

**Tissue selective estrogen receptor α agonists reverse weight gain without
causing mammary gland or uterine proliferation**

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Abstract

Long-term estrogen deficiency increases the risk of obesity, diabetes and metabolic syndrome in postmenopausal women. Menopausal hormone therapy containing estrogens might prevent these conditions, but its prolonged use increases the risks of breast cancer, strokes and thromboembolic events. Animal studies indicate that the beneficial effects of estrogens in adipose tissue and adverse effects in the mammary gland and uterus are mediated by estrogen receptor alpha (ER α). One strategy to prevent obesity, diabetes and metabolic syndrome is to improve the safety of estrogens by developing tissue selective ER α drugs that act as agonists in adipose tissue, but not in the mammary gland and uterus. To date, tissue selective ER α agonists have not been identified. We considered plant extracts as a source of tissue selective ER α agonists and screened multiple extracts using transfection assays. Eighteen plant extracts were screened for ER α activity by transfecting U2OS cells with the classic estrogen responsive element (ERE) upstream a minimal thymidine kinase promoter linked to the luciferase reporter gene (ERE tk-Luc) and an expression vector for human ER α . Extracts from two plants, Radix *Glycyrrhiza uralensis* (RG) and Radix *Pueraria lobata* (RP) selectively activated multiple ER α responsive reporters, and reversed weight gain and fat accumulation comparable to estradiol in ovariectomized obese mice maintained on high fat diet. Unlike estradiol, RG and RP did not induce proliferative effects on the mammary gland and uterus. Gene expression profiling demonstrated that RG and RP induced estrogen-like regulation of genes in abdominal fat, but not in the mammary gland and uterus. RG and RP also behaved differently than the SERMs, raloxifene and tamoxifen, because they did not antagonize the effects of estradiol. The compounds in extracts from RG and RP might

constitute a new class of estrogens to prevent and/or reverse weight gain, fat accumulation, metabolic syndrome and other conditions in postmenopausal women and comprise the first class of tissue selective ER α agonists.