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Neuroprotective Epigenetic and DNA-Damage-Repairing Molecular Mechanisms of *Centella Asiatica* Extract (CAE) on Experimentally Induced Parkinsonism in Aged Sprague-Dawley Rats

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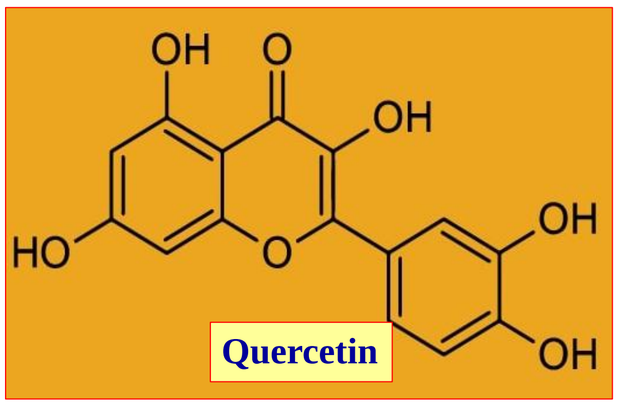
INTRODUCTION & AIM

Parkinson's disease (PD) is a degenerative disease causing motor and non-motor symptoms. Animal models reproducing the main cellular processes of PD, such as oxidative stress (OS), neuroinflammation, and DNA damage, which leads to dopaminergic neuronal loss. Studies documented that *Centalla asiatica* herbal extract enriched with antioxidants exerts cytoprotective effects against aging and age-related neurodegenerative diseases.

Centella Asiatica



Quercetin

METHOD

The present study was designed to investigate whether the CAE would ameliorate MPTP-induced neurotoxicity in aged SD rats. Aged male SD rats (26 months old) were divided into three groups: control, MPTP alone (20mg/kg b.wt, i.p, twice at 20 min intervals), and MPTP with CAE (300mg/kg b.wt and/or quercetin (QN) (100mg/kg b.wt, orally) for 21 days. We investigated the aqueous extract of CAE based on OS biomarkers , inflammation, oxidative DNA damage (8-OHdG), DNA, ATP, GSH, neurotransmitter (NT) levels, and DNA repair enzymes in discrete brain regions associated with PD.

RESULTS & DISCUSSION

MPTP-intoxicated rats elicited a highly significant elevation in the concentration of $NO^{\bullet}$ (a biomarker of OS), inflammation (IL-6, IL-1β, and TNF-α), 8-OHdG, XO, nitric oxide synthase, NADPH oxidase, and PARP-1 ($p<0.001$) when compared with controls. There was a significant decrease in total antioxidant capacity, ATP, GSH, DA, NE, and SN contents with animals treated with MPTP. The co-administration of CAE and/or QN significantly ($p<0.01$) decreased biomarkers of OS and inflammation, as well as DNA repair enzymes, and significantly increased NT levels, which are due to antioxidant and iron-chelating effects of CAE bioflavonoids.

Table 1. Neuroprotective Epigenetic and DNA-Damage-Repairing Molecular Mechanisms of *Centella Asiatica* Extract (CAE) on MPTP- Induced Parkinsonism in Aged Sprague-Dawley Rats

No	Parameters	Group-1 Control	Group-2 MPTP	Group-3 MPTP + CAE	Group-4 MPTP + CAE +QN
1	$NO^{\bullet}$ (ppm in serum)	17.49±1.47	32.58±2.30*	27.50±1.89†	22.76±2.25†
2	IL-6 (pg/mg)	5.44 ± 0.95	10.54±0.98#	9.34±1.32 †	8.45±1.73†
3	IL-1β ($ng \cdot g^{-1}$ wet wt)	187±7.6	294±9.43†	257± 8.72#	228±9.93†
4	TNF-α (pg/ml)	58.39±4.02	78.80±5.65#	71.5±6.70†	63.73±7.60†
5	8-OHdG (fmol/µg DNA)	18±1.14	32±1.34†	27.4±1.28†	23.80±1.30†
6	XO (µM/mg protein)	3.27±0.04	4.84±0.03†	3.75±0.05#	3.45±0.62†
7	NOS (nmol of Nox/g wet tissue/hr)	123±8.5	243±9.4†	238±11.6†	230±9.60†
8	NADPH oxidase (RLU/µ ptn)	187±14	342±20†	286±19#	239±21†
9	PARP-1 (Units/mg protein)	6.74±0.34	9.58±0.37†	7.85±0.28†	7.14±0.29†
10	ATP (mM/kg wet tissue wt)	3.35±0.23	2.65±0.19†	3.20±0.27†	3.31±0.28†
11	GSH (µmole/mg protein)	14.0 ±1.9	8.56±2.3†	11.6±1.72#	12.65±2.69#
12	Dopamine (ng/g tissue)	3360±116	2376±112†	2962±123†	3152±108†
13	Norepinephrine (ng/g tissue)	362±18	274±23#	339±14*	329±21†

Values are expressed as mean± SD for 8 animals in each group. On comparing groups, Group 2 with Group-1 ; Groups-3-4 with Group-2. *P<0.05, #P< 0.01, †P<0.001.

CONCLUSION

Knowledge of the epigenetic and molecular mechanisms involved in theprogressive neurodegeneration in this model is the key to identifying potential therapeutic targets for PD with antioxidants which exerts iron-chelating anti-inflammatory and antioxidant effects.

Key Words: Parkinsonism, Neurodegeneration, Oxidative Stress, Inflammation, *Centella Asiatica* Bioflavonoids, DNA damage-repair.

FUTURE WORK

Bioflavonoids are the natural potential of PARP-inhibitors (PARP-i) enriched in herbs, fruits and spices which can be isolated and its molecular structures can be elucidated and evaluated for its possible neuroprotective effects in a variety of neurodegenerative diseases such as Senile dementia, Alzheimer's disease and Parkinsonism.

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