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Research Paper

Aqueous Extract of *Urtica Dioica* Makes Significant Inhibition on Adenosine Deaminase Activity in Prostate Tissue from Patients with Prostate Cancer

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KEY WORDS

Urtica dioica, prostate cancer, adenosine deaminase

ABSTRACT

Aim: Investigation of possible effects of aqueous extract of *Urtica dioica* leaves on adenosine deaminase activity in prostate tissue from patients with prostate cancer.

Methods: Ten prostate tissues from patients with pathologically proven localized prostate cancer (Gleason scores 4 to 7) were used in the study. In the tissues, ADA activities with and without preincubation with different amounts of *Urtica dioica* extracts were performed.

Results: Aqueous extract of *Urtica dioica* results in significant inhibition on adenosine deaminase (ADA) activity of prostate tissue.

Conclusion: ADA inhibition by *Urtica dioica* extract might be one of the mechanisms in the observed beneficial effect of *Urtica dioica* in prostate cancer.

INTRODUCTION

Prostate cancer is one of the most common diseases in elderly men.[1] Since conventional treatments fail to offer the hope of a cure in most cases, many cancer patients try alternative ways. A systematic review resulted in an estimated average prevalence of 31% in this regard.[2] The most popular complementary medicine type is herbal medicine. Among them, *Urtica dioica* is the most frequently used herb in cancer therapy including prostate cancer.[3] Both roots and leaves of this plant were used; generally as an infusion after boiling. In fact, it is a traditional herb used as an adjuvant therapeutic agent in several diseases including rheumatoid arthritis.[4] Some evidence of immuno-modulator properties of *Urtica dioica* has also appeared in the literature.[5,6] In prostate diseases, phytopharmaceuticals are commonly prescribed.[7] For example, it has been observed that β-sitosterol which is rich in *Urtica dioica* causes significant improvement in symptoms and urinary flow parameters of patients with prostate diseases.[8] In fact, drugs derived from plants have a long tradition in the medical treatment of prostate diseases. Although neither mechanism of action nor precise classification of the active compounds for many of these drugs have yet been established, substantial symptom improvement has been reported.[7] In an animal study, it has been found that methanolic extract of *Urtica dioica* significantly inhibited experimentally induced prostate growth.[9] In another study, a research group has documented that *Urtica dioica* causes significant antiproliferative activity on human prostatic epithelial cells.[10] They suggested that its antiproliferative effect was biologically relevant and could be responsible for the beneficial outcome in the treatment of prostate diseases. Despite all this evidence, neither molecular mechanism nor active component(s) have been clarified for *Urtica dioica* yet.

Since ADA is a key enzyme in DNA turn-over and nucleotide metabolism and some ADA inhibitors like fludarabin have previously been used for chemoterapeutic purposes in some types of cancers like leukemia,[11,12] we thought that it would be helpful, for the elucidation of the relevant molecular mechanism(s), to investigate possible effect of aqueous extract of *Urtica dioica* on ADA activity in prostate tissue from cancer patients.

MATERIALS AND METHODS

Ten prostate tissues from patients with pathologically proven localized prostate cancer (Gleason scores between 4 and 7) were used in the study. The tissues were first washed with distilled water, homogenized in physiologic saline solution, centrifuged at 5000 rpm for 15 minutes and then, upper clear supernatants were removed to be used in the analyses.[13] Protein level of the supernatants was studied by Lowry's method[14] and adjusted to equal concentrations. Dried *Urtica dioica* leaves (5 gr) were incubated in 100 ml ethyl alcohol (5% v/v) for one week at room temperature. Following the incubation it was homogenized and centrifuged at 5000 rpm for 10 minutes at room temperature. Upper clear layer was used as the aqueous extract of *urtica dioica* in the experiments. The supernatants of tissue homogenates (25 µl) were preincubated with the extract in different amounts

Table 1 **Inhibitory Effects of Aqueous Extract of *Urtica dioica* on ADA Activity in Prostate Tissue from Patients with Prostate Cancer**

Amounts	ADA activity (mIU/mg) (Mean ± Standard Deviation)
A-No aqueous extract of *Urtica dioica*	14.8 ± 6.8
B-25 µl aqueous extract of *Urtica dioica*	13.35 ± 4.24
C-50 µl aqueous extract of *Urtica dioica*	6.49 ± 2.38
D-100 µl aqueous extract of *Urtica dioica*	0.98 ± 0.76
Wilcoxon Signed Ranks Test	
A-B	P > 0.05
A-C	P < 0.01
A-D	P < 0.02
B-C	P < 0.01
B-D	P < 0.02
C-D	P < 0.02

Table 2 **Effects of Different Amounts of Aqueous Extract of *Urtica dioica* on Inhibition % Values of ADA Activities**

Amounts	Inhibition % (Mean ± SD)
A-No aqueous extract of *Urtica dioica*	0
B-50 µl aqueous extract of *Urtica dioica*	59.4 ± 9.2
C-100 µl aqueous extract of *Urtica dioica*	92.8 ± 5.3
Wilcoxon Signed Ranks Test	
A-B	P<0.02
A-C	P<0.02
B-C	P<0.02

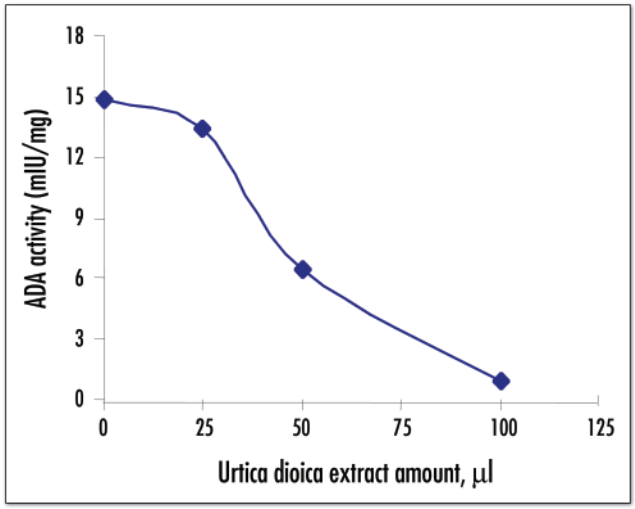

Figure 1 (Above). Prostate tissue ADA activities at different amounts of aqueous extract of *Urtica dioica*.

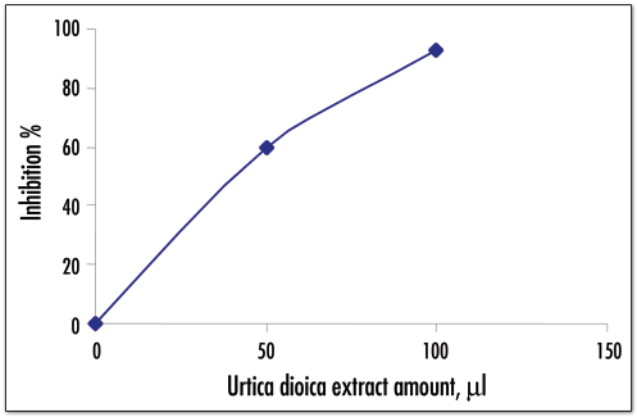

Figure 2 (Above). Effects of different amounts of aqueous extract of *Urtica dioica* on inhibition percent of ADA activities.

(0, 25, 50 and 100 µl) for 30 min. Then, ADA activity was measured as described previously[15] and the results were expressed as mIU/mg.

In the statistical analyses of the results, Wilcoxon signed ranks test was used. P values lower than 0.05 was judged as significant.

RESULTS

Results are given in Tables and Figures. The ADA activity in the sample with no extract of *Urtica dioica* was 14.8 ± 6.8 mIU/mg (Mean ± Standard deviation), with 25 µl of the extract 13.35 ± 4.24 mIU/mg, with 50 µl of the extract 6.49 ± 2.38 mIU/mg and, with 100 µl of the extract 0.98 ± 0.76 mIU/mg, respectively. As seen from the results, aqueous extract of *Urtica dioica* caused significant inhibitions on the ADA activity of prostate tissue from cancer patients. This inhibition was found to be dose-dependent.

DISCUSSION

In some countries, plant-derived drugs are widely used in the treatment of some prostate diseases and, although controversial, represent one of the most frequently used therapeutic approaches.[8,16] Rückle was the first physician who regularly used tea from *Urtica dioica* in cases of urine retention.[17] Since these first observations, various extracts of *Urtica dioica* were commonly used in the treatment of prostate diseases.[18] Some extracts from *Urtica dioica* roots were demonstrated to exert proliferation-reducing effects in an in vivo animal model.[9,19]

The effects of *Urtica dioica* extracts in prostate diseases are still controversially discussed as no clear mechanism(s) has yet been established. Different modes of actions are proposed in this regard. For example, it has been observed that some sterols and hydroxy fatty acids, even they exist at low concentrations in *Urtica dioica*, can inhibit aromatase, which is a key enzyme in steroid hormone metabolism mediating the conversion of androgens into estrogens.[20] In another, an aqueous extract of *Urtica dioica* roots demonstrated a dose dependent inhibition of the binding globulin to its receptor.[21] In another clinical trial, β-sitosterol was found to significantly improve the symptoms and urinary flow of the patients.[8] Another component of *Urtica dioica* root extracts was shown to directly inhibit cell proliferation of HeLa cells and to block binding of epidermal growth factor (EGF) to its receptor.[22] All these observations need however further verifications since none of them has given satisfactory explanations.

Under the lights of all this evidence, how can our results be evaluated? In our opinion, our results might be of importance because ADA is a key enzyme in nucleotide metabolism and DNA

turn-over and, some ADA inhibitors like fludarabine have been succesfully used in some cancer types. Indeed, as seen from the results, the aqueous extracts of *Urtica dioica* leaves cause significant inhibitions on ADA activities in prostate tissues from prostate cancer patients. This inhibition is dose-dependent. At higher amounts of the extract, ADA is almost inhibited completely. However, there are some limitations in the evaluation of our results as always observed in the in vitro experiments, since the circumstances in the living cells are certainly very different from the laboratory conditions. Despite this fact, our results may lead to preliminary understanding of the subject and provoke further studies on the subject including in vivo animal models.

In conclusion, it is possible that ADA inhibition created by *Urtica dioica* extracts is one of the mechanisms leading to improvement in the patients using it.

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