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Improvement of ovarian health and insulin resistance by Pancreastatin inhibitor PSTi8 in a DHEA-HFD-Induced PCOS rat model

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Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder characterized by hyperandrogenism and commonly associated with insulin resistance (IR). According to the WHO 2025 report, PCOS affects 6–13% of women of reproductive age, and up to 70% of affected women remain undiagnosed worldwide. Although insulin sensitizers such as metformin are frequently used to manage PCOS, they are often prescribed off-label and may cause adverse effects. Therefore, there is a need for novel therapeutic candidates capable of disrupting the pathological cycle linking metabolic and reproductive dysfunction. In this study, we investigated the therapeutic potential of the pancreastatin inhibitor PSTi8, an emerging insulin-sensitizing molecule, in a PCOS rat model. The model was established by daily high-fat diet feeding combined with subcutaneous administration of dehydroepiandrosterone at a dose of 60 mg/kg body weight for 21 days, followed by 21 days of treatment with either PSTi8 (10 mg/kg) or metformin (300 mg/kg). Throughout the study, we monitored estrous cycle progression, glucose tolerance, and insulin tolerance. Additionally, ovarian morphology, oxidative stress and inflammatory markers, steroidogenic hormone levels, protein expression, lipid parameters, and insulin signaling pathways were evaluated to assess the therapeutic effects of PSTi8. Our findings indicate that PSTi8 improved IR and

significantly lowered serum levels of insulin, testosterone, estradiol, progesterone, sex hormone-binding globulin, and the LH/FSH ratio. Moreover, PSTi8 restored normal ovarian morphology, normalized the estrous cycle, and corrected dyslipidemia. Treatment with PSTi8 also reduced oxidative stress markers (T-SOD, GSH-Px), and improve gene expression of the inflammatory markers (TNF- α , IL-4). Furthermore, PSTi8 normalized steroidogenic protein expression and enhanced PI3K/Akt phosphorylation in PCOS rats. Collectively, these results demonstrate that PSTi8 exhibits therapeutic efficacy comparable to metformin in ameliorating IR and ovarian dysfunction in this PCOS model.

Biography

Shubhi Yadav is a Senior Research Fellow and a fourth-year PhD research scholar at CSIR–Central Drug Research Institute (CDRI), Lucknow, Uttar Pradesh, India. She has published more than 12 research papers in reputed peer-reviewed journals. She is currently pursuing her doctoral research in biological sciences, focusing on advanced topics in metabolic disorders, reproductive biology, and molecular mechanisms underlying disease pathology. Her work integrates cellular, molecular, and in vivo approaches to explore novel therapeutic interventions. She has actively contributed to multiple collaborative research projects and has presented her findings at national and international conferences. With strong expertise in cell biology, animal handling, biochemical assays, and molecular techniques, she aims to advance scientific understanding and contribute to the development of innovative treatment strategies.

