uterine horns and adrenal glands were determined, followed by analysis of serum hormone levels (LH, FSH and estradiol).
Results*: Aqueous extract of Cola cordifolia caused a significant (p> 0.05) increase in body mass of ovariectomized juvenile rats at 50 and 100 mg /kg body mass. Treatment of ovariectomized rats with estradiol alone or the combination of estradiol + 50 and 100 mg /kg body weight of the aqueous extract of Cola cordifolia showed a vaginal opening (100%) compared to that of controls treated with distilled water. At the same doses, the extract caused a significant (p<0.05) increase in fresh uterine horn mass. A highly significant increase (p<0.001) was recorded in LH level at the doses of 50 and 100 mg /kg of mc. As for serum FSH level, administration of aqueous extract showed a significant (above threshold) increase (p>0.05) at the dose of 200 mg / kg mc compared to controls.*
Conclusion: The results showed that the aqueous extract of C. cordifoliabarks would contain estrogenic substances or estrogen agonist substances. This extract would act by the central way (the hypothalamo-hypophyseal way) and by the peripheral way according to a dose-dependent mechanism with a strong estrogenic potential at doses 50 and 100 mg / kg of bw.

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I. Introduction

Humanity has always used medicinal plants to solve certain health problems [1]. The use of plants in the treatment of pathologies goes back several millennia [2]. The African pharmacopoeia has always been the main means of access to health care for populations living in regions without health centers[3]. In some African countries, more than 80% of the population use plants exclusively as a source of treatment [4]. Among the ills from which humanity suffers, infertility occupies an important place and often constitutes a reason for the separation of couples in Africa and psychological disorders in the West [5]. Infertility is the inability of a couple to procreate after one year of regular unprotected sexual intercourse [6]. According to Barillier, the causes of infertility can be female (30% of cases), male (20% of cases), mixed (40% of cases) or idiopathic (10% of cases)[7]. In several African countries, particularly in West Africa, the infertility rate is globally higher than 30%, whereas in the rest of the world, the frequency of infertile couples is on average 5%[8].Infertility is considered a real catastrophe for many couples, a real disaster especially in African countries. It is a real burden for the demography as well as for the happiness of a part of the population [9]. The treatments proposed by modern medicine to treat these diseases are often very expensive while their success rates are very low [10]. The use of

medicinal plants is an alternative way for rural populations to solve the problem of infertility. Plants used to treat infertility are not widely used in Sub-Saharan Africa [11]. While, to treat infertility, several plants have been studied and revealed an important estrogenic potentiality [12]. Some plants such as *C. cordifolia*, very well known in traditional medicine in the treatment of infertility have not received much attention. *C. cordifolia* is a plant of the Malvaceae family which is known for its activities in the treatment of many pathologies such as: fever, diarrhea, stomach pain, incurable wounds, lung diseases, but also to improve fertility in humans [13].The aim of this study is to determine the mechanism of actions of the aqueous extract of the bark of *C. cordifolia* on the reproductive system of female rats.

II. Material and Methods

Plant material.

The bark of Cola cordifolia (wâlè in Baule) was collected in May in the commune of Daoukro (Iffou department), in the central-eastern part of Côte d'Ivoire. A sample of this plant was identified at the Centre National Floristique (CNF) of the Université Felix Houphouët-Boigny under N°9837.

Animal material

The animal material used in the present study consisted of young female rats of the species Rattus norvegicus (Muridae) of Wistar strain. These animals come from the vivarium of the School Normal Superior (SNS) of Abidjan. The rats used were four to six weeks old and had a mass between 60 and 80 g. The animals were fed daily add libitum. The choice of this animal species was based on availability and sensitivity to estrogenic substances. These female rats were used to study the mechanism of action of Cola cordifolia on the reproductive system.

Method of extraction.

The fresh bark of *C.cordifolia* was washed and then air-dried in a room protected from the sun for two months. The dried peels were pulverized using an electric grinder type IAMAG-RCT®. A 50 g portion of the obtained powder was macerated in 1.25 l of distilled water five times three min in a blender (Single®, Singapore). The macerate was filtered three times on white cloth and then successively on absorbent cotton and on Wattman paper N°1. The filtrate obtained was evaporated in an oven at 50°C for 48 [14]. The extract obtained was used for different tests.

Treatment of young ovariectomized rats

Formulation of the ethinyl estradiol solution

Estradiol ethinyl was used as the reference molecule for the uterotrophic study of the aqueous extract of *C. cordifolia*. A mass of 50 µg of estradiol/tablet was gently ground. The resulting powder was mixed with virgin olive oil extract.The whole was carefully homogenized with a spatula. A concentration of 2.10^{-2}mg/kg bw (body mass) was taken in a volume of 1 ml of olive oil (virgin extract) and administered to each rat by gavage.

Administration protocol for the different substances

The young ovariectomized rats were divided into eight batches of six animals. Each batch was treated daily for seven days with different doses. Lot 1 (controls) received distilled water. Lot 2 animals received 17β-estradiol. Lots 3, 4, and 5 received 50, 100, and 200 mg/kg bw of aqueous extract of *C.cordifolia*, respectively. As for Batch 6, 7, and 8, they received 50, 100, and 200 mg/kg bw of aqueous *C.cordifolia* extract associated with the dose of 2.10^{-2} mg/kg bw of 17β-estradiol, respectively.

Treatment of ovariectomized animals.

The young ovariectomized rats were weighed daily for seven days. Each morning at a fixed time (08:00) during the 7 days of treatment, the young ovariectomized rats were inspected for the state of opening of the vaginal meatus. The number of young rats with an open meatus was recorded according to the treatment and the dose of products administered. Vaginal smears were taken on the seventh day of treatment on selected rats.

Effect of aqueous extract of *Cola cordifolia* on uterine horn and adrenal gland mass of young ovariectomized rats

On the 7th day of treatment and 24 h after the last dose, the animals in each batch were sacrificed by decapitation after ether anesthesia. The uterine horns and adrenal glands were removed by opening the abdominal cavity. These organs were rinsed in 0.9% NaCl, wrung out in paper towels, and weighed for fresh mass. These organs were subsequently oven dried at 100°C for 24 h and weighed again to determine the dry mass. To demonstrate estrogen agonists, measurements were made to determine the ratio of the average uterine mass of animals in the treated lots to that of animals in the control lot.

Effects of aqueous extract of *Cola cordifolia* on serum hormones of young ovariectomized rats

Blood collected from dry tubes was centrifuged at 3000 rpm for 4 min. An aliquot of serum was collected in Eppendorf tubes and kept in the freezer in order to assay pituitary hormones (LH and FSH) and gonadal hormone (estradiol) using a VIDAS type automaton (BIOMERIEUX, France).

Statistical Analyses

Statistical analyses were performed using Graph Pad Prism 7.0 software. The values were presented as means ± Standard Error on the Mean (SEM). The analysis of variance (ANOVA) applied to the results obtained allowed to assess the effects of the different treatments with a significance level of 5%. The Turkey-Kramer multiple comparison test and Student's t-test were used to make comparisons between the means.

III. Results

Effect of aqueous extract of *Cola cordifolia* on vaginal opening and epithelial cell presence in young ovariectomized rats

After seven days of treatment, ovariectomized rats treated only with aqueous extract of *Cola cordifolia* at doses of 50, 100 and 200 mg/kg bw showed 45, 68 and 37% vaginal opening, respectively. The values obtained with the extracts were not significant ($p>0.05$) compared with those of the controls given distilled water.

Ovariectomized rats that received estradiol only had their vaginas fully opened; i.e., a 100% opening rate. This value is significantly high ($p<0.05$) compared to that of ovariectomized rats treated only with aqueous extract of *Cola cordifolia* at different doses. In addition, administration of estradiol combined with the 100 mg/kg mc dose of the aqueous extract of *Cola cordifolia* showed 100% vaginal opening. This was highly significant ($p<0.001$) compared with that of ovariectomized rats given only distilled water. In contrast, combinations of estradiol ethinyl at doses of 50 or 200 mg/ kg bw yielded vaginal opening rates of 82 and 70%, respectively. The values obtained with the combinations of estradiol ethinyl and extracts were nosignificant ($p>0.05$) compared with those of controls that received only distilled water (Table I).In ovariectomized rats treated only with 50, 100, and 200 mg/ kg bw of aqueous extract of *C.cordifolia*, a significantly ($p< 0.05$) high number of eosinophilic cells was determined compared with controls (distilled water). No eosinophilic cells were determined in these same controls. Treatments combining estradiol +100 mg/kg bw of aqueous extract of *C. Cordifolia* showed a significant ($p<0.05$) number of eosinophilic cells compared to ovariectomized rats receiving estradiol alone. Treatments combining estradiol +50 mg and œstradiol+200mg/kg bw of aqueous extract of *C.cordifolia* showed no significant ($p>0.05$) difference in the number of eosinophilic cells compared to rats given estradiol only (Table I).

Table I: Effects of aqueous extract of *Cola cordifolia* on the opening and presence of epithelial cells in young ovariectomized rats

Traitements	Vaginal openings(%)	Presence of eosinophiliccells
Controls	0	_
EE	100	++
EACCD50	45	+
EACCD100	68	+
EACCD200	37	+
EE+EACCD50	82	++
EE+EACCD100	100	+++
EE+EACCD200	70	++

─: Absence of eosinophilic cells, +: Weak presence of eosinophilic cells, ++: Strong presence of eosinophilic cells, +++: Very strong presence of eosinophilic cells,

EE: Estradiol ethinyl (20µg / kg of body weight). EACC/D50: Aqueous extract of *Cola cordifolia* (50 mg /kg of body weight). EACC/D100: Aqueous extract of *Cola cordifolia* (100 mg /kg of weight). EACC/D 200: Aqueous extract of *Cola cordifolia* (200 mg /kg of weight). Data were presented as mean ± Error on Mean (EoM) (n=5/batch) Turkey test was used for comparisons to controls.

Effects of aqueous extract of *Cola cordifolia* on body mass of young ovariectomized rats.

The body mass of young ovariectomized rats treated with different doses (50, 100 and 200 mg/kg bw) of aqueous extracts of Cola cordifolia alone increased progressively during the seven days of treatment. However, this evolution of the mc of the controls was always higher than that of the young ovariectomized rats until the end of the treatment. Similarly, ethynil estradiol alone administered to young ovariectomized rats caused an increase in body mass compared to those treated with the combination of ethynil estradiol + 50, 100 and 200 mg/kg bw (Fig 1).

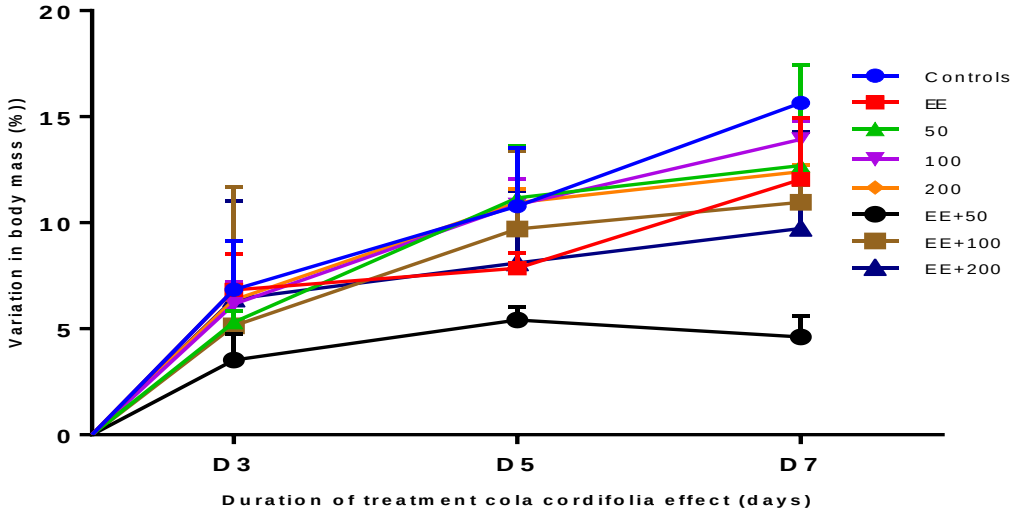

Fig 1: Effect of aqueous extract of Cola cordifolia on the body mass of young ovariectomized rats.

50: 50 mg/kg of *Cola cordifolia*, 100: 100 mg/kg of Cola cordifolia, 200: 200 mg/kg bw of *Cola cordifolia*. EE: Estradiol ethinyl (20.10-2mg / kg bw), EE +50 mg/ kg bw: Estradiol ethinyl (20.10-2mg / kg bw+50 mg/ kg bw of *Cola cordifolia*, EE + 100 mg/kg bw: œstradiolethinyl (20.10-2mg / kg bw) +100 mg/ kg bw of *Cola cordifolia*, EE+ 200 mg/ kg bw: œstradiolethinyl (20.10-2mg / kg bw) +200 mg/kg bw of *Cola cordifolia*, data were presented as mean ± Error on Mean (EoM) (n=5/batch) test Turkey was used for comparisons to controls.

Effect of aqueous extract of *Cola cordifolia* on fresh and dry weights of the adrenal gland and uterine horns in young ovariectomized rats

Young ovariectomized rats treated only with aqueous extract of *Cola cordifolia* at the dose of 100 mg/ kg bw caused a significant ($p < 0.05$) increase in adrenal gland fresh weights compared to those of controls given distilled water. This same dose, combined with ethinyl estradiol also resulted in a highly significant ($p < 0.001$) increase in the rats compared to those given ethinyl estradiol alone.

The dry masses of the adrenal glands of ovariectomized rats treated with different doses of aqueous extract of *C. cordifolia* on the one hand and the combination of estradiol + 50, 100 and 200 mg /kg bw of aqueous extract of *C. cordifolia* on the other hand, showed a non-significant ($p < 0.05$) reduction of these organs compared to that of the controls (Fig 2).

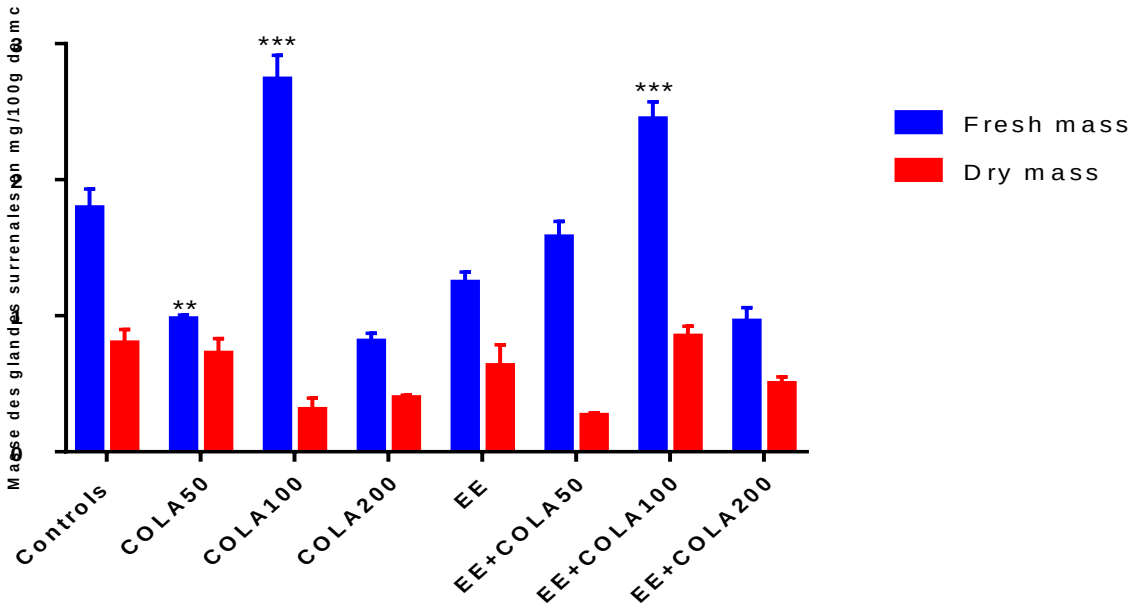

Fig 2: Effect of aqueous extract of *Cola cordifolia* on fresh and dry weight of adrenal glands.

COLA50: Aqueous extract of *Cola cordifolia* (50 mg/ kg b.w.); COLA100: Aqueous extract of Cola cordifolia 100 mg/kg bw; COLA200: Aqueous extract of *Cola cordifolia* 200 mg/ kg bw; EE+COLA50: Combination of Estradiol Ethinyl + 50 mg/ kg bw of the aqueous extract of *Cola cordifolia* 50 mg/kg bw; EE+COLA100: Combination of estradiol ethinyl + the aqueous extract of *Cola cordifolia* 100 mg/kg bw; EE+COLA200: Combination of estradiol ethinyl +200 mg/kg bw of the aqueous extract of *Cola cordifolia*. Data were taken as mean± Error on Mean (EoM) (n=6/lot). Turkey's test was used to make comparisons to the control: *: $p<0.05$; **$p<0.01$; ***$p<0.001$. For values without a star (*) $p>0.05$.

Fresh uterine horn masses were also evaluated in this study. Indeed, young ovariectomized rats treated with the aqueous extract of *C.cordifolia* at doses of 100 mg/kg of mc, as well as those with the combination of estradiol +50 or 100 mg /kg of mc of the aqueous extract of *C.cordifolia*showed a significant increase ($p < 0.05$; $p<0.001$) compared to controls treated with estradiol only. These uterine weights were very highly significant ($p<0.001$) compared with controls treated with distilled water. However, the fresh masses of the uterine horns of ovariectomized rats given the aqueous extract of *C.cordifolia* at the doses of 50 and 200 mg / kg mc did not vary significantly ($p > 0.05$) when compared to controls given distilled water.

Evaluation of uterine horn dry masses of treated ovariectomized juvenile rats showed no significant variation ($p> 0.05$) when compared to the control that received distilled water. However, rats that received the combination of estradiol ethinyl and *C.cordifolia* aqueous extract at the dose of 100 mg/kg bw to reveal a significant increase ($p < 0.05$) compared to the control treated with estradiol ethinyl alone (Fig 3).

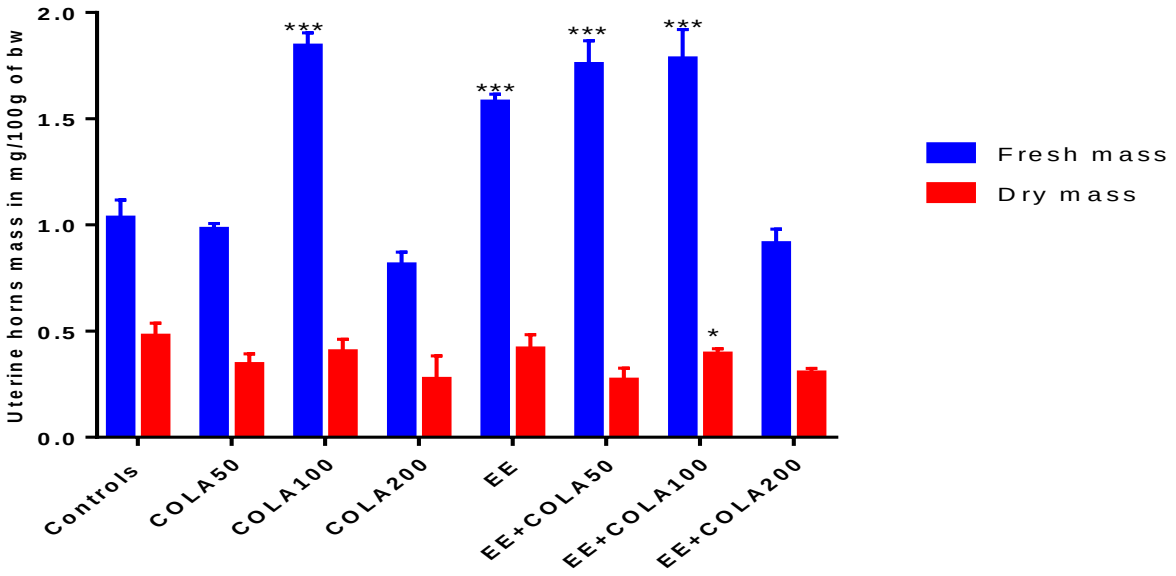

Fig 3: Effect of aqueous extract of *Cola cordifolia* on fresh and dry weight of uterine horns.

C. ut: Uterine horn; COLA50: Aqueous extract of Cola cordifolia 50 mg/kg bw; COLA100: Aqueous extract of Cola cordifolia 100 mg/kg bw; COLA200: Aqueous extract of Cola cordifolia (200 mg/kg bw; EE. +COLA50: Combination of Estradiol Ethinyl + 50 mg /kg bw of the aqueous extract of Cola cordifolia 50 mg/kg bw; EE+COLA100: Combination of Estradiol Ethinyl + the aqueous extract of Cola cordifolia 100 mg/kg bw; EE+COLA200: Combination of Estradiol Ethinyl +200 mg/kg bw of the aqueous extract of Cola cordifolia. Data were taken as mean± Error on Mean (EoM) (n=6/lot). Turkey's test was used to make comparisons to the control: (*): p<0. 05;**p<0. 01; ***p < 0.001. For values without a (*); p>0, 05.

Effect of aqueous extract of *C. cordifolia*on serum pituitary hormone (FSH and LH) and estradiol levels.

Young ovariectomized rats given aqueous extract of *C. cordifolia* alone, at doses of 50, 100 and 200 mg/kg bw showed highly significantly($p<0.001$) elevated serum FSH levels compared to the control (distilled water). The same results were observed with respect to serum LH levels. Administration of aqueous extract of *C. codifolia* alone at the dose of 200 mg/kg bw caused a very highly significant ($p < 0.001$) increase in serum LH level compared to the control. However, serum LH levels of young ovariectomized rats treated with 50 and 100 mg/ kg bw of aqueous extract of *C. cordifolia* alone were approximately equal to that of controls (<0.1mIU/ml). Young ovariectomized rats treated with 50 and 200 mg/ kg mc of the aqueous extract of *C. cordifolia* showed estradiol levels substantially equal to that of controls given distilled water (< 9.00). However,

in young ovariectomized rats, all doses of extracts (100 mg / kg mc of extract and the combination of estradiol ethinyl +100 mg / kg mc of aqueous extract of *Cola. Cordifolia* resulted in significantly ($p < 0.001$ and $p < 0.01$) elevated estradiol levels compared to that of controls obtained with distilled water and ethinylestradiol (Table II).

Table II: Effect of aqueous extract of *C. cordifolia* on pituitary (FSH and LH) and ovarian serum (estradiol) hormone levels

Treatments	FSH (mUI/ml)	LH (mUI/ml)	EE (Pg/ml)
Controls (distilled water)	< 0.1	< 0.1	< 9.00
COLA50 (50 mg/kg de pc)	0.47±0.063	< 0.1	<9±0.09
COLA100 (100 mg/kg de pc).	0.24±0.063	< 0.1	9.56±0.09***
COLA200 (200 mg/kg de pc).	1.46±0.25	0.32 ± 0.54	<9.00
EE (Pg/ml).	3.736±0.401	1.035 ± 0.77	12.18±2.09
EE+COLA50 (50 mg/kg de pc).	<0.1	0,1	8.003±2.476
EE+COLA100 (100 mg/kg de pc).	0.21	6.301±2.565	13.51±2.73**
EE+COLA200 (200 mg/kg de pc).	<0.33	0.45±0.08	7.56±1.38

COLA50: Aqueous extract of *Cola cordifolia* 50 mg/ kg bw; COLA100: Aqueous extract of *Cola cordifolia* 100 mg/ kg bw; COLA200: Aqueous extract of *Cola cordifolia* 200 mg/kg bw; EE+COLA50: Combination of Estradiol Ethinyl + 50 mg /kg bw of the aqueous extract of *Cola cordifolia*50 mg/kg bw; EE+COLA100: Combination of estradiol ethinyl + aqueous extract of *Cola cordifolia* 100 mg/kg bw; EE+COLA200: Combination of estradiol ethinyl +200 mg/kg bw of aqueous extract of *Cola cordifolia*. Data were pre-taken as mean±Error of Mean (EOM) (n=6/lot). Turkey's test was used to make comparisons to the control: (*): $p<0.05$; **$p<0.01$; ***$p<0.001$. For values without a star (*); $p>0.05$.

IV. Discussion

Determination of the body mass of young ovariectomized rats treated with aqueous extract of *C.cordifolia* at doses of 50, 100 and 200 mg/kg bw and the combination of ethinyl estradiol with 50, 100 and 200 mg/kg bw of *C.cordifolia* extract for seven days showed no significant difference ($p >0.05$) compared to controls. These results could suggest that the treatment time at these different doses would not be sufficient to induce the estrogenic effect to influence the mass of ovariectomized rats. These results are in agreement with those of Blahi [15]. This author showed that the body mass of ovariectomized immature rats treated with Sarcocephalus latifolius extract at different doses was proportional to that of those treated with 17ß-estradiol at 2.10^{-3} mg/kg of bw.

However, these results obtained on body mass differ from those of Kouakou [16]. Indeed, according to the work of this author, the treatment of young ovariectomized rats with Arachishypogaea and Phaseolus vulgaris extracts caused an increase in body mass

The results of the young ovariectomized rats administered only with the aqueous extracts of *C.cordifolia* at the doses of 50, 100 and 200 mg/kg bw showed a good early vaginal opening on the 07th day of treatment while in the young ovariectomized control rats receiving distilled water the vagina remained closed. The good early vaginal opening on the 07th day was also observed in the rats treated with the combination of ethinyl estradiol with 50 and 200 mg/kg of bw of *C.cordifolia* extract. On the other hand, treatment of ovariectomized rats with the combination of estradiol + 100 mg /kg de bw of aqueous extract of *C.cordifolia*, as well as those receiving estradiol alone induced a highly significant ($p < 0.001$) vaginal opening compared to controls (distilled water). These extract-induced vaginal openings in young ovariectomized rats would be evidence of the presence of phytoestrogens in the extract. Indeed, phytoestrogens are chemical groups that occur naturally in plants with estrogenic properties allowing them to act as estrogen agonists [17].

The results of the vaginal opening obtained after the 7 days of treatment are similar to those of Landry et *al.* [18]. These authors found a highly significant vaginal opening following administration of the aqueous extract of the leaves and stem of *Seneciobiafrae* (Asteraceae) in immature female rats at the dose of 64 mg/kg bw. In addition, several investigators have shown that phytoestrogens induce early vaginal opening in rodents [19]. However, these results are contrary to those of Koneri et *al.*[20]. Indeed, these authors showed that the ethanoic extract of *Momorsdicacynbalaria* roots has no effect on vaginal opening in ovariectomized female rats.

The results showed significant ($p > 0.01$) increases in adrenal gland fresh mass of young ovariectomized rats treated with aqueous extract of *C. cordifolia* compared to that of controls given distilled water. However, these values are highly significant ($p<0.01$) in ovariectomized rats treated with the combination of estradiol + 100 mg / kg mc of aqueous *C. cordifolia* extract compared to the adrenal gland fresh mass of young ovariectomized rats treated with ethinyl estradiol alone. These increases in adrenal gland fresh mass,

especially in those treated with aqueous extract of *C.cordifolia*, are thought to be due to the presence of secondary metabolites that may result in cell multiplication on different parts of the adrenal cortex and medulla in young ovariectomized rats. These results are similar to those of Mariotti et al.[21] who observed gains in fresh and dry adrenal gland masses in the study of estrogenic and anti-estrogenic activities of Gunnera manicata root extracts.

For uterine horn mass, the aqueous extract of *C.cordifolia*at the doses of 50, and 200 mg/kg of mc revealed a non-significant increase($p<0.05$) in uterine horn mass compared to that of controls (distilled water). It was similarly noted that young ovariectomized rats treated with aqueous extract of *C.cordifolia* at the dose of 100 mg/kg mc had a highly significant ($p<0.001$) increase in uterine horn mass compared to controls. Analyses also revealed a highly significant ($p<0.001$) increase in uterine horn mass in young ovariectomized rats treated with ethinyl estradiol alone and ethinyl estradiol in combination with aqueous extract of *C.cordifolia* at 50 and 100 mg/Kg of mc compared to young ovariectomized control rats given distilled water. This increase in uterine horn mass was thought to be due to increased estrogen production. Estrogen has been known to stimulate the contents of the uterus, thus modifying the uterine environment leading to a chain of reactions, allowing the biosynthesis of bio macromolecules (DNA, RNA) and the increase in the weight of these organs, mainly the ovary and uterus [22]. These results are consistent with those of Bayala et*al.*[23]. who also showed an increase in uterine horn mass from aqueous extracts of Holarrhena floribunda leaves. However, these results are contrary to those of Chukwuka and Thomas [24]. These authors administered a high dose of 800 mg/kg bw of the aqueous extract of *Spondiasmombin* (Anacardiaceae) to female rats and found a decrease in uterine horn mass of the rats.

Serum FSH determination in ovariectomized juvenile rats showed that administration of aqueous extract of *C.cordifolia* at doses of 50, 10 and 200 mg/kg bw resulted in a highly significant increase in serum FSH levels compared to controls. This increase in FSH levels, observed in this work, could suggest that *C.cordifolia* bark contains phytooestrogenic substances that act on the hypothalamic-pituitary complex. These results are similar to those ofShinnosuke and Massahico[25]. who showed that after administration of estradiol benzoate to ovariectomized immature rats, the serum FSH level increased. This same result was obtained by Isabel et *al.* [26] on the activation of hypothamo-hypophyseal estrogen receptors (ERβ and ERα). Other authors have obtained this same result in vivo in mice by stimulation of estrogen receptors-α at the level of the hypotalamo-pituitary complex [27]. However, these results are contrary to those obtained by Rimoldi et *al.* [28]who showed a decrease in serum gonadotropin levels following the administration of 17-β-oestradiol at different doses to ovariectomized adult rats for a period of 90 days. They are also contrary to those of Najmeh et *al.* [29] obtained through oral administration of diethylstilbestrol (DES) (100 µg/kg bw) for 21 days to male rats.

V. Conclusion

The aqueous extract of *Cola cordifolia* barks in repeated treatment in immature ovariectomized rats would exert central effects on the hypothalamo-hypophyseal complex. It stimulates the synthesis of gonadotropins by peripheral way, by the production of estradiol, thanks to the phytoestrogens which it contains. Although disrupting the estrous cycle of rats, the aqueous extract of *Cola cordifolia* bark stimulates all the parameters of reproduction and also increases the serum level of hormones. These increases would be induced by the aqueous extract of *Cola cordifolia*at different doses. The study showed that the aqueous extract of *Cola cordifolia* would act through two specific pathways: the central pathway, through the production of LH and the peripheral pathway, through the production of estradiol or its estrogen-like action.

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