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*Article*

# The Effect of Micronutrients on PSA Dynamics In Prostatic Disease: A Controlled Pilot Study

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**Abstract:** Background: The present study investigated the effects of a micronutrient combination with proven impact on prostate cell metabolism and growth with regard to PSA dynamics. Methods: In an open single-arm multicenter study, 46 men with different baseline situations were recruited: 16 men with constantly elevated PSA values and negative prostate biopsy (group A), and 30 men with low risk prostate cancer on Active Surveillance (Group B). Results: In group A, 12 out of 16 men (75%) showed a decrease of PSA after 6 months from an average 9.26 to an average 8.84 ng/ml (4.5%), whereas in group B, PSA level decreased in 16, increased in 12 men, and remained unchanged in 1 man. The average PSA in group B dropped from 7.47 to 6.82 ng/ml (8.6%). Both PSA decreases were not statistically significant. Conclusion: The results of the present study are consistent with previous findings on the positive effects of individual micronutrients on prostate health. Longer administration of micronutrients or different dosage or combinations may further improve PSA outcomes.\_

**Keywords:** micronutrients; prostate cancer; PSA dynamics

## 1. Introduction

The incidence of prostatic diseases is increasing with age, and, consequently, the majority of men > 60 years experience some kind of prostate related symptoms. While on one side prostate cancer, the most prevalent malignant disease in men, is a potentially life-threatening disease, benign prostatic enlargement (BPE), also known as prostatic hyperplasia (BPH), may cause bothersome changes in micturition.

There is a wide range of surgical and medical therapeutic options for all kinds of prostatic diseases. However, an increasing number of men tend to alternative or phytotherapeutic therapies as a first choice, even though there is scarce scientific evidence to support this [1].

For detection of prostate cancer and discrimination from benign disease, prostate-specific antigen (PSA) is the present tumor marker of choice [2]. Despite its limited specificity, it can detect most prostate cancers at curable stages. In cases when tumors are detected at very early stages (low volume/low risk tumors), active treatment may be postponed and active surveillance initiated [3]. PSA monitoring is the base in this situation, supported by magnetic resonance imaging or re-biopsy as needed.

The limited specificity of PSA means that men may have constantly elevated or rising PSA levels without cancer being detected in biopsies. This places a psychological burden on the men affected, and no standard treatment can be offered in this situation.

Common phytotherapeutics for prostatic disease (*Serenoa repens*, Saw palmetto) may have positive effects on micturition, but not on PSA levels or the progression of prostate cancer [1]. In contrast, various herbal compounds have shown effects on prostate cancer transformation/growth and PSA-levels in in-vitro studies and in published trials [4,5].

Decades ago, epidemiologic data showed that the incidence of prostate cancer in East Asian men was significantly lower than in Western countries [6]. This was attributed to the regular consumption of soy products in Asian countries, since these contain a variety of isoflavones [7]. Isoflavones are phytoestrogens with hormonal activity and found in relevant concentrations in soy beans, red clover and kudzu roots. The best investigated isoflavones are daidzein, genistein, formononetin and biochanin. They have been shown to block cell proliferation, dedifferentiation and angiogenesis in prostate cancer cell lines, as well as in rat studies [8–10].

In a clinical pilot study, PSA-reduction of 33% was observed in men without proven prostate cancer after one year administration of a standardized isoflavone preparation. No side effects, particularly with regard to sexuality, were observed in this study [11].

Similar in vitro antiproliferative effects on prostate cancer cells have been demonstrated for catechines (epigallocatechingallat – EGCG, from green tea), phytosterole ( $\beta$ -sitosterol from pine nuts), tannins (elagitannine/gallotannine from pomegranate), and lycopin (from tomatoes), as well as for vitamines D3, B6, and zinc [12–20].

This led to the hypothesis that a combination of all these compounds could have a beneficial effect on prostate cells growth and, thus, on the PSA value.

2. Materials and Methods

In an open single-arm multicenter study (office-based at 7 centers), 2 patient groups of men > 45 years were recruited:

Group A: men with constantly elevated PSA values and negative prostate biopsy

Group B: men with low risk/low volume prostate cancer on Active Surveillance [21]

All men gave their written consent to participate in the study and to take 2 capsules of the study compound (Table 1, source Lenus Pharma GesmbH) per day for 6 months.

Table 1. Ingredients per capsule.

Ellagic acid (pomegranate)	46mg
Catechins (green tea)	73mg
Phytosteroles (pine nuts)	59 mg
Isoflavones	25mg
Microencapsulated Lycopene	5mg
Vitamine D3	13,6 $\mu$ g
Vitamin B6	5mg

Inclusion criteria:

- For patients in group A, a minimum of 3 elevated PSA values (> the age-adjusted normal range) within the last 12 months was required for study inclusion.
- For patients in group B, bioptic evidence of a low risk-low/volume prostate cancer ( $\leq$  2 positive biopsies with < 50% tumor volume, Gleason grade 3+3 or 3+4, PSA < 10 ng/ml at the time of biopsy [21]) was a prerequisite for study inclusion. These men had to opt for active surveillance after being informed of all possible treatment options for their prostate cancer, and at least three elevated PSA values (> the age-adjusted normal range) within the last 12 months were required.

Exclusion criteria:

- Long-term anti-inflammatory medication.
- Antihormonal medication.
- Active urinary tract infection.
- Cycling (sport).
- Participation in another study.

Before initiation of study medication, laboratory values (PSA, free PSA, testosterone, liver transaminases), prostatic volume (by transabdominal ultrasound) and IPSS (International Prostate-Symptom-Score) were determined. Histologic reports of prostate biopsies and medication lists were recorded.

The same assessment was repeated after 6 months of medication. In addition, adverse effects were recorded.

After 3 months, an interim telephone interview was conducted to ask patients about compliance (capsule intake) and possible adverse effects.

Routine active monitoring was not part of the study protocol and performed as to discretion of the responsible urologist.

Primary study-endpoint was the change in PSA from baseline to end of the study after 6 months of study compound intake. Secondary endpoints were changes in any of the additional parameters recorded.

Statistical evaluation of PSA changes from baseline to end of study was performed with Student's t-Test. A study population of 45 people was calculated for a power of 95%. Significance was assumed for p-values < 0.05. Statistical evaluation was performed with assistance of SPSS Statistics Version 27.

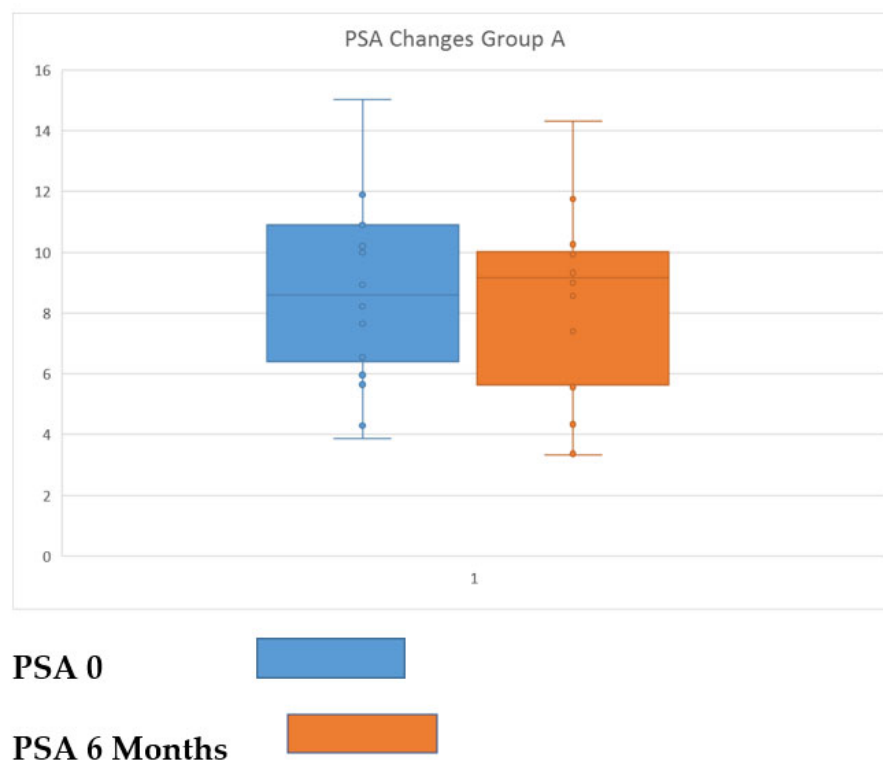
The study protocol was reviewed and approved by the local ethics committee (Ethics Committee for the Federal Province of Lower Austria, St. Pölten, Austria)

### 3. Results

A total of 46 men were included in the study, 16 in group A and 30 in group B. Of the patients under Active Surveillance, 27 were diagnosed with low volume prostate cancer Gleason 3+3, and 3 with Gleason 3+4.

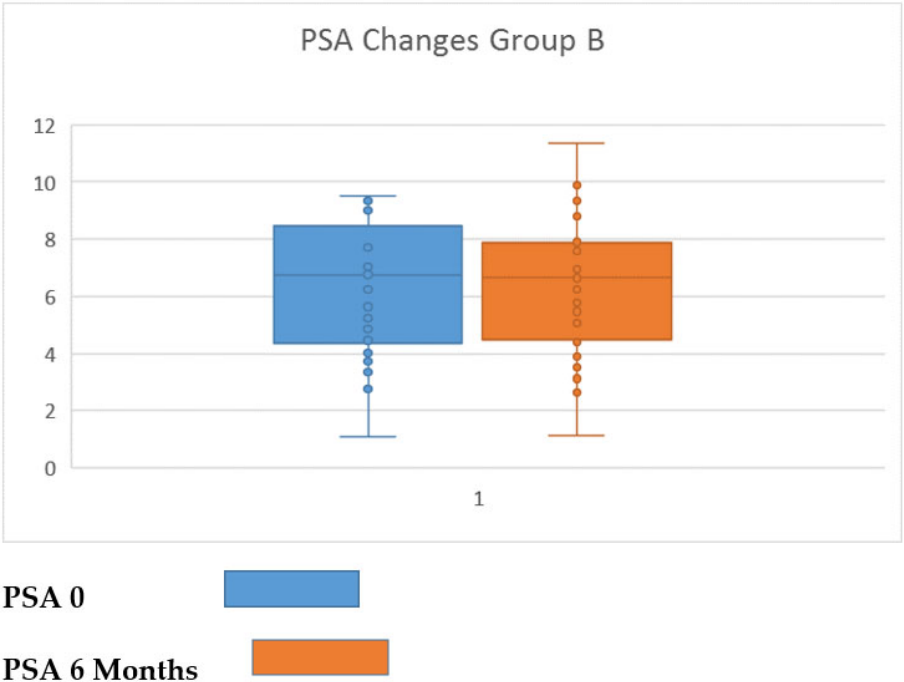
One group B patient discontinued the medication after 2 months due to an adverse event (headache) that was most likely not related to the study compound. Thus, a total of 45 men were evaluated.

In group A, 12 out of 16 men (75%) showed a decrease of PSA after 6 months from an average 9.26 to an average 8.84 ng/ml (4.5%), which was not statistically significant ( $p=0.095$ ) (Figure 1).



**Figure 1.** PSA Changes after 6 months of nutraceutical combination intake in group A.

In group B (Active Surveillance), PSA level decreased in 16 and increased in 12 men, and remained unchanged in 1 man. The average PSA dropped from 7.47 to 6.82 ng/ml (8.6%), which was not statistically significant ( $p=0.177$ ) (Figure 2).



**Figure 2.** PSA Changes after 6 months of nutraceutical combination intake in group B.

Changes of other parameters recorded at baseline and after 6 months are shown in Tables 2 and 3 and did not reach significance at any point. Interestingly, average testosterone levels increased in both groups during the study period: from 3.98 to 4.4 ng/ml in group A, and from 5.45 to 6.30ng/ml in group B. Liver transaminases showed a mild increase of average values in both groups: Glutamat-oxalacetat-transaminase (GOT) from 25.35 to 28.77 U/l and from 29.23 to 30.84 ng/ml; Glutamat-pyruvat-transaminase (GPT) from 26.28 to 28.70 U/l and from 35.46 to 38.53 U/l, whereas Gamma-glutamyl-transferase (gGT) values decreased from 43.85 to 40.17 U/l and from 54.64 to 42.23 U/l.

**Table 2.** Changes of average values in Group A after 6 months micronutrients.

	baseline	6 months
GOT (U/l)	29,23	30,84
GPT (U/l)	35,46	38,53
gGT (U/l)	54,64	42,23
IPSS	9,84	9,30
Testosterone (ng/ml)	5,45	6,30
Prostate Volume (cc)	58,11	55,00

**Table 3.** Changes of average values in Group B after 6 months micronutrients.

	baseline	6 months
GOT (U/l)	25,35	28,77
GPT (U/l)	26,28	28,70
gGT (U/l)	43,85	40,17
IPSS	7,88	6,611
Testosterone (ng/ml)	3,97	4,40
Prostate Volume (cc)	46,96	47,77

The IPSS decreased in both groups: from an average 7.88 points to 6.61 and from 9.84 to 9.30. The sonographically assessed average prostate volumes remained roughly stable: 46.96 and 47.77cc for group 1 and 58.11 and 55cc for group 2.

#### 4. Discussion

Prostatic diseases are a significant health problem for aging men. They occur in various forms, such as benign prostatic hyperplasia (BPE) and prostate cancer. These diseases not only affect quality of life, but may also lead to significant morbidity. Conventional therapeutic approaches often harbour unpleasant side effects and/or lack efficacy, thus, many men favour phytotherapeutic medications despite limited scientific evidence [22,23].

PSA serves as an important tumor marker in the detection and monitoring of prostate cancer, albeit with known limitations in terms of specificity [24]. Persistent elevated PSA values with no malignant findings in biopsy represent a clinical dilemma and psychological burden for those men affected [25]. Although conventional drug therapies can provide relief for BPE symptoms, the uncertainty from tumor marker elevation persists.

Initiated from epidemiologic studies on populations with lower incidence of prostate cancer, the evidence on a link between dietary factors and prostate health is steadily growing. An antiproliferative effect on prostate cancer cells was first shown for isoflavones in vitro and in vivo, which to a great extent are found in soy products [8–10]. Other phytochemicals such as green tea catechins (epigallocatechin gallate - EGCG), phytosterols, tannins, lycopene, as well as certain vitamins and minerals, have also demonstrated promising anti-cancer properties in preclinical studies [12–20,26]. These findings were the base for the present controlled pilot study investigating the effects of a specific combination of micronutrients on PSA dynamics in prostate diseases. It was hypothesized that a synergistic effect of these bioactive compounds could modulate prostate cell metabolism and growth and consequently influence PSA levels.

In the present study, two patient groups were followed for 6 months (Group A with elevated PSA values and negative prostate biopsy, Group B with low risk/low volume prostate cancer on Active Surveillance), and an average reduction of PSA values < 10% was observed in both patient groups, which did not reach statistical significance. A PSA reduction of 33% had been described in a prior study with isoflavone administration alone [11]. These historic data have been used for calculation of the prospective study population in the present study, however, by this the total number of probands may have been too small to reach statistical significance. In addition, isoflavone treatment was continued for 1 year in the prior study, and no cancer patients had been included. Dosages in both studies were slightly different: 50mg isoflavone extract per day in the present study compared to 60mg per day in the former investigation. These different study settings may have contributed to the fact that the PSA reduction under the micronutrient combination was lower compared to isoflavone alone and did not reach statistical significance.

In total, the results showed a nuanced response to the intervention. While a significant decrease in PSA levels was not observed across the board, notable trends emerged. In group A, 75% of the study participants showed a decrease in PSA levels, as did 55% in group B. Since prostate cancer patients usually show an increase of PSA over time, this PSA reduction in group B is most remarkable (and may be an argument for stabilization of disease with micronutrients in active surveillance cases). As PSA also constantly increases with age, which is reflected in age-dependent normal ranges [27], the PSA decrease is also unexpected in group A and may be interpreted as micronutrient effect. Thus, the results of the present study are consistent with previous findings on the positive effects of individual micronutrients on prostate health.

The observed increase in testosterone levels raises interesting questions about underlying mechanisms. While the exact mechanisms of action are still unclear, it may be assumed that the bioactive compounds of the micronutrients can influence endocrine function, possibly by interaction with steroidogenic enzymes or hormone receptors. Isoflavones possess estrogenic and anti-estrogenic effects that are able to modulate testosterone synthesis and metabolism [28]. However, a metaanalysis did not find a significant change of testosterone under isoflavone intake [29]. Thus, any other compound of the micronutrient combination may have been responsible for the testosterone increase observed. Importantly, since PSA levels are testosterone dependent [30], any increase of testosterone should also be reflected by a PSA increase, which was not observed in the study. Possibly, without this testosterone increase, the decrease of PSA would have been more pronounced in the present study.

Additional analyses revealed non-significant changes in other parameters that indicate possible metabolic and physiological effects of the intervention. Liver transaminases showed diverging



patterns suggesting metabolic modulation without a significant increase or decrease. This is important, since a recent publication reports that almost 5 percent of the US population regularly take nutraceutical compounds with potential hepatotoxicity [31].

IPSS scores showed improvements in urinary symptoms, especially in group A. Prostate volume remained relatively stable throughout the study, suggesting that there were no significant anatomical changes attributable to the study product.

## 5. Conclusions

While the results of the present study are preliminary, they provide valuable insight into the complex interplay between micronutrients and prostate health. New compounds with proven in-vitro activity in prostate cells may be added to the present formulation to enhance efficacy. In addition, elucidating the underlying mechanisms behind the observed effects is critical to refine therapeutic strategies and optimize patient outcomes in prostate disease.

In summary, the study contributes to the evolving landscape of integrative approaches in the treatment of prostate disease and highlights the potential of micronutrient combinations as complementary therapies. The short duration of the study may have prevented significant reductions in PSA levels, as changes in prostate health markers often need longer periods to become apparent. Longer-term studies are needed to fully evaluate the effectiveness of micronutrient interventions targeting prostate health.

**Author Contributions:** Claus Riedl was responsible for the study protocol, data analysis and manuscript writing.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Dataset available on request from the authors.

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**Conflicts of Interest:** Claus Riedl declares no conflict of interest concerning the presented study.

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