



TREATMENT OF VASOMOTOR SYMPTOMS WITH THE ISOPROPANOLIC CIMICIFUGA RACEMOSA EXTRACT ICR: INSIGHT INTO ITS MODE OF ACTION

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Context & Objective: Vasomotor symptom (VMS) pathophysiology has not been fully elucidated, yet. Estrogen depletion affects serotonin (5-HT) and norepinephrine (NE) synthesis and the corresponding neurotransmitter pathways to the hypothalamic thermoregulatory center as the putative site responsible for thermoregulatory dysfunction. iCR extract has shown its efficacy for VMS in a multitude of clinical studies but does not exhibit estrogen-like effects. Therefore, potential central nervous (CNS) and other pharmacological effects, which may contribute to the amelioration of VMS, are discussed.

Methods, Interventions & Main Outcome Measures: Literature (e.g. MEDLINE, EMBASE, BIOSIS) was collected till 2017 and analyzed for iCR's CNS effects (interaction with CNS receptors, modulation of brain metabolism and activity) and further pharmacological properties which may contribute to iCR's mechanism of action for VMS relief.

Results: iCR extract binds to several CNS receptors involved in thermoregulation and acts partially agonistic at 5-HT_{1a}R, 5-HT₇R and μ OR. Hypothalamic 5-HT_{1a}R and 5-HT_{2a}R expression increases after ovariectomy (OVX) and decreases with additional iCR or estradiol (E2) treatment. The impact of OVX on 5-HT and NE synthesis and the corresponding projections of 5-HT and NE fibres to the preoptic anterior hypothalamus is normalized by iCR or E2 treatment. In women, iCR increases μ OR availability in estrogen-sensitive brain regions; however, these effects are not estrogen-like. OVX-induced impairment of hypothalamic nerve cells, presenting in a decrease of c-fos protein, is compensated by iCR or E2 treatment. Furthermore, iCR produces changes in electrical brain activity in line with dopaminergic, serotonergic and glutaminergic activity. Additionally, iCR exhibits antioxidant effects.

Conclusions: The beneficial effects of iCR on VMS are not estrogen-like but mediated by the CNS receptors responsible for thermoregulation. The iCR extracts binds to and modulates these receptors and induces favourable changes in brain metabolism and activity. Antioxidant effects could further lead to improvement of neuronal function. Synergistically, all these effects may contribute to functional recovery of the hypothalamic thermoregulatory center leading to amelioration of VMS.

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