

SAFETY EVALUATION OF AN EXTRACT OF PELARGONIUM SIDOIDES DC (EPS®7630) ON RATS

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Commercial extract from the roots of *Pelargonium sidoides* DC (EPS®7630) showed antibacterial, antiviral, immunomodulatory, antioxidant, and tissue-protective activity. This extract is used for a treatment of infectious and inflammatory respiratory diseases as a part of complex therapy in different dosage forms.

In the present study, we aimed to evaluate the safety of EPS®7630 in the form of a tablet and solution for oral administration.

Two groups of ten females and males albino rats for each formulation and one group of placebo (starch slime) were used in the experiment. The solution for oral administration (300 and 3000 mg/kg/day/rat) and suspension of tablets (5 and 50 mg/kg/day/rat) were administered to the rats by the gavage for 30 days. Clinical analysis of blood was done on 30 and 45 days, biochem-

ical analysis of serum was done on 31 and 46 days. The effect of the extracts on organs weights and histological observation of the organs were assessed.

Some signs of toxicity were registered in 30% of animals on the days from 21 to 30 of an experiment after administration of the highest dose. It was tousled wool, depression and diarrhea. All the symptoms of intoxication were reversible and wasn't defined on the day 31–45. While the pathological alterations in the rat's organs and blood were not observed. The statistical analysis hasn't revealed differences of experimental groups from control.

Results of this animal study showed that extract of *Pelargonium sidoides* DC (EPS®7630) has no overall toxic effect on the health of animals. Symptoms of intoxication were reversible.

INVOLVEMENT OF EPOXYEICOSATRIENOIC ACID IN THE DEVELOPMENT OF TAMOXIFEN-RESISTANT BREAST CANCER

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Epoxyeicosatrienoic acid (EET)s production via Cytochrome P450 (CYP) epoxygenases closely correlates with the progression of breast cancer, however its roles in the development of chemoresistant breast cancers have been uncovered.

Cell proliferation was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Tumorigenesis and angiogenesis were determined by Chick chorioallantoic membrane (CAM) assay. Cell migration was analyzed by trans-well migration assay.

Here we found that CYP3A4 expression was enhanced in tamoxifen (TAM)-resistant breast cancer cells (TAMR-MCF-7) compared to control MCF-7 cells and its epoxy-product, 11,12-epoxyeicosatrienoic acid (11,12-EET) was selectively increased. Treatment of TAMR-MCF-7 cells with ketoconazole (selective

CYP3A4 inhibitor) or 14,15-epoxyeicosa-5(Z)-enoic acid (14,15-EEZE, EET antagonist) inhibited cell proliferation and recovered the sensitivity to 4-hydroxy tamoxifen. CAM and trans-well migration analyses showed that the enhanced angiogenic, tumorigenic and migration intensities of TAMR-MCF-7 cells were also significantly suppressed by ketoconazole and 14,15-EEZE. We have revealed that Pin1, a peptidyl prolyl isomerase is a crucial regulator for higher angiogenesis and epithelial-mesenchymal transition characteristic of TAMR-MCF-7 cells. EET inhibition suppressed the E2F1-dependent Pin1 gene transcription and, Pin 1 silencing by lentiviral shRNA transduction also blocked cell proliferation, angiogenesis and migration of TAMR-MCF-7 cells.

Our finding suggests that CYP3A4-mediated EET pathway is a potential therapeutic target of tamoxifen resistant breast cancer.