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Ginsenoside-Rb1 from *Panax ginseng C.A. Meyer* Activates Estrogen Receptor Alpha and Beta, Independent of Ligand Binding

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ABSTRACT

Ginseng has been used to enhance stamina and immune function, and its use continues to rise with the increasing popularity of complementary and alternative medicine (1). It is one of the best-selling herbs in the United States (2). Although many studies have examined the pharmacological action of ginseng extracts, a detailed mechanism has yet to be determined. The major pharmacologically active components of ginseng are ginsenosides, which are steroidal saponins comprising 3-6% of ginseng (3). It has been shown that ginsenosides decrease the levels of total cholesterol and triglyceride via cAMP production, and inhibit the accumulation of calcium ions in liver cells (4). Ginsenosides potentiate analgesia and inhibit analgesic tolerance (5). The cardioprotective action of ginsenosides is due to effects on vasodilation via nitric oxide (NO) release (6,7). Other activities, such as anticarcinogenic and neurologic effects, have also been reported for ginsenosides (8,9).

In the United States, ginseng is used to alleviate menopausal symptoms, as are black cohosh (*Cimicifuga racemosa*), chaste tree berry (*Vitex agnus-castus*), dong quai (*Angelica sinensis*), evening primrose oil (*Oenethera biennis*), motherwort (*Leonurus cardiaca*), red clover (*Trifolium pratense*), and licorice (*Glycyrrhiza glabra*) (10). One recent randomized controlled clinical trial showed that only black cohosh had a beneficial effect on postmenopausal hot flashes (10). Other *in vitro* studies have measured estrogenic activity in red clover and licorice, which was not demonstrated in black cohosh (11). Various studies have indicated that ginseng has estrogenic activity, although no clinical trials have demonstrated real efficacy as an estrogen-replacement therapy (10). Ginseng extracts are able to stimulate the growth of estrogen receptor (ER)-positive cells (12). Ginsenoside-Rg1 and -Rh1 have been shown to contain estrogen-like activity (13, 14), but more comprehensive data are needed to adequately evaluate this

activity.

Among 26 identified ginsenosides, ginsenoside-Rb1, -Ro, -Rg1, -Rc, and -Re are highly abundant. In particular, ginsenoside-Rb1 makes up 0.37-0.5% of ginseng extracts, depending on manufacturing and processing methods, and belongs to the protopanaxadiol class of ginsenosides (15). We have previously reported that ginsenoside-Rb1 has estrogenic activity (16). In the present study, we studied the estrogenic activity of a component of *Panax* ginseng, ginsenoside-Rb1. The activity of ginsenoside-Rb1 was characterized in a transient transfection system, using estrogen receptor isoforms and estrogen-responsive luciferase plasmids, in COS monkey kidney cells. Ginsenoside-Rb1 activated both α and β estrogen receptors in a dose-dependent manner with maximal activity observed at 100 μM, the highest concentration examined. Activation was inhibited by the estrogen receptor antagonist ICI 182,780, indicating that the effects were mediated through the estrogen receptor. Treatment with 17β-estradiol or ginsenoside-Rb1 increased expression of the progesterone receptor, pS2, and estrogen receptor in MCF-7 cells and of AP-1-driven luciferase genes in COS cells. While these data suggest that it is functionally very similar to 17β-estradiol, ginsenoside-Rb1 failed to displace specific binding of [^{3}H]17β-estradiol from estrogen receptors in MCF-7 whole-cell ligand binding assays. Our results indicate that the estrogen-like activity of ginsenoside-Rb1 is independent of direct estrogen receptor association.

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