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## EVALUATION OF *ALOE BARBADENSIS* MILL. GEL ON LETROZOLE INDUCED POLYCYSTIC OVARIAN SYNDROME (PCOS) RAT MODEL- A DOSE DEPENDENT STUDY

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### Keywords:

Polycystic Ovarian Syndrome, Metabolic syndrome, Anovulation, Letrozole, *Aloe vera* gel, Insulin resistance

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**ABSTRACT:** Aim of the present study was to investigate the dose dependent effect of *Aloe vera* gel [5 mg, 10 mg, 15 mg of dry weight for 60 days each group] on Polycystic Ovarian Syndrome (PCOS) rat model. Charles Foster adult female (200-225 g weight) rats were treated orally with letrozole (non-steroidal aromatase inhibitor) at a dose of 0.5 mg/kg body weight daily for 21 days for PCOS model development, that were further treated orally daily with *Aloe vera* gel (AVG) at various doses of [5 mg, 10 mg, 15 mg of dry weight for 60 days. Parameters that were evaluated included glucose tolerance profile, estrus cyclicity, ovarian steroidogenic enzymes activities along with hormonal profile (Insulin, Progesterone, Testosterone, and Estradiol). Treatment of AVG daily at doses of 10 mg and 15 mg for 60 days in PCOS rat model demonstrated most beneficial effect by restoring the ovarian steroid status, by modulation of key steroidogenic activities, along with structural changes. This could be attributed to phyto-components present in the extract. The preliminary study explores the effective dose of *Aloe vera* gel extract as a possible therapeutic agent in prevention and management of such type of infertility.

**INTRODUCTION:** Polycystic Ovarian syndrome (PCOS) is the most common endocrine disorder among women of reproductive age<sup>1, 2</sup>. Polycystic Ovary Syndrome is characterized by Hyperandrogenism, insulin insensitivity and chronic anovulation<sup>3</sup>. Newer data from literature has indicated PCOS is an important metabolic disorder, which is associated with an increased risk of type 2 diabetes mellitus as well as for the metabolic syndrome<sup>4</sup>. In PCOS, ovarian hyperandrogenism is mainly attributed to steroidogenic defects in theca cells of ovary.

Increased Luteinising hormone (LH) and increased insulin levels mainly amplify the intrinsic abnormality of thecal steroidogenesis<sup>5</sup>. Excess androgen activity may hinder gonadotropin-induced estrogen and progesterone synthesis in PCOS follicle<sup>5</sup>. Normally, testosterone and androstenedione are converted to estradiol and estrone respectively with help of P450 aromatase, which plays an important role in the hormonal balance in the ovary. However, decreased activity of this enzyme results in the increased ovarian androgen production; thus, leading to development of PCOS condition<sup>6, 7</sup>.

Women having PCOS condition suffering from insulin action and secretion. As central core of PCOS is insulin resistance, current available mode of treatment is use of insulin sensitizers like metformin<sup>8, 9</sup>. But, these drugs have their own side effects upon

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prolong usage<sup>10</sup>. Hence, currently researchers are exploring alternative therapy to treat and manage the infertility disorders<sup>11, 12</sup>. In this context, many scientists have demonstrated the role of medicinal plants in the control of hyperglycemic condition<sup>13, 14, 15</sup>. One such plant, which has been explored, Recently, *Aloe barbadensis* Mill. that has shown to have several medicinal effects including hypoglycemic effect<sup>16, 17, 18, 19, 20</sup>. As explained earlier, PCOS is linked with insulin resistance; thereby it could be plausible that *Aloe vera* gel could possibly manage this disorder. In view of the above hypothesis, the present study was to study the efficacy of *Aloe vera* gel in dose dependent manner, which could be act as a possible therapeutic dose which could manage and prevent the metabolic syndrome.

## MATERIALS AND METHODS:

**Chemicals:** Dihydroepiandrosterone (DHEA), 17  $\beta$ -estradiol, Bovine serum albumin (BSA) was obtained from Sigma Inc, USA. Indole Nitro tetrazolium (INT), reduced NAD, Tween-20, NAD were purchased from Sisco research laboratories Ltd., Mumbai, India. ELISA Kits purchased from Dia Metra, Germany. All other chemicals were purchased locally. Letrozole, GOD-POD (Glucose oxidase-Peroxidase) kits purchased locally.

**Animals:** Adult Charles foster female albino rats (weight 180–225 g) were used for the study All animals were housed in cages maintained in an ambient temperature of  $25 \pm 1$  °C and 45.5% relative humidity, with a photoperiod cycle of 12 h: 12 h (light and dark) with food and free access of water as per recommendations. All the experimental protocols were ethically cleared by institutional committee as per CPCSEA guidelines (Reg.no. 938/A/06/CPCSEA).

**Development of PCOS in Rats:** Adult virgin female rats (3-4 month) exhibiting regular estrus cyclicity, weighing 180- 225 g was maintained under controlled conditions of light and temperature; with having free access to diet and water. Animals were treated orally with Letrozole (0.5 mg/kg body weight) daily<sup>21, 22</sup> for 21 days, while control group received carboxymethylcellulose (1% CMC). All

experimental animals that were induced for PCOS phenotype, exhibited glucose intolerance, irregular ovarian cyclicity with presence of cysts and altered steroidogenic activity were considered as chosen for AVG treatments.

**Preparation of *Aloe vera* gel:** *Aloe barbadensis* Mill. (Voucher no. PSN 723) was compared with the specimen (Bhatt 2486, 653, 279, JVJ 448) lying with the nationally recognized BARO Herbaria of the Department of Botany, The M.S. University of Baroda, Vadodara, Gujarat, India was selected for preparation of extract.

Fresh mature *Aloe vera* leaves (3.5 years old) were taken and washed with water. Later, the leaves were incised with the sterilized knife and allowed to stand by for two hrs in order to remove the aloin. Later, the gel was removed by separating the epidermis and was sonicated to get a homogenous gel.

***Aloe vera* gel (AVG) Treatment:** PCOS positive animals were further divided into 2 groups- one group contained animals which was treated with Letrozole for PCOS model and these rats that did not receive any treatment and served as control rats. Letrozole induced rats were considered for study showed altered estrus cyclicity, altered steroid levels. These PCO rats were divided into various groups and received *Aloe vera* gel in dose dependant manner.

Following were the group of animals: a) 5 mg for 60 days; b) 10 mg for 60 days; c) 15 mg for 60 days. It is important note that 60 days were chosen as treatment period as *Aloe vera gel* is stable up to 60 days evaluated by HPTLC profiling (data not shown). All the groups were continuously monitored for cyclicity, body weight and insulin sensitivity by OGTT test. At the end of treatment, rats were sacrificed; tissues were excised and assessed for various biochemical parameters.

**Histological analysis:** Ovary was removed and fixed in Bouins fixative. Histological examinations of ovary from all groups were carried out using standardized histological methods. Section of 5  $\mu$ m thickness were cut and stained with Hematoxylin-Eosin<sup>21</sup>. Histological sections were made using five samples of each group under light microscope.

**Oral Glucose Tolerance Test (OGTT):** OGTT was performed after 12 hrs fasting in all rats by the protocol<sup>22</sup>. Blood samples were collected in sodium fluoride-coated bulb. Later, glucose (1 g/Kg body wt) was orally fed to the rats and blood samples were collected at the different time intervals {0', 30', 60', 90', 120', 150'}. Blood was subjected to 3000 rpm for 10 min and plasma was separated. Plasma glucose was estimated using GOD-POD based kit. Those animals that demonstrated unresponsiveness to glucose load after 90 min and exhibited elevated blood glucose at 90' and later time points levels were considered to be positive for PCOS phenotype.

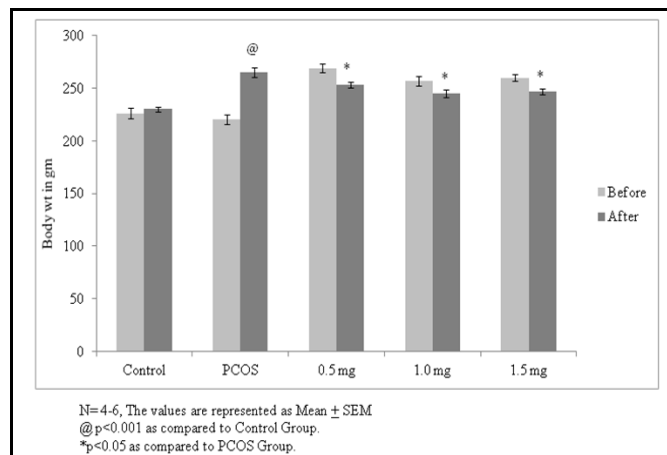
**Enzyme assays:** The key steroidogenic enzymes - 3  $\beta$  Hydroxy Steroid Dehydrogenase (3  $\beta$  HSD) and 17  $\beta$  Hydroxy Steroid Dehydrogenase (17  $\beta$  HSD) were assayed<sup>21</sup>. In brief, 10% ovarian homogenate was prepared in 0.1 M Tris-HCl buffer (pH-7.8) and centrifuged at 10,000 g for 30 min at 4°C. The supernatant was used as a source of steroidogenic enzyme assay and protein content was monitored.

The enzyme assays were carried out in 0.1 M Tris-HCl buffer (pH 7.8) containing NAD (500 $\mu$ M) and the substrate DHEA (100 $\mu$ M) for 3  $\beta$  hydroxy steroid dehydrogenase or 17  $\beta$  estradiol (100 $\mu$ M) for 17  $\beta$  hydroxy steroid dehydrogenase in a total volume of 3 ml. The reaction started by adding the enzyme (100 $\mu$ l) and INT, a color reagent and incubated at 37°C for 1hr. The reaction terminated by the addition of 2.0 ml of phthalate buffer (pH 3.0) and read at 490 nm. The enzyme activity was calculated from the standard curve of NADH and expressed as nmoles NADH formed hr<sup>-1</sup>mg<sup>-1</sup> protein.

**Hormone profile:** Serum insulin level and steroid hormones levels were checked in all animal groups using ELISA kits procured from Diametra Inc, Germany. Sensitivity for method for Insulin is 2 $\mu$ IU/ml; for Testosterone is 0.075 ng/ml; for Progesterone is 0.05ng/ml and for 17  $\beta$  estradiol (8.68pg/ml) at 95% confidence limit. The variability within run replicate is 2% for Insulin, 4.6% for Testosterone ;  $\leq$  5.9% (Progesterone),  $\leq$  9% (17  $\beta$  estradiol) whereas between assay variability 6% (Insulin), 7.5% (Testosterone),  $\leq$  10.5% (Progesterone),  $\leq$  10% (17  $\beta$  estradiol).

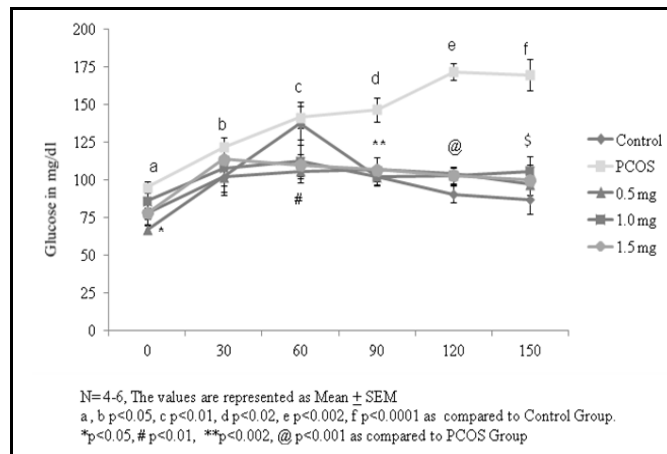
## RESULTS:

*Aloe vera* gel treatment at different doses has been represented in **Figure 1**. PCO untreated rats exhibited significantly increase in body weight (@<0.001) as compared to control. *Aloe* treated PCOS rats (i.e., 5 mg, 10 mg and 15 mg of dry weight of *Aloe gel* doses at 60 days of treatment) (\*p<0.05) demonstrated significant difference as compared to PCOS positive rats. Also, AVG treated rats exhibited regular estrus cyclicity similar to control rats at all doses.



**FIG: 1 DOSE DEPENDENT EFFECT OF ALOE VERA GEL ON BODYWEIGHT IN LETROZOLE INDUCED PCOSRAT MODEL**

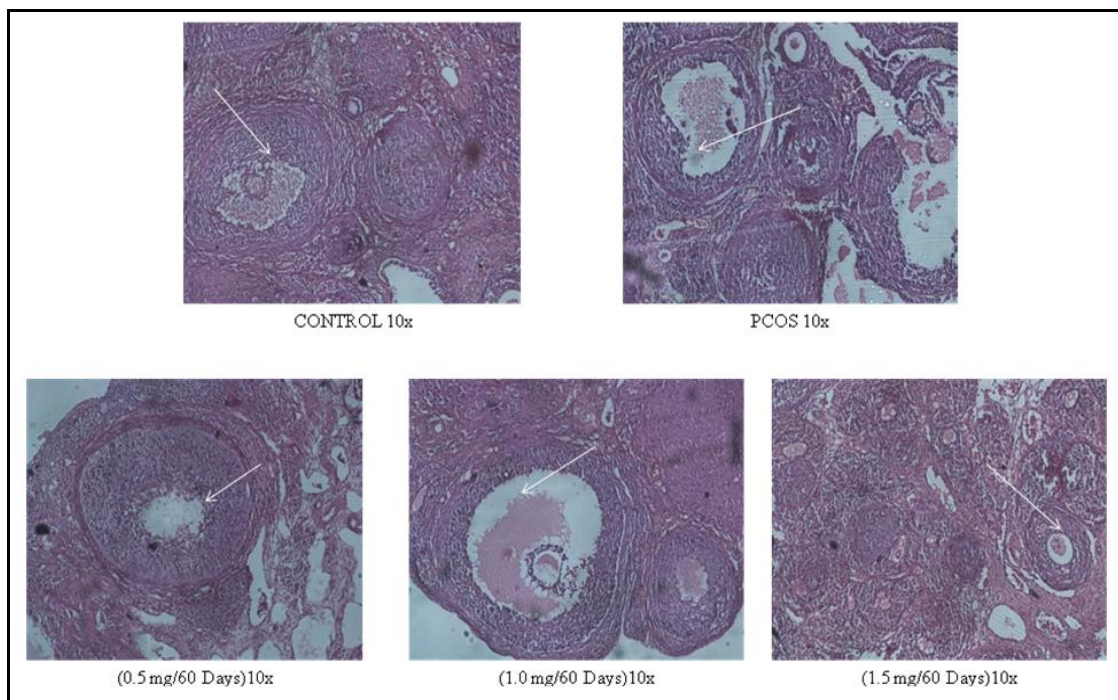
In **Figure 2**, OGTT profile of letrozole induced PCOS group demonstrated a significant glucose intolerance as compared to control group whereas the remaining all groups treated with *Aloe vera* Gel (5, 10, 15 mg) reverted back from glucose intolerant to tolerant stages (\*p<0.05, # p<0.01, \*\*p<0.002, @ p<0.001) as compared to control group.



**FIG 2: DOSE DEPENDENT EFFECT OF ALOE VERA GEL ORAL GLUCOSE TOLERANCE TEST (OGTT) IN LETROZOLE INDUCED PCOS RAT MODEL**

Histological sections of PCOS positive rat ovary exhibits small cysts present in follicles as compared to normal ovary wherein AVG treatment in all groups (5, 10, 15 mg) caused a change in ovarian structure. It is interesting to note that *Aloe*

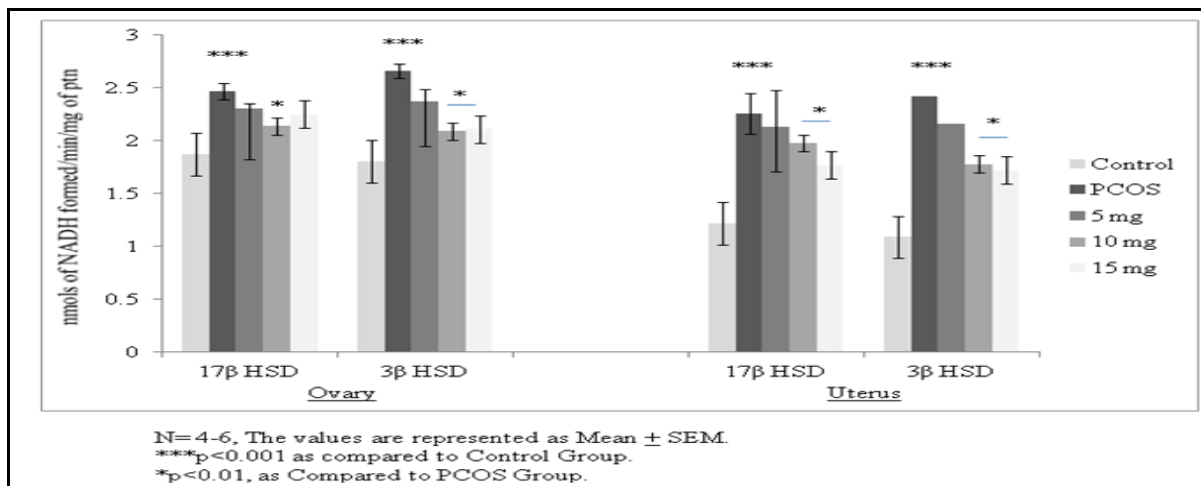
treatment with high dose for longer period causes decrease in atretic follicles and reverting ovary to normalcy when compared to PCOS rat ovary (**Figure 3**).



**FIG 3: DOSE DEPENDENT EFFECT OF ALOE VERA ON OVARIAN HISTOLOGY IN LETROZOLE INDUCED PCOS RAT MODEL**

A significant dose dependent effect was observed on ovarian  $3\beta$  hydroxy steroid Dehydrogenase activity ( $3\beta$  HSD) and  $17\beta$  hydroxy steroid Dehydrogenase ( $17\beta$  HSD) activities Activities (\*\* $p < 0.001$ ) (**Figure 4**). Letrozole induced PCOS group demonstrated a significant increase in activity of  $3\beta$  HSD enzyme as compared to control group wherein *Aloe vera* gel treated groups

demonstrated that modulation of the steroid enzyme activity as similar to control group. *Aloe* treated PCO rats in group of 10 mg and 15 mg demonstrated a significant change in activities as compared to 5 mg dose ( $*p < 0.05$ ) whereas with increase in treatment of dose exhibited more significant change in steroidogenic activity and were comparable to control (**Figure 4**).



**FIG 4: DOSE DEPENDENT EFFECT OF ALOE VERA GEL ON OVARIAN STEROIDOGENIC ENZYME ACTIVITY IN LETROZOLE INDUCED PCOS RAT MODEL**

The serum insulin and steroid hormones - Testosterone, Progesterone, and Estradiol levels measured from all the different groups of animals is represented in **Table 1**. The plasma insulin level was high in untreated PCOS rats (\*\*p<0.001) as compared to control group whereas *Aloe* treated PCOS rats exhibited significantly reduced insulin level in all groups of dose (<sup>@</sup>p<0.001). Further, HOMA-IR index also has been evaluated to check insulin resistance. The PCOS rats demonstrated insulin resistance (HOMA IR- 4.2) whereas *Aloe* treatment reduced the resistance in all group as similar to control group (HOMA IR <3).

In steroid hormones status, testosterone level was altered in PCOS rats (<sup>@</sup>p<0.01) with higher testosterone content. *Aloe* treatment in dose dependent manner caused the testosterone level to be gradually decreased significantly in 10 mg and 15 mg dose to normal levels similar to control group whereas 5 mg dose exhibited non significant change. Other steroid hormones progesterone and estradiol exhibited non significant change in PCOS rats as well AVG treated PCO rats in dose dependent manner.

**TABLE 1: DOSE DEPENDENT EFFECT OF ALOE VERA GEL ON HORMONE PROFILE IN LETROZOLE INDUCED PCOS RATS.**

G GROUPS	Testosterone (ng/ml)	Estradiol (ng/ml)	Progesterone (ng/ml)	Insulin ( $\mu$ IU/ml)	HOMA-IR
CONTROL	0.41 $\pm$ 0.08	0.75 $\pm$ 0.1	46.0 $\pm$ 3.0	7.33 $\pm$ 1.66	1.19 $\pm$ 0.22
PCOS	1.13 $\pm$ 0.15**	0.34 $\pm$ 0.02*	27. $\pm$ 6.24	17.66 $\pm$ 0.88***	4.2 $\pm$ 0.12***
5mg/60 Days	0.65 $\pm$ 0.1	0.56 $\pm$ 0.10	42.6 $\pm$ 2.9	5.0 $\pm$ 0.28###	0.83 $\pm$ 0.04###
10mg/60 Days	0.59 $\pm$ 0.05 <sup>@</sup>	0.66 $\pm$ 0.02 <sup>@</sup>	43.3 $\pm$ 3.70	4.46 $\pm$ 0.14 <sup>@</sup>	0.95 $\pm$ 0.06 <sup>@@@</sup>
15mg/60 Days	0.64 $\pm$ 0.06 <sup>@</sup>	0.67 $\pm$ 0.06 <sup>@</sup>	56.7 $\pm$ 5.4	4.66 $\pm$ 0.44 <sup>@</sup>	0.85 $\pm$ 3.7 <sup>@@@</sup>

N=4 $\pm$ SEM,

P<0.05; \*\*P<0.01; \*\*\*P<0.001 as compared to Control group.

###p<0.001; <sup>@</sup>p<0.01 <sup>@@@</sup>p<0.001 as Compared to PCOS Group

**DISCUSSION:** It has been well documented that PCOS is positively correlated with insulin resistance<sup>8</sup>. The developed PCOS rat model was hyperglycemic, hyperinsulinemic<sup>23, 24</sup> and characteristics of metabolic syndrome<sup>25, 26</sup>. It is proposed that insulin resistance may arise due to increased truncal fat and high level of free fatty acids. The treatment with *Aloe vera gel* decreases glucose insensitivity and thus could prevent an increase in body fat as shown in earlier study<sup>22</sup>. Our Earlier study also exhibited that AVG treatment can alter hyperlipidemic to normo-lipidemic status<sup>23</sup>.

Dose dependent treatment irrespective of dose could cause a reversion to normo-glycemic condition from hyperglycemic condition. However, AVG treatment with higher dose (10, 15 mg for 60 days) demonstrated more significant effect as compared to low dose (5 mg). This could be attributed to the nutritionally rich phytosterols and phyto-phenols component present in the plant<sup>15, 27</sup> that helps to recover the syndrome and could be able to sensitize the insulin receptors for the glucose uptake. Also, it should be noted that *Aloe*

*vera gel* has enriched fibers that could increase transit time for diet to be get absorbed which could modulate glucose homeostasis<sup>28</sup>.

In our study, PCO rat's demonstrated the formation of empty cysts with follicular fluid which is similar to ovarian histology was reported earlier<sup>21, 29</sup>. PCOS rats that were treated with AVG demonstrated normal follicular growth which could be correlated with regular estrus cyclicity as demonstrated in this study. The phytosterols present in AVG could be active components and could alter the steroidogenesis and expression of steroidogenic proteins which alter the PCO condition<sup>30</sup>.

It has been indicated that hyper-insulinemia is also positively correlated with estrogen deficiency as in PCOS phenotype<sup>31</sup>. As the estrogen synthesis is inhibited by the use of inhibitor in our model; the 3 $\beta$  HSD activity was higher as compared to 17 $\beta$  HSD activity and androgen production will be higher rather than estrogen production<sup>32</sup>; this will affect the hormonal balance (LH: FSH ratio). In present study, AVG treatment reversed the activity

of  $3\beta$  HSD activity of PCO rats to normalcy and was comparable to control. The reversion in steroid status could be positively correlated with phytosterols present in the AVG. Recent reports have suggested the presence of phytosterols like sitosterol, stigmasterol and other sterols may contribute to cholesterol lowering effect<sup>33,34</sup>.

*Aloe vera* gel is well known for different rich phyto-components, one of it phyto-component namely,  $\beta$ -sitosterol reported that long term exposure decreases plasma testosterone concentration and alter gonadal steroidogenic acute regulatory protein (StAR) expressions<sup>30</sup>. Phytosterol mixture and its oxidation products have a modulatory effect on steroidogenesis in gold fish<sup>35</sup>. Many flavonoids have been reported to have direct effect on  $3\beta$  hydroxysteroid dehydrogenase ( $3\beta$  HSD) and control the hormones production (Cortisol and Testosterone)<sup>36, 37</sup>. These phyto-components present in gel may act important role in modulation of ovarian steroidogenesis and H-P-G axis.

Our previous study demonstrated that AVG is rich in phytosterols and polyphenols that could be the active component to control the hyperglycemic condition and modulate steroidogenesis<sup>28, 30</sup>. Hypoglycemic potential of phytosterols has been reported by several workers<sup>15</sup>. In addition, polyphenols are powerful agents for diminishing glucose absorption and modifying glucose and insulin levels in diabetic mice<sup>38</sup>. Also, one report has reported the role of polyphenol rich extract from green tea as insulin receptor sensitizer in mice<sup>39</sup>.

Hormone profile in the present study clearly demonstrates that *Aloe* have potential to sensitize the insulin receptor and reduced insulin level; thereby reverting insulin resistant state to sensitive status as shown by HOMA-IR change. Interestingly, the extract also has a potential to decrease androgens and increase estrogen in PCO phenotype after AVG treatment. The change in hormones correlate with change in steroidogenic activity as represented in the current study. However, there is no report wherein effect of phytosterols or polyphenols on steroidogenic enzymes has been observed.

This study has clearly evaluated the efficacy of *Aloe vera* gel in dose dependent manner on letrozole induced PCOS rat model which suggests 10 mg dry weight of AVG treatment for 60 days is the potent dose for the reversion of PCO phenotype. Lower dose of AVG was unable to demonstrate significant change in steroid status suggesting that the amount of phytosterols was insufficient to modulate its effect. It is to be noted at high concentration of 15 mg of AVG was showing similar effect as 10 mg. This may be due to saturation in concentration of phytosterols that might have achieved, thus showing similar effect at both 10 mg and 15 mg doses. However, saturation kinetics needs to be evaluated to emphasize this hypothesis.

Thus, it can be concluded from the present study that 10 mg dry weight of *Aloe vera* gel for 60 days seems to be optimum dosage to render maximum efficacy. However, several detailed studies still remain to be done, to identify the active ingredient at this concentration that could help us in management and prevention of this epidemic of future.

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