Original Article

Synergistic Role of Fisetin and Dapagliflozin in Ameliorating Oxidative Damage & Insulin Resistance in Dehydroepiandrosterone Induced Polycystic Ovarian Syndrome in Rats

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Abstract

Objective: This study aims to test how fisetin and dapagliflozin—alone and combined—affect reproductive cycles, blood markers, hormones, oxidative stress, and tissue changes in DHEA-induced PCOS rats.

Materials and methods: This study used 30 female rats split into five groups of six animals each: normal controls, PCOS disease controls, fisetin treatment, dapagliflozin treatment, and combination treatment. PCOS was created by giving the rats DHEA injections under the skin for 21 days, followed by 28 days of treatment. The researchers measured body weight, reproductive cycles, organ weights, hormone levels (LH, FSH, testosterone, insulin), cholesterol profiles, oxidative stress markers (MDA, SOD), inflammation markers (TNF-α, IL-6), and examined tissue samples under a microscope.

Results: PCOS induction in rats caused estrous cycle disruption (shown through vaginal cytology), weight gain, elevated LH/testosterone/insulin levels, and compromised antioxidant status. Individual fisetin and dapagliflozin treatments significantly ameliorated these abnormalities, but their combination demonstrated the most comprehensive therapeutic benefits, effectively restoring reproductive cycles, hormonal balance, and metabolic parameters while reducing oxidative damage.

Conclusion: Fisetin and dapagliflozin, particularly when used together, helped reduce PCOS-related problems by fighting inflammation, protecting against cellular damage, and improving insulin function. This likely works by influencing the PI3K/AKT cellular signaling pathway.

Keywords: Polycystic Ovary Syndrome (PCOS); Fisetin; Dapagliflozin; PI3K/AKT Pathway; SGLT2 Inhibitor; Insulin Resistance; Metabolic Syndrome; Dyslipidaemia

Introduction

Polycystic Ovary Syndrome (PCOS) is a complicated hormonal condition that involves ongoing mild inflammation throughout the body, disrupted hormone levels and metabolic health in women of childbearing age (1-3). Beyond irregular menstrual cycles, excess androgens, and infertility, PCOS involves widespread hormonal imbalances and metabolic dysfunction, making diagnosis and treatment challenging due to its variable presentation

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and overlapping reproductive and metabolic symptoms (2, 3). Globally, PCOS affects an estimated 5–15% of reproductive-aged women—roughly 65–70 million cases—yet up to 70% remain undiagnosed, highlighting an urgent need for improved screening and awareness; prevalence is especially high in urban populations, likely driven by lifestyle and environmental factors (4, 5).

Insulin resistance lies at the heart of PCOS, occurring in both lean and overweight women and reflecting intrinsic defects in insulin signaling beyond excess adiposity (6, 7). This metabolic dysfunction significantly increases the likelihood of developing type 2 diabetes: more than 50% of women with PCOS will develop diabetes before reaching 40 years of age, with occurrence rates 2.6 times higher compared to women without PCOS and an age-standardized prevalence that is nearly 6.8 times greater during middle-aged years (8, 9). Impaired insulin receptor and IRS-1 phosphorylation weaken insulin's metabolic effects, while ensuing hyperinsulinemia drives ovarian androgen production, creating a vicious cycle that worsens both metabolic and reproductive outcomes (10-13).

PCOS also features chronic inflammation, oxidative stress, and mitochondrial dysfunction, evidenced by elevated TNF-α and IL-6 and dysregulation of signaling pathways such as AMPK, NF-κB, TGF-β, and PI3K/AKT, which are critical for cell survival and ovarian function (14, 15). Treatments that address both metabolic and inflammatory components—like metformin, which activates AMPK to reduce hepatic glucose output, boost peripheral glucose uptake, lower insulin levels by about 40%, and achieve mean weight loss of 5.8%—have proven most effective, although side effects and residual cardiovascular risks limit its benefit (16).

Recently, SGLT2 inhibitors such as dapagliflozin have emerged as promising alternatives. By promoting glycosuria independent of insulin, dapagliflozin lowers blood glucose, induces modest weight loss, and improves blood pressure and cardiovascular markers (17). It also attenuates hyperinsulinemia, lipotoxicity, oxidative stress, and inflammation via modulation of NF-κB and NLRP3 inflammasome pathways.[17] Early data suggest combining dapagliflozin with metformin enhances glycemic control, further reduces insulin levels, improves lipid profiles, and boosts anti-inflammatory effects—offering a more holistic approach to PCOS management (17, 18).

This study examines whether dapagliflozin can effectively replace metformin in a PCOS model by evaluating insulin sensitivity, hormonal balance, inflammatory markers, and metabolic outcomes. By pairing dapagliflozin with the senotherapeutic flavonoid fisetin, we aim to reveal synergistic or complementary actions that could inform multi-targeted treatments to alleviate PCOS symptoms and reduce long-term risks of diabetes and cardiovascular disease (17, 19, 20).

Materials and methods

Fisetin (≥98% purity) was purchased from Ottokemi Pvt. Ltd., Mumbai, and dapagliflozin was sourced from local pharmacies. Dehydroepiandrosterone (DHEA) for PCOS induction in immature female Wistar rats was also obtained from Ottokemi Pvt. Ltd., Mumbai. All chemicals and reagents used for biochemical, hormonal, and oxidative stress assays were of analytical grade. Histological sections were processed and treated with hematoxylin and eosin staining (H&E) using standard protocols.

Animal and Ethics

Adult female Sprague–Dawley rats (180–220 g) were procured from the Central Animal House, JSS College of Pharmacy, Ooty. Animals were maintained in polypropylene cages under controlled conditions (12 h light/12 h dark cycle, 22 ± 2 °C, 55 ± 5% humidity) with free access to standard rodent chow and water. All procedures were approved by the Institutional Animal Ethics Committee (IAEC/PHARM/2023/07) and adhered to CPCSEA guidelines.

PCOS Induction and Experimental Design

After a one-week acclimatization, rats were randomized into five groups (n = 6 each):

Group I (Normal Control): Received sesame oil (s.c.) for 21 days, then distilled water orally for 28 days.

Group II (PCOS Control): Received DHEA (6 mg/100 g, s.c., dissolved in sesame oil) for 21 days, followed by distilled water orally for 28 days.

Group III (Fisetin): After DHEA induction, treated with fisetin (20 mg/kg/day, p.o., dissolved in DMSO and PBS) for 28 days.

Group IV (Dapagliflozin): After DHEA induction, treated with dapagliflozin (1 mg/kg/day, p.o., in 0.9% saline) for 28 days.

Group V (Combination): Following DHEA induction, received both fisetin (20 mg/kg/day, p.o.)

and dapagliflozin (1 mg/kg/day, p.o.) concurrently for 28 days.

PCOS induction was confirmed by persistent diestrus in daily vaginal smears and significant weight gain relative to controls.

Estrous Cycle Monitoring

Vaginal smears were collected daily using saline-moistened swabs, air-dried, stained, and examined under a light microscope to identify proestrus, estrus, metestrus, and diestrus phases (Figure 1).

Sample Collection

At study end, rats were fasted overnight and anesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood was drawn from the retro-orbital plexus, allowed to clot, and centrifuged to obtain serum. Ovaries and uteri were excised, cleared of fat, and weighed (21, 22).

Biochemical and Hormonal Measurements

Serum LH, FSH, testosterone, insulin, and glucose were quantified using commercial ELISA kits. Lipid profile (total cholesterol, triglycerides, HDL, LDL) was measured via enzymatic colorimetric assays. Oxidative stress markers—MDA and SOD—were determined using TBARS and pyrogallol autoxidation methods, respectively. TNF-α and IL-6 levels were measured by rat-specific ELISA kits.

Histopathology

One ovary per rat was fixed in 10% neutral buffered formalin for 48 h, dehydrated, embedded in paraffin, sectioned at 5 µm, and stained with H&E. Sections were examined for follicular development, cyst formation, corpora lutea, and stromal changes.

Statistical Analysis: Results are expressed as mean ± SEM. Group comparisons were performed using one-way ANOVA followed by Tukey's post hoc test in GraphPad Prism. A p-value < 0.05 was considered significant.

Results

Changes in Body Weight and Organ Measurements: Following 21 days of DHEA administration, rats in the PCOS control group (Group II) showed a notable weight gain compared to normal controls (Group I) ($p < 0.01$). Both ovarian and uterine masses were considerably elevated in the PCOS group. Individual treatments with fisetin (Group III) and dapagliflozin (Group IV) led to moderate reductions in body and ovarian weights, while the combined treatment group (Group V) demonstrated statistically significant decreases ($p < 0.001$) in both measurements, returning values close to normal ranges.

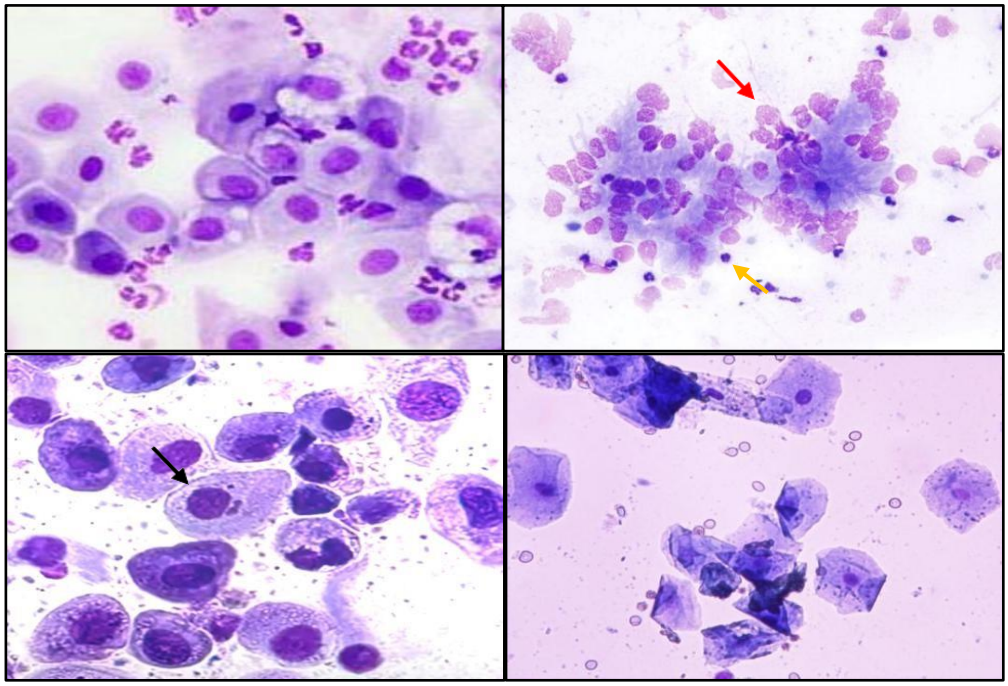

Figure 1: Three predominant cell types identified in vaginal smear samples: nucleated epithelial cells (black arrows); cornified squamous epithelial cells (red arrows); and leukocytes (yellow arrows).

Table 1: Effect of Fisetin & Dapagliflozin on body weight, Estrous cycle and Organ weight DHEA- Induced PCOS Rats

Group	Body Weight (g)	Estrous Cycle (days)	Ovarian Weight (mg)
Control	115.5±0.58	18.3±0.91	63.8±4.7
Disease control (PCOS)	124.4±0.89 #	19.6±1.0 #	62.2±4.94 #
Fisetin	118.4±0.7 *	20.6±0.6 *	61.4±5.3 *
Dapagliflozin	112.5±0.56 *	19.5±0.6 *	61.4±4.6 *
Combo	109.5±0.71 *	17.6±0.9 *	63.8±4.7 *

The data are presented as mean ± SEM (n=6) and #Against control, *Against Disease control.

Changes in Reproductive Cycle: Animals in the PCOS control group remained in persistent diestrus throughout the monitoring period, confirming successful establishment of non-ovulatory cycles. Rats receiving fisetin or dapagliflozin monotherapy showed partial recovery of reproductive cyclicity, with increased occurrence of proestrus and estrus phases. Most remarkably, the combination treatment group showed the greatest improvement, with 83% of animals displaying normalized cyclic patterns by treatment completion (Table 1).

Changes in Hormone Levels: DHEA-treated PCOS rats showed increased serum concentrations of luteinizing hormone (LH), testosterone, and insulin, accompanied by reduced follicle-stimulating hormone (FSH), indicating hormonal disruption. Both fisetin and dapagliflozin treatments markedly reduced LH and testosterone concentrations while improving the LH/FSH ratio ($p < 0.05$). The combination therapy achieved the most significant hormonal correction, with testosterone levels approaching those observed in normal controls (Table 2).

Changes in Lipid Parameters and Blood Sugar: The PCOS control group exhibited substantial increases in total cholesterol (TC), triglycerides (TG), and LDL concentrations, along with decreased HDL levels, reflecting dyslipidemia. Fisetin and dapagliflozin monotherapies modestly improved lipid imbalances. However, combined administration significantly decreased TC, TG, and LDL while increasing HDL ($p < 0.01$). Fasting glucose levels, which were markedly elevated in the PCOS control group, were effectively normalized across all treatment groups, with combination therapy showing the most substantial improvement ($p < 0.001$) (Tables 2, 3).

Changes in Oxidative Damage: PCOS rats displayed significantly increased serum MDA concentrations and reduced SOD activity, indicating oxidative damage. Fisetin and dapagliflozin each independently decreased MDA and pro-inflammatory cytokines while increasing SOD activity. The combination therapy proved significantly more effective ($p < 0.01$), demonstrating superior antioxidant (Table 3).

Microscopic Tissue Analysis: Microscopic evaluation of ovarian sections from normal control rats showed multiple healthy follicles at various developmental stages and well-formed corpora lutea. Conversely, PCOS-induced rats displayed multiple cystic follicles with thinned granulosa cell layers and thickened theca interna, along with stromal overgrowth. Fisetin and dapagliflozin monotherapies partially restored normal follicular structure. However, the combination group showed near-complete restoration of ovarian tissue architecture, including presence of healthy antral follicles and cyst regression (Figure 2).

Discussion

PCOS represents a complex endocrine condition affecting reproductive-aged women, characterized by multiple pathophysiological disruptions including excessive androgen production, irregular ovulation, insulin resistance, and distinctive ovarian changes, frequently accompanied by metabolic dysfunction and systemic inflammation.

Table 2: Effect of Fisetin & Dapagliflozin on FBS, FINS and sex Hormones in DHEA-Induced PCOS Rats

Group	LH (ng/L)	FSH (IU/L)	Testo (ng/mL)	Estradiol (pg/mL)	FBG (mmol/L)	FINS (mU/L)
Control	1.6±0.30	1.8±0.24	0.912±0.19	50±6.98	105.4 ±8.1	12.04 ±1.77
PCOS	1.61±0.27 #	1.84±0.27 #	0.902±0.20 #	50.4±7.44 #	106.4 ±9.2 #	11.96 ±1.65 *
Fisetin	1.58±0.30 *	1.78±0.23 *	0.88±0.19 *	48.8±7.22 *	105.2 ±8.9 *	12.26 ±1.80 *
Dapagliflozin	1.64±0.27 *	1.84±0.27 *	0.918±0.20 *	49.8±6.78 *	106.8 ±9.6 *	11.98 ±1.72 *
Combo	1.56±0.30 *	1.82±0.24 *	0.908±0.21 *	49.4±7.31 *	106 ±8.7 *	12.16 ±1.65 *

The data are presented as mean ± SEM (n=6) and #Against control, *Against Disease control

Table 3: Effect of Fisetin & Dapagliflozin on Serum lipid Profiles and on anti-oxidant markers in DHEA-Induced PCOS Rats

Group	LDL (mmol/L)	HDL (mmol/L)	Triglycerides (mmol/L)	SOD (U/mg)	CAT (U/mg)	TBARS (nmol/mg)
Control	42.6±5.1	48.6±3.6	97±14.2	99±8.4	34.8±4.1	4±0.6
PCOS	43.2±5.3 #	48±3.7 #	97.2±14.7 #	98.8±9.1 #	34.6±4.5 #	4.04±0.6 #
Fisetin	42.2±4.8 *	48.6±3.4 *	96.8±13.9 *	99.4±8.2 *	35±3.8 *	3.94±0.5 *
Dapagliflozin	43±5.1 *	48.4±3.5 *	97±14.5 *	99.2±8.5 *	34.8±4.2 *	4±0.6 *
Combo	42.2±5.0 *	47.6±3.5 *	96.8±14.5 *	99.2±8.7 *	34.8±4.2 *	3.9±0.6 *

The data are presented as mean ± SEM (n=6) and #Against control, *Against Disease control

In our study, we evaluated the therapeutic potential of fisetin, a plant-derived flavonoid compound recognized for its oxidative stress-reducing and inflammation-fighting capabilities, alongside dapagliflozin, an SGLT2 inhibitor recognized for its metabolic advantages, using an established DHEA-induced PCOS rat model. The rationale behind testing this combination stemmed from the hypothesis that these compounds might work through complementary or synergistic mechanisms targeting different pathophysiological aspects of PCOS.

The DHEA-treated control group displayed characteristic biochemical and morphological changes consistent with PCOS pathology. These animals showed markedly elevated serum testosterone levels, increased LH/FSH ratios, hyperinsulinemia, and reduced estrogen and progesterone concentrations. Histological examination supported these biochemical findings, demonstrating cystic follicle formation, reduced corpora lutea, and enlarged ovarian stroma, closely resembling human PCOS characteristics. These observations confirm the effectiveness of DHEA in creating a functional PCOS phenotype appropriate for therapeutic assessment (23).

Treatment with fisetin alone resulted in significant improvement of oxidative stress indicators.

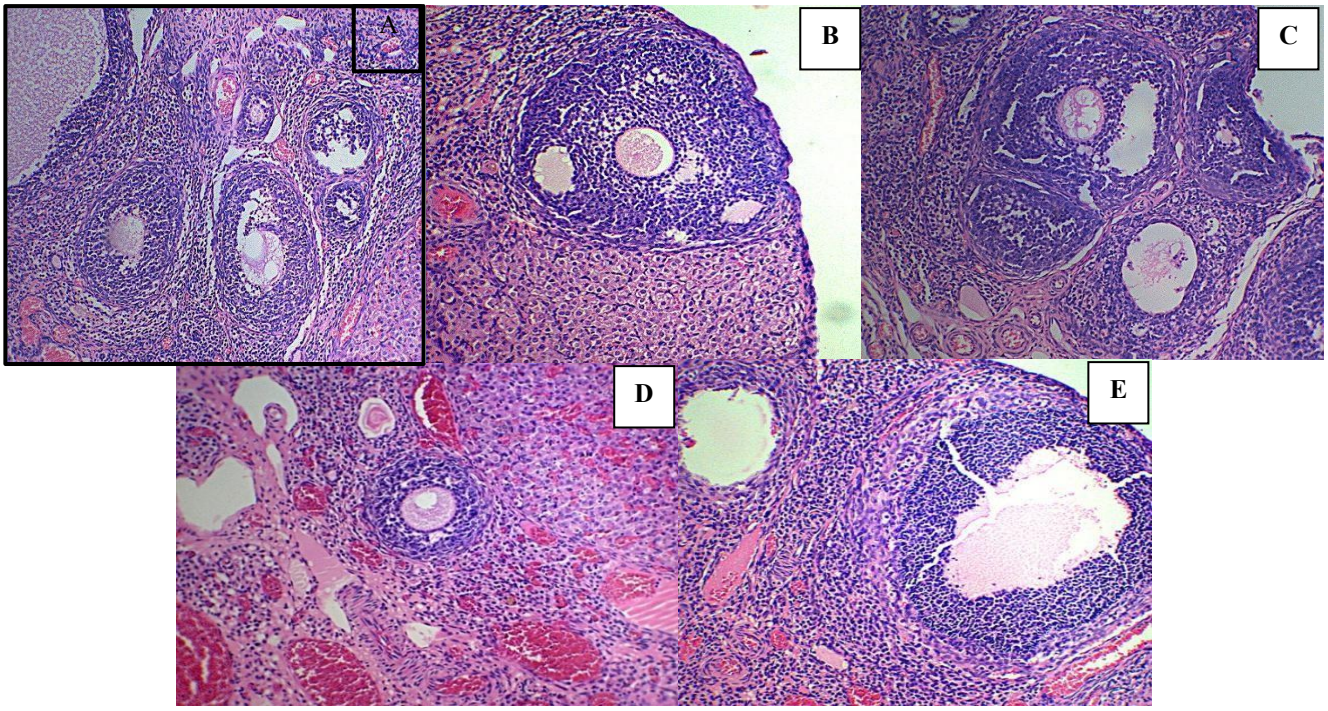

Figure 2: Group A (Control) exhibited normal ovarian architecture with healthy follicles and corpora lutea. Group B (DHEA-induced PCOS) showed numerous cystic follicles, thickened theca layers, and absence of corpora lutea, indicating disrupted folliculogenesis. Treatment with fisetin (Group C) and dapagliflozin (Group D) individually resulted in partial restoration of ovarian morphology, with reduced cystic follicles and reappearance of developing follicles. Notably, Group E (Combination therapy) demonstrated significant histological improvement, closely resembling the control group, suggesting synergistic effects in restoring normal ovarian structure.

Enhanced concentrations of endogenous antioxidants including SOD, catalase, and GSH, combined with substantial reduction in MDA levels, demonstrated decreased lipid peroxidation and overall oxidative damage. These modifications likely contributed to improved follicular maturation, since oxidative stress represents a known factor in follicular developmental arrest and cell death in PCOS. Fisetin also influenced steroidogenic enzyme regulation, particularly affecting 17β-HSD and CYP17A1, both showing downregulation, resulting in a beneficial shift in androgen-to-estrogen conversion. These effects align with previous research highlighting flavonoids' capacity to restore hormonal equilibrium through enzyme regulation and free radical neutralization.

Conversely, dapagliflozin primarily affected metabolic and inflammatory markers. Treated animals showed reduced serum glucose and insulin concentrations, indicating restored insulin sensitivity. Since hyperinsulinemia worsens ovarian androgen production by stimulating theca cells, the observed hormonal improvements may partly result from metabolic correction (24). Dapagliflozin also reduced inflammatory cytokine concentrations, especially TNF-α and IL-6, which are commonly elevated in PCOS and contribute to ovarian dysfunction. This anti-inflammatory action further demonstrates its therapeutic benefits beyond glucose control (25).

Most notably, the fisetin and dapagliflozin combination produced more comprehensive improvements across all measured parameters. Hormonal profiles showed normalized LH/FSH ratios, decreased testosterone, and increased estrogen and progesterone levels, indicating restoration of hypothalamic-pituitary-ovarian axis function. Ovarian tissue examination reflected these biochemical improvements with enhanced follicular development, reduced cyst formation, and restored corpora lutea. Antioxidant and anti-inflammatory markers also showed significant improvement compared to single treatments, suggesting additive or synergistic effects when both compounds were administered together. These findings highlight the important relationship between oxidative stress, insulin resistance, and inflammation in PCOS development. Treatment strategies that simultaneously target these pathways may produce superior clinical results. While fisetin and dapagliflozin address different mechanisms, their combination provides a multi-targeted intervention approach particularly suited for a complex disorder like PCOS.

However, this study has limitations. Molecular or receptor-level mechanistic insights were not explored, and omics-based or pathway-specific analyses such as network pharmacology or molecular docking were outside this work's scope. Future studies should concentrate on clarifying the precise signaling pathways and targets involved, along with evaluating long-term safety and effectiveness in translational models (26).

Conclusion

Taken together, our findings suggest that both fisetin and dapagliflozin exert beneficial effects on DHEA-induced PCOS in rats, addressing key hormonal, metabolic, and inflammatory disruptions. Fisetin primarily improved oxidative balance and modulated steroidogenesis, while dapagliflozin enhanced insulin sensitivity and reduced systemic inflammation. When administered in combination, these agents delivered superior therapeutic efficacy, likely through complementary mechanisms. This dual treatment approach holds promise for integrated PCOS management and provides a compelling basis for further preclinical and clinical exploration into multi-targeted interventions.

Conflict of Interests

Authors declare no conflict of interests.

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