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Review Article

Can Spearmint Be a Natural Alternative to Spironolactone in Treating Increased Androgen Levels?

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Abstract

Medical spironolactone and the natural spearmint plant have been studied to determine their antiandrogenic effects and influence on conditions associated with elevated levels of androgens such as polycystic ovary syndrome and acne. Spironolactone functions as an androgen receptor antagonist and combats the effects of excess testosterone. Spearmint is a member of the mint family and contains carvone, which contributes to its antiandrogenic effects. This review will introduce each of these treatments and compare recent studies to previous research investigating topics such as the expected amount of time it will take either spironolactone or spearmint to lower androgen levels, as well as the efficacy and safety of each option.

Keywords: Acne; Androgens; Polycystic Ovary Syndrome; Spearmint; Spironolactone

Abbreviations: ACE: angiotensin-converting enzyme; BMI: Body Mass Index; DHEA: Dehydroepiandrosterone; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; NSAID: Non- steroidal Anti-Inflammatory Drug; PCOS: Polycystic ovary syndrome; SHBG: Sex Hormone Binding Globulin

Introduction

Spironolactone is a mineralocorticoid receptor antagonist commonly used to help treat primary hyperaldosteronism, congestive heart failure, essential hypertension, and hypokalemia [1]. However, it also as an off-label use in treating acne. It is frequently used as an androgen receptor antagonist. In this way, it acts to reduce excess sebum from hyperandrogenism [1]. Because excess sebum is thought to be a main contributing factor to hormonal acne, spironolactone can effectively be used as a treatment.

Mentha spicata Labiatae (spearmint) and Mentha piperita (peppermint) come from Eastern Asia and have been used over the years for many illnesses [2]. Within the mint family, not all types are as effective in fighting acne. Spearmint has been determined to be a stronger antimicrobial agent than peppermint against the bacteria Propionibacterium acnes [3]. In different research studies that were done to determine the effect of spearmint on androgen levels, initial findings were positive. However, there may be certain circumstances where a stronger alternative, such as spironolactone is needed to combat excess androgens and reduce related symptoms. Additional research evaluating the properties of spearmint can help this treatment become more widely recognized as a safe and natural alternative to the medication spironolactone.

This study reviewed electronic databases (ScienceDirect, Google Scholar, ResearchGate, and PubMed) to gather data about the usefulness of spearmint as an alternative to spironolactone in lowering elevated androgen levels in females and determine the length of time required before any anti-androgenic effects were realized. Studies analyzing the effectiveness of each treatment by recording various hormone levels and also by grading the severity of the physical manifestations of elevated androgens, such as acne, were used to reveal how spearmint can be a viable alternative to spironolactone in cases where symptoms may not be so severe and where it is given enough time to be an effective treatment. The search was performed using Spearmint for acne, Spironolactone for acne, Spearmint vs Spironolactone, Spearmint and androgens, and Spironolactone and androgens.

Results and Discussion

Spironolactone

A search for spironolactone for acne on PubMed yielded over 230 results including its uses in treating acne in both women and adolescent girls, dermatology, and for specific medical conditions like PCOS.

In J. W. Charny's study in 2016, 110 female patients were given spironolactone to reduce their acne. A comprehensive severity scale (CASS) was used to grade the severity of the participants' acne [1]. The grading was done both before they began the medication and at each of their following visits. Throughout the study, 94 of the 110 women saw a reduction in their acne, and 61 of the 110 women observed that spironolactone cleared all their acne [1]. The greatest reduction in acne for these women was seen on the back, followed by the chest, and then the face [1]. Taking spironolactone is safer than acne medications such as isotretinoin because isotretinoin use can potentially cause depression and is also teratogenic [1]. However, spironolactone does not come without its own side effects. Of the 110 participants in Charney's study, fifty-one experienced side effects from spironolactone. Six of the study's participants felt the side effects were too severe to continue their participation in the research. Conversely, the remainder felt that their decreased levels of acne outweighed the adverse effects of breakthrough bleeding, amenorrhea, and lightheadedness [1].

The authors believed spironolactone could be used as the first-line treatment for women who have acne but felt that there was a need for more research before this point could be reached. While this study did have more patients than some other studies done with spironolactone, it is important to note that it did have its own limitations. While effective, it would have produced more accurate results if the patients had first discontinued their use of any other acne-inhibiting products or medications. The patients in this study did not stop their use of other acne treatments during this period, and many of them were still using topical acne medications such as benzoyl peroxide, topical clindamycin and retinoids, and oral contraceptive pills which confounded any potential findings.

Spironolactone and Androgen Levels

Studies with spironolactone are not only a recent occurrence. In one study done on androgen levels and spironolactone almost forty years ago, it was found that the medication was able to improve acne and reduce sebum excretion when compared to a placebo. The study was unique at the time because it used a combination of both male and female patients whose ages ranged from eighteen to thirty-eight. Thirty-six participants were treated for three months with either spironolactone or a placebo, but only twenty-six individuals completed the study [4]. Spironolactone amounts used in the study were either 50 mg, 100 mg, 150 mg, or 200 mg, with the doses of 150 mg and 200 mg showing the greatest improvement in participants [4].

Since the five participants with the most severe acne had the highest levels of free androgens [4], the study was able to determine that androgen levels play a large role in the severity of acne. Findings consisted of reduced sebum excretion in both genders, but specifically, in all of the females who completed the study, spironolactone was able to lessen androgen levels causing sebum excretion [4], which was the main cause of their acne.

This study also considered the importance of the time period as a factor in these types of studies. It found that more time would be needed to truly see maximum improvement in acne. Without considering this, how can it be determined for certain if acne severity could decrease even more or if findings would simply plateau after a certain point? However, it would be important to keep in mind that including males in a longer study with spironolactone would be difficult because they potentially could experience adverse effects of low levels of androgens such as gynecomastia or impotence [4], and that is likely why many similar studies include females only. Male participants did not experience those side effects in this study, however, because the duration was too short. An interesting aspect of Goodfellow's study was that unlike other studies involving spironolactone and the reduction of acne, this study did not include any female participants who were currently using oral contraceptives. Additionally, any female participants involved in the study were asked to switch to non-hormonal contraceptive measures, if necessary. This method is helpful since it ensures that any improvement of acne was almost definitely caused by the spironolactone.

Acne likely affects up to 20-30% of women and is generally classified using hormonal and inflammatory factors when compared to acne in teenagers [5]. The cost of acne in the United States is predicted to exceed 1 billion United States Dollars per year [5]. A study run in 2020 using 200 female patients provided evidence that many therapies used for acne are difficult to manage. Cyclins can lead to bacterial resistance, zinc salts are less effective than cyclines, antiandrogenic therapies can cause phlebitis, and isotretinoin is teratogenic [5]. The authors of this study support that spironolactone provides another option by blocking 5-a reductase receptors and inhibiting luteinizing hormone [5]. While this particular research consisted of a double-blind randomized study to compare low doses of spironolactone (< 200 mg/day) to cyclines in patients with at least ten inflammatory lesions, it is the consideration of the side effects of each type of treatment that this review article is interested in touching upon. This study cites that there have been 10 other randomized control trials where women

with acne were treated with spironolactone that measured results by the lesion count. This study used a new scale called the Adult Female Acne Scoring Tool (AFAST) to assess acne on the face and the mandibular region [5]. Spironolactone has been prescribed for more than thirty years in the USA to treat women's acne, but that is an off-label use, meaning sometimes it may not be the first treatment a provider considers prescribing even if it may be helpful [5]. However, since spironolactone is a potassium-sparing diuretic, it does come with the potential side effect of hyperkalemia. Consequently, this study took special measures to prevent the use of any other substances that could increase potassium such as potassium supplements, ACE inhibitors, angiotensin II antagonists NSAIDs, and heparin [5], while participants were enrolled in the study. It was found that 14% of women enrolled in the study that were taking spironolactone experienced menstrual irregularities as the most common side effect. Additionally, up to 1% of women may have also experienced uncommon side effects such as postural hypotension, depression, diarrhea, muscle pain, palpitations, and drowsiness to name a few [5].

Considerations for Spironolactone Use

An additional study was done on spironolactone two years after Goodfellow's research provided more support for its efficacy as a treatment for acne in women [6]. Twenty-one women were observed over the course of three months. When compared to Goodfellow's study, the women participating in Muhlemann's study all took a standardized 200 mg daily amount of spironolactone. This study used a similar grading method as in Goodfellow's study where assessments were objective, photographic, or subjective.

It was found that levels of SHBG did decrease, but there were no real changes in plasma testosterone or free testosterone [6]. It was also stated that oral contraceptives did not change results significantly [6]. This is an interesting finding because, in Goodfellow's similar study, individuals were not included if they took oral contraceptives. The result of Muhlemann's study found that a majority of the patients saw improvement after using spironolactone and no change when using the placebo. It is important to note, however, that the most reported side effect during this study was menstrual irregularity which occurred in nearly all the patients, eleven out of fifteen. One month after discontinuing their use of spironolactone, their cycles returned to normal. While spironolactone is shown to be effective in the reduction of acne, side effects such as altered menstrual cycles may cause some patients to be more comfortable with natural acne treatments such as spearmint.

Spironolactone and PCOS

Altered levels of androgen can even influence fertility. PCOS can be associated with metabolic disorders and can increase rates of infertility [7]. Spironolactone can be used to help treat the androgen levels and resulting hirsutism seen in PCOS. Although this review article is focused on exploring means of reducing androgen levels in humans, a study done by Olaniyi, et al. in 2020 attempted to evaluate the antiandrogenic properties of a low dose of spironolactone in female rats. A group treated with vehicle, another treated with letrozole (1 mg/kg), and a third group treated with letrozole and low-dose spironolactone (.25 mg/kg) once daily for twenty-one days were used for this research [7]. Letrozole was used as an artificial means of inducing PCOS for the purpose of the study. Considering that PCOS likely causes around 70-80% of cases of infertility in women and plays a role in upsetting the certain metabolic processes that cause anovulation and cause acne hirsutism [7], the study sought to find if spironolactone could correct the androgenic imbalance. This was done by evaluating the relationship between levels of adiponectin and the severity of PCOS symptoms. While not known for certain, there are strong associations between insulin resistance and PCOS. This stems from the realization that insulin resistance and resulting hyperinsulinemia stimulate ovarian tissue which consequently decreases aromatase activity [7]. Aromatase is an enzyme that would have converted the androgens into estrogens, but now this ability is compromised. This results in altered levels of sex steroids and sex hormone-binding globulins which result in increased levels of androgens, resulting in infertility [7]. The study asserts that using spironolactone as a mineralocorticoid receptor antagonist can help manage symptoms of PCOS but is best used in small doses to minimize side effects. The study found that the group of rats treated with low doses of spironolactone had significantly reduced body weight, ovarian weight gain, and levels of testosterone when compared to untreated rats, as well as undisrupted follicles and granulosa cells when compared to untreated PCOS rats [7]. Low doses of spironolactone were found to increase circulating adiponectin levels, as well as decrease circulating testosterone, which is why the authors of the study felt that spironolactone was an effective treatment.

Spearmint

Over the years, more natural remedies have been tested to determine their effects on lowering androgen levels, but studies on natural remedies are less commonly known and more research with positive findings would likely have to be done to increase public awareness. In 2007, research was conducted in Turkey to evaluate the efficacy of spearmint in combating increased androgen levels in women. Other members of the mint family, such as peppermint, are not comparable to spearmint in the treatment of high androgen levels. This stems from the fact that the high efficacy of spearmint is due to carvone, of which spearmint generally has anywhere from 29-74% [2]. In the past, different studies had been done with spearmint in rats. Taking into account that although this is a different body than a human's, it was found that spearmint was able to lower their androgen levels which then set into action research done in Turkey by Akdogan and Tamer that attempted to determine if spearmint could have the same effect in women with hirsutism. In more recent years, additional research was also done by other researchers such as Grant and Tamilselvi to evaluate how potent the antiandrogenic properties of spearmint are.

Spearmint and Androgens

It is now evident that spearmint's androgen-lowering abilities can improve the effects of hirsutism in females. Hirsutism is described as higher than normal levels of male-patterned hair growth in women, caused by the effect of high androgen levels on hair follicles [2]. In this study, twenty-one females in the follicular

phase of their menstrual cycle, beginning on the first day of their period and ending with the first day of ovulation, drank a 250 mL cup of herbal tea with spearmint (% 20g/L) twice a day over five days. It was found that their levels of free testosterone declined, and levels of luteinizing hormone and follicle-stimulating hormone increased [2].

These results stemmed from spearmint acting as an inducer of the liver enzyme CYP3A4. Inducing this enzyme results in reductions in the concentration of different sex hormones in the blood [2]. It was also thought in this study that spearmint was able to help increase levels of SHBG. SHBG normally would decrease from the effects of androgens like testosterone [2], but since spearmint is able to lower the levels of androgens in the blood, this allows levels of SHBG to rise. The study also found that spearmint influenced triglyceride levels in women with hirsutism. After taking spearmint to combat high androgen levels, the women's levels of triglycerides now appeared to decrease. Women with high levels of androgens many times have high levels of triglycerides because these are correlated with insulin resistance and obesity [2]. The researchers for this study believe treating elevated androgen levels is the key to helping women with hirsutism. This effect has already been proven by the medication spironolactone, which works by blocking androgen action, but this research makes it evident that spearmint can also provide a natural remedy to high levels of androgens.

Spearmint Use and Physical Appearance

In Paul Grant's study done in 2009, a randomized control trial was done to evaluate the antiandrogenic properties of spearmint in women with hirsutism who had the condition PCOS [8]. Completed two years after Akdogan and Tamer's research in Turkey, Grant's research acknowledged the findings of Akdogan and Tamer, but wanted to go one step further and link lower androgen levels caused by spearmint to a clinical improvement in the severity of hirsutism experienced by individuals.

Grant's study took place over thirty days using forty-two volunteers who were randomly given either spearmint tea twice a day for one month or a placebo herbal tea twice a day for one month [8]. Their hirsutism was graded using two different methods: objectively using the Ferriman-Gallwey index and subjectively using the Dermatology Quality of Life Index (DQLI). This method of measuring the effects of spironolactone on acne had some similarities to Goodfellow's previously mentioned research on spironolactone, where two different methods were used to evaluate any improvements in hirsutism.

Additionally, Grant's study resulted in similar findings to the 2007 Akdogan and Tamer research, but in addition to the previously noted lower free testosterone levels and increases in levels of LH and FSH, Grant's research also found that total testosterone was much lower in the group that took spearmint tea.

The study concluded that spearmint is an effective, natural way to lower levels of androgens in women with PCOS, but that it takes time to actually see the effects of these lower levels of male hormones on follicular hair growth and cell turnover time [8]. The 2007 spearmint study done in Turkey by Akdogan and Tamer took place over 5 days and this 2009 study by Grant took place over 30 days, which provided a much greater time period to see results and support the idea of spearmint being able to provide a natural solution in combating high androgen levels. However, an even longer study would be beneficial to show the effects of spearmint over an extended period of time.

Spearmint Use and Hormone Levels

In 2018, more research was done to evaluate the effects of androgen levels in young women with PCOS. In this condition, ovulation is disturbed by cysts forming near the ovaries [9]. While it may not seem common, PCOS affects an estimated one in five women worldwide. It is one of the most common female endocrine disorders, with between 5%-10% of women of reproductive age experiencing symptoms [9]. The research was done to see if females with this condition could modify their lifestyles and drink spearmint tea to lower their levels of androgens. If successful, this would then act to decrease the effects of PCOS.

The process would use a pretest and posttest for both the experimental and control groups. This consisted of blood tests for levels of FSH, LH, blood glucose, and testosterone, as well as an ultrasonogram of the pelvis and a Body Mass Index (BMI) calculation [9]. The sample size for this study was small and only studied seven women with PCOS over the course of one month [9], 50 mL of mint powder, a modified diet, and exercise were found to be effective in helping PCOS [9]. The participants in both the experimental and control groups recorded self-assessment scores. For the experimental group, the pretest score was 57.14 and the post-test score was 36.36 [9]. Based on study results, considering herbal remedies to treat PCOS could be beneficial.

Additionally, this research referenced Paul Grant's previous research, which suggested that a longer study should be done. This is because the effects of hirsutism can take a long time to improve [9].

The five individuals who completed the study did experience regular menstruation, ovarian cysts that decreased in size, and a lower BMI [9]. However, the small sample size could be a potential drawback to this study. An additional shortcoming in this particular study was the fact that various socioeconomic levels were not represented. The study was mainly confined to a specific socioeconomic group; therefore, it is difficult to predict the outcome of the study if it were done on a group of individuals with a greater variation in socioeconomic backgrounds.

It has also been supported in a 2020 study done in rats that spearmint and flaxseed extract can be used to improve PCOS by reducing androgen levels [10]. In this study, 24 rats with regular cycles were divided into 4 groups. The treatment group received 40 mg/kg spearmint extract and 200 mg/kg flaxseed extract for 30 days, which was seven weeks after an injection of estradiol valerate to induce PCOS in the treatment group and the untreated PCOS group [10]. In the group of rats that were treated with spearmint and flaxseed, a decrease in testosterone and cystic follicles was observed. In women with the disorder, a higher level of luteinizing hormone and a lower level of follicle-stimulating hormone is usually observed [10]. Some medications used to control manifestations of PCOS such as metformin, clomiphene citrate,

glucocorticoids, and anastrozole can contribute to some women feeling burdened by side effects such as nausea, abdominal pain, and vaginal bleeding [10]. For this reason, natural alternatives that provide control levels of excess androgens such as spearmint may begin to gain favor. Spearmint decreases FSH, LH and DHEA levels [10]. Additionally, this particular study also supported that the lignan and phytoestrogen in flaxseed may be able to alter levels of aromatase that are off-balance in patients with PCOS and decrease levels of 5-α reductase and free testosterone levels. Because of these positive findings, treatment with spearmint and flaxseed was recommended for PCOS in women.

Conclusion/Future Directions

In the world in which we live, there has been increasing amounts of interest every year in skincare, with a large part of the concern going toward improving the appearance of acne. There is also greater knowledge than ever before in managing medical conditions such as PCOS. A factor both of these conditions share is increased androgen levels. Utilizing natural methods can not only decrease levels of androgens but can also reduce some noticeable androgenic symptoms such as acne and hirsutism from PCOS that can result if levels are elevated. Taking spearmint instead of spironolactone can provide a way to lower elevated androgen levels that causes these conditions. Also, spearmint can work as a more natural alternative that can be easily incorporated into the diet. With that being said, it is important to consider that spearmint may not work for everyone. There is still a need for spironolactone in any of these conditions where androgen levels are too high for what previously tested levels of spearmint are able to lower. Even though some of the researchers tried to extend the duration of their studies, overall, each of them concluded that even more time would be needed to truly see the effects of the natural remedy of spearmint on decreasing levels of androgens as much as spironolactone. Therefore, it seems reasonable to conclude that spearmint has value in being an option for those with the previously stated conditions without extreme severity and who would like to avoid the potential side effects of spironolactone.

Acknowledgement

None.

Conflict of Interest

The authors declare that there is no conflict of interest.

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