Asian Research Journal of Gynaecology and Obstetrics

Volume 8, Issue 3, Page 5-11, 2022; Article no.ARJGO.94581

The Role of Alpha-Lactalbumin with Myoinositol in the Treatment of PCOS: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/94581

Review Article

Received: 02/10/2022
Accepted: 07/12/2022
Published: 10/12/2022

ABSTRACT

Polycystic Ovary Syndrome (PCOS) presents commonly in women of reproductive age group, and has a multifactorial pathogenesis involving insulin resistance and androgen excess, influenced by obesity, diet, lifestyle, metabolic factors, stress, and environmental factors. Inositols (myoinositol-MI, D-chiro inositol-DCI) are part of the therapy options to address insulin resistance in PCOS. However, many women may be inositol nonresponsive due to competitive reduction of inositol intestinal absorption, gut dysbiosis and chronic inflammation. Addition of alpha-lactalbumin can help increase intestinal absorption of inositols, as well as improve gut dysbiosis and inflammation, along with reducing insulin resistance. Presented here is a review of studies that have shown improved rates of ovulation, MI absorption and levels, as well as metabolic and hormonal parameters, when alpha-lactalbumin is added to myoinositol.

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Keywords: PCOS; myoinositol; insulin resistance; alpha-lactalbumin; inositol resistance.

1. INTRODUCTION

"Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders in premenopausal women, and presents with signs and symptoms of androgen excess and ovarian dysfunction" [1]. "Androgen excess (hyperandrogenaemia) causes increased insulin production, female hormonal imbalance (increasing luteinizing hormone LH to follicular stimulating hormone FSH ratio), acne and hirsutism" [2]. "Hyperandrogenism inhibits follicular development, that can lead to microcysts in the ovaries, anovulation, and menstrual abnormalities like oligomenorrhea or amenorrhea. The prevalence of infertility in women with PCOS can be as high as 70-80%, while almost 80% of anovulatory infertility cases are due to PCOS" [3].

"PCOS affects 5% to 10% of females in the reproductive age group. Studies from India have shown prevalence rates of 9-18% in young adolescent females, with up to 22.5% in urban women" [4]. "More and more evidence suggest that multiple factors are involved in the etiology and pathogenesis of PCOS that can range from insulin resistance and hyperinsulinemia, obesity, diet and lifestyle, metabolic factors, stress, and environmental influences. Women with PCOS are at an increased risk of developing metabolic syndrome, type II diabetes mellitus, abnormal lipoprotein levels, and cardiovascular diseases" [5].

"There is a high incidence of insulin resistance in PCOS patients independent of obesity, and insulin resistance is a major mechanism in developing clinical symptoms and other metabolic complications of PCOS" [6]. Resistance to insulin leads to an increase in free androgen availability, increased insulin concentration, reduced sex hormone binding globulin SHBG, and increased free testosterone level.

Treatment of PCOS comprises of agents that improve insulin sensitivity, and hormonal therapy to attain regular menses and ovulation. There is a renewed interest towards natural therapies in India to treat PCOS holistically and minimize drug related side effects and tolerability issues [7]. Inositols are such a class of therapy in PCOS management that have clinically documented efficacy without side effect concerns.

2. ADDRESSING INSULIN RESISTANCE IN PCOS MANAGEMENT

"Therapies to address insulin resistance like the most well-known metformin (MET) as well as inositols (myoinositol - MI, D-chiro inositol-DCI), are part of PCOS management. MI acts as an insulin sensitizer by restoring the diminished GLUT-4 protein levels and cellular glucose uptake in PCOS, through sodium/myo-inositol transporter (SMIT-1) and phosphorylated AMP-activated protein kinase (p-AMPK) dependent mechanism. MI also exerts its insulin-sensitizer effects by metabolism and generation of Phosphatidylinositol (4,5)-bisphosphate (PIP2) and Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) that act as a second messenger in the insulin pathway through the activation of the enzyme phosphatidylinositol-3-kinase/protein Kinase B (PI3K/AKT)" [8]. Therefore, the insulin sensitizing action of metformin will be limited when deficiency of inositols is present.

A study comparing myo-inositol 1g twice daily with metformin 500 mg thrice daily for 24 weeks, showed that both interventions significantly improved insulin resistance seen by improvement in glucose/ insulin ratio and lipid profile, and decrease in HOMA-IR values [9]. "On comparing both the groups, no statistically significant difference was observed, suggesting that myo-inositol is a useful alternative to metformin for PCOS treatment. Other studies have also shown that metformin and myo-inositol significantly improved insulin sensitivity in PCOS women, and while metformin is still used as first line therapy in PCOS, both MI and MET were found to be almost equally effective in improving biochemical profile. Research has also shown the benefit of synergetic effect of metformin plus myo-inositol versus metformin alone in infertile women with PCOS undergoing ovulation induction, with significant improvement in menstrual cycles (cycle length and bleeding days) and live birth rate in the combination group" [10]. "While MET and MI have been found comparable in parameters like fasting insulin, HOMA (Homeostatic Model Assessment for Insulin Resistance) index, testosterone, SHBG levels and body mass index, there was strong evidence of an increased risk of adverse events among women receiving MET compared to those receiving MI (RR =5.17, 95% CI: 2.91-9.17, p<.001)" [11]. "Metformin, significantly induces nausea, abdominal distress and diarrhea,

thereby reducing patients' compliance while MI is generally well tolerated across the range of therapeutic dosages" [12].

"D-chiro-inositol (DCI), accelerates the dephosphorylation of glycogen synthase and pyruvate dehydrogenase, the rate limiting enzymes of non-oxidative and oxidative glucose disposal" [13]. "The presence of abnormal ovarian ratios of myo-inositol (MI) to D-chiro-inositol (DCI) is seen in PCOS due to hyperinsulinemia, and elevated DCI causes increased androgen production and poor reproductive outcomes" [14]. Therefore DCI should be given only with MI in a 40:1 ratio of MI: DCI for maximum benefit [15]. Studies have shown that combinations of 40:1 ratio of MI:DCI are more effective in reducing the risk of metabolic syndrome, improving metabolic and endocrine parameters, as well as in enhancing the ovarian functions as compared to a mono therapy with MI [16,17]

3. INOSITOL RESISTANCE

Although inositol supplementation is an effective treatment for a large proportion of PCOS patients, around 35% are inositol nonresponsive (inositol resistant) [18]. Myo-inositol and D-chiro-inositol after oral intake, are absorbed at the duodenum and jejunum level. Inositols are taken into the enterocyte using the same transporters as other sugars (i.e., glucose, galactose, etc.): SGLT-1 (Sodium-Glucose Transporter), through which inositols are co-transported with sodium from the intestinal lumen across the intestinal cell, and GLUT-2 (Glucose transporter) by which inositols are released into the bloodstream.

Inositol intake during meals may result in the intestinal co-presence of different sugars that may compete for the same transporters, causing a marked decrease in inositol absorption. Inositol-based drugs or food supplements, the combined presence of sugary excipients such as maltodextrin, sucrose, galactose, etc. may be responsible for a reduction of inositol absorption due to the competition for the same transporters. The presence of a chronic inflammatory state in PCOS leads to gut dysbiosis and metabolic disturbance [19]. This can further reduce absorption of inositols, as well as increase insulin resistance.

4. ALPHA-LACTALBUMIN

"Alpha-lactalbumin is a globular whey protein that constitutes approximately 22% of the proteins in human milk and approximately 3.5% of those in bovine milk. It is an important source of essential amino acids, including tryptophan, lysine, branched-chain amino acids like leucine, and sulfur-containing amino acids, along with bioactive peptides, which possess prebiotic, antibacterial properties, anti-inflammatory and immunomodulatory activities" [20]. Administered orally, it passes undisturbed through the stomach, unlike all the other proteins that precipitate in the gastric environment.

Alpha-lactalbumin (α-LA) offers a novel approach to treat inositol nonresponsive PCOS patients. It can stimulate the secretion of GLP-2 (glucagon-like peptide) [21]. This in turn increases the gene expression of SGLT-1 and GLUT-2 transporters [22,23]. Alpha-lactalbumin also improves the permeability at the tight junctions of the intestinal cells that improves direct absorption of inositols [24]. Co-administration of inositol plus alpha-lactalbumin may be more effective than giving inositols alone, providing a clinical efficacy even in the so-called inositol resistant patients. Therefore, such combinations for PCOS therapy have been developed globally, and MI-DCI with alpha-lactalbumin as chewable tablets is now available in India (Ovamystic™).

"Alpha-lactalbumin and its peptides are involved in various biological processes that can open new additional applications in PCOS. Majority of women with PCOS exhibit gut dysbiosis, which is implicated in PCOS pathogenesis. Due to its prebiotic effect, α-LA can restore gut flora, reduces dysbiosis, and improves insulin resistance, obesity and intestinal inflammation, that are often associated with PCOS" [25-27].

5. SCIENTIFIC EVIDENCE

"The effect of combining alpha-lactalbumin with myoinositol (MI) has been studied in vitro as well as in humans. In a study, 37 PCOS patients, with anovulation and infertility > 1 year were included" [28]. In a preliminary phase aimed at determining MI-resistant PCOS patients, 2g MI twice daily was given for 3 months, and insulin resistance by HOMA (Homeostatic Model Assessment for Insulin Resistance) index and plasma MI levels was assessed. In the main phase, previously selected MI-resistant patients received the same daily amount of MI plus 50 mg α-LA twice daily for 3 months. Ovulation was assessed using ultrasonography, on days 12, 14 and 20 of the cycle. The HOMA index, lipid profile, hormone and MI plasma levels were detected at baseline and at the end of this phase. Following MI

treatment alone (preliminary phase), 23 of 37 women (62%) ovulated, while 14 (38%) were resistant and did not ovulate. In the latter group, MI plasma levels did not increase, and the HOMA-IR did not show a decrease. After this combined treatment, 12 (86%) of women unresponsive to MI earlier, now ovulated. Their MI plasma levels were found to be significantly higher (almost double of baseline). Hormonal and lipid profile parameters also showed significant improvement (Fig. 1).

In another study, 34 normal weight or overweight patients (14 in Mexico and 20 in Italy), aged 18 to 40 years, with anovulation and infertility > 1 year and insulin resistance diagnosed by HOMA-index, were evaluated [29]. Patients were given 2 g MI + 50 mg alpha-lactalbumin with 200 ug folic acid for 6 months. Significant decrease at 3 and 6 months was seen in HOMA-index, insulin levels, androgen (testosterone and androstenedione) levels, and metabolic parameters (Fig. 2). The improvement was more relevant when the starting point was further away from the normal range. The reductions in testosterone and lipid parameters in this study were similar to the study discussed earlier (Fig. 1). No significant adverse effects were detected in both groups of patients. It was concluded that myoinositol given with alpha-lactalbumin improves important parameters in PCOS patients with insulin resistance.

Women diagnosed with gestational diabetes in a study were randomly treated with myo-inositol 2g plus 50mg α-lactalbumin plus folic acid 200ug (treated group) or folic acid 200 ug (control group), for 2 months [30]. Average insulin resistance (HOMA-index) was significantly decreased in the MI +Alpha-LA from 5.2 at baseline to 3.1 at 2 months, while it increased in the control group from 4.5 to 6.1 at 2 months. The difference in HOMA-index between test and control group at 2 months was significant (P=0.0002). Only 6.7% required insulin in treated group compared to 20.3% in control group (P=0.03). The pre-term births were seen to be nil in the treated group compared to 15.2% in the control group. (p = 0.007). No significant difference was seen between groups in other parameters like birthweight or low for gestational age babies, cesarean delivery rate, admissions to neonatal ICU, or development of hypertension.

In a volunteer study, the enhancement of myoinositol absorption with the addition of alpha-lactalbumin was studied [24]. In phase I of this study, subjects, all fasting for 12 hours, received orally 6 g MI in powder form as single dose dissolved in 80 ml water. In phase II, after a washout period of 7 days, the same subjects, fasting for 12 hours, were given an oral dose of 6 g MI and150 mg alpha-LA in powder form, dissolved in 80 ml water. Blood samples were

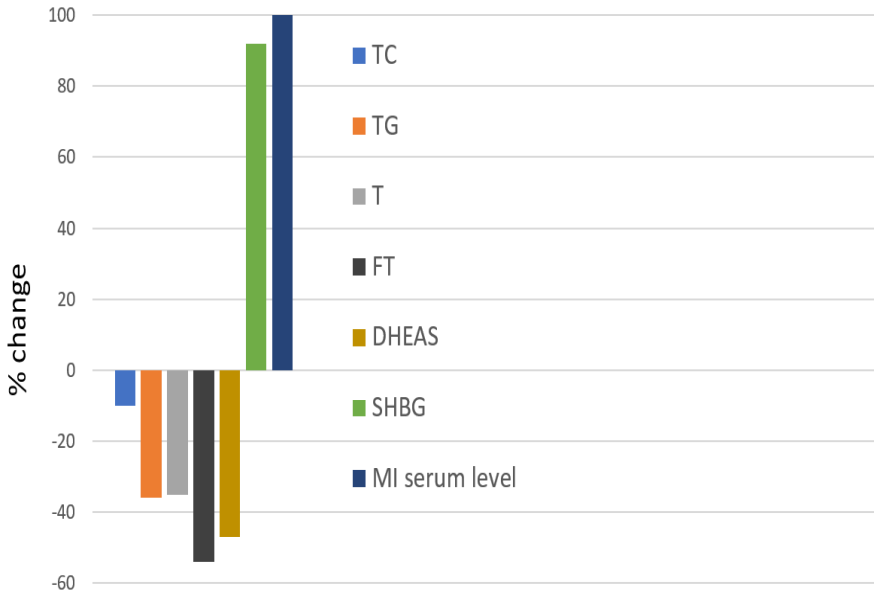

Fig. 1. Percentage change in hormonal and metabolic parameters with Myoinositol+ *Alpha-Lactalbumin* treatment at 3 months in women with resistance to Myoinositol [25]

P<0.05 for all parameters. TC: Total cholesterol; TG: Triglycerides; T: Testosterone; FT: Free Testosterone; DHEAS: Dehydroepiandrosterone sulphate; SHBG: Sex hormone binding globulin; MI: Myoinositol

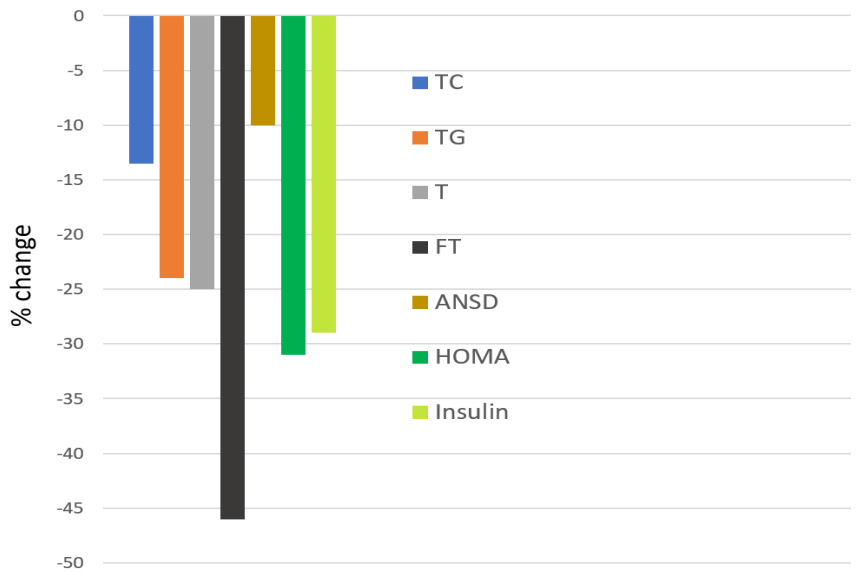

Fig. 2. Average percentage change in HOMA-index, Insulin, hormonal and metabolic parameters with Myoinositol+ *Alpha-Lactalbumin* treatment at 3 months[26]

TC: Total cholesterol; TG: Triglycerides; T: Testosterone; FT: Free Testosterone; ANSD: Androstenedione; HOMA: Homeostatic Model Assessment for Insulin Resistance

collected at pre-dose, (time point 0), and 60, 120, 180, 240 and 300 minutes post-dose. A significant increase in myoinositol absorption was seen on adding alpha-lactalbumin with a 32.4% and 27.5% higher increase in maximum blood concentration (Cmax), and area under the curve (AUC_{0-300}) respectively, as compared to MI alone. While the MI Cmax showed a 3-fold rise from baseline when given alone, there was a 4-fold rise in MI Cmax from baseline when given with alpha-lactalbumin. The same study also had an in vitro component that evaluated monolayer permeability of Caco-2 cells following different experimental treatments. After 4 h transport experiments, TEER (transepithelial electrical resistance) expressed as % of control cells maintained in saline was measured, and MI trans-epithelial passage in Caco-2 cells was assayed (transport rate was expressed as % of MI concentration in the apical compartment / h). The MI transport was 4-times more and the TEER was 3 times less with MI + 10mg/ml alpha-lactalbumin as compared to that seen with MI alone.

6. CONCLUSION

Inositol supplementation is one of the treatment options for managing insulin resistance in PCOS patients, however more than one third women may be inositol nonresponsive or resistant. This is due to competitive reduction of inositol intestinal absorption resulting from the presence of substances using common gut transporters, as well as gut dysbiosis and chronic inflammation. Addition of alpha-lactalbumin helps increase intestinal absorption of inositols, as well as improve gut dysbiosis, inflammation, and insulin resistance. Reviewed studies have shown improved rates of ovulation, MI levels, as well as metabolic and hormonal parameters when alpha-lactalbumin was combined with myoinositol. Larger clinical and real-world studies can add further insights and value in this direction of PCOS therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

Corresponding author is engaged in research on the mentioned brand.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Escobar-Morreale HF. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018; 14(5):270-284.
2. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: A review of treatment options with a focus on pharmacological approaches. P T. 2013;38(6):336-55.
3. Melo AS, Ferriani RA, Navarro PA. Treatment of infertility in women with polycystic ovary syndrome: approach to clinical practice. Clinics (Sao Paulo). 2015;70(11):765-9.
4. Ganie MA, Vasudevan V, Wani IA, Baba MS, Arif T, Rashid A. Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India. Indian J Med Res. 2019;150(4):333-344.
5. Ali AT. Polycystic ovary syndrome and metabolic syndrome. Ceska Gynekol. 2015;80(4):279-89.
6. Shirazi FKH, Khodamoradi Z, Jeddi M. Insulin resistance and high molecular weight adiponectin in obese and non-obese patients with Polycystic Ovarian Syndrome (PCOS). BMC Endocr Disord. 2021:21:45.
7. Pandya MR, Khandheria K, Golwala D. Evaluation of clinical efficacy and safety of ovaryl tablet a herbalformulation in Poly Cystic Ovarian Syndrome (PCOS). Indian Journal of Obstetrics and Gynecology Research. 2015;2(2):73-91.
8. Cabrera-Cruz H, Oróstica L, Plaza-Parrochia F, Torres-Pinto I, Romero C, Vega M. The insulin-sensitizing mechanism of myo-inositol is associated with AMPK activation and GLUT-4 expression in human endometrial cells exposed to a PCOS environment. Am J Physiol Endocrinol Metab. 2020;318(2): E237-E248.
9. Nehra J, Kaushal J, Singhal SR, Ghalaut VS. A comparative study of myoinositol versus metformin on biochemical profile in polycystic ovarian syndrome in women. International Journal of Pharmaceutical Sciences and Research. 2017;8(4):1664-1670.
10. Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: Randomized controlled trial. Gynecol Endocrinol. 2019;35(6):511-514.
11. Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with Polycystic Ovarian Syndrome (PCOS): A meta-analysis of randomized clinical trials. Gynecol Endocrinol. 2019;35(3):198-206.
12. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. Endocr Connect. 2017;6(8):647-658.
13. Larner J. D-chiro-inositol--its functional role in insulin action and its deficit in insulin resistance. Int J Exp Diabetes Res. 2002;3(1):47-60.
14. Unfer V, Dinicola S, Laganà AS, Bizzarri M. Altered ovarian inositol ratios may account for pathological steroidogenesis in PCOS. Int J Mol Sci. 2020;21(19):7157.
15. Nordio M, Basciani S, Camajani E. The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: Comparison with other ratios. Eur Rev Med Pharmacol Sci. 2019;23 (12):5512-5521.
16. Nordio M, Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. Eur Rev Med Pharmacol Sci. 2012;16(5):575-81.
17. Benelli E, Del Ghianda S, Di Cosmo C, Tonacchera M. A combined therapy with Myo-Inositol and D-Chiro-Inositol improves endocrine parameters and insulin resistance in PCOS young overweight women. Int. J Endocrinol. 2016;2016: 3204083.
18. Unfer V. Use of alpha-lactalbumin for the management of PCOS in inositols resistant women. European Review for Medical and Pharmacological Sciences. 2018;22:1873-1874.
19. Zhao X, Jiang Y, Xi H, Chen L, Feng X. Exploration of the relationship between gut microbiota and Polycystic Ovary Syndrome (PCOS): A review. Geburtshilfe und Frauenheilkunde. 2020;80(2):161–171.
20. Layman DK, Lönnerdal B, Fernstrom JD. Applications for α-lactalbumin in human nutrition. Nutr Rev. 2018;76(6):444-460.
21. Izum IH, Ishizuk AS, Inafune A, Hira T, Ozawa K, Shimizu T, Takase M, Hara H. A-Lactalbumin hydrolysate stimulates

glucagon-like peptide-2 secretion and small intestinal growth in suckling rats. J Nutr. 2009;139:1322-1327.

22. Au A, Gupta A, Schembri P, Cheeseman CI. Rapid insertion of GLUT2 into the rat jejunal brush-border membrane promoted by glucagon-like peptide 2. Biochem J. 2002;367:247-254.
23. Petersen YM, Elnif J, Schmidt M, Sangild PT. Glucagon-like peptide 2 enhances maltase-glucoamylase and sucrase-isomaltase gene expression and activity in parenterally fed premature neonatal piglets. Pediatr Res. 2002;52:498-503.
24. Monastra G, Sambuy Y, Ferruzza S, Ferrari D, Ranaldi G. Alpha-lactalbumin effect on Myo-inositol intestinal absorption: *In vivo* and *In vitro*. Curr Drug Deliv. 2018;15(9):1305-1311.
25. Cardinale V, Lepore E, Basciani S, Artale S, Nordio M, Bizzarri M, Unfer V. Positive effects of α-lactalbumin in the management of symptoms of polycystic ovary syndrome. Nutrients. 2022;14:3220.
26. Yamaguchi M, Yoshida K, Uchida M. Novel functions of bovine milk-derived alpha-lactalbumin: Anti-nociceptive and anti-inflammatory activity caused by inhibiting cyclooxygenase-2 and phospholipase A2. Biol. Pharm Bull. 2009;32(3):366-71.
27. Gao J, Guo K, Du M, Mao X. Bovine α-lactalbumin-derived peptides attenuate TNF-α-induced insulin resistance and inflammation in 3T3-L1 adipocytes through inhibiting JNK and NF-κB signaling. Food & Function. 2022; 13:2323-2335.
28. Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women. J. Ovarian Res. 2018; 11(1):38.
29. Hernandez Marin I, Picconi O, Laganà AS, Costabile L, Unfer V. A multicenter clinical study with myo-inositol and alpha-lactalbumin in Mexican and Italian PCOS patients. Eur Rev Med Pharmacol Sci. 2021;25(8):3316-3324.
30. D'Anna R, Corrado F, Loddo S, Gullo G, Giunta LD, Benedetto A. Myoinositol plus α-lactalbumin supplementation, insulin resistance and birth outcomes in women with gestational diabetes mellitus: A randomized, controlled study. Sci. Rep. 2021;11:8866.

Peer-review history:
The peer review history for this paper can be accessed here:
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