Research Article

Effects of aqueous extract of *Albizia glaberrima* on the reproductive system of female adult Wistar albino rats

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Abstract

Objective: The objective of this study was to investigate the effects of the aqueous extract of *Albizia glaberrima* (AEAG) on the reproductive system of female adult Wistar albino rats. **Material and method**: Fifteen healthy adult female Wistar rats were divided into 3 groups of 5 animals each and given orally for 28 consecutive days distilled water (group 1), AEAG 200 mg/kg b.w (group 2), and AEAG 400 mg/kg b.w (group 3). Vaginal smears were performed daily from each rat and at the end of treatments, rats were sacrificed to collect ovary and uterus which were weighed and stored in 10% formalin for histological analysis. **Results and conclusion**: Results showed that AEAG induced a disturbance of the estrous cycle characterized by an augmentation of the duration of the estrous phase. Furthermore, this extract did not change the ovary wet weight while it increased significantly the relative wet weight of the uterus. These effects were corroborated by the histological architecture of these organs since the ovary of the extract-treated rats showed Graafian follicle and newly formed corpora lutea and their uterus exhibited a proliferated endometrium with large columnar epithelium cells. These data suggested that *A. glaberrima* exerted estrogenic effects on the female reproductive system of Wistar rats due probably to its phytoconstituents such as flavonoid, sterols, polyterpenes, and polyphenols.

Keywords: *Albizia glaberrima*, estrogenic effects, ovary, uterus, endometrium proliferation

Introduction

Infertility is a global public health problem today. More than 15% of couples of childbearing ages are affected by this disease worldwide (WHO, 2010). In sub-Saharan Africa, the prevalence varies from 9% to 30% depending on the country (Parrott, 2014; Hollos and Whitehouse, 2014; Asemota and Klatsky, 2015). Infertility is defined by the World Health Organization as the inability of a couple to achieve conception and carry a pregnancy to term after a year or more of regular, unprotected sex (WHO, 2018). This disease can concern both men and women. Indeed, 30% of infertility cases are thought to be female, 20% are male in origin, 40% are of mixed origin and 10% are unexplained. However, there are two types of infertility, namely primary infertility when the couple has never conceived and secondary infertility when the couple can no longer give birth after having a child (Tabong and Adongo, 2013). The secondary form is thought to affect around 30% of women aged 25 to 49 in sub-Saharan Africa (WHO, 2010). In Africa, the child is considered a precious

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wealth, a source of pride and social well-being, of the perpetuation of the family, and marriage only really makes sense if the couple manages to conceive a child (Dyer, 2007; Tabong and Adongo, 2013; Chimbatata and Malimba, 2016). As a result, infertility is a source of social stigma, exclusion, various humiliation, stress, anxiety, physical or psychological violence, divorce, polygamy, withdrawal into oneself (Nieuwenhuis et al., 2009; Naab et al., 2013; Anokye et al., 2017). Although many of the causes of infertility are male, women are more often held responsible and endure the worst psychosocial consequences of this disease (Donkor and Sandall, 2009; Odinga, 2011).

To find a solution to their problem and regain their dignity, infertile women have recourse either to modern medicine for the wealthy or to traditional medicine for cultural or economic reasons (Brochard, 2014; Koman et al., 2019). But modern methods of treating infertility include surgical procedures, various stimulation, and assisted reproduction techniques which are too expensive and generally beyond the reach of the overwhelming majority of women. Indeed, in sub-Saharan Africa, 41% of the population in general and women in particular live below the poverty line (UNCEA, 2017). In addition, recourse to modern medicine sometimes ends in failure, leading women, even the wealthiest, to turn to traditional medicine (Angone et al., 2009). This medicine is essentially based on the use of medicinal plants that are easily accessible and have real effectiveness in the treatment of many diseases. Thus, aware of the role played by traditional medicine in providing healthcare for most poor populations, the Ivorian government has set up a national program for the promotion of traditional medicine. This program encourages research on medicinal plants, including research and development, local production, and the use of improved traditional medicines (MSLS, 2014).

Albizia glaberrima (Fabaceae) is a plant that is part of the rich floristic heritage of the Ivory Coast. Authors have already demonstrated its analgesic, anti-inflammatory, antipyretic, anxiolytic, and anticonvulsant properties (Adebesin et al., 2015; Ogbiti et al., 2017). But no study has yet revealed its potential usefulness in the treatment of women's infertility although it is traditionally used to treat this disease.

The objective of this study was therefore to investigate the effects of the aqueous extract of *Albizia glaberrima* on the reproductive system of female adult Wistar albino rats.

Material and methods

Plant material

The fresh leaves of *A. glaberrima* were collected near Daloa, the capital city of the Haut-Sassandra region, in the Center-West of Ivory Coast. The plant was identified at the National Floristic Center where a sample was kept under the number A2C59R16E3F3.

Animals

Adult female albino Wistar rats were obtained from the animal house of Jean Lorougnon Guédé University for the experiments. The animals were acclimatized under laboratory conditions for 14 consecutive days prior to experiments beginning. They were kept at room temperature (28±2°C) with a photoperiod of 12 hours light/dark. The hygrometry was 50-60% and they were free allowed to water and commercial food (15% protein, 5.3% fat) provided from the IVOGRAIN industry (Abidjan, Ivory Coast). Experiments were conducted according to the EU Directive 2010/63/EU for animal experiments.

Preparation of the extract

The leaves of *A. glaberrima* were dried under ambient temperature without exposure to sunlight and pulverized using an electric grinder (RETSCH SK100/C, Germany). A quantity of 25g of the obtained powder was macerated in 1 L of distilled water under a magnetic agitator (JANKE & KUNKEL RH, Germany) for 24 h and double filtered using hydrophilic cotton and Whatman filter paper number 1. The solution obtained after filtration was evaporated in an air circulating oven (MEMMERT UF55, Germany) at 50°C for seven days until total dryness. The aqueous extract was then recovered and stored at 4°C in a refrigerator for the tests. The same procedure was repeated eight times in order to obtain a sufficient quantity of extract for the experiments. An average extraction yield was then calculated from the quantity of extract obtained according to the formula:

$$\text{Yield} = \frac{\text{Extract obtained (g)}}{\text{Leaves powder used(g)}} \text{X } 100$$

Phytochemical screening

Standards methods were used for a qualitative evaluation of secondary metabolites in the leaves of *A. glaberrima* (Ouattara et al., 2021). The above aqueous extract prepared was used to test compounds such as sterols, polyterpenes, polyphenols, flavonoids, saponosides, quinones, alkaloids, catechic and gallic tannins.

Experimental design

This experiment was carried out according to the method used by Bleu (2013). Healthy adult female albino rats weighing from 160 to 200g were divided into 3 groups of 5 animals each and treated with the aqueous extract of *A. glaberrima* (AEAG) as follows:

Group 1: distilled water (control)

Group 2: 200 mg/kg b.w of the extract

Group 3: 400 mg/kg b.w of the extract

All these treatments were given for 28 consecutive days by

oral route using an intragastric sound. The rats were weighed every week and vaginal smears were performed daily from each rat at the same time (7:00 a.m.) to determine the effect of treatments on the estrous cycle. On the day after the last treatment, the rats were sacrificed by decapitation under ether anaesthesia. An incision was made in the abdomen of the rats, then the ovaries and uterus free of fatty adhesions were removed and immediately weighed. After weighing, these organs were preserved in 10% formalin for histological studies (Bleu, 2013).

Histological examination

After 48 hours of storage, the ovary and uterus were immersed in successive alcohol solutions (70 °, 80 °, 90 °, and 100 °) to be dehydrated and then were embedded in hot paraffin (58°C). Section of 4 µm in thickness was cut using a microtome (MICROM HM 310, France) and stained with haematoxylin-eosin. The sections were then observed under a microscope (OPTIKA B192, Italia) for the analysis of the histological structure of these organs, and photomicrographs were taken.

Statistical analysis

Statistical analysis of experimental results was performed using GraphPad Prism 7.00 software (Microsoft, USA). Values were presented as mean ± standard error on the mean. The data were evaluated by the one-way ANOVA analysis method followed by the Tukey multiple comparison test at the 5% level to assess the degrees of significance observed between the treated and the control groups. If $p<0.05$, the difference between the values was considered significant, and if $p<0.01$ this difference was considered highly significant.

Results

Extraction yield

The extraction from 200g of leaves powder of *A. glaberrima* in distilled water gave 18.54g of aqueous dry extract, which corresponded to an extraction yield of 9.27%.

Chemical compounds

The secondary metabolites present in the leaves aqueous extract of *A. glaberrima* consist of sterols, polyterpenes, polyphenols, flavonoids, alkaloids, quinones, catechic tannins, and saponosides. However, this extract did not contain gallic tannins (Table 1).

Effect of the extract on the estrous cycle

The 28 days administration of the aqueous extract of *A. glaberrima* induced a dose-dependent disturbance of the estrous cycle of rats characterized by a significant augmentation ($p<0.05$) of the duration of the estrous phase. This phase was increased from week 2 to week 4 at the treatment dose of 200 mg/kg b.w whereas it was increased by the dose of 400 mg/kg b.w from week 1 to week 4 in rats when compared to controls (Table 2).

Table 1. Secondary metabolites the from leaves of *A. glaberrima*

Chemical compounds	Tests used	Aqueous extract
Sterols	Liebermann test	+
Polyterpenes		+
Polyphenols	$FeCl_3$ test	+
Flavonoids	Cyanidin test	+
Catechic tannins	Stiasny test	+
Gallic tannins	Stiasny + $FeCl_3$ test	-
Quinones	Borntraeger test	+
Alkaloids	Bouchardat and Dragendorff test	+
Saponosides	Foam test	+

(-): absence; (+): presence.

Table 2. Duration of the estrous phase of the estrous cycle in rats per week

Treatment groups	Duration (days)			
	Week 1	Week 2	Week 3	Week 4
Group 1 (control)	1.60±0.54	1.80±0.44	1.60±0.54	1.40±0.54
Group 2 (200 mg/kg)	2.40 ± 1.51^{ns}	$2.80\pm0.83^{*}$	$3.60\pm0.89^{**}$	$3.00\pm0.70^{**}$
Group 3 (400 mg/kg)	$2.40\pm0.54^{*}$	$3.20\pm1.09^{*}$	$3.20\pm0.83^{**}$	$3.60\pm1.14^{**}$

Results are presented as mean ± SEM (n=5). $^{*}p<0.05$, $^{**}p<0.01$ vs control group; ns: not significant

Effects on the body weight

When administered at the dose of 200 mg/kg of b.w, the aqueous extract of *A. glaberrima* induced a significant reduction ($p<0.05$) in body weight gain of rats only at week 4. However, the treatment at a dose of 400 mg/kg b.w results in a significant decrease ($p<0.05$) in body gain of rats from week 1 to week 4 except week 2 in comparison to controls (Table 3).

Effect on the relative wet weight of ovaries and uterus

The treatment of rats with doses of 200 mg/kg and 400 mg/kg b.w of AEAG for 28 days did not cause any significant change ($p>0.05$) in the relative wet weight of the ovaries when compared to the controls (Figure 1A). However, the administration of AEAG at doses of 200 and 400 mg/kg b.w to rats resulted in a significant increase ($p<0.05$) in the uterine relative wet weight in comparison to controls (Figure 1B). In addition, the uterus of treated rats was filled with fluid and the volume was augmented unlike the uterus of controls which exhibited a normal appearance.

Histological structure of ovaries and uterus

The analysis of the histological architecture of ovaries showed the presence of Graafian follicles and newly formed corpora lutea in 60% of rats treated with both the dose of 200 and 400 mg/kg b.w. However, the ovaries of control rats exhibited degenerated corpora lutea in 80% of cases (Figure 2). Treatment of rats with these doses resulted in significant

Table 3. Body weight gain of rats treated with the aqueous extract of *A. glaberrima*

Treatment groups	Body weight gain (%)			
	Week 1	Week 2	Week 3	Week 4
Group 1 (control)	4.94±1.70	4.95±1.24	8.81±1.67	11.21±2.13
Group 2 (200 mg/kg)	3.71±1.11^{ns}	4.28±1.37^{ns}	6.48±1.13^{ns}	7.16±1.13*
Group 3 (400 mg/kg)	1.08±0.58*	4.18±1.01^{ns}	5.36±2.25*	5.17±1.32**

Results are presented as mean ± SEM (n=5). *p<0.05, **p<0.01 vs control group; ns: not significant

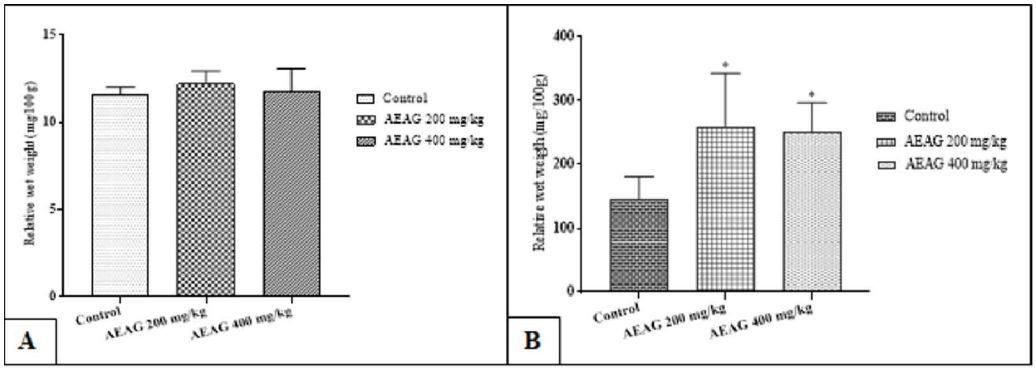

Figure 1. Effect of AEAG on the relative wet weight of ovaries and uterus of rats. Results are presented as mean ± SEM (n=5). *p<0.05 vs control group. (A) effect on ovaries; (B) effect on uterus. AEAG caused a significant increase of the relative wet weight of uterus.

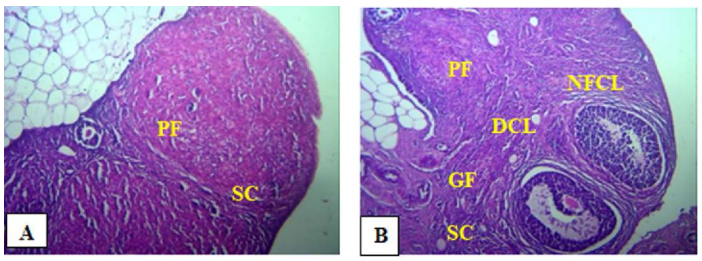

Figure 2. Photomicrograph of ovaries of rats treated with AEAG A: ovary of control, B: ovary of treated rats. DCL: degenerated corpora lutea, GF: Graafian follicle, NFCL: newly formed corpora lutea, PF: primary follicle, SC: stroma cells. Original magnification x 10; stained: hematoxylin-eosin. Ovaries of rats treated with AEAG showed Graafian follicle and newly formed corpora lutea.

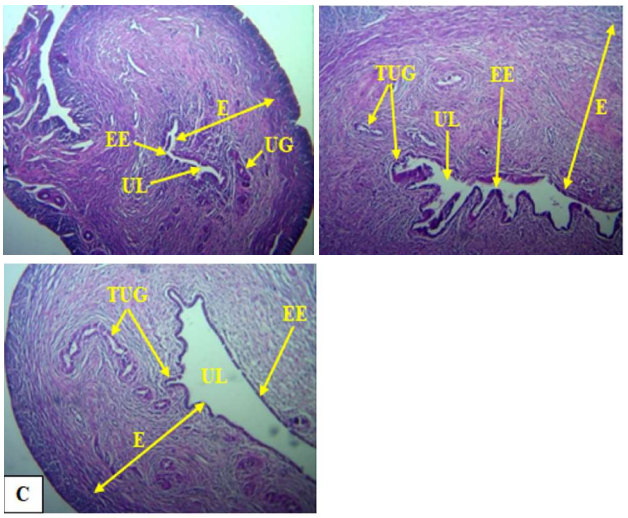

Figure 3. Photomicrograph of uterus of rats treated with AEAG. (A) uterus of control, (B) uterus of 200 mg/kg treated rats, (C) uterus of 400 mg/kg treated rats. E: endometrium, EE: endometrium epithelium, TUG: tortuous uterine glands, UG: uterine gland, UL: uterine lumen. Original magnification x 10; stained: hematoxylin-eosin. The uterus of rats treated with AEAG showed endometrial proliferation.

changes in the structure of the uterus. Enlargement of the uterine diameter, proliferation, and thickening of the endometrium, development of the uterine glands which got more numerous and tortuous was observed in 80% of rats. The endometrial epithelium has also consisted of large columnar cells. These effects were dose-dependent since they were more pronounced in rats given the dose of 200 mg/kg than those treated with 400 mg/kg. The uterus of 80% control rats did not show endometrial proliferation and the epithelial cells were small (Figure 3).

Discussion

The preparation of the aqueous extract of *A. glaberrima* from 200g of dry leaf powder gave 18.54g of a brown dry extract with an extraction yield of 9.27%. This yield was higher than the 5.3% yield of the aqueous extract of leaves of the same plant boiled for 30 min (Adebesin et al., 2015) but lower than that of the aqueous extract of leaves of *Albizia lebbeckoides*

(Fabaceae) macerated for 24 h which was 11.21% (Hajrawati et al., 2019). The extraction yields depend on the polarity, the extracting power of the solvents, the method of preparation, the species, the organ used, and the content of chemical compounds (Bouzid et al., 2011; Dhanani et al., 2017). Calculating the yields allows assessing the quantities of extracts that can be obtained from each organ of a species. This extraction yield also makes it possible to consider the quantity of organs to be removed for a scientific study and to make the use of medicinal plants more rational and sustainable.

Phytochemical analysis revealed that this extract contained sterols, polyterpenes, polyphenols, flavonoids, quinones, saponosides, alkaloids, and catechic tannins. The presence of Polyphenols, tannins, steroids, terpenoids, saponosides, and flavonoids has also been demonstrated in the aqueous extract of this plant by Adebesin et al. (2015). In addition, all these secondary metabolites were present in the leaves of *Albizia lebbeckoides* (Hajrawati et al., 2019). The presence of these phytoconstituents should explain the various medicinal uses of *A. glaberrima* (Lemmens, 2007; Lawal et al., 2010). Then the study of its pharmacological effects on the reproductive system of rats was carried out. Thus, when administered orally for 28 consecutive days to female rats, AEAG induced a disturbance of the estrous cycle marked by a significant increase in the duration of the estrous phase. The same disturbances were observed in rats by Bleu et al. (2012a) for two weeks of treatment with an aqueous extract of *Passiflora foetida* (Passifloraceae) and by Affi et al. (2019) with the methanol extract of *Amaranthus viridis* for 28 day-treatment in rats. The estrous cycle of rats is characterized by a cyclical renewal of the vaginal mucosa which occurs through tissue changes in the epithelium under the influence of cyclical variations in the activity of the ovaries. This cycle includes four phases which are proestrus, estrous, metestrus, and diestrus, and vaginal smears allow to assess each phase. The estrous phase is characterized by a vaginal cornification with abundant anucleated keratinized epithelial cells which get large and acidophilic/eosinophilic (Marcondes et al., 2002; Paccola et al., 2013; Cora et al., 2015). The vaginal epithelium is a target tissue for estrogen, an ovarian hormone that induces epithelial stratification and full cell keratinization through its α receptors (Miyagawa and Iguchi, 2015). In this experiment, the increase in the duration of the estrous phase in rats treated with AEAG means that this extract would contain phytoconstituents with an estrogenic effect which stimulates the keratinization of epithelial cells. This effect was dose-dependent as it was more rapid at the dose of 400 mg/kg. Since the estrous cycle depends on the cyclical variation in the activity of the ovary (Cora et al., 2015), the effects of the extract were studied on the wet weight and the histological structure of this organ. At the doses of 200 and 400 mg/kg b.w, AEAG induced a slight non-significant increase of the relative wet weight of the ovaries and the histological examination showed the presence of Graffian follicle and newly formed corpora lutea in 60% of rats unlike that of 80% control rats which exhibited degenerated corpora lutea. In mammals, estrogen can exert a positive feedback effect on the brain by stimulating GnRH surge which induces preovulatory pituitary gonadotropins LH and FSH surge at the end of a follicular phase or proestrus phase, and this action induces ovulation that occurs in the estrous phase (Herbison, 2008; Radovick et al., 2012; Uenoyama et al., 2021). The effects of AEAG should be explained by the presence in this extract of phytoestrogens or estrogen-like substances which acted as endogenous estrogen by a positive feedback on the hypothalamic-pituitary complex or by potentializing its effect as it has been demonstrated by Zougrou et al. (2018) with the aqueous extract of *Cnestis ferruginea* (Connaraceae) and by Bleu et al. (2012b) with the aqueous extract of *Passiflora foetida*. In addition, AEAG at doses of 200 and 400 mg/kg b.w induced a significant dose-dependent increase in the relative wet weight and volume of the uterus in 80% of rats compared to controls. These changes were confirmed by the histological examination of this organ. The same effects were obtained on the uterus by several authors (Bleu et al., 2012b). Like the vaginal epithelium, the uterus is a target tissue for ovarian hormones. During the proestrus phase, estrogen, whose synthesis becomes important, binds to its uterine receptors ERα (Nephew et al., 2000; Blesson et al., 2012) and induces endometrial hyperplasia then stimulates the development of the uterine glands which become tortuous with an increase in their glycogen secretion. These effects of estrogen are accentuated by progesterone during the estrous phase (Russell, 2008) and result in an increase in uterine volume and wet weight. On the other hand, it has been established that quercetin, a bioflavonoid phytoestrogen directly promotes ovarian steroidogenesis of progesterone, testosterone, and estrogen in rabbit ovary (Sirotkin et al., 2019). Other authors demonstrated that phytoestrogen naringenin, quercetin, and coumestrol induce the activity of aromatase, an enzyme involved in estrogen synthesis in the ovary (Solak et al., 2014). It was possible that phytoconstituents in AEAG stimulated the uterine growth in rats by a direct action on the ovary as well as these phytoestrogens, probably by binding on estrogen receptors, by stimulating the estrogen precursor's synthesis and/or inducing aromatase activity. Finally, the presence in AEAG of phytoconstituents such as flavonoids, sterols, polyterpenes, polyphenols, saponosides, alkaloids which are known for their estrogenic activity (Nikolić et al., 2017) could explain the effect of this extract on the rat reproductive system.

Conclusion

The aqueous extract of *A. glaberrima* induced estrogenic effects on the female reproductive system of Wistar rats. It increased the duration of the estrous phase of the estrous cycle and then stimulated ovulation and endometrial proliferation in the uterus. These effects would be due to its phytoconstituents such as flavonoids, sterols, polyterpenes, polyphenols, saponosides, alkaloids, and tannins tested in a preliminary phytochemical screening. Further studies must be carried out to identify the chemical components responsible for this estrogenic activity.

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