

## ABOUT THE HORMONE OF YOUTH

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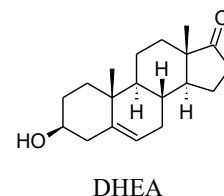
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There are many secondary metabolites around us that have a significant (either positive or negative) impact on human, animal and plant health. This journal touches on them not infrequently in its review articles, because the editors believe that it is necessary to combat the growing (especially Internet) obscurantism that clouds the field with much nonsense, such as the "white evil" of sugars, vinegar, salt, flour, and so on, which spreads harmful untruths, such as that "white distilled vinegar and wine vinegar (in which the predominant substance is "acetic acid") ... is produced by the fermentation of acid alcoholic liquids"<sup>1</sup>. Thus, this article loosely follows articles on flavours and colours<sup>2,3</sup>, alkaloids<sup>4</sup>, cannabis<sup>5</sup>, caffeine<sup>6</sup>, and the like in order to provide the public with sensible information.

Let us have look at the title compound called DHEA; chemically it is (3 $\beta$ )-3-hydroxyandrost-5-en-17-one, also known by the names 17-chetovis; 17-hormophorin; 3 $\beta$ -hydroxy- $\Delta^5$ -androst-17-one; androst-17-one; astenil(e); dehydroepiandrosterone (DHEA, also DHA); deandros; dehydroisoandrosterone; diandron(e); EM 760; GL 701; IM 28; immunor; intrarosa; NSC 9896; prasterone; psicosterone; siscelar plus; *trans*-dehydroandrosterone (TDA);  $\Delta^5$ -androstene-3 $\beta$ -ol-17-one, is a substance that is also known as the "hormone of youth" (but also as the "mother of hormones", "miracle pill", "fountain of youth", or "anti-aging antidote" (cit.<sup>7</sup>) either alone or in the conjugated form of its ester with sulfuric acid (DHEAS)<sup>8,9</sup> whose levels are much higher in the body. It has been called the hormone of youth because between the ages of 20 and 30 its levels begin to decline rapidly in humans<sup>10</sup>, and because its supplementation in older people has been shown not only to improve sexual function but also to reduce the incidence of depression and anxiety, along with an improved sense of well-being<sup>11,12</sup> even though there are voices that disagree with the above<sup>13</sup>. Unfortunately, the

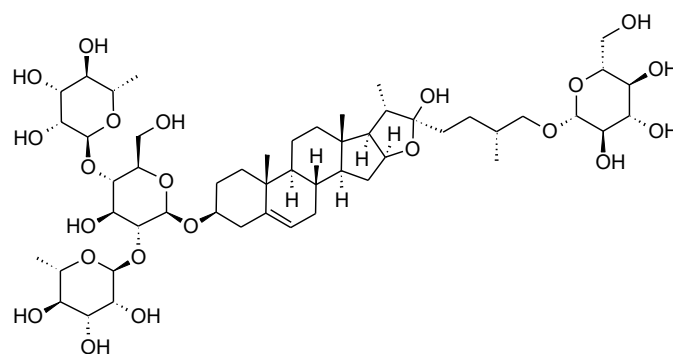


use of the abbreviation DHEA can also be found for other compounds, such as docosahexaenoyl-ethanolamine (2-amino-1-hydroxytetracos-4,6,8,10,12,14-hexaen-3-one) and the abbreviation DHA for docosahexaenoic acid, both of which also have a role on the CNS and are being investigated in the context of endocannabinoids<sup>14</sup>.

It is not surprising that nature has chosen the conjugated form for DHEA, because while DHEA has a log $P$  = 3.44, DHEAS has 1.94, resulting in much better water solubility and thus bioavailability<sup>15</sup>. The body makes this steroid from cholesterol (cholesterol  $\rightarrow$  pregnenolone  $\rightarrow$  17-OH-pregnenolone  $\rightarrow$  DHEA) and is secreted in the adrenal cortex<sup>16</sup>. As a steroid hormone, it plays an important role as an indirect intermediate in the metabolic pathway to androgens and oestrogens. Men derive 50 % of their testosterone and women 75 % of their oestrogens from DHEA. In postmenopausal women, even 100 % of their oestrogens. Interestingly, DHEA does not exhibit typical anabolic properties, although it is considered an androgenic anabolic; in this context, it is worth noting that an increased ratio of serum cortisol to DHEAS may be a risk factor for sarcopenia (a type of muscle loss) in elderly patients with diabetes<sup>17</sup>. However, there are also studies that describe a reduction in overall weight gain in obesity<sup>18</sup>. DHEA improves overall sugar metabolism and even reduces oxidative stress caused by diabetes<sup>19</sup>. DHEA lowers LDL, so it seems to be a suitable sparring partner for 24-epibrassinolide in this area<sup>20</sup>.

Based on the known immunomodulatory properties of DHEA, research has been conducted on its use in autoimmune diseases such as systemic *lupus erythematosus*<sup>21</sup>. The immunomodulatory and anti-inflammatory effects of DHEA have also been investigated in the treatment of asthma and other diseases such as Crohn's disease and ulcerative colitis, among others<sup>22</sup>. People infected with HIV have very low levels of DHEA concentrations<sup>23</sup>. Studies show that both men and women infected with HIV showed improved mental function and increased immunity after taking DHEA<sup>24</sup>. DHEA can block disease reactivation, especially in HIV-1.

A decrease in DHEA concentration (by about 2 % per year) eventually leads to blockage of the arteries of the heart and to myocardial infarction, especially in men<sup>25</sup>. DHEA supplementation reduces the degree of hyperten-



protodioscin

sion, the risk of coronary artery disease and atherosclerosis. The evidence for an inverse relationship between DHEA levels and cardiovascular risk is quite strong<sup>26</sup>. There is also evidence for a beneficial effect of DHEA on a major disease of the pulmonary circulation: pulmonary hypertension<sup>27</sup>. There have also been papers that recommend investigating the effect of DHEA<sup>28</sup> on COVID-19.

DHEA may improve bone mineral density in both women and men with osteoporosis and osteopenia<sup>29</sup>. There are many studies that show the positive action of DHEA against “aging”. The already cited decrease in DHEA concentration with age leads to a higher incidence of serious diseases. Maintaining the level of DHEA concentration has an effect on the patient's overall picture; it also contributes to the maintenance of muscle activity and physical performance. A study in rodents has shown that DHEA can prolong life by up to 50 %, with the experimental subjects looking youthful and non-greyish<sup>30,31</sup>.

It is likely that after menopause, DHEA may help maintain the concentration of desirable steroids. It may facilitate fertilization; improve sexual function, metabolism and well-being. DHEA supplementation has been shown to be useful in managing post-traumatic conditions and improving abstinence in addictions. The effects of DHEAS as an anxiolytic and aggression suppressant have been found. Overall, DHEA(S) contributes to promoting “well-being” and positive emotions, possibly increasing attention and overall working memory<sup>32–34</sup>.

It seems that it can reduce the incidence of breast<sup>35</sup> and endometrial cancer, however, here it is recommended to administer DHEA hand in hand with a physician, as there is a risk of hormone-sensitive tumors<sup>36</sup>, which is however also downplayed<sup>37</sup>.

DHEA supplementation in men with erectile dysfunction has been shown to improve erections to a sufficient level<sup>38</sup>. DHEA even improves semen quality in men with fertility disorders<sup>39</sup>.

In general, DHEA is important in endocrinology and neuroendocrinology. Many receptors are activated by DHEA, but often at different levels than conventional ligands. DHEA is an important regulatory tool for many brain functions. It acts as a ligand on some signalling channels<sup>40</sup> and is directly produced by brain tissue. These

findings indicate a wide range of activities attributed to DHEA<sup>41</sup>. Physicians and endocrinologists in our country have long fought for the possibility of using DHEA for its multiple biological activities, but have still faced the obstacle that this substance, and its derivatives (7 $\alpha$ -hydroxy-DHEA, 7 $\beta$ -hydroxy-DHEA and 7-keto-DHEA) are still considered anabolic androgenic steroids, doping<sup>42</sup> and, moreover, not available in our country<sup>43</sup>. Today, it is freely sold as a dietary supplement, e.g., in Hungary and Slovakia. Even in the literature, however, we read about the anabolic effect of DHEA in sarcopenia<sup>44</sup> and anorexia<sup>45</sup>.

Our sphere of “pure” sport relies on the information that from the steroidal glycoside protodioscin (from *Tribulus terrestris*, apparently imported as an extract from China and sold also in pharmacies as a means to improve our sexual fitness, performance and healthy hormonal activity) DHEA is produced by the body itself. Given the structure, this is highly doubtful.

However, medicinal product Intrarosa, which contains DHEA as the active ingredient, received a positive opinion from the EMA in 2017, as a medicine used to treat postmenopausal women with moderate to severe symptoms of vulvar and vaginal atrophy. In women with vulvar and vaginal atrophy, the wall of the vagina and surrounding tissues thin and can cause symptoms such as dryness, irritation and soreness in the genital area and painful intercourse. Intrarosa has been shown to improve the structure of vaginal tissues and to have a mild pain-relieving effect during intercourse and has an acceptable safety profile<sup>46</sup>. SÚKL has no information about its availability in the Czech Republic<sup>47</sup>.

In the Czech “grey” literature there is a common opinion, based on the fact that DHEA is converted in the body into testosterone, which was confirmed by men who took DHEA or DHEAS almost secretly for a long time, who were mostly experimenters, who favourably evaluated libido and erection, but also an increase in physical strength and mental abilities, including improved memory<sup>43</sup>; however, excess male sex hormones have also been linked to certain malignant diseases, such as prostate tumours in men<sup>48</sup>. EMA states that the most common side effect of Intrarosa (which can affect up to 1 in 10 people) is vaginal discharge. Intrarosa should not be used in pa-

tients with the following conditions: Genital bleeding with no diagnosed cause, diagnosis or suspicion of breast cancer or oestrogen-dependent cancer, previous breast cancer, untreated endometrial hyperplasia (thickening of the uterine lining), acute (short-term) liver disease, previous liver disease, where liver function tests are still abnormal, previous or current venous thromboembolism (blood clots in the veins), thrombophilic disorders (abnormal blood clotting), active or recent arterial thromboembolic disease (caused by blood clots in the arteries), porphyria (inability to break down chemicals called porphyrins).

It is therefore useful to know about substances such as DHEA that are widely used in scientific research, sports medicine and the grey market<sup>49</sup>.

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### Abstract

DHEA, prasterone, (3 $\beta$ )-3-hydroxyandrost-5-en-17-one, is a natural secondary metabolite that is, mainly in its sulphated form present in young humans. After the age of 30 its concentration gradually lowers. When it is supplemented to the elderly people their well-being and sexual functions grow up together with mental capacity. Alternatively it may help to cure number of diseases. However, as it is considered to be anabolic androgen, doping, its use is in the Czech Republic limited on the medical prescription only.

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