Quercetin interferes with the fluid volume and receptivity development of the uterus in rats during the peri-implantation period

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ABSTRACT
Hypothesis: Quercetin could induce changes to the fluid volume and receptivity development of the uterus during peri-implantation period.

Methods: Female rats were treated with quercetin (10, 25 and 50 mg/kg/day) subcutaneously beginning from day-1 pregnancy. Uterus was harvested at day-4 (following three days quercetin treatment) for morphological, ultra-structural, protein and mRNA expression changes and plasma sex-steroidal levels analysis. In another cohort of rats, implantation rate was determined at day-6 (following five days quercetin treatment).

Results: Administration of 50 mg/kg/day quercetin causes increased in uterine fluid volume and CFTR expression but decreased in γ-ENaC, AQP-5, AQP-8, claudin-4, occludin, E-cadherin, integrin αvβ3, IGF, lHh and bFGF expression in the uterus. PINopodes were poorly developed, tight junctions appear less complex and implantation rate decreased. Serum estradiol levels increased but serum progesterone levels decreased.

Conclusions: Interference in the fluid volume and receptivity development of the uterus during peri-implantation period by quercetin could adversely affect embryo implantation.

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1. Introduction

Uterine receptivity is a period when the uterus is receptive to the implanting embryo [1]. In humans, uterine receptivity occurs in the mid-secretory phase of the menstrual cycle [2] while in rats, receptivity occurs between day-4-5 of the estrous cycle [3]. During receptivity period, the newly formed blastocyst attaches to the uterine epithelium [4]. For implantation to occur, complex interplay between hormones, adhesion molecules, extracellular matrix and pacificin factors in the uterus are needed. The hormones that are essential for implantation are estrogen and progesterone as indicated by increased expression of estrogen and progesterone receptors in the endometrium [5]. Several protein molecules are reported to be expressed in the endometrium exclusively during the uterine receptivity period, and therefore could serve as the uterine receptivity markers [6].

During the uterine receptivity period, ultrastructural changes have been reported to occur in the endometrium. These changes include formation of pinopodes, which are the progesterone-dependent projections. Pinopodes can be found at the apical surface of the endometrium in rats [7] and humans [8]. In rats and mice, pinopodes have been shown to be involved in the fluid uptake that could assist in uterine closure [9]. In addition to pinopodes, changes in the tight junction morphology were also reported in the early pregnancy period. Tight junction (TJ) serves as a barrier that controls the movement of solutions between the different uterine compartments [10]. During implantation, the depth and comple-