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Plant extracts for the treatment of menopausal women: Safe?

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Abstract

Objectives: The recently published data concerning putatively dangerous effects of classical hormone therapy resulted in increased sales of plant derived substances, which claim beneficial effects on climacteric and postmenopausal complaints and diseases. Soy and red clover extracts containing isoflavones have estrogenic effects in cell biological and animal experimental models but commercial advertisements often claim beneficial effects in mammary glands by preventing occurrence of malignancies. Black cohosh preparations are also increasingly used, and they appear to be devoid of estrogenic effects in the uterus. Their effects in the mammary gland have not yet been thoroughly studied.
Methods: Therefore, we studied the effects of genistein, the main isoflavone in soy or red clover preparations and of the black cohosh extract *Cimicifuga racemosa* (CR) or *Actea racemosa* BNO 1055 in the uterus and mammary gland of ovariectomized (ovx) rats and compared them with the effects of estradiol. Serum LH levels were also measured as an indicator of a hypothalamic/pituitary effects of the test substances.
Results: Genistein and E2, both stimulated uterine weight and several estrogen regulated genes. Lobulo-alveolar growth of 20 mammary glands as well as the expression of the nuclear protein proliferating cell nuclear antigen (PCNA, a proliferation marker) was also stimulated by E2 and genistein. The CR extract BNO 1055 was devoid of such estrogenic effects in the uterus and mammary gland. E2 and to lesser degree CR inhibited serum LH levels whereas genistein had no effects on this hormone.
Conclusions: E2 and genistein share uterotropic and mammatropic effects in ovx rats. If occurring in postmenopausal women this may endanger these organs to develop malignancies. Serum LH levels were inhibited by E2 and the CR BNO 1055 extract whereas genistein had no estrogenic effect in the hypothalamus and it is therefore unlikely that genistein inhibits climacteric complaints.

Keywords: Soy; Isoflavones; Estradiol; Black cohosh; Uterus; Mammary gland

Why phytoestrogens? The recently published results of the Heart and Estrogen/Progestin Replacement Study (HERS), the Women's Health Initiative (WHI) study for reviews [1–3] and the Million Women Study have resulted in a tremendous increase of sales of

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plant derived substances which supposedly ameliorate climacteric complaints and in addition sales companies of soy or red clover products claim beneficial effects in the mammary gland and bone. Soy and red clover products contain isoflavones, amongst others genistein and daidzein. An efficient way to test whether estrogenic substances act in the hypothalamus to ameliorate hot flushes is measurement of LH levels. Hot flushes are associated with an overactivity of the hypothalamic GnRH pulse generator. Therefore, substances which reduce serum concentrations of this hormone are likely to reduce hot flushes also.

Black cohosh (*Cimicifuga racemosa* (CR) or *Actea racemosa*) grew initially in North America and was used by Indians to treat gynaecological disorders. Its name stems from its smell that made bedbugs escaping (cimex fugare). Extracts of the rhizome of CR, which is now cultivated in many European mediteranean countries, has been used since more than 50 years for the treatment of climacteric complaints. Evidence concerning the efficacy of Cimicifuga extracts in ameliorating climacteric complaints, however, was scarce and only recently double-blind placebo-controlled studies have been performed and published [4–6]. In peri- and postmenopausal women suffering from climacteric complaints, *C. racemosa* extracts proved to be an efficient alternative to classical hormone therapy. Also soy or red clover derived isoflavones claim such effects on psychosomatic symptoms in the perimenopausal period. Evidence that they are efficient however, is scarce: from 33 double-blind, placebo-controlled studies published hitherto 25 yielded results, which were not statistically better than placebo effects. For both Cimicifuga extracts and isoflavones, antiosteoporotic effects were proposed [7] and have been demonstrated [4,8–10] also controversial data demonstrating no effect of isoflavones on the development of osteoporosis have been reported [11–13].

1. Mechanism of action

An important question, i.e., whether *C. racemosa* or soy/red clover-derived products are safe for the uterus and the mammary gland is not satisfactorily solved hitherto. The active ingredients in soy and red clover products are claimed to be the isoflavones of which genistein and to some degree also daidzein have been thoroughly studied under many cell biological and animal experiment conditions [14–16] including mammary cancer models [17–19]. These isoflavones cause transactivation of both estrogen receptors (ERs) with a slight preference for ERß over ERα [20]. We know very little about the function of ERß but the desired estrogenic effects in the hypothalamus or bone and the undesired effects in the endometrium or mammary gland of postmenopausal women are mediated via the ERα [21–25]. Since isoflavones do not only address the ERß but also the ERα the question rises whether treatment of climacteric or postmenopausal women is efficient and safe.

Active compounds in CR were originally thought to be estrogenic in nature [26,27]. Later it was proposed that CR has selective estrogen receptor modulator (SERM) activity [28]. Substances in extracts of black cohosh addressing directly the estrogen receptor however, have not been identified [28]. Since CR has also antiosteoporotic effects in estrogen-deprived animal models such mechanism may also take place in the bone. In the hypothalamus neurotransmitter-like effects of CR extracts have been postulated and serotoninergic, dopaminergic and cholinergic mechanisms have been described [29–32]. The nature of the substance(s) exerting these effects remains largely unknown. The only hint that some estrogenic mechanisms may be involved comes from studies, in which cytosolic extracts of endometrial tissue of a variety of species including the human were shown to displace radiolabeled estradiol from an estrogen binding protein which is neither ERα nor ERß [28]. Something else must be present in these cytosolic extracts. Indeed, we succeeded recently to demonstrate that the aryl hydrocarbon receptor may bind yet unidentified compounds of CR extracts [33]. An interaction of the AhR and aryl hydrocarbon receptor nuclear translocator (ARNT) with estrogen receptors has been reported recently [34,35]. Such interactions of CR-extracts with the AhR/ARNT complex and thereby with estrogen receptor may be the reason for antiosteoporotic and the mild vaginotropic effects of CR extracts. In view of the many open questions concerning uterine or mammary gland safety of both genistein or extracts of *C. racemosa* we performed experiments in ovariectomized (ovx) rats and tested these compounds for estrogenic actions. In the uterus estrogenicity was tested by determining weight of the organ and the expression of