ABSTRACT

Polycystic Ovary Syndrome is a heterogenous endocrinopathy in reproductive-aged women associated with clinical pregnancy complications, an increased rate of spontaneous abortion/early pregnancy loss, and preterm delivery. Currently, assisted reproductive technology has been used to help numerous infertile couples to have their babies. However, molecular alterations in PCOS pregnancy that originates from the mother, embryo, or both are still under debate. Therefore, the motive of the current study was to investigate the probable molecular cascade to decipher the early pregnancy complications in the letrozole-induced PCOS mouse model. Results from the previous study clearly show that letrozole (an aromatase inhibitor) able to induce PCOS in rodents similar to the human PCOS condition. In the current study, letrozole-treated PCOS animals were developed and allowed to mate with age-control males. These animals exhibited decreased fertility index and disrupted ovarian structure-function on the day-6^{th} of pregnancy. Moreover, the steroid-stimulated control of key regulatory markers (steroid receptors, adhesion phase markers, decidualization marker, proteases, and their inhibitors, key mediators of the LIF-STAT pathway) of early pregnancy was deranged in the embryo implanted region of the uterus in PCOS condition. This could be due to the reduced progesterone signalling and its responsiveness that results in dysregulated molecular cascade, leading to poor pregnancy outcomes in PCOS. Further, targeting them for therapeutic interventions could help us in the management of early pregnancy complications linked to PCOS pathology. In this direction, the present study was an attempt to elucidate the therapeutic potential of phytocompounds present in petroleum ether (PE) extract of *Aloe barbadensis (Aloe vera* gel-AVG 25 and 75 µg/kg/day) when given as a pre-conceptive agent in the improvement of embryo-uterine transmission for the establishment of pregnancy in letrozole induced PCOS mouse model. Our results indicate that phytosterol-containing extract derived from *Aloe vera* gel restores ovarian functions and fertility rate in PCOS animals. The possible mechanism may be due to its regulatory role in the transcription and/or translation of steroid receptors and key early pregnancy marker proteins, mainly by acting as a progestogenic agent. Remarkably, PE extract of AVG is similarly potent as AVG and metformin (a drug used for the treatment of PCOS) towards control of pregnancy complications associated with PCOS, indicating that oral administration of PE extract of AVG in the dose of 25 µg/kg/day before conception for 30 days is adequate for treatment of PCOS pregnancy complications without causing any adverse effect to animals. However, the

study warrants the further characterization of non-polar phytocompounds of AVG that could possibly play a role as a ligand in modifying the targets of pregnancy directly or indirectly. Thus, understanding the possible interaction of the phytocomponents with key molecules of early pregnancy is vital. Although, the screening of molecular interaction between each phytocompounds and target molecules becomes tedious and impractical. Interestingly, our earlier data suggested that campesterol and n-Hexadecanoic acid are possible bio-functional of *Aloe vera* that has proven to have the best efficacy as fertility agents in the non-pregnant state of PCOS. With this rationale, we attempted the molecular docking study of n-Hexadecanoic acid and Campesterol with pivotal pregnancy targets. *In silico* data from the current studies visualized that campesterol has well-established bonds in the binding pocket of the progesterone receptor with the highest docking score. Also, the *in-silico* study has laid the foundation for identifying the best target for phytosterol that mimics, progesterone in early pregnancy molecular events. Thus, the correlation between the *in vivo* data and the binding affinities could impart valuable insight into the therapeutic procedure which may help in the pregnancy complications associated with infertility like PCOS. ***Overall, this is the first study to dissect the pathways of molecular aberration at the maternal-fetus interfaces underlying PCOS mothers. Also, this is a study where campesterol containing a fraction of Aloe vera gel could be considered an indigenous herbal alternative to be a pre-conceptive drug for the management of PCOS fertility, without adverse effects, thereby adding new efficacy to economic important herb "Aloe".***