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### ACCEPTED MANUSCRIPT

Hesperetin and it nanocrystals ameliorate social behavior deficits and oxidoinflammatory stress in rat model of autism

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#### Highlights

- Prenatal injection of VPA not only induces anxiogenic-like behavior but also remarkable decrease in social interaction, increased repetitive behavior and oxido-inflammatory stress.
- Mother administration of Hst and nano-Hst can ameliorate autistic-like behaviors and oxidoinflammatory parameters in animal model of autism based on prenatal exposure to VPA.
- Histopathological findings suggests that Hst and nano-Hst protected Purkinje cells of cerebellum in in animal model of autism.

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#### **Abstract**

Prenatal exposure to valproic acid (VPA) induces behavioral disorders and enhancement of oxido-inflammatory stress in Autism Spectrum Disorders (ASDs). The aim of this study was to investigate the comparative effects of hesperetin (Hst) and nano-hesperetin on social behavior deficits and oxido-inflammatory indexes in prenatally valproic acid-exposed rat offspring. Pregnant Wistar rats on embryonic day 0 (E0) were segregated into six groups; Group-1 served as vehicle, received distillated water orally (PO) from E1 until the end of lactation and saline intraperitoneally (i.p) on E12.5. Group-2 received sodium valproate (500 mg/kg in 0.9 % saline, i.p) on E12.5 was considered as VPA-exposed group, Group-3 to 6 were VPA-exposed which received hesperetin and nano-hesperetin (10 and 20 mg/kg/day, PO) from E0 until the end of lactation respectively. Social interaction and open field tests were conducted on postnatal day 28 (PND 28) and PND 30, cerebral antioxidant enzymes activity and biochemical indexes, the level

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