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Does 2'-hydroxygenistein inhibit the endometrial proliferation? A preliminary study

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ABSTRACT

Isoflavones, due to their claimed or demonstrated beneficial biological activities, have attracted great interest and gained popularity among the public. On the risk of endometrial hyperplasia, conflicting findings for such compounds have been reported and genistein has been intensively studied. Studies also indicated that 2'-hydroxylation of isoflavones can lead to beneficial components with superior bioactivity compared to isoflavones lacking this substituent. Till now there is no study evaluating the effect of 2'-hydroxygenistein on endometrial hyperplasia *in vivo*. In line with this, a 3-day uterotrophic assay was carried out to evaluate the effect of 2'-hydroxygenistein on the uterus as its endometrial hyperplasia is of significant clinical concern. Daily subcutaneous administration of 2'-hydroxygenistein significantly ($p \leq 0.05$) increased uterine wet weight at 2 and 8 mg/kg/day, while it reduced ($p \leq 0.05$) uterine epithelial height at all tested doses. In contrast, no significant variation was observed on vaginal epithelial height. As global result, it appears that 2'-hydroxygenistein might exhibit anti-proliferative effects in the uterus, while having no effect on the vagina. However, this aspect needs to be further investigated.

Keywords: 2'-Hydroxygenistein, uterotrophic assay, endometrial proliferation.

INTRODUCTION

Endometrial hyperplasia (EH) characterized by an excessive proliferation of endometrial glands and stromal structures lining the uterine cavity is a significant clinical concern that can be a precursor of endometrial carcinoma [1], one of the most common cancer in women worldwide [2]. Its simple form is rarely directly transformed to cancer, but can evolve to atypical hyperplasia which is a precancerous lesion [3]. This pathological condition is commonly observed in postmenopausal women at the age of 60-80. To avoid hysterectomy at high risk, patients seek conservative treatments [4] consisting of progestogens and follow-up biopsies every 3-6 months [5]. However, in many cases this option is ineffective, or shows relapse after remission, with the risk of progression to invasive disease [6]. In that context, there is a need for alternatives and natural substances remain the most inspiring source in the development of antiproliferative or anti-cancer agents.

Over the last decades, phytoestrogens have attracted great interest and gained popularity among the public due to their claimed or demonstrated beneficial biological activities. Genistein (GEN; 4',5,7-trihydroxyisoflavone), the best-known and a major isoflavone found at high concentrations in plants from *Leguminosae* family, has been intensively studied. Sharing structural features with 17β-estradiol (Figure 1), it displays its effects through estrogen receptor (ER)-mediated and non-ER-mediated pathways [7, 8]. Beyond its ability to reduce menopausal symptoms and related diseases [9], the antiproliferative/antitumor properties of GEN have been intensively described in estrogen-dependent and -independent tumors/cancers [8, 10-15]. At the dose of 50 mg/kg, it induced a marginal decrease of the tumor wet weight in a RUCA I-cell endometrial carcinoma tumor model [16]. There is a growing body of evidence suggesting that the hydroxylated isoflavones can function as beneficial components for human health with superior bioactivity to genuine isoflavones [17]. For instance, Choi *et al*. [18] showed that the 2'-hydroxylation of GEN enhanced its antiproliferative activity in MCF-7 cells. Although uterus and breast display a tissue specific regulation of transcription, we hypothesized based on these studies that 2'-hydroxygenistein (2'-HG) might be antiproliferative towards the endometrium. Studies dealing with the biological activities of this isoflavone are scarce. Therefore, the present study was designed to investigate the impact of 2'-HG on the uterus using a 3-day uterotrophic assay.

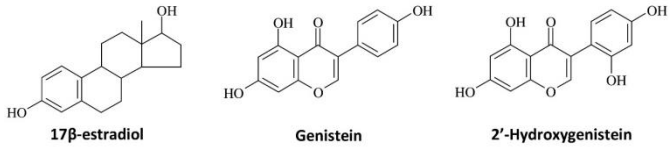

Figure 1: Chemical structures of 17β-estradiol, genistein and 2'-hydroxygenistein

MATERIAL AND METHODS

Chemicals

Estradiol benzoate and genistein were obtained from Sigma-Aldrich (Taufkirchen, Germany). 2'-Hydroxygenistein was isolated from *Eriosema laurentii* [19, 20].

Animals

Young adult female Wistar rats, 10-12 weeks old, were bred in the production facility of the Animal Physiology Laboratory, University of Yaounde I (Cameroon) and kept under a standard soy-free rat chow. They were housed in plastic cages under natural conditions (ambient temperature, cycles of ~12 h light/dark) and had free access to diet and water *ad libitum*. The animals were handled and the experiments were carried out in conformity with the European Union on Animal Care (CEE Council 86/609) guidelines adopted by the Institutional Ethics Committee of the Cameroon Ministry of Scientific Research and Technological Innovation.

Experimental protocol

In this experiment, five sham operated (Sham) and thirty ovariectomized (OVX) rats were used. Fourteen days after ovariectomy, animals were randomly allocated in six groups of five animals each. The first (Sham) and the second (OVX) groups received vehicle only (corn oil). The third group received estradiol benzoate (E2B) at the dose of 2 µg/kg, while the forth received genistein at the dose of 8 mg/kg. The three further groups were treated with 2'-hydroxygenistein (2'-HG) at 0.5, 2 and 8 mg/kg. Animals were subcutaneously treated (0.5 mL/100 g) once daily for 3 days between 9 to 10 a.m. Twenty-four hours after the last administration animals were sacrificed under diazepam/ketamine *i.p.* anesthesia (10 and 50 mg/kg BW, respectively, *i.p.*). Uteri and vaginas were removed. Prior to the fixation of uteri and vaginas in 10% formaldehyde solution for histological analysis, uterine wet weight was determined.

Histological analysis

Histological analyses of the 5-µm paraffin embedded sections of uterus and vagina were performed following hematoxylin-eosin staining. Using a Zeiss Axioskop 40 microscope, and MRGrab 1.0 and AxioVision 3.1 software programs installed in a computer, the microphotographs were transferred to the computer and analyzed.

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM) and were analyzed by the Mann & Whitney *U* non-parametric test using the GraphPad Prism 5.03 software. Differences were considered to be significant with $p \leq 0.05$.

RESULTS

Effect on uterus

Following a 3-day treatment, GEN (8 mg/kg) induced an increase of uterine wet weight (UWW) by 25.12% compared to OVX controls (Figure 2A), but this increase was statistically not significant. Administration of 2'-HG induced a significant increase of UWW at 2 (85.29%; $p \leq 0.01$) and 8 mg/kg (48.06%; $p \leq 0.05$) whereas at 0.5 mg/kg a non-significant increase (23.48%) was observed.

The uterine epithelial height (UEH) of animals treated with 2'-HG is depicted in figure 2B. The 3-day administration of GEN induced a significant ($p \leq 0.05$) decrease of UEH by 23.02%. Similarly, 2'-HG displayed a significant decrease ($p \leq 0.05$) of UEH by 30.24%, 30.25% and 27.15% at 0.5, 2 and 8 mg/kg, respectively.

The microphotographs of ovariectomized controls (OVX group) as well as those from OVX animals treated with GEN and 2'-HG showed a thin layer of cubic cells (Figure 2C). Epithelia of animals receiving GEN and 2'-HG appeared less developed than those of negative control (OVX).

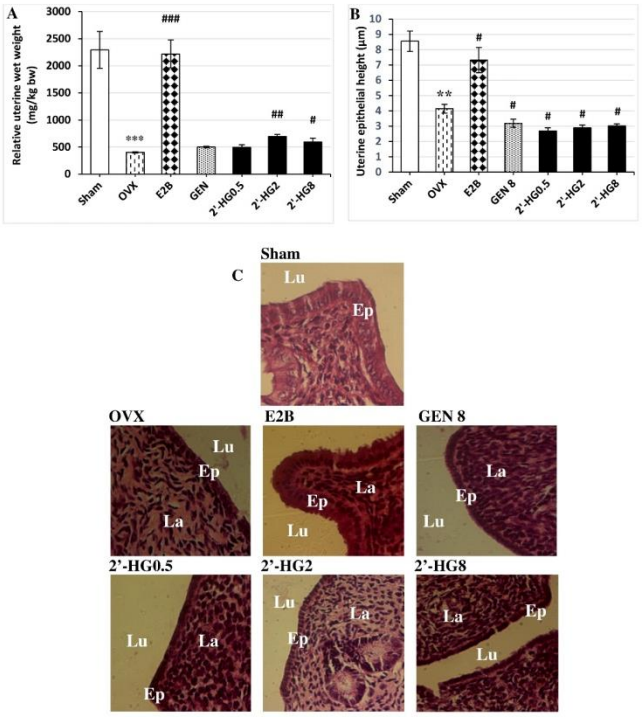

Figure 2: Wet weight (**A**), epithelial height (**B**) and microphotographs (400x, hematoxylin-eosin staining) (**C**) of uterus after a 3-day subcutaneous treatment (n = 5). Sham: Non-ovariectomized animals, OVX: ovariectomized animals receiving vehicle (corn oil), E2B: OVX animals treated with estradiol benzoate (2 µg/kg), GEN: OVX animals treated with genistein at 8 mg/kg, 2'-HG: OVX animals treated with 2'-hydroxygenistein at the doses of 0.5, 2 and 8 mg/kg, Lu: Lumen, Ep: epithelium, La: lamina propria. $^{**}p \leq 0.01$ and $^{***}p \leq 0.001$ compared with Sham, $^{\#\#}p \leq 0.01$ and $^{\#\#\#}p \leq 0.01$ compared with OVX.

Effect on vaginal epithelium

Compared to ovariectomized control (OVX), treatment with 2'-HG at all tested doses did not significantly affect vaginal epithelium height (VEH) whereas estradiol benzoate (2 µg/kg) induced a significant ($p \leq 0.01$) increase of VEH by 321.05% (Figure 3A).

As compared to OVX control group, microphotographs of vaginal epithelium of OVX animals treated with GEN (8 mg/kg) and 2'-HG at 0.5, 2 and 8 mg/kg showed the presence of a thin stratum germinativum consisting of few cell layers whereas E2B induced the proliferation, stratification and cornification of vaginal epithelium (Figure 3B).

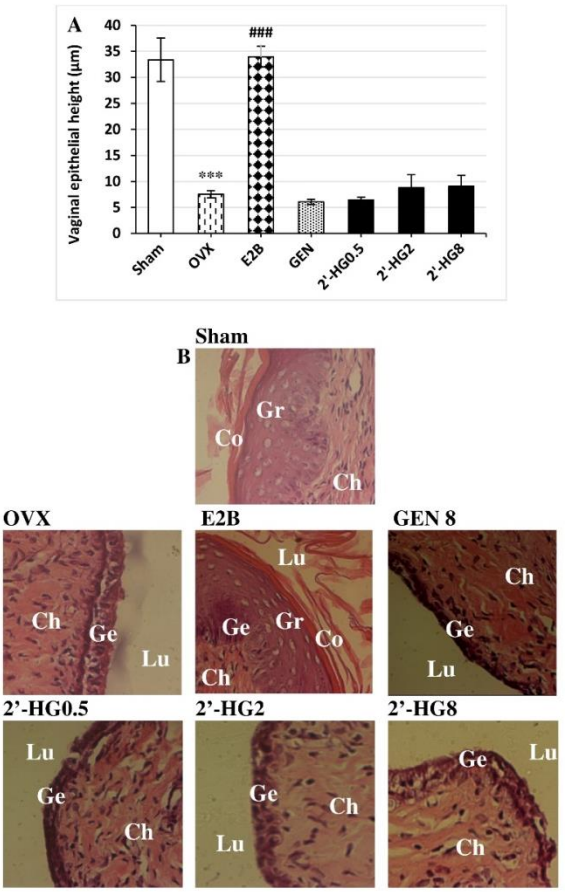

Figure 3: Epithelial height (**A**) and microphotographs (400x, hematoxylin-eosin staining) (**B**) after a 3-day treatment (n = 5). Sham: Non-ovariectomized animals, OVX: ovariectomized animals receiving vehicle (corn oil), E2B: OVX animals treated with estradiol benzoate (2 µg/kg), GEN: OVX animals treated with genistein at 8 mg/kg, 2'-HG: OVX animals treated with 2'-hydroxygenistein at the doses of 0.5, 2 and 8 mg/kg, Lu: Lumen, Co: stratum corneum, Gr: stratum granulosum, Ge: stratum germinativum, Ch: chorion. ***$p \leq 0.001$ compared with Sham, $^{###}p \leq 0.001$ compared with OVX.

DISCUSSION

Aberrant cell proliferation is known to be a defining hallmark of tumors. When excessive proliferation occurs within the endometrium (epithelium and chorion), it can lead to the development of endometrial carcinomas. Although allowing to avoid hysterectomy, conservative treatments are inefficient in many cases or show relapse after remission [6]. Thus, alternatives are still needed for women who want to preserve their health. Over the last decades, compounds from medicinal plants are intensively studied for better managing proliferative diseases.

Our results showed that a 3-day subcutaneous administration of 2'-hydroxygenistein (2'-HG) to ovariectomized animals (OVX) induced a significant increase of uterine wet weight (UWW) at the doses of 2 and 8 mg/kg, respectively. Genistein (GEN; 8 mg/kg) increased UWW by 25.1% as compared to OVX control. A similar increase in UWW was previously observed with 8 mg/kg/day GEN (21.7%) after a 14-day oral treatment [21] and 10 mg/kg/day GEN (~25%) for 3 days' subcutaneous treatment [22]. However, by contrast to Diel *et al.* [22] who did not observe any effect on uterine epithelial height (UEH) after a 3-day repeated subcutaneous administration of 10 mg/kg GEN, GEN (8 mg/kg) and 2'-HG (at all tested doses) by the same route led to a slight but significant decrease of the UEH in our study. Uterotrophic response has been described to be biphasic, including hyperemia and uterine water imbibition in the early phase, and epithelial gland/cell proliferation and differentiation in the late phase [23, 24]. All these steps are mediated through ERα, much more expressed than ERβ in all endometrial cell types during the proliferative phase [24, 25]. According to our results, 2'-HG probably induced hyperemia and water imbibition, while inhibiting cell proliferation. The uteri of all ovariectomized animals are lined by low cuboidal epithelial cells that characterized the diestrus phase, those of 2'-HG-treated animals being less developed than in OVX control and GEN-treated animals. The increase in the endometrium thickness is known to be related to the proliferative effect to endometrial cells. The thicker the endometrium, the less cell proliferation occurs. Accordingly, 2'-HG might inhibit the endometrial cell proliferation. Although both GEN and 2'-HG have been reported to be full ERα agonists [19], the 2'-hydroxylation of GEN significantly reduced its ERα binding affinity [26] and ERα β-galactosidase activity [19]. There is a large body of literature indicating that the ERβ generally counteracts the ERα-mediated cell proliferation in tissues such as uterus and breast, suggesting that its selective activation may be exploited to obtain an antiproliferative or antitumor effect [27-29]. GEN has been shown to bind ERβ with much higher affinity (~40 fold) than to ERα [30, 31]. Studies indicated that the OH-5 group is the most important structural element contributing to this selectivity [32, 33]. Although no study on the ERα/ERβ binding affinity of 2'-HG has been published yet, the presence of this OH-5 group might orient towards an ERβ-binding selectivity. On the other hand, Diel *et al.* [22] showed that in estradiol-induced proliferation in the uterine endometrium, the ERα/ERβ ratio shift dramatically towards ERα. In line with this, the effect of 2'-HG observed on endometrium is probably due to its capacity to bind preferentially ERβ or shift the ERα/ERβ ratio towards ERβ dominance.

The problems of vulvovaginal atrophy including dyspareunia and vaginal dryness result from the regression of the vaginal epithelium [34]. Our results showed that GEN and 2'-HG did not increase the vaginal epithelial height of OVX animals suggesting that at the tested doses they were not able to induce vaginal proliferation, stratification and cornification and therefore may not alleviate vaginal dryness. Genistein has been reported to increase the height of vaginal epithelium in ovariectomized Wistar rats but only at higher doses (>50 mg/kg BW for 3 days) [16, 35].

CONCLUSION

In this study we evaluated for the first time the effects of 2'-hydroxygenistein on uterine growth using a 3-day uterotrophic assay. The compound induced a slight but significant increase in uterine wet weight, while decreasing uterine epithelial height in ovariectomized rats. Globally, these effects are stronger than those of genistein and need to be further investigated.

Conflict of interests

The authors declare the absence of any commercial or financial relationships that could lead to a conflict of interest.

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