Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : https://ijpsdronline.com/index.php/journal

Research Article

To Examine the Potential Effectiveness of *Psidium guajava* in Letrozole-Induced Polycystic Ovarian Syndrome in Female Albino Rats

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ARTICLE INFO

Article history:

Received: 18 September, 2024

Revised: 30 October, 2024

Accepted: 12 November, 2024

Published: 30 November, 2024

Keywords:

Clomiphene citrate, Hormone disturbance, Oxidative stress, Polycystic ovarian syndrome, Pro-inflammatory.

DOI:

10.25004/IJPSDR.2024.160610

ABSTRACT

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder characterized by hormonal imbalances, metabolic disturbances, and ovarian dysfunction. This study aimed to investigate the therapeutic potential of methanol extract from *Psidium guajava* leaves as a natural remedy for alleviating PCOS symptoms in female albino rats. The experimental approach involved assessing critical physiological and biochemical markers both before and after treatment, including body weight, blood levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), ovarian weight, and the FSH/LH ratio. Anti-inflammatory effects were evaluated by measuring inflammatory markers like TNF-α and lipid-derived mediators. Furthermore, a histological analysis of ovarian tissue was performed to observe changes in follicular development and ovarian structure. The results showed that *P. guajava* treatment significantly improved hormonal profiles, reduced inflammation markers, and promoted the regeneration and maturation of ovarian follicles, counteracting hyperandrogenism and inflammation associated with PCOS. These findings suggest that *P. guajava* leaf extract could be a promising adjunct therapy for managing PCOS, supporting endocrine balance, ovarian health, and inflammation reduction. However, further studies are needed to understand the underlying mechanisms and long-term effects of this botanical treatment.

Introduction

The most prominent hormonal ailment harming women is PCOS and is because of overloaded stress, food habits and lifestyle.[1] PCOS causes 6 to 10% of reproductive-age females and is usually related to obesity, insulin resistance, along infertility. However, because of heterogeneity, the exact etiology of PCOS is yet uncertain.[2] PCOS is a complex syndrome marked by hyperandrogenism (hirsutism, acne and alopecia), anovulation (oligo menorrhea, irregular cycles of menstruation, amenorrhea) as well as histology of polycystic ovaries, a variety of metabolic diseases are linked to PCOS, which include atherosclerosis, hypertension, dyslipidemia, cardiovascular and disease type 2 diabetes.[3] Endocrinologically, PCOS patients exhibit high circulating concentrations of testosterone that is unbound in their blood along with a lack of a globulin that binds to sex hormones, with varied elevations of overall testosterone levels. In around 60% of these individuals, the LH/FSH ratio is 3:1 or greater.[4] PCOS has been mostly diagnosed using the Rotterdam standards, which consist of the original National Institutes of Health criteria: Findings of anovulation or oligo- on ultrasonography, The overabundance of testosterone, clinical and ovarian polycystic. [5] The plant *Psidium guajava*, widely known as guava, is indigenous to Asian countries, Mexico, Northern South America and Central America, belonging to the family Myrtaceae.[6] Traditional medicine has employed various phytochemicals to treat diseases such as malaria, nausea, gastroenteritis, diarrhea, digestive disorders, toothache, wounds, sore throat, ulcers, coughs, swollen gums, and a variety of others. This herb is additionally utilized to treat life-threatening illnesses like hypertension, diabetes

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

as well as obesity.[7] The phytochemical examination of the guava leaf revealed that it contains alkaloids, anthocyanins, carotenoids, triterpenes, vitamin C,[8] phenols and tannins, and glycosides. Antioxidants found in guava, especially flavonoids and polyphenols, may mitigate oxidative stress. Guava's antioxidant properties may offer therapeutic advantages because oxidative stress is associated with PCOS and might worsen insulin resistance and reproductive dysfunction. And also has some promising properties like anti-inflammatory, hormonal regulation, Improvement in insulin sensitivity, etc. The leaf extract is rich in antioxidants, which help combat oxidative stress, which is linked to PCOS-related metabolic disturbances and follicular dysfunction. *P. guajava's* safety profile in conventional medicine backs its identification as a naturally occurring, non-toxic solution for PCOS.[7] These properties, along with *P. guajava's* rich history in traditional medicine and diverse biochemical composition, make it a promising candidate for addressing the complex pathology of PCOS. Given that PCOS requires lifelong management rather than a cure, this research aims to examine how this herb and PCOS symptoms are related. Specifically, it seeks to establish how *P. guajava* may contribute to follicular regeneration and maturation, potentially reducing the formation of cysts and alleviating key symptoms associated with PCOS. This research could pave the way for *P. guajava* as a natural, supportive therapy for managing of PCOS.

Materials And Methods

Experimental Animals

The study used healthy adult female Wistar Albino rats of weights 160 to 200 g. While the study was being conducted, all animals were acclimatized for two weeks under standard conditions as mentioned in CPCSEA and animals had free access to a standard diet. IAEC approved the protocols for the research, KCP/IAEC/11/22-23/06/22/12/22

Collection of the Plant Material

Guava leaves were collected from Hebbal, Bangalore, Karnataka, India in the month of May 2023. It was then authenticated by Dr. V. Rama Rao, Central Ayurveda Research Institute, Kanakapura, Bangalore, SMPU/CARI/BNG/2023-24/407.

Preparation of the Plant Extract

P. guajava leaves were collected, rinsed with water then let it dry in the shade. After drying, the leaves were crushed into a very fine powder. Methanol and soxhlation were used to extract the chemical components found in the leaves. For each 100 g of *P. guajava* leaf powder, 500 mL of methanol was utilized. A rotary evaporator is then employed to evaporate the solvent and allowed to air dry for a full day. About 17 g of solvent leaf extracts were found after air drying, and the extract was collected, preserved, and examined further.[9]

Induction of PCOS

Except for the normal control (NS 10 mL/kg,b.w.) group, all of the test animals received treatment with letrozole. For 21 days, where 1-mg/kg was dissolved in 0.5% CMC was taken orally on a daily basis.[10] To confirm PCOS induction, vaginal smears were taken on a regular basis and microscopically examined with Giemsa stain. The doses for the study were selected from the previously published research article.[8,10]

Study Design

The study involved the equal division of 30 female Wistar Albino rats into five groups;

Group 1: The control group, this group administered only normal saline (10 mL/kg b.w) orally from day 1 to 36;

Group 2: The disease control group received letrozole (1-mg/kg b.w) [10] orally from day 1 to 21;

Group 3: Standard drug group, the animals of this group received letrozole (1-mg/kg b.w) orally from day 1 to 21 and clomiphene citrate (1-mg/kg b.w)[10] orally from day 22 to 36 after the confirmation of PCOS;

Group 4: Test drug group, the animals of this group received letrozole (1-mg/kg b.w) orally from day 1 to 21 and Methanolic extract of leaves of *P. guajava* (MEPG) (200 mg/kg b.w)[8] orally from day 22 to 36 after the confirmation of PCOS;

Group 5: Test drug group, the animals of this group received letrozole (1mg/kg b.w) orally from day 1 to 21 and Methanolic extract of leaves of *P. guajava* (MEPG) (400 mg/kg b.w) [8] orally from day 22 to 36 after the confirmation of PCOS.

The disease group animals after 21th day and the animals from other groups on 36th day were deprived overnight and were anaesthetized using Phenobarbital. The cardiac puncture was used to collect blood. The serum was isolated using centrifugation at 1200 rpm. It was used for the determination of pre and post-treatment body weights and ovary weight, serum levels of FSH, LH, testosterone, LH/FSH ratio, lipid peroxidation (LPO), a pro-inflammatory cytokine, and antioxidant enzymes and histopathological study of ovary tissue. (Each rat's ovaries were extracted in formalin (10%) solution for histological examination.)

Vaginal Smear Examination

To examine the estrous cycle, a sample of smear was obtained from rat's vaginal lining using the pipette smear technique. A tiny pipette was used for flushing 0.2 to 0.3 mL, injecting regular saline into the vagina of the rat, and the fluid was then obtained. Then, a coverslip was placed over the drop of the suspension of cells on a microscope slide. In order to stain, WBC dilution fluid was utilized, and the resulting slide was viewed through 10X and 45X microscope lenses. [10]

Statistical Analysis

One-way ANOVA and Tukey's multiple comparison tests, Statistical analysis was performed on the data, and the results were displayed as mean ± standard error of mean. $p < 0.05$ was deemed significant statistically. The statistical analysis was conducted using the Graph Pad Prism 10 program.

RESULTS

Body Weight

The rats' body weight was recorded from the beginning till the study's conclusion. Animals included in the research showed approximately equal initial body weight, which resulted in $p > 0.05$ (non-significant) (Fig. 1). However, final body weights showed significant differences in the disease control group in contrast to normal control and also with the other two treatment groups. The animal's body weights in the letrozole-induced control group increased considerably in comparison to the healthy animals ($^{####}p < 0.0001$) (Fig. 2), whereas the standard group revealed a substantial ($^{**}p < 0.01$) decline in comparison to letrozole induced group. Moreover, the MEPG (400 mg/kg) revealed a noteworthy decrease ($^{*}p < 0.05$) in the rat's body weights following treatment groups.

Effect of MEPG on ovary weights against letrozole-induced PCOS in female Wistar albino rats

Disease control group readings of the ovary weights were found to be increased drastically ($^{####}p < 0.0001$) compared to the control. Clomiphene citrate group animals showcased a significant reduction ($^{****}p < 0.0001$) in ovary weights when correlated with disease control. Whereas both the test groups MEPG (200 mg/kg) and MEPG (400 mg/kg) showed significant decrease ($^{****}p < 0.0001$) in comparison with the control group (Fig. 3).

Effect of MEPG on FSH serum levels against letrozole-induced PCOS in female Wistar albino rats:

Fig. 4 showed that in disease control, the FSH serum levels were found to be increased significantly ($^{\#}p < 0.05$) in contrast to normal control. The standard group's increase was noticeably mild ($^{**}p < 0.01$) in FSH serum levels when compared to the disease control group. In contrast, the MEPG (400 mg/kg) showed a significantly mild increase ($^{*}p < 0.05$) in contrast to a letrozole-induced group. MEPG (200 mg/kg) did not show ($^{ns}p > 0.05$) any significant changes.

Effect of MEPG on LH and serum testosterone levels against letrozole induced PCOS in female rats

LH serum levels were observed to be considerably higher in the group that was given letrozole ($^{####}p < 0.0001$) compared to healthy animals (Fig. 5). The clomiphene citrate group showed a significant reduction ($^{****}p < 0.0001$)

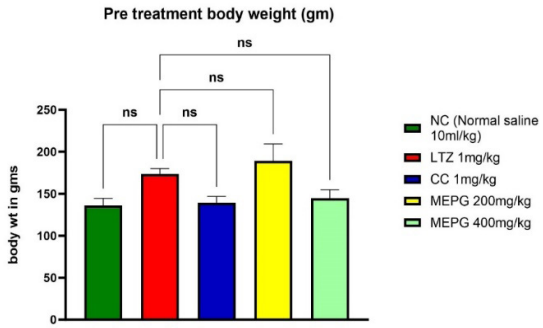

Fig. 1: Pre-treatment body weights. Values are expressed as Mean ± S.E.M, n = 6. $p > 0.05$ ns between the groups

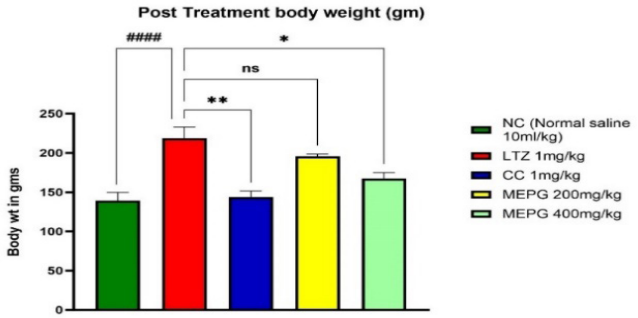

Fig. 2: Post-treatment body weights Values are expressed as Mean ± SEM, n= 6. $^{####}p < 0.0001$ compared to Normal control, $^{**}p < 0.01$, $^{*}p < 0.05$, ns $p > 0.05$ compared letrozole induced group.

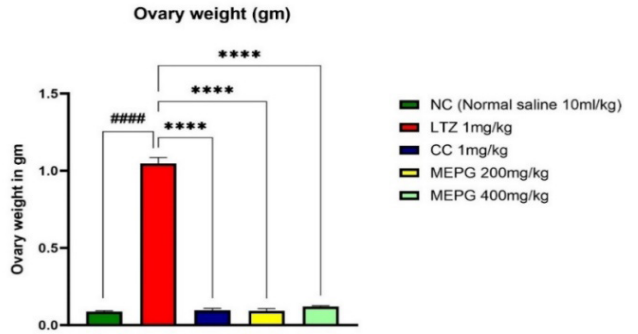

Fig. 3: Values are expressed as Mean ± SEM, n = 6. $^{####}p < 0.0001$, compared to Normal control, $^{****}p < 0.0001$ compared to disease control, Letrozole

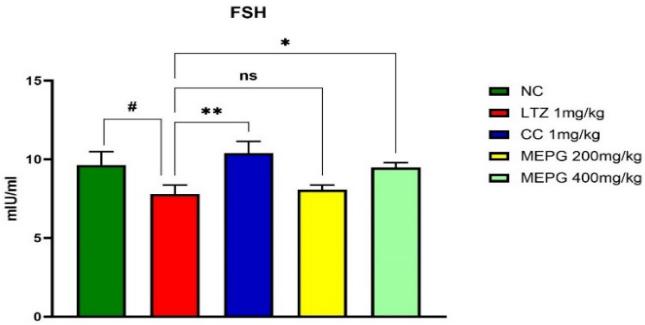

Fig. 4: Effect of MEPG on FSH Values are expressed as Mean ± SEM, n = 6. $^{\#}p < 0.05$ compared to Normal control, $^{**}p < 0.01$, $^{*}p < 0.05$, nsp>0.05 compared to disease control, Letrozole.

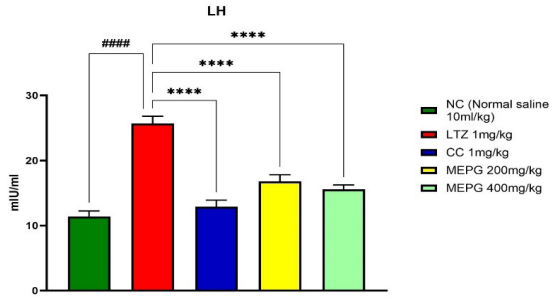

Fig. 5: Effect of MEPG on LH. Values are expressed as Mean ± SEM, n= 6. $^{\#\#\#\#}p < 0.0001$, compared to Normal control, $^{****}p < 0.0001$ compared to disease control, Letrozole.

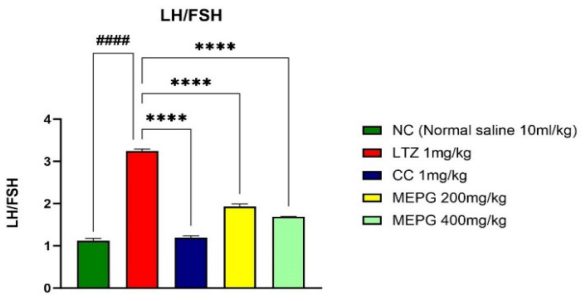

Fig. 7: Effect of MEPG on LH-FSH ratio Values are expressed as Mean ± SEM, n= 6. $^{\#\#\#\#}p < 0.0001$, compared to Normal control, $^{****}p < 0.0001$ compared to disease control, Letrozole.

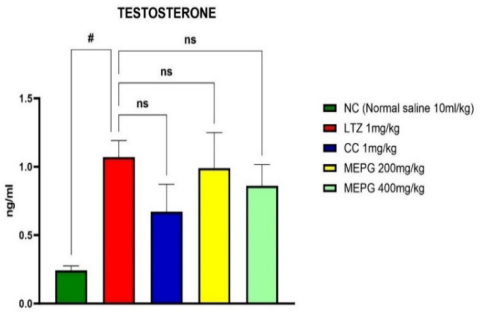

Fig. 6: Effect of MEPG on testosterone. Values are expressed as Mean ± S.E.M, n = 6. $^{\#}$p<0.05 compared to Normal saline, p>0.05ns between disease control and treatment the groups.

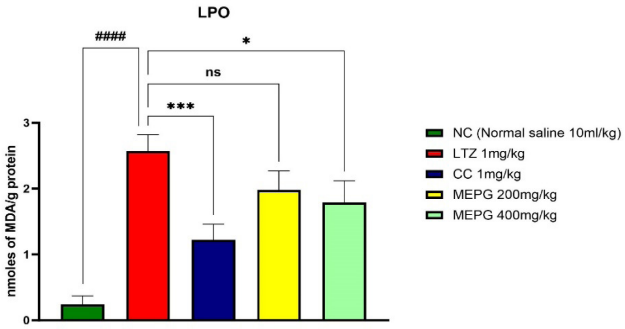

Fig. 8: Effect of MEPG on LPO. Values are expressed as Mean ± SEM, n= 6. $^{\#\#\#\#}$p<0.0001 compared to Normal control, ***p<0.001, *p<0.05, nsp<0.05 compared to disease control, Letrozole.

in serum LH levels in compared to letrozole induced group. Whereas both the treatment groups MEPG (200 mg/kg) and MEPG (400 mg/kg) revealed significant reduction ($^{****}p$ <0.0001) when compared with the letrozole induced group. Fig. 6 demonstrated noteworthy elevated ($^{\#}p$ <0.05) levels of serum testosterone in letrozole induced group in contrast to normal control, ^{ns}p >0.05 (non-significant) between letrozole-induced compared and treatment of the groups. It has been shown in the changes at the level of testosterone but not statistically significant when compared to letrozole-induced PCOS.

Effect of MEPG on LH-FSH Ratio against disease control in female wistar albino rats

In the disease-induced group, the LH-FSH ratio was found to be significantly increased ($^{\#\#\#\#}p$ <0.0001) when compared with normal control. The standard control animals showed a significant decrease ($^{****}p$ <0.0001) in the ratio of LH-FSH-when compared with letrozole induced group. Whereas both the post-treatment groups MEPG (200 mg/kg) and MEPG (400 mg/kg) showed a significantly decreased ($^{****}p$ <0.0001) compared to the letrozole group (Fig. 7)

Effect of MEPG on LPO levels against letrozole-induced PCOS in female wistar albino rats

Fig. 8 revealed a significant rise ($^{\#\#\#\#}p$ <0.0001) in LPO levels in disease control in comparison with normal

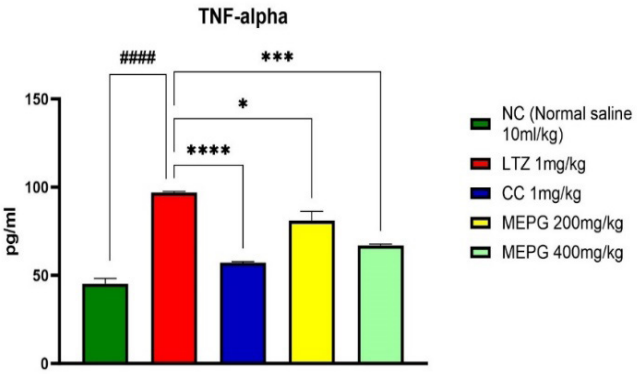

Fig. 9: TNF-alpha, Values are expressed as Mean ± SEM, n= 6. $^{\#\#\#\#}$p<0.0001 compared to Normal control, ****p<0.0001, ***p<0.001, *p<0.05 compared to disease control, Letrozole

control. The clomiphene citrate group showed a significant reduction ($^{***}p$ <0.001) in LPO plasma levels in comparison to disease control. MEPG (200 mg/kg) did not show (^{ns}p >0.05) any significant variations. In contrast, the post-treatment groups MEPG (400 mg/kg) showed a significantly mild decrease ($^{*}p$ <0.05) in comparison to the letrozole-induced group.

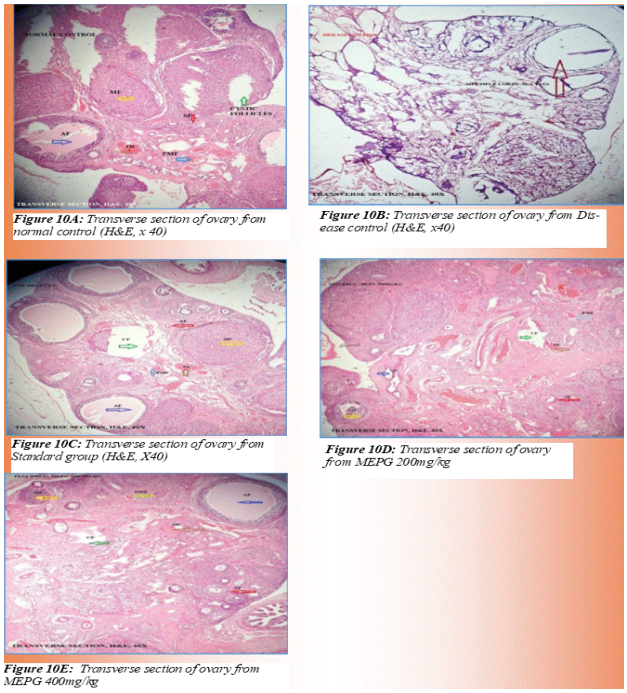

Fig. 10: Histopathological examination: ovary

Effect of MEPG on TNF-α level against letrozole induced PCOS in female Wistar albino rats

There was a notable spike ($^{####}p < 0.0001$) in levels of TNF-α in letrozole-induced rats in comparison with normal control. The standard group displayed a notable decline ($^{****}p < 0.0001$) in TNF-α levels compared to the group that was letrozole-induced. Whereas the treatment group MEPG (400 mg/kg) showed a notable decline ($^{***}p < 0.001$) and MEPG (200 mg/kg) revealed a significant decrease ($^{*}p < 0.05$) when compared with the letrozole-induced group (Fig. 9).

Histopathological examination

Ovary sections from animals in the control group (Fig. 10A) revealed healthy follicles containing 10 to 16 normal maturing follicles, several corpora lutea and two cystic follicles (green arrow), the presence of oocyte (Brown arrow), along with the presence of antral follicles (Blue arrow), presence of PMF (light blue arrow). Letrozole-treated rats exhibited (Fig. 10B) the presence of multiple cysts. The clomiphene citrate treated group (Fig. 10C) showed recovery containing 13 to 14 normal maturing follicles (yellow arrow), corpora lutea and 1 cystic follicle (green arrow) in the cortex also shows the presence of antral follicles (blue arrow), oocyte (brown arrow) and PMF (light blue arrow). Whereas sections from MEPG (200 mg/kg b.w) group (Fig. 10D) exhibited minor recovery containing 8 to 10 normal maturing follicles (yellow arrow), corpora lutea and 2 cystic follicles (green arrow) in the cortex also shows the presence of antral follicles (blue arrow), oocyte (brown arrow). And sections from the MEPG (400 mg/kg b.w) group (Fig. 10F) showed 12 to 13 normal maturing follicles (yellow arrow), corpora lutea and 1 cystic follicle (green arrow) in the cortex also shows the presence of antral follicles (blue arrow), oocyte (brown arrow) and PMF (light blue arrow).

Discussions

This study's main objective was to look into the potential medicinal advantages of *P. guajava* (MEPG) leaf methanolic extract in alleviating symptoms of PCOS in female wistar Albino rats caused by letrozole.[11] The hallmarks of PCOS include metabolic dysfunctions and hormonal imbalances, including hyperandrogenism and oligo-menorrhea, which contribute to a range of physiological issues[12,13], such as increased body weight, altered sex hormone levels, and ovarian cysts. Studies have shown that various plants, including cinnamon, fenugreek, *Vitex agnus-castus, Curcuma longa, Glycyrrhiza glabra,* guggul, and tea tree oil, have potential therapeutic effects on polycystic ovary syndrome (PCOS). It has been shown that cinnamon extract helps women with PCOS with their lipid profiles and insulin sensitivity, suggesting its role as a supportive dietary intervention for managing symptoms.[14] *Trigonella foenum-graecum* (Fenugreek seed extract has been shown to ameliorate insulin resistance and enhance reproductive functions in a rat model of PCOS, making it a promising candidate for natural management strategies.[15] *V. agnus-castus* (Chaste Tree) has been found to improve menstrual cycle irregularities and balance hormone levels in women with PCOS.[16] Curcumin, the active ingredient in turmeric, has been shown to reduce hyperandrogenism and enhance reproductive health in PCOS-induced rats.[17] Licorice extract has been shown to lower androgen levels and improve ovarian function in PCOS models, potentially addressing hyperandrogenic symptoms.[18] *Comiphora mukul* (Guggul) extract has been found to enhance insulin sensitivity and ovulatory function in women with PCOS,[19] suggesting its potential as an effective herbal remedy. Finally, *Melaleuca alternifolia* (Tea tree oil) has been shown to alleviate some PCOS symptoms, particularly acne and hirsutism, due to its anti-androgenic properties.[20] Collectively, these studies underscore the potential of various herbal remedies in managing PCOS and its associated metabolic and reproductive disturbances. The therapeutic effects observed in these plants, ranging from improved insulin sensitivity and hormonal balance to reductions in hyperandrogenism and inflammation, highlight their roles as adjunctive therapies. By addressing the multifactorial nature of PCOS, these natural remedies may offer a complementary approach to conventional treatments, ultimately enhancing the quality of life for women affected by this condition.

Each experimental outcome was systematically analyzed to understand how MEPG influences these parameters, aligning with the study's aim of identifying *P. guajava* as a natural remedy for PCOS symptoms. Letrozole induces

PCOS by inhibiting the conversion of testosterone to estrogen, resulting in hyperandrogenism, a characteristic of PCOS. The disease control showed a noticeable rise in body weight, corresponding to elevated androgen levels, a common PCOS trait. However, treatment with MEPG (200 mg/kg as well as 400 mg/kg) resulted in a reduction of body weight in comparison to a disease control group. This outcome suggests that *P. guajava* may counter the weight gain often seen in PCOS, likely due to the flavonoid content in guava, which has antiobesity properties.[21] This finding supports the objective of exploring the metabolic benefits of MEPG in PCOS management. In PCOS diagnosis, serum levels of sex hormones, particularly testosterone, FSH, and LH, are critical indicators. The letrozole-induced group exhibited elevated testosterone and LH levels with reduced FSH levels, characteristic of PCOS-related hormonal imbalance. MEPG at 400 mg/kg significantly reduced LH levels while increasing FSH, restoring balance in the LH/FSH ratio. This outcome aligns with the objective of assessing MEPG's potential to correct hormonal dysregulation in PCOS, showing that MEPG may help modulate the abnormal LH/FSH ratio observed in PCOS. The letrozole-induced PCOS group demonstrated elevated levels of LPO and TNF-α, markers associated with oxidative stress and inflammation, which are commonly elevated in PCOS.[22] Treatment with MEPG (400 mg/kg) significantly lowered both LPO and TNF-α levels compared to the disease control group, suggesting that *P. guajava* mitigates oxidative stress and inflammatory responses in PCOS. These anti-inflammatory and antioxidant effects align well with the study's aim of evaluating the protective efficacy of MEPG in managing PCOS-related inflammation. Letrozole-induced ovarian cyst formation and follicular maturation disruption are linked to PCOS. Histological examination revealed that the standard treatment (Clomiphene citrate) group exhibited 13 to 14 normal maturing follicles, while the follicle development improved in groups treated with MEPG in a dose-dependent manner. The MEPG (200 mg/kg) group displayed 8 to 10 maturing follicles with some cystic formations, whereas the MEPG (400 mg/kg) group had 12 to 13 normal maturing follicles and fewer cystic formations. This histological outcome supports the study's objective of evaluating MEPG's influence on follicle maturation and cyst reduction, highlighting its potential to restore normal ovarian morphology.

The study outcomes collectively support the aim of investigating *P. guajava* as a natural remedy for PCOS symptoms. MEPG exhibited significant benefits in reducing body weight, improving hormonal balance, lowering inflammatory markers, and promoting healthy follicular development, thereby addressing key aspects of PCOS pathology.

Despite these promising findings, limitations remain. The study was restricted to a single extract type (methanolic) and two doses, leaving the potential effects of other extract types and dosages unexplored. Additionally, the study was conducted in an animal model, which may not fully replicate human responses. Future research should delve into the molecular mechanisms by which MEPG exerts its effects, explore diverse extraction methods, and include clinical trials to confirm its efficacy and safety in human PCOS management.

Conclusion

The study suggests that *P. guajava* leaf methanolic extract may be a natural remedy for managing letrozole-induced PCOS. The extract, when administered at 400 mg/kg, showed moderate positive effects when comparable to the standard treatment, clomiphene citrate. The extract may support ovarian function and restore hormonal balance, which is crucial for improving ovarian function. Treatment with *P. guajava* reduced body weight, positively influenced serum hormone levels, and showed anti-inflammatory and antioxidant properties. It also resulted in fewer cystic formations and more normal maturing follicles in contrast to an untreated control group. The research indicates that *P. guajava* can be a valuable alternative therapy for controlling PCOS by improving hormonal balance, promoting ovarian function, and addressing metabolic issues.

Acknowledgment

The author acknowledges Karnataka College of Pharmacy for their support and contributions.

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HOW TO CITE THIS ARTICLE: Shree RR, Jha DK. To Examine the Potential Effectiveness of *Psidium guajava* in Letrozole-Induced Polycystic Ovarian Syndrome in Female Albino Rats. Int. J. Pharm. Sci. Drug Res. 2024;16(6):997-1003. **DOI:** 10.25004/IJPSDR.2024.160610