Herbal supplements effect on ameliorating biochemical and clinical features of elevated androgen levels (hyperandrogenism) in young women with Polycystic Ovary Syndrome (PCOS): A systematic review

Amy Wagner, RD, LDN

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**Abstract**

*Objective:* To identify what effect herbal supplements have on reducing androgens in young women with Polycystic Ovary Syndrome (PCOS).

*Methods:* An electronic literature search was conducted during May and June of 2021 to identify studies published between 2004 and 2021via the following databases: Academic Search Ultimate, Agricola, Biological Abstracts, E- Journals, MEDLINE Complete, Alt Health Watch and CINAHL Complete through eBook Clinical Collection (EBSCO), as well as Google Scholar. Participants were women with PCOS aged 18-42 and treated with various herbal supplements. Articles included in this systematic review were critically appraised via the Quality Criteria Checklist (QCC).

*Results:* There was a total of five studies included and evaluated in this systematic review. Two of the five articles are randomized controlled trials (RCT) (Ainehchi et al., 2020; Grant, 2010) and the remaining three articles are experimental studies (Akdogan et al, 2007; Armanini et al., 2007; Luan & Sun, 2015). All studies evaluated how androgen levels were affected by herbal supplement treatments on the study populations.

*Conclusion:* Based on the studies from this systematic review, it is evident that herbal supplements (spearmint, ginger, cinnamon, sweet orange groups, glabridin) can significantly lower biochemical androgen levels and can significantly improve clinical features (acne and hirsutism) of elevated androgens in young women with PCOS. Further research must be conducted on human subjects with PCOS. Further research should also include studies that look at isolated, individual herbal supplement treatment on this population without medicine or multiple herbal components in one study or review.

**Introduction**

Polycystic Ovary Syndrome or Polycystic Ovarian Syndrome (PCOS) is a lifelong chronic disease and hormonal disorder and affects the endocrine system of women or those who have female reproductive organs, significantly during reproductive ages (Polycystic ovary syndrome [PCOS], 2020).The etiology and pathogenesis of PCOS is unknown and further research is needed to understand why PCOS affects six to twelve percent (approximately five million women) of reproductive-aged women in the United States alone (PCOS, 2020; PCOS and diabetes, 2020; Rosenfield & Ehrmann, 2016). Originally, in 1935, Stein and Leventhal defined PCOS as being a syndrome with the following characteristics: oligomenorrhea, polycystic ovaries, acne, hirsutism, overweight and obesity (Rosenfield & Ehrmann, 2016; Stein & Leventhal, 1935).

Today, the most widely used diagnostic criteria for PCOS is the Rotterdam Criteria which requires patients to meet two of the following three diagnostic criteria in order to be diagnosed with PCOS: polycystic ovaries, oligomenorrhea, and hyperandrogenism (PCOS, 2020). Polycystic ovaries can be defined as ovaries that have multiple cysts or fluid-filled sacks on or in the ovaries causing them to be enlarged (PCOS, 2020). These cysts can often appear and are commonly referred to as “a string of pearls” when seen via a pelvic ultrasound. Oligomenorrhea can be defined as irregular menstrual cycles such as those that miss or skip menses (a regular bleeding period) (PCOS, 2020). Oligomenorrhea can also refer to menses that result in too light or too heavy in flow, or those that are too long or short in duration as compared to an average cycle length (PCOS, 2020). Oligomenorrhea can be determined via biochemical laboratory testing on blood, physical examinations, pelvic ultrasounds, and observations of menstrual cycles. Finally, hyperandrogenism can be defined as elevated androgen levels in women which can result in elevated testosterone levels in the blood (such as free testosterone and total testosterone), elevated levels of dehydroepiandrostenedione sulphate (also referred to as dehydroepiandrosterone sulfate) (DHEAS; a type of androgen or male sex hormone), dehydroepiandrosterone (DHEA; a type of androgen), androstenedione (a type of androgen), androstenediol (a type of androgen), hirsutism (excessive hair growth to the face, back, and chest such as that of male patterned hair growth), alopecia (hair loss), acne, and central obesity (PCOS, 2020; Oakley, 2014). Hyperandrogenism can be determined via biochemical laboratory blood tests (androgen levels detected via blood tests: testosterone, DHEAS, DHEA, androstenedione and androstenediol) and through observations of clinical manifestations such as acne, hirsutism and alopecia.

Many animal studies have analyzed the effectiveness of herbal supplements on treating hyperandrogenism in PCOS, however very few human studies have analyzed this relationship. The unwanted clinical features and manifestations of hyperandrogenism related to POCS, such as hirsutism and acne, can cause extreme emotional distress in those, specifically those identifying as women with PCOS. Hopefully this systematic review can shed light on the whether or not herbal supplements and remedies that may alleviate signs and symptoms of hyperandrogenism in women with PCOS. The purpose of this review is to identify what effect herbal supplements have on reducing androgens in young women with Polycystic Ovary Syndrome (PCOS).

**Methods**

**Search Strategy**

 An electronic literature search was conducted during May and June of 2021 to identify studies via the following databases: Academic Search Ultimate, Agricola, Biological Abstracts, E- Journals, MEDLINE Complete, Alt Health Watch and CINAHL Complete through eBook Clinical Collection (EBSCO), as well as Google Scholar. The reference list for identified studies was searched for eligible studies including randomized controlled trials, randomized clinical trials, placebo controlled randomized studies, non-controlled trials, before and after studies, and experimental studies. Studies between 2004 and 2021 were eligible for review based on the time frame. A larger time frame was necessary to obtain enough viable studies to review and include in this systematic review. Only English language studies were eligible for review and animal studies were excluded. The aim of this systematic review is to identify what effect herbal supplements have on reducing androgens in young women with Polycystic Ovary Syndrome (PCOS). The following search terms were use in various combinations: “spearmint”, “hyperandrogenism”, “androgen”, “pcos”, “polycystic ovarian syndrome”, “polycystic ovary syndrome”, “baicalin”, “lavender”, “licorice”, “hirsutism”, “women”, “glabridin”, “oral”, “before and after study”, “testosterone”. MESH terms and phrases that were used with the chosen databases are listed below; refer to Table 1.

Table 1

*Search Strategy*

|  |  |  |
| --- | --- | --- |
| **MeSH Terms** | **“AND” Terms** | **Related Lab Values** |
| PCOSPolycystic ovarian syndromePolycystic ovary syndromeHirsutismWomen | Spearmint BaicalinLavenderLicoriceGlabridin | TestosteroneAndrogenAndrogensHyperandrogenism  |

Pre-defined inclusion and exclusion were used to select studies for this review. Studies that were randomized controlled trials, randomized clinical trials, placebo controlled randomized studies, non-controlled trials, before and after studies, and experimental studies published in English between 2004-2021 were included. It was necessary to only include studies written in English because the researcher is only literate in English. Studies that included young women participants with Polycystic Ovary Syndrome (PCOS) were included. Studies that included an herbal treatment alone or a drug or medicinal treatment along with an herbal treatment were included. Studies and articles that were review articles, systematic review articles, meta-analysis, literature reviews, academic review articles, dissertation papers, handbooks, academic article without a study or trial, and textbooks were excluded. Studies written prior to 2004 were excluded. Studies that had a study population of children, males, postmenopausal women, or animal participants were excluded. Articles that did not discuss PCOS or PCOS treatment were excluded. Studies that included herbal treatments combined with laser hair removal treatments were excluded; refer to Table 2.

Table 2

*Inclusion and Exclusion Criteria*

|  |  |
| --- | --- |
| **Inclusion Criteria** |  **Exclusion Criteria** |
| Species: HumanGender: FemaleAge: Young womenNutrition Related Problem/ Condition: Polycystic Ovary Syndrome (PCOS)Study Design Preference: Randomized Controlled Trials, Randomized Clinical Trials, placebo controlled randomized studies, non-controlled trials, before and after studies, and experimental studiesYear Range: 2004-2021Language: EnglishFull text accessibility: YesInternational Studies (including US Studies)Treatments: herbal treatment alone or drug/ medicine treatment along with herbal treatments were included | Species: Animal studies (such as rat studies/models)Genders: any gender other than femaleAge: children, postmenopausal womenStudy Design/ Article type: review articles, systematic reviews, meta-analysis, literature reviews, academic review articles, dissertation papers, handbooks, academic articles without a study or trial, textbooksYear Range: prior to 2004Language: Articles not published in EnglishNo accessibility to full text articles/studiesArticles not on the subject of hirsutism and hirsutism treatment.Treatment: herbal treatments combined with laser hair removal treatments were excluded. |

 Pre-defined inclusion and exclusion criteria were used to select studies for this review to minimize bias from the researcher during the selection process. To minimize bias, all studies that met the inclusion criteria and did not meet the exclusion criteria were all reviewed regardless of the effectiveness the herbal remedies had on reducing androgens in women with hirsutism. Also, articles were included in the review regardless of their Quality Criteria Checklist (QCC) ratings.

**Data Extraction and Quality Assessment**

 Each study that is included in this systematic review (a total of five studies) had information extracted and compiled into a Data extraction Table. This table includes information on the study design, author(s), year, overall quality assessment rating, database, purpose of the study, study population, intervention, outcomes, conclusion and limitations; refer to Table 3.

 The QCC for Primary Research was used to evaluate and assign a rating to each article. Articles were given a rating of positive, neutral or negative depending on how they scored based of the QCC for Primary Research guidelines regarding relevance (four questions) and validity (ten questions). Articles were awarded a positive (+) rating if the majority of questions from the QCC were answered with a “yes” (Y) including questions numbered 2,3,6 and 7, and at least one additional “yes”. Articles were awarded a neutral (Ø) rating if questions numbered 2,3,6 and 7 were not found to be exceptionally strong with a “yes”. Articles were awarded a negative (-) rating if the majority of the questions (at least six of the ten validity questions) were answered with a “no” (N). Of the five articles, the two RCT were awarded a positive rating, and the three experimental studies were awarded a neutral rating. No article was awarded a negative rating; refer to Table 4.

Table 3

*Data Extraction*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author/Year****Study design****Quality Assessment Rating** | **Purpose of Study** | **Study population** | **Intervention** | **Outcomes** | **Conclusion** | **Limitations** |
| Ainehchi et al., 2020, RCT, **+** Academic Search Ultimate | To evaluate the effect of a herbal mixture (i.e., *Mentha spicata, Zingiber officinale, Cinnamomum zeylanicum,* and *Citrus sinensis*) alone and in combination with clomiphene citrate (CC) compared to CC on the treatment of polycystic ovary syndrome (PCOS).*-****Mentha spicata***(Spearmint)*-****Zingiber officinale***(Ginger)*-****Cinnamomum zeylanicum***(True cinnamon tree) -***Citrus sinensis***(Sweet orange group such as blood oranges and navel oranges) | 60 infertile women with Polycystic Ovary Syndrome (PCOS) aged 18-35 years old with a BMI between 26.5-28.5kg/m2 and willing to be pregnant.Women were selected from the infertility clinic of Alzahra Hospital in Tibriz (Iran). Group 1: *n* = 20Group 2: *n* = 20Group 3: *n* = 20\*Original study size: 75 participants; 15 women dropped out of the study resulting in 60 women completing the study (20 per group). There was a 25% probable- dropout for each group.**Inclusion Criteria:**Women were included if they met: PCOS determined by Rotterdam Criteria (2003), primary or secondary infertility, aged between 18-35 years, and BMI <30kg/m2.**Exclusion Criteria:**Women were excluded if they had: diabetes mellitus, thyroid disorders, current use of medications that aid in ovulation or insulin sensitizers and cholesterol-lowering drugs, smoking, current treatment of infertility, HTN, CVD, Cushing’s Syndrome, and allergy to spearmint, ginger, cinnamon, and *C. Sinensis.*  | \*Treatments were given after spontaneous progestin-induced withdrawal bleeding. \*Participants were randomized to 3 groups and given a single injection of 100mg progesterone at the end of 35th day of their menstrual cycle after beta-hCG test for ruling out pregnancy.\***Blinding:** Statistician was blind to the study.**Group 1:** treated with 50-150mg CC for the duration of 3 menstrual cycles from the 3rd to 5th day of menstruation for 5 days. **Group 2:** treated with 700 mg capsule per day for 3 months of an herbal mixture consisting of: 250mg spearmint, 200mg ginger, 150mg cinnamon, 100mg *C. Sinensis.***Group 3:** treated for 3 months with 50-150mg CC + the 700mg capsule per day of the herbal mixture consisting of: 250mg spearmint, 200mg ginger, 150mg cinnamon, 100mg *C. Sinensis.* | Outcomes of the study found that total testosterone (TT) in group 2 and free testosterone (T) in group 3 both had significant differences compared to group 1. 🡪 A significant decrease of TT only in group 2 was found (*p* = .003).🡪 TT significantly decreased in group 2 (*p* = .022) and was significant compared to group 1.🡪 T in group 2 (*p* = .204) was not significant compared to group 1. 🡪 TT in group 3 (*p* = .099) was not significant compared to group 1.🡪 T significantly decreased in group 3 (*p* < .001) and was significant compared to group 1.🡪 No significant changes between the groups regarding T in groups 1 and 2, and TT in groups 1 and 3 (*p* > .05).Clinical outcomes significantly improved in all 3 groups (*p* < .05).🡪 Acne significantly improved in all 3 groups after 3 months of interventions compared to baseline: group 1 (*p* = .011), group 2 (*p* = .008), group 3 (*p* < .001).🡪 There was no significant difference between the 3 groups before and after interventions (*p* > .05).🡪 Hirsutism improved significantly in all groups: group 1 (*p* = .023), group 2 (*p* = .001), group 3 (*p* = .001). 🡪 No significant difference between groups before intervention, but there was a significant difference between the groups after treatment (*p* < .001). \*A *p*-value </= .05 was considered statistically significant. | The reduction of T in group 3 (treatment of CC + herbal mixture) was more significant as compared to group 1 (CC only group). Also, TT in group 2 (herbal mixture only group) decreased significantly as compared to group 1 (CC only group). Overall, the study showed that the treatment of the herbal mixture used in this study along with CC was able to improve free testosterone and clinical features of PCOS in PCOS women.\*It is important to note that using CC for > 6 cycles contributes to a high risk of ovarian cancer in this population. Therefore, the herbal mixture alone could be used as a long-term treatment for this population regarding the reduction of total testosterone (TT) and clinical features (acne and hirsutism) of PCOS without side effects. \*Herbal Mixture: 250mg spearmint, 200mg ginger, 150mg cinnamon, 100mg *C. Sinensis.* | The authors listed no conflict of interest for this study. Authors listed their sample size of 60 being small, and the duration of 3 months being short, and therefore both being limitations of the study.Some other limitations noted include that acne and hirsutism data was obtained subjectively from the participants and therefore, the data was not as reliable as it would have been if it were objectively measured.  |
| Akdogan et al., 2007, Experimental Study, **Ø**MEDLINE Complete | To observe the effect of spearmint herbal tea on the androgen levels in women with hirsutism. \*Hirsutism is a clinical manifestation /feature of elevated androgens. | 21 women aged 18-40 years old with hirsutism were selected (12 with Polycystic Ovary Syndrome (PCOS), and 9 with idiopathic hirsutism) as the study population. **Treatment group:** *n* = 21Other Inclusion criteria and exclusion criteria were not noted.Women admitted to the endocrinology outpatient clinic who complained of hirsutism were included. (Unidentified location of clinic).  | All women in the study were treated with 250mL of herbal tea steeped with *M. Spicata* (Spearmint) (%20 g/L) 2 times per day for 5 days during the follicular phase of the participants menstrual cycles. Leaves were steeped for 5-10 min and all teas were prepared daily.  | Outcomes of the study found that after 5 days of treatment there was a statistically significant decrease in free testosterone (FT) (*p* < .05). There was not a significant decrease in total testosterone (TT) and dehydroepiandrostenedione sulphate (DHEAS) levels after the 5-day treatment- (*p* > .05) for both TT and DHEAS.**FT:**Pre-treatment: 5.49 +/- 2.94 pg/mLPost-treatment: 3.92 +/- 2.80 pg/mL**TT:**Pre-treatment: 0.75 +/- 0.40 ng/mLPost-treatment: 0.67 +/- 0.35 ng/mL**DHEAS:**Pre-treatment: 189.41 +/- 92.73 μg/LPost-treatment: 192.60 +/- 88.02 μg/L\*A *p*-value < .05 was considered statistically significant. | Overall, the study found that spearmint tea can be used to significantly decrease FT in women with hirsutism (this includes women with PCOS with hirsutism). They found spearmint tea can be used as an alternative treatment for mild hirsutism as compared to spironolactone, oral contraceptives and other medicines which block androgen actions.  | Limitations and conflict of interest were not addressed in the study.A limitation of the study was the small sample size of 21 women. Another limitation was that treatment only lasted for 5 days during the follicular phase of participants menstrual cycles and were not followed for more than one cycle. The treatment period was not long enough to show a reliable outcome.A significant limitation is that the researchers did not separate the participants with idiopathic hirsutism from the women with PCOS, therefore the results are mixed between the two different conditions and results may be inaccurate.  |
| Armanini et al., 2007, Experimental Study, **Ø** Google Scholar | To compare the effect of spironolactone (SP) (antagonist of mineralocorticoid and androgen receptors) versus spironolactone (SP) plus licorice (agonist of mineralocorticoid receptors and mild inhibitor of androgen synthesis) on plasma renin activity, aldosterone and androgen levels in women with polycystic ovary syndrome (PCOS). | 32 hirsute women aged 21-28 years old with PCOS were alternatively divided into 2 groups. Group 1: *n* = 16Group 2: *n* = 16**Inclusion Criteria:**Hirsute women with PCOS (meeting PCOS Rotterdam criteria) following a free normocaloric diet with normal physical activity. \*All women in the study had to either abstain from intercourse or use mechanical contraceptive deceives to prevent pregnancy during the study.**Exclusion Criteria:**Women with HTN, DM, or women who were taking medications within the 3 months before the study were excluded. Women with 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia, Cushing’s syndrome, and androgen-secreting tumors were excluded from the study. | Group 1 was treated with 100mg spironolactone per day for 2 months.Group 2 was treated with 100mg spironolactone + 3.5g of licorice per day for 2 months.\*Licorice treatment: dried extract of boiled licorice root. | Outcomes of the study found that there were no statistically significant changes in total testosterone nor free testosterone in the group receiving spironolactone + licorice. After 2 months of treatment with spironolactone + licorice the following was found compared to baseline:**Total testosterone:**Baseline: 88.7 +/- 13 ng/dL2 months: 82.1 +/- 9.7 ng/dL(*p* > .05)**Free testosterone:**Baseline: 5.6+/- 2.8 ng/dL2 months:5.2 +/- 2.5 ng/dL(*p* > .05)\*A *p*- value < .05 was considered statistically significant. | Overall, the study found that spironolactone + licorice does not have a significant effect on reducing androgen levels such as total testosterone and free testosterone in women with PCOS (over the course of a 2-month treatment period).The authors did, however, conclude that treatment of spironolactone + licorice “may have possible therapeutic applications in hyperandrogenic women” because licorice and spironolactone have “opposite effects on the mineralocorticoid effector mechanism and a potential synergic negative effect on the androgen effector mechanism”. This theory would need to be analyzed for effectiveness in a study with a longer duration of treatment.  | A limitation to this study was that the sample size was small consisting of 32 women total (16 per group) which was noted in the limitations section of the study. The study should have had at lease 30 participants per treatment group with a minimum total of 60 women. Another limitation was that the follow up period of 2 months was too short to produce a reliable outcome and results of the study.  |
| Grant, 2010, RCT, **+** MEDLINE Complete | To expand on previous work regarding whether a reduction in androgen levels can be brought about by spearmint tea, translating to clinical improvement in hirsutism. The aim was to include subjective and objective monitoring of the hirsutism and to extend the duration of exposure to the spearmint tea treatment. | 42 women aged 19-42 years with confirmed PCOS (in adherence to Rotterdam 2003 criteria) and hirsutism were chosen from the endocrinology outpatient setting from two hospitals within the same National Health Service trust to participate in this study. Participants were randomized into 2 groups. No other inclusion and no exclusion criteria were noted in the study.  | Treatments started on the first clear (no bleed) day after menstrual cycle bleeding ceased. One group was given spearmint tea and one was given “camomile” tea. Teas were given 2x per day for 30 days (duration of 1 average menstrual cycle).\*Researchers were blinded to which participants received which teas. \*1 person dropped out due to not liking the taste of chamomile tea. **Spearmint Tea Group:** (*n* = 21)**Camomile Tea Group 2:** (*n* = 21 \*originally) (*n* = 20 \*after 1 person dropped out).\*Teas were composed of “herbal tea bags with standard contend of dried tea leaves”.  | Outcomes of the study found that free testosterone and total testosterone had significantly decreased in participants after the treatment of spearmint tea (*p* < .05). It was found that DHEAS had not significantly decreased in participants after treatment of spearmint tea (*p* > .05). It was also found that subjective assessment of degree of hirsutism (based on the modified Dermatology Quality of Life Index (DQLI)) had significantly decreased after treatment of spearmint tea (*p* < .05). The objective hirsutism scores (Ferriman- Galwey ratings) did not show a significant reduction of hirsutism between the two treatment groups (*p* = .12). \*A *p* - value < .05 was considered statistically significant.**Spearmint Group androgens:****Free Testosterone:**0 days tx: 5.12 +/- 2.14 pg/mL30 days tx 3.64 +/- 2.67 **Total Testosterone:**0 days tx: 0.81 +/- 0.39 ng/mL30 days tx: 0.62 +/- 0.34 ng/mL**DHEAS:**0 days tx: 184.5 +/- 82.1 mcg/mL30 days tx:183.3 +/- 87.8 mcg/mL**DQLI (Subjective Hirsutism):**0 days tx: 17 (10-24)30 days tx: 11 (8-18)**Ferriman-Galwey (Objective Hirsutism):**0 days tx: 17 (12-22)30 days tx: 16 (10-23) | Overall, the study found that treatment of spearmint tea twice per day for 30 days can reduce testosterone (FT and TT) levels in women with PCOS who have hirsutism. | Limitations of the study that were noted by the author include that the duration of the study was too short, and that the duration of treatment must be longer to determine the effectiveness of spearmint on reducing all androgen levels and hirsutism in women with PCOS.Another limitation was that the population size of participants was small and should have been at least 30 women per group.  |
| Luan & Sun, 2015, Experimental Study, **Ø** Google Scholar | To investigate the hypoglycemic effects of glabridin from licorice in patients with PCOS.-**Glabridin**(found in licorice root extract) | 32 women with PCOS aged 26.5 +/- 4.2 years were included in the study. **Inclusion Criteria:**Participants were included in the study if they had 2 of the following 3 features: oligo- or anovulation, clinical Ferriman-Gallwey score >8, and or biochemical signs of hyperandrogenism and polycystic ovaries. These participants were included if their thyroid, renal, and hepatic functions were normal.**Exclusion Criteria:** Participants were excluded if they were pregnant, used oral contraceptives within 6 months of the start of the study, anti- androgens, anti-diabetics, and those with CVD. \*It was noted that there were no participants who dropped out of the study. | All participants were treated with 10 μM of glabridin (from licorice) daily for a duration of 12 months. **Treatment group**: *n* = 32 | Outcomes of the study found that 12 months of 10 μM of glabridin treatment daily resulted in a statistically significant decrease in serum testosterone within this population. The study also found that there was a significant reduction in “Hirsutism Score” (not Ferriman-Gallwey Scores) after treatment from 12.8 +/- 3.2 to 7.0 +/- 3.5 (*p* – value not listed in study). **Ferriman-Gallwey Scores:**Before tx: 9.8 +/- 1.8After tx: 9.2 +/- 1.6(*p* = .11) Not statistically significant.**Testosterone:**Before tx: 89.7 +/- 31.7 ng/dLAfter tx: 49.5 +/- 13.3 ng/dL(*p* = .04)Statistically significant. \*A *p* - value < .05 was considered statistically significant. | Overall, the study found that treatment of glabridin for 12 months can decrease androgen production in women with PCOS.  | Authors did not list any limitations within the discussion or conclusion of their study.A limitation of this study would be that there was no control group to compare results of the treatment after 12 months.  |

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| --- |
| Table 4*Quality Criteria Checklist* |
| **Author(s)**  | **Design** | **Q1a**  | **Q2b**  | **Q3c**  | **Q4d** | **Q5e** | **Q6f** | **Q7g** | **Q8h**  | **Q9i**  |  **Q10j** |  **QAk** |
| Ainehchi et al.Akdogan et al. Armanini et al.GrantLuan & Sun | Randomized Controlled Clinical Trial – Single Blind, ParallelExperimental StudyExperimental StudyRandomized Controlled TrailExperimental Study | YYYYY | YUCYYY | YUCYYN/A | YNNYN/A | YNNYN | YUCUCYY | YYYYY | YYYYY | YUCYYUC | YUCUCUCUC | **+**Ø Ø**+**Ø |

qQ1=Question 1: Was the research question clearly stated?

bQ2=Question 2: Was the selection of study subjects/patients free from bias?

cQ3=Question 3: Were study groups comparable?

dQ4=Question 4: Was method of handling withdrawals described?

eQ5=Question 5: Was blinding used to prevent introduction of bias?
fQ6=Question 6: Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?

gQ7=Question 7: Were outcomes clearly defined and measurements valid and reliable?

hQ8=Question 8: Was the statistical analysis appropriate for the study design and type of outcome indicators?

iQ9=Question 9: Are conclusions supported by results with biases and limitations taken into consideration?

jQ10=Question 10: Is bias due to study’s funding or sponsorship unlikely?

kQA= quality assessment; l+=positive; m-=negative; nØ=neutral; oY=yes; pUC=unclear; qN/A=not applicable; rN=n

**Results**

After completing a scoping search, the systematic review research question was developed, and the remainder of the search was based off the PICO research question. During the search for review articles, MeSH terms and phrases were used in various combinations across several databases, as previously stated, to find quality articles that could be included in the systematic review. A total of sixty-three articles were found through various databases across eBook Clinical Collection (EBSCO), and throughout Google Scholar. A full list of databases that were searched through eBook Clinical Collection (EBSCO) is recorded under the Search Strategy section of this systematic review. A total of twenty-seven duplicate studies were removed and the remaining thirty-six articles were screened. Of the thirty-six screened articles, twenty-eight were excluded because they did not meet the inclusion criteria. Of the thirty-six screened articles, eight were eligible to be analyzed to determine whether or not they were appropriate to be included in this study. Of the eight full text articles analyzed, three of them were excluded due to the following reasons: studies were excluded if they did not have any human participating subjects (*n* = 2); studies were excluded if they did not include outcomes identified in the inclusion criteria (*n* = 1). This left a total of five viable articles to be analyzed and included in this systematic review; see Figure 1, PRISMA Diagram.

## Identification

## Screening

## Eligibility

## Included

Full-text articles excluded, with reasons
(*n* = 3)

* Excluded if study does not have human participating subjects used in study (*n* = 2)
* Excluded if study did not include outcomes identified in inclusion criteria (*n* = 1)

Records after duplicates removed
(*n* = 36)

Records screened
(*n* = 36)

Records excluded
(*n* = 28)
)

Records identified through database searching
(*n* = 63)

Additional records identified through other sources
(*n* = 0)

Studies included in qualitative synthesis
(*n* = 5)

Full-text articles assessed for eligibility
(*n* = 8)

*Figure 1.* PRISMA Flow Diagram

**Study Designs**

 There was a total of five studies included and evaluated in this systematic review. Two of the five articles are Randomized Controlled Trials (RCT) (Ainehchi et al., 2020; Grant, 2010) and the remaining three articles are Experimental Studies (Akdogan et al, 2007; Armanini et al., 2007; Luan & Sun, 2015). The first RCT by Ainehchi et al. (2020) evaluated the effect an herbal mixture plus clomiphene citrate (CC); a drug used to treat female infertility) had on treating symptoms of PCOS. The second RCT by Grant (2010) expanded on previous research in order to evaluate whether or not spearmint tea can reduce androgen levels and improve clinical features of PCOS in PCOS women. The first experimental study by Akdogan et al. (2007), evaluated the effect spearmint tea had on androgen levels in women with hirsutism and PCOS. The second experimental study by Armanini et al. (2007) evaluated the effect spironolactone (SP; a drug which is an “antagonist of mineralocorticoid and androgen receptors”) plus licorice had on androgen levels in women with PCOS. Finally, the third experimental study by Luan and Sun (2015) evaluated what hypoglycemic effects glabridin (from licorice) had on women with PCOS, but during their study, they were able to evaluate what effect glabridin had on testosterone levels and hirsutism in women with PCOS.

**Biochemical Androgen Testing**

All five studies analyzed data on how an herbal supplement affects biochemical androgen levels. Androgens that were analyzed through biochemical testing across all five studies include testosterone, free testosterone, total testosterone, and DHEAS. Four of the five studies found a statistically significant decrease in androgen levels in young women with PCOS after treatment of herbal supplements (herbal supplements treated with or without medications) including studies done by Ainehchi et al. in 2020, Akdogan et al. in 2007, Grant in 2010, and Luan and Sun in 2015.

The first study found that women who were treated with an herbal mixture (700 mg herbal mixture composed of *Mentha spicata, Zingiber officinale, Cinnamomum zeylancium,* and *Citrus sinensis)* daily for three months had a statistically significant decrease in total testosterone levels after treatment (*p* = .022) as compared to the women treated with only clomiphene citrate (CC), but did not result in a statistically significant decrease in free testosterone levels after treatment (*p* = .204) as compared to women treated with only CC (Ainehchi et al., 2020). After treatment, free testosterone was significantly decreased in women who were treated with the herbal mixture plus 50-150mg CC daily for three months (*p* < .001) but did not result in a statistically significant decrease in total testosterone levels after treatment (*p* = .099) as compared to women treated with only CC (Ainehchi et al., 2020). The second study found that PCOS young women who were treated with for five days with 250mL of herbal tea consisting of *M. Spicata* (spearmint) twice a day over the course of 5 days during their follicular phase of their menstrual cycles, had a statistically significant decrease in free testosterone (*p* < .05), but no significant decrease in total testosterone (*p* > .05) nor DHEAS (*p* > .05) after treatment (Akdogan et al., 2007). The third study did not find any statistically significant changes in total testosterone (*p* > .05) and free testosterone (*p* > .05) after treatment of 100gm spironolactone plus 3.5gm licorice twice a day over a duration of two months in young women with hirsutism and PCOS (Armanini et al., 2007). The fourth study found that young women with PCOS had a statistically significant decrease in both free testosterone (*p* < .05) and total testosterone (*p* < .05) levels but not DHEAS (*p* >.05) levels after the treatment of spearmint tea (unspecified dose) twice a day over the course of one average menstrual cycle length (Grant, 2010). Finally, the fifth study found that young women with PCOS treated with 10 μM of glabridin (a licorice extract) per day had a statistically significant decrease in serum testosterone levels (*p* = .04) after twelve months of treatment Luan & Sun, 2015). Overall, most of the studies in this systematic review found that herbal supplements can help lower biochemical androgen levels in young women with PCOS including, serum testosterone, free testosterone, total testosterone, and DHEAS. Therefore, the data collected from this systematic review supports the notion that herbal supplements can improve biochemical androgen levels in young women with PCOS.

**Clinical Features and Manifestations of Hyperandrogenism**

Three of the five studies analyzed clinical features and manifestations of hyperandrogenism in young women with PCOS including Ainehchi et al. (2020), Grant (2010), and Luan and Sun (2015). Clinical features include acne and hirsutism. The study done by Ainehchi et al. (2020), found that young women with PCOS who were treated with an herbal mixture (previously mentioned), or an herbal mixture plus 50-150mg CC daily for three months had a statistically significant improvement in both hirsutism (herbal only treatment (*p* = .001); herbal plus CC (*p* = .001)) treatment and acne (herbal only treatment (*p* = .008); herbal plus CC (*p* < .001)). The study done by Grant (2010) found that young women with PCOS, treated with spearmint tea (unspecified dose) twice a day over the course of one average menstrual cycle length, had a statistically significant decrease in hirsutism based on a subjective assessment (modified DQLI) (*p* < .05) after treatment but did not have a statistically significant improvement in hirsutism based on an objective assessment score (Ferriman-Galwey scores) (*p* = .12) after treatment. Finally, the study done by Luan and Sun (2015) found that young women with PCOS, treated with 10 μM of glabridin per day for a duration of 12 months, had a statistically significant decrease in “Hirsutism Scores” (*p* value not listed), but did not have a statistically significant decrease in hirsutism based on objective Ferriman-Gallwey scores (*p* = .11). Overall, there is not enough information and data to determine whether or not herbal supplements can improve clinical features and manifestations of hyperandrogenism such as hirsutism and acne based on the studies from this systematic review. Therefore, at this time, it is inconclusive to determine the effect herbal supplements have on improving clinical manifestations of hyperandrogenism in young women with PCOS.

**Discussion**

The purpose of this review is to identify what effect herbal supplements have on reducing androgens in young women with Polycystic Ovary Syndrome (PCOS). Two studies included in the review were RCT’s and the remaining three were experimental studies. All studies agreed, to some degree, that elevated androgen levels in women with PCOS can be decreased by the treatment of various herbal supplements (Ainehchi et al., 2020; Akdogan et al., 2007; Armanini et al., 2007; Grant, 2010; Luan & Sun, 2015). It’s difficult to compare findings from each study to one another because they do not study the exact same herbal supplement treatment. Some studies have combined treatments of several herbs, some have herbal supplements with medications, and some have one isolated herb as a supplement (such as spearmint alone). This is a major reason why more studies need to be conducted to determine what effect individual or isolated herbal supplements have on androgen levels in women with PCOS. This will help determine how effective each supplement is on lowering androgen levels in this population.

What all studies included in this review have in common is that they all had small study populations ranging between twenty-one to sixty participants per study (Ainehchi et al., 2020; Akdogan et al., 2007; Armanini et al., 2007; Grant, 2010; Luan & Sun, 2015). Another quality that all the studies have in common is that four of the five studies had exceptionally short treatment periods ranging from five days to three months which is not long enough for accurate and valid results (Ainehchi et al., 2020; Akdogan et al., 2007; Armanini et al., 2007; Grant, 2010). The only study in this review that had an acceptable treatment period to determine valid results was the study conducted by Luan and Sun (2015).

The studies which had spearmint as the isolated treatment or combined in an herbal mixture treatment found the following results (Ainehchi et al., 2020; Akdogan et al., 2007; Grant, 2010). One of the RCT found that spearmint treatment resulted in a significant decrease in both total testosterone and free testosterone (Grant, 2010). Another RCT found that an herbal mixture treatment containing spearmint resulted in a significant decrease in total testosterone but not free testosterone (Ainehchi et al., 2020). The same RCT along with one of the experimental studies both found that the treatment of either spearmint alone or the treatment of an herbal mixture containing spearmint with CC resulted in significantly decreased free testosterone levels but did not result in significantly decreased total testosterone levels (Ainehchi et al., 2020; Akdogan et al., 2007). An experimental study and a RCT that evaluated DHEAS levels both found that the treatment of spearmint tea twice per day did not significantly decrease DHEAS levels in the two study populations (Akdogan et al., 2007; Grant, 2010).

 Only one experimental study evaluated what effect an herbal mixture treatment containing spearmint alone and with the additional supplementation of CC had on acne. The results found that both the herbal mixture alone and the herbal mixture with CC were able to significantly improve acne in the participants (Ainehchi et al., 2020). Lastly, one of the experimental studies and one of the RCT found that the treatment of spearmint alone or spearmint contained in an herbal mixture (both with and without additional supplementation of CC) resulted in a significant decrease in hirsutism based of subjective assessments from participants (Ainehchi et al., 2020; Grant, 2010). However, the RCT that assessed hirsutism assessed it both subjectively (with DQLI) and objectively (with Ferryman-Galwey ratings) resulting in different outcomes. The subjective results were previously mentioned, and the objective results showed that there was not a significant reduction hirsutism in the subjects (Grant, 2010).

The two remaining experimental studies had treatments consisting of licorice extract or a substance (glabridin) from licorice (Armanini et al., 2007; Luan & Sun, 2015). The treatment of licorice had mixed results between the two studies. The first study found that there were no significant changes in total testosterone nor free testosterone in participants who were treated with the combination of licorice extract and spironolactone (Armanini et al., 2007). On the other hand, the second study found that there was a significant decrease in serum testosterone and “Hirsutism Scores” after the treatment of glabridin (Luan & Sun, 2015). However, there was not a significant reduction in hirsutism based on the objective Ferryman-Gallwey Scores after the treatment of glabridin (Luan & Sun, 2015).

In the scoping search for this review, an overwhelming ratio of animal to human studies were identified regarding the effect herbal treatments had on reducing androgen levels in PCOS. Some rodent studies found that spearmint supplementation can successfully reduce testosterone levels in PCOS rats (Ataabadi et al., 2017; Mehraban, Jelodar & Rahmanifar, 2020). Rodent studies on baicalin, a “potent bioactive flavonoid isolated from the radix of Scutellaria baicalensis” which is a Chinese medicinal herb, found that baicalin supplementation was able to successfully reduce testosterone production in rats with PCOS (Wang et al., 2019; Jin Yu et al., 2019). This suggests that both baicalin and spearmint may have a beneficial impact on reducing elevated androgen levels in women with PCOS. Unfortunately, there were no human studies identified that looked at the effects baicalin had on androgen levels that fit the inclusion criteria for this review, therefore, an evaluation on the supplementation of baicalin was not included in this review. Further research must be conducted to determine what effects both spearmint and baicalin have on androgen levels in human subjects with PCOS.

**Strengths and Limitations**

Only two of the five studies in this systematic review were gold standard RCT’s. The RCT’s evaluated in this review both used randomization and blinding to reduce the chance of bias, and both RCT’s made note of their limitations within their respected discussions (Ainehchi et al., 2020; Grant, 2010). The RCT’s were both rated as strong studies with positive (+) ratings from the QCC. The remaining three studies were all experimental studies, all of which resulted in neutral (Ø) ratings from the QCC due to the majority of the three studies lacking clarity and answering “no” or “unclear to questions numbered 3, 4, 5, 6, and 10 in the QCC; refer to Table 4 (Akdogan et al., 2007; Armanini et al., 2007; Luan & Sun, 2015). Major limitations to most of the studies in this review were that they had small sample sizes and too short of treatment periods to determine accurate effects of the relationship of the respected treatments on androgen levels (Ainehchi et al., 2020; Akdogan et al., 2007; Armanini et al., 2007; Grant, 2010). The limitation of the last study was that there was no control group to compare results of the treatment (Luan & Sun, 2015). Another limitation was that some studies obtained data on acne and hirsutism subjectively, which provides data that is not as reliable and valid as objectively measured data (Ainehchi et al., 2020; Grant, 2010).

An overall limitation of the systematic review was that the inclusion and exclusion criteria resulted in only five studies fitting the criteria to be reviewed and included in this systematic review. Because studies were limited to English, this could mean that quality studies were excluded from being reviewed and adding quality information to this review. Another limitation was that multiple herbal remedies were included in the review and the search was not limited to one herb’s effect on androgens because there were not enough human studies on a single herb. Therefore, the search broadly evaluated the effect several herbs had on androgens rather than looking at several studies showing data on one herb’s effect on androgens in this population. A strength of this review was that all study populations consisted of young (premenopausal) women with PCOS who presented with elevated androgens.

**Implications for Future Research**

 As previously mentioned, during the search for articles to include in this review, it became evident that there was an overwhelming amount of animal (rodent) studies regarding the effects various herbal supplements had on androgen levels in those with PCOS but very few studies with human participants. It is essential that there be further future research with human participants to determine stronger conclusions on how various herbal supplements effect androgen levels in women with PCOS for treatment purposes. Based on the small sample sizes and short treatment periods in the majority of the studies in this review, further studies are needed with larger sample sizes and longer treatment periods to better understand and obtain more accurate data on the effects of various supplements on androgen levels in this population. Finally, further studies need to be conducted on individual herbal supplements alone, such as the supplement of spearmint alone without medications or other herbal supplements combined, on women with PCOS to determine the isolated effect each herbal supplement has on androgen levels in this population.

**Conclusion**

Based on the studies from this systematic review, it is evident that herbal supplements (spearmint, ginger, cinnamon, sweet orange groups, glabridin) can significantly lower biochemical androgen levels and can significantly improve clinical features (acne and hirsutism) of elevated androgens in young women with PCOS. It is impossible at this time to give a definitive answer on what supplement, how much, and for how long women with PCOS would need treatment for to ameliorate elevated androgen symptoms due to the fact that the treatment was not identical across all studies included in this review. For example, some studies had an intervention consisting of spearmint, while others had an intervention consisting of a mix of several herbal supplements.

As a collective, the articles of this review scored between I (good) and III (limited) on the conclusion grading table consisting of five categories. Quality scored II overall, consistency scored I overall, quantity scored III overall, clinical impact scored II overall, and generalizability scored III overall. This resulted in a final grade of II (fair) overall; refer to Table 5. Further research must be conducted on human subjects with PCOS. Further research should also include studies that look at isolated, individual herbal supplement treatment on this population without medicine or multiple herbal components in one study or review.

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| Table 5*Conclusion Grading Table* |
| **Strength of Evidence Elements** | **Grades** |
| **I****Good** | **II****Fair** | **III****Limited** | **IV****Expert Opinion Only** | **V****Grade Not Assignable** |
| **Quality** Scientific rigor/validityConsiders design and execution | Studies of strong design for questionFree from design flaws, bias and execution problems | Studies of strong design for question with minor methodological concerns, OROnly studies of weaker study design for question | Studies of weak design for answering the questionORInconclusive findings due to design flaws, bias or execution problems | No studies availableConclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research | No evidence that pertains to question being addressed |
| **Consistency** Of findings across studies | Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most | Inconsistency among results of studies with strong design, ORConsistency with minor exceptions across studies of weaker design | Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies | Conclusion supported solely by statements of informed nutrition or medical commentators | NA |
| **Quantity** Number of studiesNumber of subjects in studies  | One to several good quality studiesLarge number of subjects studiedStudies with negative results have sufficiently large sample size for adequate statistical power | Several studies by independent investigatorsDoubts about adequacy of sample size to avoid Type I and Type II error | Limited number of studiesLow number of subjects studied and/orinadequate sample size within studies | Unsubstantiated by published research studies | Relevant studies have not been done |
| **Clinical Impact**Importance of studied outcomesMagnitude of effect | Studied outcome relates directly to the questionSize of effect is clinically meaningfulSignificant (statistical) difference is large  | Some doubt about the statistical or clinical significance of the effect | Studied outcome is an intermediate outcome or surrogate for the true outcome of interestORSize of effect is small or lacks statistical and/or clinical significance | Objective data unavailable | Indicates area for future research |
| **Generalizability** To population of interest | Studied population, intervention and outcomes are free from serious doubts about generalizability | Minor doubts about generalizability | Serious doubts about generalizability due to narrow or different study population, **intervention or outcomes studied** | Generalizability limited to scope of experience | NA |

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