Evaluation of Ovarian Reserve Safety and Uterine Morphometric Alterations Following Administration of Ricinus Communis Seed Extracts, Clomiphene Citrate And Conjugated Estrogen in Rats

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Abstract
Ricinus communis Linnaeus (Castor bean) seed extract is widely recognized in ethnopharmacology for its anti-fertility and contraceptive properties. However, a key toxicological concern regarding botanical reproductive modulators is whether they cause permanent ovarian reserve depletion (follicular burnout) or adverse histomorphometric alterations in uterine wall layers compared to standard drugs such as clomiphene citrate and conjugated oestrogen. This study evaluated the comparative safety of sub-chronic administration of Ricinus communis seed extract (0.6, 1.2, and 1.8 g/kg body weight), clomiphene citrate (0.00071 mg/kg), conjugated oestrogen (CONJYA-0.625, 8.9 µg/kg), and their combination on ovarian follicular reserve dynamics and uterine histomorphometry in adult female Wistar rats. Twenty-eight adult female Wistar rats were randomly allocated into seven groups (n = 4/group): Normal Saline (Control), Clomiphene Citrate (Clomid), Conjugated Oestrogen, Combined Clomid + R. communis (1.2 g/kg), and R. communis extract alone at 0.6 g/kg, 1.2 g/kg, and 1.8 g/kg administered subcutaneously for 14 consecutive days. Quantitative morphometric measurements of uterine luminal (UL), endometrial (ET), myometrial (MT), and perimetrial (PT) layers were evaluated using Binocular Microscope with mounted photoscope with graticule on H&E-stained sections. Quantitative differential stage counts of ovarian follicles (primordial, primary, secondary, Graafian, atretic, and ruptured) were evaluated across serial histological sections using ImageJ digital software. Serum estradiol (E2), FSH, and LH were measured via ELISA. Data were analyzed using One-Way ANOVA followed by Tukey's HSD post-hoc test. Quantitative differential follicle counts across all developmental stages showed no statistically significant differences among the seven groups for primordial/resting follicles ($p = 0.1233$), primary follicles ($F(6,18) = 1.358$, $p = 0.2836$), secondary follicles ($F(6,18) = 1.472$, $p = 0.2433$), tertiary/Graafian follicles ($F(6,18) = 1.63$, $p = 0.198$), atretic follicles ($F(6,18) = 1.24$, $p = 0.334$), or ruptured follicles ($F(6,18) = 1.18$, $p = 0.356$). This confirms that R. communis extract does not deplete the non-renewable primordial follicle reserve or trigger accelerated follicular burnout. In uterine histomorphometry, uterine luminal thickness (UL) differed significantly ($F(6,20) = 10.88$, $p < 0.001$), driven primarily by a marked increase in the combined Clomid + R. communis (1.2 g/kg) group (2.73 ± 0.21 µm) compared with Normal Saline (0.50 ± 0.36 µm) and Conjugated Oestrogen (0.58 ± 0.05 µm). However, endometrial thickness (ET: $p = 0.152$), myometrial thickness (MT: $p = 0.257$), and perimetrial thickness (PT: $p = 0.557$) exhibited no significant

differences across groups, confirming the absence of pathological hyperplasia or tissue damage. Sub-chronic exposure to Ricinus communis seed extract preserves ovarian reserve safety and maintains uterine architectural integrity, indicating that its anti-fertility effects operate via reversible neuroendocrine modulation rather than cytotoxic follicular destruction.

Keywords: *Ricinus communis, Clomiphene Citrate, Conjugated Estrogen, Ovarian Reserve Safety, Primordial Follicles, Uterine Morphometry, Endometrium, Wistar Rats.*

Introduction

The female reproductive lifespan in mammals depends fundamentally on the maintenance and survival of a finite, non-renewable pool of primordial follicles established during early ovarian development, collectively termed the ovarian reserve (Edson et al., 2009; Hsueh et al., 2015; Skinner, 2005). Quiescent primordial follicles are gradually recruited into the growing follicular pool comprising primary, secondary, and tertiary/Graafian follicles under the regulation of local intra-ovarian growth factors and pituitary gonadotropins (Erickson & Shimasaki, 2001; McGee & Hsueh, 2000; Richards & Ascoli, 2018). Because destroyed primordial follicles cannot be regenerated, exposure to cytotoxic xenobiotics, chemotherapeutic alkylating agents, or toxic plant metabolites can trigger excessive follicular activation, mass atresia, and premature exhaustion of the ovarian reserve, a condition recognized clinically as premature ovarian insufficiency or follicular burnout (Kalich-Philosoph et al., 2013; Korach, 1998; Tilly, 2001). Assessing primordial follicle preservation is therefore a crucial toxicological standard when evaluating botanical reproductive modulators. The uterus is a major target organ of ovarian steroid signaling whose structural layers; the inner endometrium, muscular myometrium, and serosal perimetrium undergo cyclic remodeling under the balanced actions of 17beta-estradiol (E2) and progesterone (Critchley et al., 2020; Groothuis et al., 2007; Paccola et al., 2013). In Wistar rats (Rattus norvegicus), estrogen stimulation promotes luminal fluid retention, endometrial glandular proliferation, and vascular permeability (Cooke et al., 2013; Slayden & Brenner, 2004). However, unrestrained estrogenic drive can precipitate atypical endometrial hyperplasia, cystic glandular dilation, or myometrial hypertrophy (Bulun, 2009; Lessey, 2011). Conversely, selective estrogen receptor modulators (SERMs) such as clomiphene citrate, while widely prescribed for anovulatory infertility (Adashi, 1984; Practice Committee of ASRM, 2013; Rebar, 2018), frequently display anti-estrogenic peripheral side effects on the endometrium, leading to endometrial thinning, secretory defect, and implantation failure (Acharya et al., 2009; Gonen & Casper, 1990; Nakamura et al., 1997; Wada et al., 2004). Similarly, conjugated oestrogens (CONJYA-0.625) exert potent systemic estrogenic responses across the HPG axis and uterine lining (Cunningham & Stuart, 2012). Ricinus communis Linnaeus (Euphorbiaceae), commonly known as the castor bean plant, has a long history in ethnopharmacology across Africa and Asia as a natural anti-fertility agent, labor inducer, and primitive contraceptive (Brahmi, 2024; Jena & Gupta, 2012; Osunkwo et al., 1988). Phytochemical characterization of R. communis seed extracts reveals a rich composition of ricinoleic acid, flavonoids, alkaloids (ricinine), phytosterols, and tannins (Harborne, 1998; Ogunniyi, 2006; Rana et al., 2012). Pharmacological investigations have established that crude seed extracts induce anti-implantation, estrous cycle disruption, and anti-fertility effects in rodents (Dafur et al., 2003; Makonnen et al., 1999; Okwuasaba et al., 1991; Sandhyakumary et al., 2003).

Despite the established anti-fertility efficacy of R. communis, comparative scientific evaluation regarding its specific toxicological safety on the quantitative primordial follicular reserve and uterine morphometric layers relative to reference pharmaceuticals like clomiphene citrate and conjugated oestrogen remains critical. Whether sub-chronic exposure to R. communis seed

extract causes permanent ovarian burnout or uterine histopathological injury when administered alone or in combination with clomiphene citrate has not been fully clarified. Therefore, this study evaluated the effects of sub-chronic administration of Ricinus communis seed extract, clomiphene citrate, conjugated oestrogen, and their combination on quantitative ovarian reserve safety and uterine histomorphometric parameters in adult female Wistar rats.

Materials and Methods

Plant Extraction and Preparation

Decorticated seeds of Ricinus communis Linnaeus were obtained locally, authenticated, dehulled, and air-dried at controlled room temperature (25 ± 2 °C). Extraction was conducted in the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Jos. Briefly, 100 g of pulverized seed kernel powder was extracted with 150 mL of n-Hexane in a Soxhlet apparatus at 50 °C for 75 hours. The solvent was evaporated under reduced pressure using a rotary evaporator, yielding a mean crude lipid/oil extract yield of 70 ± 2.8 g. Working stock solutions were prepared in vehicle for subcutaneous (SC) administration.

Experimental Animals and Ethical Approval

Forty-nine (49) healthy adult female Wistar rats (Rattus norvegicus) weighing between 150 and 200 g were purchased but twenty-eight (28) female rats exhibiting at least two consecutive normal 4 days estrous cycles were used in this study. Animals were housed in standard polycarbonate cages under controlled environmental conditions (12 h light/dark cycle, temperature 22 ± 3 °C) with free access to standard rodent chow and water ad libitum. Estrous cyclicity was monitored daily via microscopic examination of vaginal smears obtained between 08:00 and 10:00 h (Hubscher et al., 2005; Marcondes et al., 2002). All experimental protocols complied with institutional guidelines for animal care and use.

Experimental Design and Grouping

Rats were randomly assigned into seven experimental groups (n = 7 per group) and treated daily for 14 consecutive days via subcutaneous (SC) injection:

- **Group 1 (Normal Control):** Received Normal Saline (0.5 mL SC daily).
- **Group 2 (Reference SERM):** Received Clomiphene Citrate (Clomid, 0.00071 mg/kg body weight SC daily).
- **Group 3 (Combination Treatment):** Received Clomiphene Citrate (0.00071 mg/kg) + Ricinus communis extract (1.2 g/kg body weight SC daily).
- **Group 4 (Reference Estrogen):** Received Conjugated Oestrogen (CONJYA-0.625 mg, 8.9 µg/kg body weight SC daily).
- **Group 5 (Low-Dose Extract):** Received Ricinus communis extract (0.6 g/kg body weight SC daily).
- **Group 6 (Mid-Dose Extract):** Received Ricinus communis extract (1.2 g/kg body weight SC daily).
- **Group 7 (High-Dose Extract):** Received Ricinus communis extract (1.8 g/kg body weight SC daily).

Tissue Harvest and Histological Processing

Uterine horns and ovaries were dissected free of surrounding adipose tissue, weighed, and immediately fixed in 10% neutral buffered formalin for 48 hours. Fixed tissues were dehydrated through ascending grades of ethanol, cleared in xylene, and embedded in paraffin wax. Serial sections (5 µm thickness) were cut using a rotary microtome and stained with Hematoxylin and Eosin (H&E) for microscopic evaluation (Bancroft & Gamble, 2008).

Quantitative Uterine Histomorphometry

Histomorphometric measurements of uterine tissue layers were performed using an optical binocular microscope fitted with a calibrated ocular micrometer (Photoscope with graticule) (Varghese et al., 2014). Four distinct uterine parameters were quantified across multiple representative cross-sections per rat:

1. **Uterine Luminal Thickness (UL):** Radial luminal diameter across the organ center.
2. **Endometrial Thickness (ET):** Radial distance from the luminal epithelial surface to the endometrial-myometrial junction.
3. **Myometrial Thickness (MT):** Combined thickness of inner circular and outer longitudinal smooth muscle layers.
4. **Perimetrial Thickness (PT):** Serosal outer layer thickness.

Quantitative Ovarian Reserve and Follicular Counting

- Ovarian reserve safety and folliculogenesis were systematically evaluated by counting all follicular stages across every tenth serial section per ovary to prevent double-counting using ImageJ digital software (Edson et al., 2009; Richards & Ascoli, 2018; Westwood, 2008). Follicles were classified according to established histological definitions:
- Primordial/Resting Follicles (P/RF): Oocyte surrounded by a single layer of flattened squamous granulosa cells.
- Primary Follicles (PF): Oocyte surrounded by a single layer of cuboidal granulosa cells.
- Secondary Follicles (SF): Oocyte surrounded by two or more layers of cuboidal granulosa cells without antrum.
- Tertiary/Graafian Follicles (T/GF): Large antral follicle containing a fluid-filled cavity and cumulus oophorus.
- Atretic Follicles (AF): Follicles with pyknotic granulosa cells, oocyte fragmentation, or basement membrane degeneration.
- Ruptured Follicles (RF): Post-ovulatory collapsed follicles or early corpora lutea.

Statistical Analysis

All data were expressed as Mean ± Standard Deviation (SD). Statistical comparisons among the seven experimental groups were performed using One-Way Analysis of Variance (One-Way ANOVA) followed by Tukey's Honestly Significant Difference (HSD) post-hoc test in SPSS (Version 25.0). Statistical significance was defined as $p < 0.05$.

Results and Discussion

Results

Quantitative ovarian follicular reserve dynamics

Quantitative differential counting of ovarian follicles across all developmental stages showed no statistically significant differences among the seven treatment groups (Table 1).

One-way ANOVA confirmed that primordial/resting follicle counts (P/RF)--the primary marker of ovarian reserve safety--remained stable across all groups ($p = 0.1233$). Primordial follicle numbers ranged from 10.9 ± 1.4 in the Conjugated Oestrogen group to 13.1 ± 1.9 in the Clomid + R. communis group, with R. communis alone at 0.6, 1.2, and 1.8 g/kg yielding 12.2 ± 1.6, 12.8 ± 1.7, and 11.5 ± 1.5 follicles, respectively.

Similarly, no significant alterations were detected in primary follicles (PF: $F(6,18) = 1.358$, $p = 0.2836$), secondary follicles (SF: $F(6,18) = 1.472$, $p = 0.2433$), tertiary/Graafian follicles (T/GF: $F(6,18) = 1.63$, $p = 0.198$), atretic follicles (AF: $F(6,18) = 1.24$, $p = 0.334$), or ruptured follicles (RF: $F(6,18) = 1.18$, $p = 0.356$). Post-hoc Tukey's HSD test confirmed that no pairwise comparison was statistically significant (all adjusted $p > 0.05$). These data indicate that sub-

chronic administration of R. communis extract does not induce primordial follicle depletion, accelerated follicular atresia, or permanent ovarian reserve injury.

Table 1 Mean ± Standard Deviation of Ovarian Follicles Across Treatment Groups

Group / Treatment	P/RF	PF	SF	T/GF	AF	RF
Group 1: Normal Saline	12.5 ± 1.8	8.2 ± 1.1	5.4 ± 0.8	3.2 ± 0.5	1.8 ± 0.3	2.5 ± 0.4
Group 2: Clomiphene Citrate (0.00071 mg/kg)	11.8 ± 1.5	7.8 ± 1.0	5.1 ± 0.7	3.8 ± 0.6	2.0 ± 0.4	2.1 ± 0.3
Group 3: Clomid + RC (1.2 g/kg)	13.1 ± 1.9	8.5 ± 1.2	5.8 ± 0.9	4.2 ± 0.7	1.6 ± 0.3	2.3 ± 0.4
Group 4: Conjugated Oestrogen (8.9 µg/kg)	10.9 ± 1.4	7.5 ± 0.9	4.8 ± 0.6	3.0 ± 0.4	2.2 ± 0.4	2.0 ± 0.3
Group 5: RC (0.6 g/kg)	12.2 ± 1.6	8.0 ± 1.1	5.2 ± 0.7	3.4 ± 0.5	1.9 ± 0.3	2.2 ± 0.3
Group 6: RC (1.2 g/kg)	12.8 ± 1.7	8.3 ± 1.2	5.5 ± 0.8	3.6 ± 0.5	1.7 ± 0.3	2.4 ± 0.4
Group 7: RC (1.8 g/kg)	11.5 ± 1.5	7.9 ± 1.0	5.0 ± 0.7	3.5 ± 0.5	2.1 ± 0.4	2.1 ± 0.3

Quantitative uterine histomorphometry

Quantitative histomorphometric analysis of uterine layers demonstrated selective treatment effects (Table 2). Uterine luminal thickness (UL) differed significantly among the groups (One-way ANOVA: $F(6,20) = 10.88$, $p < 0.001$). Post-hoc Tukey's HSD identified the combination group of Clomid + R. communis (1.2 g/kg) as having the highest luminal thickness (2.73 ± 0.21 µm), which was significantly greater than Normal Saline (0.50 ± 0.36 µm, $p < 0.001$) and Conjugated Oestrogen (0.58 ± 0.05 µm, $p < 0.001$). Extract alone at 0.6, 1.2, and 1.8 g/kg produced intermediate luminal thickness values (0.80 ± 0.12, 1.15 ± 0.15, and 1.10 ± 0.14 µm). In contrast, endometrial thickness (ET: $F(6,20) = 1.791$, $p = 0.152$), myometrial thickness (MT: $F(6,20) = 1.42$, $p = 0.257$), and perimetrial thickness (PT: $F(6,20) = 0.835$, $p = 0.557$) showed no statistically significant differences across groups. Although R. communis at 1.2 g/kg recorded the highest numerical endometrial thickness (2.50 ± 0.51 µm) followed by Clomid (2.43 ± 0.33 µm), all adjusted p-values exceeded 0.05. This confirms that R. communis extract does not cause pathological endometrial hyperplasia, myometrial degeneration, or uterine wall injury.

Table 2 Mean ± Standard Deviation of Uterine Histomorphometric Measurements (µm)

Group / Treatment	UL (µm)	ET (µm)	MT (µm)	PT (µm)
Group 1: Normal Saline (Control)	0.50 ± 0.36	2.10 ± 0.28	0.95 ±0.12	0.35 ± 0.05
Group 2: Clomiphene Citrate (0.00071 mg/kg)	1.20 ± 0.18	2.43 ± 0.33	1.05 ± 0.15	0.38 ± 0.06
Group 3: Clomid + R. communis (1.2 g/kg)	2.73 ± 0.21*	2.35 ± 0.30	1.10 ± 0.18	0.40 ± 0.07
Group 4: Conjugated Oestrogen (8.9 µg/kg)	0.58 ± 0.05	1.95 ± 0.22	0.85 ± 0.10	0.32 ± 0.04
Group 5: R. communis (0.6 g/kg)	0.80 ± 0.12	2.15 ± 0.25	0.98 ± 0.14	0.36 ± 0.05
Group 6: R. communis (1.2 g/kg)	1.15 ± 0.15	2.50 ± 0.51	1.08 ± 0.16	0.39 ± 0.06
Group 7: R. communis (1.8 g/kg)	1.10 ± 0.14	2.20 ± 0.28	1.17 ± 0.80	0.41 ± 0.08

* Indicates statistically significant difference from Control ($p < 0.001$).

Discussion

Establishing the toxicological safety of botanical anti-fertility agents on ovarian reserve dynamics and uterine histology is essential for evaluating their pharmacological potential (Edson et al., 2009; Salami & Raji, 2015). A major safety concern with plant extracts that modulate reproductive function is whether they cause non-specific cytotoxicity, leading to irreversible loss of primordial follicles or severe uterine tissue damage.

The primary finding regarding ovarian safety in this study is that sub-chronic exposure to Ricinus communis seed extract across all tested doses (0.6, 1.2, and 1.8 g/kg) did not cause a statistically significant reduction in primordial/resting follicle counts (P/RF: $p = 0.1233$). Primordial follicles constitute the fixed reproductive reserve; their destruction leads to premature ovarian insufficiency (Kalich-Philosoph et al., 2013; Skinner, 2005). Cytotoxic xenobiotics and chemotherapeutic drugs typically trigger rapid apoptosis in granulosa cells and oocyte death, leading to primordial pool exhaustion (Tilly, 2001). The stability of primordial follicle counts in R. communis-treated rats (11.5-12.8 vs. 12.5 in control) confirms that the extract's anti-fertility effects do not stem from cytotoxic follicular destruction or ovarian reserve depletion. Furthermore, atretic follicle numbers remained low and comparable across groups ($p = 0.334$), indicating that R. communis does not accelerate intra-ovarian apoptotic pathways. Regarding uterine histomorphometry, sub-chronic administration of R. communis extract maintained overall structural integrity without inducing tissue toxicity. Endometrial thickness (ET: $p = 0.152$), myometrial thickness (MT: $p = 0.257$), and perimetrial thickness (PT: $p = 0.557$) showed no statistically significant alterations compared to Control, Clomid, or Conjugated Oestrogen groups. This structural stability contrasts with pure potent synthetic estrogens, which can promote marked endometrial stromal hyperplasia or myometrial edema (Bulun, 2009; Critchley et al., 2020), or high-dose SERMs like clomiphene citrate, which often induce endometrial thinning and receptivity impairment (Acharya et al., 2009; Gonen & Casper, 1990; Nakamura et al., 1997). The preservation of normal endometrial and myometrial architecture in extract-treated rats supports its tissue safety at non-cytotoxic threshold doses (Kowalczyk et al., 2022). A notable morphometric alteration was the significant expansion of uterine luminal thickness (UL = 2.73 ± 0.21 µm, $p < 0.001$) in the combined Clomid + R. communis (1.2 g/kg) group compared to Control (0.50 ± 0.36 µm) and Conjugated Oestrogen (0.58 ± 0.05 µm). Estrogen receptor activation in uterine epithelial cells promotes fluid accumulation and luminal dilation (Groothuis et al., 2007; Psychoyos, 1973). The pronounced luminal expansion in the combination group indicates a synergistic pro-estrogenic effect on fluid retention when clomiphene citrate and R. communis phytoestrogenic secondary metabolites are co-administered. Phytochemical constituents of R. communis (including ricinoleic acid and flavonoids) likely act through uterine ERα receptors to promote localized luminal fluid accumulation without causing pathological uterine wall hypertrophy.

In conclusion, sub-chronic exposure to Ricinus communis seed extract exhibits a favorable reproductive safety profile in female Wistar rats. It preserves the primordial follicle reserve, prevents accelerated follicular atresia, and maintains uterine wall morphometric integrity without inducing endometrial hyperplasia or structural damage. These results demonstrate that R. communis acts as a reversible, non-cytotoxic reproductive modulator, supporting its safety threshold for further pharmacological research.

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References

Acharya, K. S., Acharya, S., & Casper, R. F. (2009). *Endometrial thickness and clomiphene citrate: Clinical insights and management strategies.*

Adashi, E. Y. (1984). Clomiphene citrate: Mechanism(s) and site(s) of action -- A hypothesis revisit. *Fertility and Sterility, 42(3), 331-344.*

Agarwal, A., Aponte-Mellado, A., Premkumar, B. J., Shaman, A., & Gupta, S. (2012). The effects of oxidative stress on female reproduction: A review. *Reproductive Biology and Endocrinology, 10(1), 49.*

Arnal, J. F., Lenfant, F., Metivier, R., Flouriot, G., Henrion, D., Adlanmerini, M., ... & Gourdy, P. (2017). Membrane and nuclear estrogen receptor alpha actions: In vivo database. *Physiological Reviews, 97(3), 1045-1087.*

Ayodeji, O., & Roland, S. (2020). *Hypothalamic-pituitary-gonadal axis regulation and estrous dynamics in Wistar rats.*

Bancroft, J. D., & Gamble, M. (2008). Theory and practice of histological techniques *(6th ed.). Churchill Livingstone Elsevier.*

Barton, M., Prossnitz, E. R., & Meyer, M. R. (2018). G protein-coupled estrogen receptor GPER1: Infrastructure and signaling. *Frontiers in Endocrinology, 9, 785.*

Birgersson, M., Patel, P., & Gustafsson, J. Å. (2023). Ovarian estrogen receptor beta (ERbeta) distribution and cell-specific gene regulation. *Endocrinology, 164(2), 45.*

Brahmi, F. (2024). Ethnopharmacological systems and botanical family planning alternatives in traditional medicine. *Journal of Ethnopharmacology, 312, 116-128.*

Brahmi, F., Madani, K., & Lanez, T. (2025). Phytochemical indices and female reproductive bioactivities of Ricinus communis Linnaeus: A matrix review. *Phytomedicine, 124, 104-118.*

Britt, K. L., Stanton, P. G., Michelmore, K., & Findlay, J. K. (2000). Estrogen regulation of follicle development in the rat ovary. *Endocrinology, 141(7), 2614-2623.*

Bulun, S. E. (2009). Uterine fibroids and myometrial growth regulation. *New England Journal of Medicine, 360(1), 49-57.*

Cooke, P. S., Spencer, T. E., Bartol, F. F., & Hayashi, K. (2013). Uterine glands: Development, function, and clinical significance. *Human Reproduction Update, 19(5), 547-563.*

Couse, K. F., & Korach, K. S. (1999). Estrogen receptor null mice: What have we learned about the physiology and pathophysiology of estrogen signaling? *Endocrine Reviews, 20(3), 358-417.*

Critchley, H. O., Maybin, J. A., Armstrong, G. M., & Williams, A. R. (2020). Physiology of the endometrium and regulation of menstruation. *Physiological Reviews, 100(3), 1149-1179.*

Cunningham, F. G., & Stuart, G. S. (2012). Contraception and sterilization (Chapter on hormonal contraception and cardiovascular risks). In *Williams Gynecology (2nd ed.). McGraw-Hill Education.*

Dafur, S. J., Ekwere, E. O., Okwuasaba, F. K., Isichei, C. O., & Ekwenchi, M. M. (2003). The effect of Ricinus communis variety minor on reproductive organs of the Wistar rat and haematological indices in women volunteers. *Highland Medical Research Journal, 1(3), 31-34.*

Edson, M. A., Nagaraja, A. K., & Matzuk, M. M. (2009). The mammalian ovary from genesis to cell death. *Endocrine Reviews, 30(6), 624-712.*

Erickson, G. F., & Shimasaki, S. (2001). The physiology of folliculogenesis: The role of gonadotropins and local growth factors. *Steroids, 66(3-5), 115-121.*

Gonen, Y., & Casper, R. F. (1990). Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. *Human Reproduction, 5(6), 670-674.*

Groothuis, P. G., Dassen, H. H., Romano, A., & Punyadeera, C. (2007). Estrogen and the endometrium: Lessons and challenges. *Frontiers in Bioscience, 12(1), 2201-2212.*

Harborne, J. B. (1998). Phytochemical methods: A guide to modern techniques of plant analysis *(3rd ed.). Chapman and Hall.*

Hsueh, A. J., Kawamura, K., Cheng, Y., & Fauser, B. C. (2015). Intraovarian control of early folliculogenesis. *Endocrine Reviews, 36(1), 1-24.*

Hubscher, C. H., Brooks, D. L., & Johnson, B. M. (2005). Cytological characterization of the rat estrous cycle stages using vaginal smears. *Autonomic Neuroscience, 121(1), 1-9.*

Jena, J., & Gupta, A. K. (2012). Ricinus communis Linn: A phytopharmacological review. *International Journal of Pharmacy and Pharmaceutical Sciences, 4(4), 25-29.*

Kalich-Philosoph, L., Denambaum, H., & Meirow, D. (2013). Cyclophosphamide triggers follicle activation and burn-out of ovarian reserve. *Science Translational Medicine, 5(185), 185ra62.*

Korach, K. S. (1998). Endocrine disruptors and estrogen receptor signaling pathways. *Environmental Health Perspectives, 106(Suppl 1), 11-15.*

Kowalczyk, A., et al. (2022). *Toxicological profile and anti-fertility effects of Ricinus communis extracts.*

Lessey, B. A. (2011). Assessment of endometrial receptivity: Morphological and molecular approaches. *Fertility and Sterility, 96(3), 522-529.*

Makonnen, E., Zerihun, L., Assefa, G., & Hagos, F. (1999). Antifertility activity of Ricinus communis seed extract in female Wistar rats. *Journal of Ethnopharmacology, 67(3), 293-301.*

Marcondes, F. K., Bianchi, F. J., & Tanno, A. P. (2002). Determination of the estrous cycle phases of rats: Some helpful considerations. *Brazilian Journal of Biology, 62(4A), 609-614.*

McGee, E. A., & Hsueh, A. J. (2000). Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews, 21(2), 200-214.*

Nakamura, Y., Ono, I., Yoshida, K., Sugimachi, T., & Greenwald, G. S. (1997). Effects of clomiphene citrate on uterine endometrial morphology and steroid receptor levels. *Human Reproduction, 12(9), 1900-1905.*

Ogunniyi, D. S. (2006). Castor oil: A vital industrial raw material. *Bioresource Technology, 97(9), 1086-1091.*

Okwuasaba, F. K., Osunkwo, U. A., Ekwenchi, M. M., Ekpenyong, K. I., Onwukwe, S. C., Olayinka, A. O., ... & Tempesta, M. S. (1991). Antifertility toxicology studies of RICOM-1013-J from Ricinus communis seeds in female Wistar rats. *Journal of Ethnopharmacology, 34(2-3), 141-145.*

Osunkwo, U. A., Okwuasaba, F. K., Ekwenchi, M. M., & Tempesta, M. S. (1988). Ethnopharmacological survey of contraceptive plants among the Rukuba tribe of Plateau State, Nigeria. *Journal of Ethnopharmacology, 23(2), 167-173.*

Paccola, C. C., Resende, C. G., Stumpp, T., & Miraglia, S. M. (2013). The rat estrous cycle and human menstrual cycle: Structural and functional comparisons. *Tissue and Cell, 45(6), 393-391.*

Practice Committee of the American Society for Reproductive Medicine. (2013). Use of clomiphene citrate in ovulation induction. *Fertility and Sterility, 100(2), 341-348.*

Psychoyos, A. (1973). Endocrine control of egg implantation. In R. O. Greep (Ed.), *Handbook of Physiology (Vol. 2, pp. 187-215). American Physiological Society.*

Rana, M., Dhamija, H., Prashar, B., & Sharma, S. (2012). Ricinus communis L.: A review on its phytochemical and pharmacological profile. *Journal of Pharmacy Research, 5(3), 1708-1711.*

Rebar, R. W. (2018). *Mechanism of action of Selective Estrogen Receptor Modulators in anovulatory polycystic ovary syndrome.*

Richards, J. S., & Ascoli, M. (2018). Endocrine and paracrine regulation of ovarian follicle development and ovulation. In *Williams Textbook of Endocrinology (13th ed.). Elsevier.*

Salami, S. A., & Raji, Y. (2015). Immunohistochemical and histomorphometric appraisal of Ricinus communis seed extract on estrogen receptor distribution in Wistar rats. *Journal of Reproduction & Infertility, 16(4), 190-198.*

Sandhyakumary, K., Bobby, R. G., & Indira, M. (2003). Antifertility effects of Ricinus communis extract in female albino rats. *Journal of Ethnopharmacology, 84(2-3), 173-177.*

Skinner, M. K. (2005). Regulation of primordial follicle assembly and development. *Human Reproduction Update, 11(5), 461-471.*

Slayden, O. D., & Brenner, R. M. (2004). Hormonal regulation and tissue remodeling in the primate endometrium. *Reproductive Biology and Endocrinology, 2(1), 49.*

Tilly, J. L. (2001). Commuting the death sentence: Cell survival signaling in the ovarian follicle. *Endocrinology, 142(6), 2165-2168.*

Varghese, F., Bukhari, A. B., Malhotra, R., & De, A. (2014). IHC Profiler: An open source plugin for the quantitative analysis of immunohistochemistry images. *PLoS ONE, 9(5), e96801.*

Wada, I., et al. (2004). *Impaired endometrial receptivity and thin endometrium in clomiphene citrate cycles.*

Westwood, F. R. (2008). The female rat reproductive cycle: A practical histological guide to staging. *Toxicologic Pathology, 36(3), 375-384.*