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*Berberis vulgaris* attenuates chronic haloperidol-induced oral dyskinesia and reinstate dopaminergic modulation in rat caudate.

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Chronic neuroleptic-induced orofacial movements in rats have been extensively employed as an animal model of Tardive dyskinesia (TD). Caudate, a region of brain involved in the control of motor activity, is rich in DA nerve terminals. Dopamine D2 receptor antagonism is postulated to be a key to antipsychotic efficacy in the treatment of schizophrenia. The present study was therefore designed to evaluate the protective effects of aqueous fruit extract of *Berberis Vulgaris Linn* (*B. Vulgaris*) in the amelioration of haloperidol-induced vacuous chewing movements (VCMs), tongue protrusions and vertical jaw movements in the rat model for TD.

Male Albino Wistar rats (n=24) were randomly assigned as: Test group (n=12) received daily haloperidol (3.0 mg/kg i.p.) and Control group (n=12) received saline injections with an equal volume of 1.0 ml/kg body weight for a period of 21 days. 10-day post-treatment, animals were further subdivided into four groups (n=6 in each group). Aqueous extract of *B. Vulgaris* (50 mg/ml) was administered daily via feeding tube in selective groups of saline and haloperidol treated rats while others groups were receiving the same treatment. Quantification of VCMs and vertical jaw movements were monitored during a 5-minute observation period successively in each group of rats. On the last day of experiments, changes in extracellular levels of dopamine (DA), dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) in caudate were determined by High Performance Liquid Chromatography with Electrochemical Detection (HPLC-EC). The protocol for experimentation was approved and performed in strict accordance with the Guide for the Care and Use of Laboratory Animals (Institutional Animal Ethical Committee IAEC; University of Karachi, Pakistan).

Behavioral data revealed that chronic haloperidol treated rats significantly (p<0.01) developed these extrapyramidal symptoms, but co-administration of *B. Vulgaris* fruit extract (50 mg/ml) exhibited significant (p<0.01) reduction in these extrapyramidal (EPS) effects. Neurochemical results showed that levels of DA and HVA in caudate were significantly (p<0.01) altered in group of rats administered with *B. Vulgaris* fruit extract (50mg/ml) followed by injections of haloperidol when compared with their respective controls. Important finding of the present study is that, treatment with haloperidol at a dose of 3.0 mg/kg daily induced tardive VCMs in 2 weeks that increased in a time-dependent manner. Co-administration of aqueous extract of *B. Vulgaris* (50 mg/ml) attenuated and absolutely reversed the VCMs in a time dependent manner. In the present study haloperidol treatment produced VCM in 30% of the treated rats and the concomitant treatment with *B. Vulgaris* altered both the prevalence and intensity of VCMs in a time-dependent manner.

In conclusion, these findings strongly suggest the role of postsynaptic DA-D2 receptors in the precipitation of haloperidol-induced EPS symptoms while long-term oral administration of aqueous *B. Vulgaris* presented neuroprotective effects in the caudate suggesting its role in attenuation of orofacial dyskinesia. Hence, this mechanism would possibly help in the development of neutraceuticals extending the nutrient therapy in schizophrenia.
