Systemic administration of defined extracts from *Withania somnifera* (Indian ginseng) and Shilajit differentially affects cholinergic but not glutamatergic and GABAergic markers in rat brain

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Abstract

Although some promising results have been achieved by acetylcholinesterase inhibitors, an effective therapeutic intervention in Alzheimer's disease still remains an important goal. Sitoindosides VII–X, and withaferin-A, isolated from aqueous methanol extract from the roots of cultivated varieties of *Withania somnifera* (known as Indian Ginseng), as well as Shilajit, a pale-brown to blackish brown exudation from steep rocks of the Himalaya mountain, are used in Indian medicine to attenuate cerebral functional deficits, including amnesia, in geriatric patients. The present investigation was conducted to assess whether the memory-enhancing effects of plant extracts from *Withania somnifera* and Shilajit are owing to neurochemical alterations of specific transmitter systems. Therefore, histochemistry to analyse acetylcholinesterase activity as well as receptor autoradiography to detect cholinergic, glutamatergic and GABAergic receptor subtypes were performed in brain slices from adult male Wistar rats, injected intraperitoneally daily with an equimolar mixture of sitoindosides VII–X and withaferin-A (prepared from *Withania somnifera*) or with Shilajit, at doses of 40 mg/kg of body weight for 7 days. Administration of Shilajit led to reduced acetylcholinesterase staining, restricted to the basal forebrain nuclei including medial septum and the vertical limb of the diagonal band. Systemic application of the defined extract from *Withania somnifera*, however, led to differential effects on AChE activity in basal forebrain nuclei: slightly enhanced AChE activity was found in the lateral septum and globus pallidus, whereas in the vertical diagonal band AChE activity was reduced following treatment with sitoindosides VII–X and withaferin-A. These changes were accompanied by enhanced M1-muscarinic cholinergic receptor binding in lateral and medial septum as well as in frontal cortices, whereas the M2-muscarinic receptor binding sites were increased in a number of cortical regions including cingulate, frontal, piriform, parietal and retrosplenial cortex. Treatment with Shilajit or the defined extract from *Withania somnifera* affected neither GABA$_A$ and benzodiazepine receptor binding nor NMDA and AMPA glutamate receptor subtypes in any of the cortical or subcortical regions studied. The data suggest that Shilajit and the defined extract from *Withania somnifera* affect preferentially events in the cortical and basal forebrain cholinergic signal transduction cascade. The drug-induced increase in cortical muscarinic acetylcholine receptor capacity might partly explain the cognition-enhancing and memory-improving effects of extracts from *Withania somnifera* observed in animals and humans.

Abbreviations

AChE, acetylcholinesterase; mAChR, muscarinic acetylcholine receptor; WS, equimolar mixture of sitoindosides VII–X and withaferin-A, prepared from *Withania somnifera*

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