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CONTEMPORARY ASPECTS OF USING VALERIANAE OFFICINALIS

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Using plants in therapy originates from far past. The skill of treating with plants has been developed in all nations and is now preserved, more or less, as traditional or popular therapy, commonly named popular medicine.

Valeriana officinalis, which has been successfully used in traditional therapy, is accepted and represents an important medicinal raw material in contemporary medicine.

Considering that clinical effects are not due to single chemical component, numerous scientists have concluded that a combination of valerian ingredients is responsible for its action. Dried root and rhizoma of Valerianae officinalis in forms of different pharmaceutical formulations achieve antioxidative, cytoprotective and neuroprotective activity.

Pharmaceutical preparations made of valeriana root and rhizoma have multiple role in treating disorders at the level of cardiovascular, gastrointestinal and central nervous systems. *Acta Medica Medianae 2010;49(3): 65-70.*

***Key words**: Valeriana officinalis, using, action, clinical effects*

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Introduction

Using plants in therapy originates from far past. Skills of treating with plants developed in all nations and is now preserved, more or less, as traditional or popular therapy, commonly named popular medicine.

Valeriana officinalis, which has been successfully used in traditional therapy, is accepted and represents an important medicinal raw material in contemporary medicine (1).

Valerianaceae family includes perennial or annual herbaceous plants, with confronted, divided or whole leaves, without offshoots, including 8 genera, with about 290 kinds (2). There are only two genera in Serbia: Valeriana and Valerianella.

The Valeriana genus includes about 170 perennial herbaceous plants and there are 8 kinds in Serbia: V. officinalis, V. dioica, V.tuberosa, V. Tripteris,V. Montana, V. sambucufolia, V. pancicii and V. bertiscea.

The drug is made of dried rhizoma with roots (*Valerianae radix et rhizoma*). Rhizoma with roots is pulled out in autumn, processed and dried at temperature not higher than 40 cº. The Rhizoma is oval, up to 5 cm long, 2-3 cm wide, mainly cut in halves vertically. On the upper part there are remnants of stalk and leaves, and on the lower part it is densly grown having long, tender, cylindrical, vertically striped roots. *Valeriana officinalis* is an aromatic plant. Raw material is slitely smelly, and the smell is intensified by drying and becomes extremely unpleasant if the drug is kept for a long period of time. The smell comes from isovalerian acid (3).

Composition

Valeriana contains over 150 chemical compounds, most of which are physiologically active. There are variations in chemical components in plants due to different sources, processing methods and ways of keeping (4).

Valeriana root and rhizoma approximately contain 0,5–1% of etherial oil. Most pharmacopoeias prescribe standards according to which the drug has to contain at least 0,5 % of etherial oil and at least 0,17 % of valerian acid and its derivatives (5).

Valeriana etherial oil contains a mixture of monoterpenic and sesquiterpenic derivatives. The most important monoterpenic derivatives are: camphene, pinenes, borneol and its esters bornilisovalerianate, bornilacetate and bornil-formiate. Besides terpenic ingredients of the etherial oil, the drug contains nonevaporable monoterpenic compounds, iridoides (valtrate, isovaltrate, acevaltrate). The

underground organs contain high quantity of valeopotriate, while low quantity is found in the upper parts of the plant (3). Because of its esterial structure, valeopotriates are very unstable in the presence of moisture, at high temperature and in the presence of acids and bases. As products of hydrolysis of valeopotriate there are decomposing products, aldehide structures: baldrinale and isopropylaldrinale.

Within nonevaporable, sesquiterpenic compounds, *Valerianae radix et rhizoma* contain mainly oxidative derivatives – acids (valerian acid, hydroxi – and acetoxivalerian acid), ketones (valeranone), alcohol (valerianol, kesylil – alcohol) and aldehides (valerianal (3).

Valerian alcaloides are present in small quantities (valerianine and actinidine). In vitro, they show cholinesterasic activity which is not proven on animals or humans (6).

Hydroxipinoresinole is a lignan present in Valerianae. Its mechanism of action is based on bonding to benzodiazepine receptors in amigdale and is considered to act synergically with bornil acetate, valerian acid and valeopotriates in achieving sedative effect of valeriana (7).

Action

Considering that clinical effects are not due to single chemical component, numerous scientists conclude that a combination of valerian ingredients is responsible for its action (8). Dried root and rhizoma of Valerianae officinalis in forms of different pharmaceutical formulations achieve antioxidative, cytoprotective and neuroprotective activities.

Antioxidative activity

In traditional medicine, valeriana can be used as alternative treatment in applying benzodiazepine in treatment of insomnia (9,10). In vivo research has proven that applying valeriana does not lead to any oxidative disorders of brain after chronical use (11). It is pharmacologically important to stress out that valeriana prevents brain damages induced by different pro-oxidants; hypoline acid, 3-nytropropionic acid, No-nytropruside, Fe (II). I Fe (II) / EDTA complex (12).

Pharmacological characteristics of certain components of valeriana indicate its antioxidative effect. Alcohol extract of valeriana root shows signifficant antioxidative activity and thus decreases lypide peroxidation provoced by Ee (II) iones (13).

Because it is known that insomnia can be accompanied by oxidative stress, valeriana can be used as means of sleep improvement (14).

Cytoprotective activity

alerianae officinalis root is rich in flavonoides, including these that act in brain (34), and some of them achieve strong neuroprotective effect (15). This effect is accompanied by antioxidative characteristics of valeriana (16).

Presence of flavonoides in valeriana extract makes this plant interesting for further research in the sense of developing neuroprotective agent for human use (13).

It is important to stress out that valeriana extract contains several different substances, so some other components can also be responsible for this action (valerianacid, valerianon, valeopotriates) (17).

Neuroprotective activity

A large number of literature data describe GABA – ergic mechanism of action of valeriana. The mechanism of biological activity of valeriana is based on increasing releasing of GABA and increasing activity of GABA – A receptors (18).

Decreasing of total excitability of brain cells leads to preventing excytotoxic neural death, increasing function of inhibitory neurotransmiternic system, and as a result, a neuroprotective effect is developed (19).

Water extract of valeriana is rich in GABA which can be responsible for perifery pharmacological efects of valeriana (51). It was not expected for GABA to be responsible for biological effects in CNS. Other components of etherial oil which can act in CNS are: valerianacid, valeranon and valeopotriates (17).

It is considered that valeriana contains still unidentified components that can pass blood – brain barrier and can be responsible for pharmacological activity of valeriana in brain (13).

Therapeutic use of Valerianae officinalis

Pharmaceutical preparations made of valeriana root and rhizoma have a multiple role in treating disorders at the level of cardiovascular, gastrointestinal and central nervous systems.

The effect of valeriana extract on cardiovascular system

At the level of cardiovascular system, valeriana extract leads to coronary dilatation and shows antiarrhytmic effect. The effect is confirmed on laboratory animals (rabbits, cats, mice). Valeopotriates prevent occurence of acute coronary insufficiency, erase arrhytmias caused by vasopresine, initiate short term increase of coronary flow, achieve positive inotropic and negative chronotropic activities (20).

The results of open multicentric study which involved 2243 participants (patients with different heart deseases) that were treated with herbal mixture (valeriana,hawthorn,camphor) showed improvement in the health state in 84% of patients (21).

The effect of valeriana extract on the gastrointestinal tract

Spasmolytic activity of valeriana has been known for a long time. Valeriana has been traditionally used in treating intestinal spasms, colics and nervous stomach. Because of their bitter taste, valeriana preparations can be used as bitter tonics treating loss of apetite and bad digestion.

In vitro researches have proven that valerian acid, valtrate and valeranone achieve spasmolytic effect on smooth muscles of Guinea pigs' ileum (22).

The effect of valeriana extract on the central nervous system

Numerous studies have justified traditional use of valeriana preparations with the aim of achieving sedative, anxiolytic and hypnotic effect as well as in treating loss of attention in hyperactive children.

Pharmacological researches of valeriana are usually focused on etherial oil components: valerian acid, valeopotriates, decomposing products - baldrinales and lignans (6). Potential mechanism of pharmacological activity of Valerianae officinalis is based on its antagonistic effect in regard to GABA, adenosine, barbiturate and benzodiazepine receptors (23-25).

The influence of valeriana on modulatory activity of GABA

γ–aminobuternic acid (GABA) is an inhibitory transmitor of CNS and it achives the effect by bonding to GABA – ergic receptors.

GABA A canals are modulated by numerous structure supstances including clinically important drugs such as: benzodiazepines, barbiturates and some general anaestetics as well as several herbal components, the most important of which are: flavonoides and monoterpenes (borneole and timolole) (26,27).

Borneole is a bicyclic monoterpene present in etherial oil of many plants including valeriana, camomile and lavander. The extracts of these plants are traditionally used for tenseness and insomnia relief (28).

In the research performed by Ganger and associates, it has been shown that borneole leads to signifficant increase of GABA activity bonding to d1β2γ2L GABA A receptors, by direct modification of the receptors' activity. The activity of (+) and (-) borneole, as enatiomere is conditioned by different order of hydroxile groups, which is of great importance for monoterpenic activity at the level of d1β2γ2L GABA A rereceptors (27).

So far, in vitro studies on brain preparations of rats have shown that the most probable effect of valerian acid is achieved by bonding to GABA A receptors (30). Khom et al. in their research have come to conclusion that signifficant activity of valerian acid is achieved by stimulation of d1β2γ2S, while low level of the activity is achieved by stimulation of γ1, α1β2 or α2β2 receptors. Use of valerian acid in high concentrations leads to direct activation of GABA A receptors and canals. The research has shown that valerian acid is an agonist with signifficantly weaker efficiency than GABA (29).

The effect of valeriana to adenosine receptors

Adenosine is an endogenic ligand that achieves its effect by bonding to adenosine receptors. Natural components: flavonoides, alcaloides, lactons show different affinity to bonding to adenosine receptors (31,32). It is considered that oily lignan valeriana derivative 4'-0-β-D glucosile-6''-deoxisaharoze is a partial agonist of adenosine A 1 receptors at submicromolar level (24).

Sedative and hypnotic effects

It is considered that valeriana extract causes mild sedative effect but its mechanism has not been completely clarified yet. In vitro researches show that amino – acids and valerian acid from valeriana extract bond to GABA (A) receptors in the rat brain (33).

In the rat cortex, water valeriana extract inhibits transmission and stimulates releasing of GABA, which leads to increase of GABA concentration in synaptic fissures (18). The effect is expected because of the presence of GABA in valeriana extract.

Valerian acid inhibits enzyme disolving of GABA in the rat brain (7). Other studies show that valeriana extract has direct effect on GABA receptors, but it also reacts with other presynaptic components of GABA – ergic neurons (36).

High concentrations of amino – acids, GABA and glutamate in water extract of valeriana root justify its sedative effect (34).

Testing on animals has shown that intraperitoneal application of valerian acid, valeranale and valerian extract to mice cause signifficant sedation, ataxia and anticonvulsive effect. Even the smell of valeriana root can cause sedative effect in mice (37).

Valeapotriates suppress the symptoms caused by stopping diazepame use. This has led many authors and clinicians to consider the usefulness of valeriana in treating benzodiazepine apstinential syndrome (38).

Ortise et al. state that low concentrations of valeriana extract initiate bonding of benzodiazepine but higher concentrationes inhibit it. It is considered that the combination of these effects is responsible for in vivo anxiolytic and sedative actions (39).

Anxiolytic effect

Assumptions that valeriana extract achieves anxiolytic effect are confirmed today by numerous researches which show that valeriana can be used as mild but efficient anxiolytic.

In an open research that included 70 hospitalized patients with different psychosomatic diagnoses, a herbal preparation based on valeriana was used in the dosage of 150-300 mg. Functional heart disorders, as tachicardia, hypertension, sweating and other disorders were positively improved using valeriana. The preparation caused mild sedative effect and was efficiant in treating anxiety and tension (40).

In a rendom, double-blind study that included 80 adult patients with different anxiety syndromes a standardized valeriana extract was used (270 mg) and it showed to be more effecient and bearable compared to the application of 30 mg of Clobazame, according to Hamilton's scale of anxiety and Leed's survey on anxiety (82).

Dosage, toxicity and caunter-indications

Valerianae officinalis root and rhizoma are used in the forms of various pharmaceutical preparations. The composition and concetration of valeriana herbal preparations differ signifficantly, so it is necessary to be cautious in dosage regime and coordination. Various commercial preparations that contain valeriana have to be standardized according to valeopotriate content. According to the European standards, the preparations have to contain at least 0,5% of valeriana etherial oil.

One cup of infusion two times a day, before sleeping is applied (42). If we use valeriana tincture, recommanded dosage is 1-3 ml of the tincture once, or three times a day (43).

Pills or capsules based on valeriana are the most frequently used pharmaceutical forms. For treating mild sleep disorders, most of the studies recommend oral usage of 400-900 mg of valeriana extract 1-2 hours before going to bed (44).

Doses applied in pediatric population have to be adjusted to interindividual and intraindividual characteristics of the age. German board E recommends valeriana extract dose of 220 mg three times a day for treating anxiety and insomnia for children at the age of 14 and younger (42,45). The European scientific cooperation of phytotherapy justifies the use of valeriana for children aged 3-12 under constant medical monitoring (46).

Potential toxicity is based on the presence of active chemical compounds. Toxicity test on rats shows that valeriana etherial oil was the least toxic of all tested etherial oils, including mint and anason etherial oils (47).

There are indications that long-term use of the preparation can lead to developing chronical intoxication which is manifested by: headache, somnolency, intense anxiety, unclear heart disorders, but there are no experimental data to confirm all this. Chronical use of high doses (5mg a day) can develope apstinency syndrome, if the use is suddenly stopped (48).

Cytotoxic effect is found in vitro, but the components responsible for the effect (valeopotriates) are rapidly disolved after oral administration (49).

Recent researches have shown the need for precaution during simultaneous use of valeriana preparations with other drugs because of possible effect of valeriana extract on cytochromal activity P450 (CYP2D6 and CYP3A4). This has been proved by the research performed by Donavan et al (50).

After using therapeutic doses of valeriana extract, side effects have not been reported. The safety of using valeriana during pregnancy and lactation has not been tested yet. Tests performed on animals showed that treating pregnant rat females with valeopotriates (for 30 days) did not influence the fertility, fetotoxicity or had any other side effect concerning both the mother and baby (51).

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SAVREMENI ASPEKTI UPOTREBE VALERIANAE OFFICINALIS

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Upotreba bilja u lečenju vodi poreklo iz daleke prošlosti. Veština lečenja biljem razvijala se kod svih naroda i sačuvala se negde više, negde manje kao tradicionalna ili narodna terapija, popularno nazvana narodna medicina, sve do danas.

Valeriana officinalis, koja se uspešno vekovima upotrebljavala u tradicionalnoj terapiji, prihvaćena je i predstavlja važnu lekovitu sirovinu u savremenoj medicini.

S obzirom da za kliničke efekte nije zadužena samo jedna hemijska komponenta, mnogi naučnici zaključuju da je kombinacija sastojaka valeriane zadužena za njeno delovanje. Osušeni koren i rizom Valerianae officinalis u vidu različitih farmaceutskih formulacija ostvaruje antioksidativnu, citoprotektivnu i neuroprotektivnu aktivnost.

Farmaceutski preparati korena i rizoma valeriane imaju višestruku ulogu u lečenju poremećaja na nivou kardiovaskularnog, gastrointestinalnog i centralnog nervnog sistema. *Acta Medica Medianae 2010;49(3):65-70.*

***Ključne reči**: Valeriana officinalis, upotreba, delovanje, klinički efekti*