ABSTRACT

Aloe barbadensis Mill., commonly known as *Aloe vera* has been widely used in the traditional medicine in several parts of the world for its health, beauty and medicinal properties. In India, Kumaryasava, a popular *Aloe vera* gel preparation has therapeutic value in treatment of female reproductive disorders like menstrual disturbances and menopausal problems. Despite their widespread use, only a limited number of studies have probed into the scientific evidence for their varied bioactivities. Previous studies have highlighted the potential of *Aloe vera* gel towards management of polycystic ovarian syndrome (PCOS) by improving the ovarian structure- function as well as the metabolic complications associated with the pathology. However, the exact phytocomponents from non-polar petroleum extract that is involved in the modulation of dysfunctional ovarian-structure function along with metabolic modulation is still not been identified. Thereby it is essential to isolate and identify of the bioactive molecule/s from *Aloe vera* gel and studying their molecular targets will underpin the treatment regime for PCOS. In this context, the current study was aimed at isolating and characterizing the bioactive non-polar phytocomponent/s of *Aloe vera* gel by different chromatographic techniques and their bioactivity was evaluated using *"in-silico", "in-vitro"* and *"in-vivo"* approaches. To achieve the above goal, Petroleum ether extract of *Aloe vera gel* was subjected to column chromatography and TLC was performed. Based on separation and bioassay, five potential fractions were isolated namely, LP1, LP2, LP3, LP4 and LP5 containing n-Hexadecanoic acid, Cholesta-3,5-diene, Campesterol acetate, b-Sitosterol and Stigmasterol acetate with an abundance of 97.07%, 96.04%, 94.03%, 92.45% and 87.49% respectively were identified as modulators of key steroidogenic and metabolic targets associated with PCOS. Further, data from *"in-silico", "in-vitro"* and *"in-vivo"* bioassays have demonstrated that amongst all the isolates, LP1 and LP3 were found to exhibited better binding affinities with Androgen Receptor, Estrogen Receptor beta, Progesterone receptor, Aromatase, Steroidogenic Acute Regulatory protein. 3 beta hydroxysteroid dehydrogenase and p-Insulin receptor. In addition to this, LP3 was found to be a potent stimulatory modulator for estradiol and progesterone biosynthesis whereas, LP1 exhibited a good anti-androgenic effect as well as it could modulate the insulin receptor expression. The possible mechanism by which LP1 and LP3 elicit their bioactivity is by modulating the gene expression of gonadotropin receptors, steroid receptors and other key steroidogenic marker proteins. With the high binding affinity of these bioactives, good pharmacokinetic (ADMET) properties and potential to modulate steroidogenic and metabolic targets. LP1 and LP3 may be used in the treatment of PCOS as an alternative to

metformin (most common therapeutic agent for PCOS). However, molecular detailing of these bioactives in pathways of PCOS phenotype still needs to understood. Overall, the study has identified potential bioactives from *Aloe vera gel*, that can be further studied and has paved way for researchers to understand their efficacy of this economical enriched herb. ***This is the first study which holistically demonstrates the bioactivity of the non-polar phytochemicals isolated from Aloe vera gel towards management of reproductive and metabolic complication associated with PCOS at the molecular level. Further, it is interesting that new facet has been added, giving an opportunity for development these bioactives independently or in combination as new indigenous "phytodrug" with safety for multiorgan endocrinopathy of PCOS.***