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AMELIORATIVE POTENTIAL OF COUMARIC ACID AND IMEGLIMIN AGAINST RESERPINE-INDUCED PARKINSONISM IN RATS

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ABSTRACT
Background: Parkinson's disease involves dopaminergic degeneration, oxidative stress, and α-synuclein aggregation. Reserpine-induced Parkinsonism mimics these deficits via VMAT-2 inhibition. Coumaric acid and imeglimin possess antioxidant and mitochondrial-protective actions. This study evaluated the individual and combined efficacy of these agents in reducing reserpine-induced behavioural and neurochemical impairments in rats. **Methodology:** PD was induced in rats by giving reserpine (1 mg/kg, s.c) alternately for three days. Pretreatment with coumaric acid (80 and 100 mg/kg, p.o.), imeglimin (100 & 200 mg/kg, p.o.), and their combination were administered for 5 days. Behavioral assessments (orofacial dyskinesia, H & B test, and rotarod) were performed on day 5, followed by biochemical oxidative stress parameters (CAT, GSH, SOD, and LPO), neurotransmitters (dopamine), and α-synuclein expression with histopathological evaluations. **Results:** Reserpine-treated rats exhibited pronounced orofacial dyskinesia, reduced motor coordination, dopamine depletion, elevated oxidative stress, and α-synuclein expression. Pretreatment with coumaric acid and imeglimin improved behavioral outcomes, restored antioxidant enzymes, reduced inflammation, and elevated dopamine levels. Combination therapy produced the greatest improvement. **Discussion:** The combined effects of coumaric acid and imeglimin likely counteract reserpine-induced dopaminergic toxicity through antioxidant enhancement and inhibition of α-synuclein expression. **Conclusion:** Coumaric acid and imeglimin combination therapy significantly mitigates reserpine-induced Parkinsonism by improving general neuronal integrity and brain function.

INTRODUCTION

About 1% to 2% of those over 60 have Parkinson's disease (PD), the second most prevalent neurological disorder after Alzheimer's disease. In addition to non-motor characteristics like depression, cognitive decline, and autonomic problems, it is clinically characterized by motor dysfunctions such as bradykinesia, tremor, stiffness, and postural instability [1]. In the substantia nigra pars compacta, dopaminergic neurons gradually

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degrade, and subsequent striatal dopamine depletion is the main pathophysiological feature of PD. In addition to dopamine deficiency, mitochondrial dysfunction, α-synuclein aggregation, and oxidative stress are recognized as central mechanisms contributing to neuronal loss and disease progression [2]. Current medications, particularly dopamine agonists and levodopa, alleviate symptoms but are unable to cease or reverse neurodegeneration. Long-term use of these agents is further limited by motor complications and reduced efficacy, thereby necessitating the exploration of novel neuroprotective interventions [3]. Reserpine-induced Parkinsonism in rodents serves as a well-established experimental model for evaluating potential therapeutic strategies. Reserpine inhibits vesicular monoamine transporter-2 (VMAT-2), thereby depleting dopamine, norepinephrine, and serotonin from presynaptic terminals [4]. This monoamine depletion produces motor impairments and biochemical alterations resembling Parkinsonian pathology. Importantly, this model highlights the roles of oxidative stress, lipid peroxidation, and inflammatory responses in nigrostriatal degeneration, providing a platform for testing antioxidant and neuroprotective compounds [5,6]. Natural polyphenols have attracted considerable interest because of their anti-inflammatory and antioxidant properties. Natural hydroxycinnamic acid, or coumaric acid, is found in a variety of fruits, vegetables, and cereals. It has demonstrated the ability to scavenge free radicals, reduce lipid peroxidation, and enhance endogenous antioxidant defenses. Its neuroprotective potential has been shown in experimental models of oxidative stress–induced neuronal damage [7]. Drug repurposing (DR), or drug repositioning, is an emerging strategy in drug development that identifies new therapeutic uses for existing drugs beyond their original indications [8]. Imeglimin was originally developed and approved as an antidiabetic agent. Beyond its glucose-lowering action, imeglimin exhibits significant antioxidant, mitochondrial-modulating, and anti-apoptotic properties, which are highly relevant to the pathophysiology of PD. In the substantia nigra, oxidative stress and mitochondrial dysfunction are major causes of dopaminergic neuronal degeneration. Imeglimin's capacity to improve mitochondrial bioenergetics and lower reactive oxygen species may help reverse these effects [9]. Therefore, repurposing imeglimin for PD represents a promising therapeutic approach that could offer dual benefits with metabolic regulation and amelioration, and also reduce the time and cost associated with *de novo* drug development. Given the complementary pharmacological profiles of coumaric acid and imeglimin, their combined administration may yield pronounced benefits by targeting oxidative stress and dopaminergic depletion. Hence, the present investigation was conducted to examine the protective role of coumaric acid and imeglimin, alone and in combination, in a reserpine-induced Parkinsonism rat model. Behavioral, biochemical, and histopathological analyses were employed to assess their efficacy in mitigating dopaminergic neurodegeneration and oxidative damage.

MATERIALS AND METHODS

The animals were male Wistar rats weighing 230-250 g, housed under standard conditions with free access to food and water (25 ± 2 °C, 12 h light/dark cycle, 50 ± 5% humidity). The animals were acclimated before the studies, and each group comprised six rats. All procedures were conducted during 08:00–16:00 h in accordance with CCSEA guidelines, and the Institutional Animal Ethics Committee (IAEC) of M.V.P.S. College of Pharmacy in Nashik approved the study protocol (IAEC/2023/01).

Drugs and chemicals: Reserpine, Imeglimin (Hi-Media Laboratories Pvt. Ltd., Mumbai, India), Coumaric acid (YUCCA enterprises, Mumbai, India), Vitamin E (Alembic Pharma Ltd., Vadodara) were used in the present study.

Rats with reserpine-induced Parkinson's disease: Nine groups of animals (n = 6) were used. Treatment with coumaric acid and imeglimin was given daily from Day 1 to Day 5, while reserpine (1 mg/kg, s.c, in 0.1% acetic acid) was administered on alternate days (Days 1, 3, and 5).

I: Control
II: Reserpine, every other day
III: Reserpine + Coumaric acid (80 mg/kg, p.o), 5 days
IV: Reserpine + Coumaric acid (100 mg/kg, p.o), 5 days
V: Reserpine + Imeglimin (100 mg/kg, p.o), 5 days
VI: Reserpine + Imeglimin (200 mg/kg, p.o), 5 days
VII: Reserpine + Coumaric acid (80 mg/kg, p.o) + Imeglimin (100 mg/kg, p.o), 5 days
VIII: Reserpine + Coumaric acid (100 mg/kg, p.o) + Imeglimin (200 mg/kg, p.o)
IX: Reserpine + Vitamin E (p.o)

Behavioral assessments

Quantification of dyskinesia-Orofacial dyskinesia was assessed by placing rats individually in a Plexiglas chamber (30 × 20 × 20 cm). After 10 min of habituation, vacuous chewing

movements and tongue protrusions were recorded for 15 min using mirrors for full visibility. Each movement was defined and counted as per standard protocols [10,11].

Digital actophotometer measurement of total locomotor activity: Using photoelectric cells, locomotor activity was monitored. A 5-minute count was conducted as the animal cut off the light beam illuminating the photocell [12,13].

Rota rod test: Rota rod equipment was used to assess the grip strength. Every animal was put on a revolving rod that rotated at 20 rpm, and the animal's latency to fall was noted for each group [14,15].

Hole-and-board test: The hole-and-board is 40 cm by 40 cm. There are 16 uniformly spaced holes on the floor, each measuring 3 cm in diameter. The animal's propensity to insert its head into the holes was noted and quantified. The total number of pokes per rat at each one minute interval was recorded [16,17].

Biochemical estimations

Dissection and homogenization:

In 0.1 M phosphate buffer (pH 7.4), a 10% (w/v) homogenate was made. To obtain the post-nuclear fraction for the catalase (CAT) assay, centrifugation was carried out at 1000 g for 20 minutes at 4 °C, and for the other enzyme assays, at 12000 g for 60 minutes at 4 °C. Enzyme activities were measured using an Elico BL200 spectrophotometer [18,19].

Estimation of catalase (CAT) levels: The Luck method, which monitors the breakdown of H_2O_2 at 240 nm, was used to measure catalase activity. 3 ml of H_2O_2 phosphate buffer (0.0125 M H_2O_2) and 0.05 ml of homogenized brain supernatant made up the assay mixture. The change in absorbance was recorded at 240 nm. The findings were presented as the number of micromoles of H_2O_2 degraded per minute per milligram of protein [20,21].

Estimation of superoxide dismutase (SOD levels): SOD activity was measured at 560 nm using the Kono method, which shows that SOD inhibits the degradation of NBT. The percentage decrease in NBT absorbance was used to express the results [22].

Lipid peroxidation assay (LPO activity): LPO activity was quantified using the Wills method. By reacting with TBA at 532 nm, the amount of malondialdehyde (MDA) produced was determined. With the use of the chromophore's molar extinction coefficient ($1.56 \times 105\ M^{-1}\ cm^{-1}$), the results were represented as nmoles of MDA/mg protein [23,24].

Estimation of α synuclein expression: Soluble α-Synuclein levels in the nigrostriatal region were quantified using an Elabscience sandwich ELISA kit. Following the addition of samples (50 µl) to antibody-coated plates, biotinylated antigen, HRP-streptavidin, and TMB substrate were incubated. At 450 nm, absorbance was measured [25,26].

Estimation of brain dopamine content: To assess dopamine (DA) levels, 1 ml of brain homogenate was combined with 1 ml each of potassium ferricyanide (1.5×10^{-2} M) and ferric chloride (1.5×10^{-2} M) in 25 ml of distilled water. After a 30-minute reaction, absorbance at 735 nm was measured using a UV-visible spectrophotometer [27].

Histopathological evaluation: The brains of the experimental and control groups were immersed in paraffin wax, treated with 10% formalin, and then cut into longitudinal sections that were 5 μm thick. Haematoxylin and eosin dye were used to stain the sections for histological examination. A 100X light microscope (Olympus, Japan) was used to view the slices, and photomicrographs were taken [28].

Statistical analysis: The mean ± SEM was used to express all results. Using GraphPad Prism 10, one-way ANOVA (analysis of variance) and Tukey's multiple comparison test were used to examine all group data.

RESULTS

1. Orofacial Dyskinesia

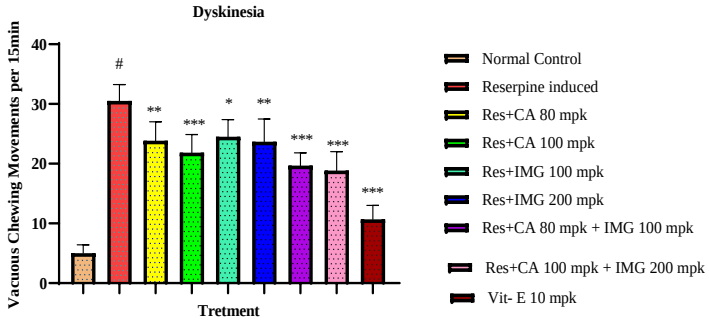

Figure 1A: Effect of coumaric acid & imeglimin, alone and in combination, on in reserpine-treated rats. Data are presented as mean ± SEM (n = 6), and Tukey's test was performed after a one-way ANOVA. $p < 0.05 vs. Coumaric acid (80 mg/kg) plus Imeglimin (100 mg/kg); @p < 0.05 vs. Coumaric acid (100

mg/kg) + Imeglimin (200 mg/kg); *p < 0.05, **p < 0.01, ***p < 0.001 vs. Reserpine; #p < 0.05 vs. Control

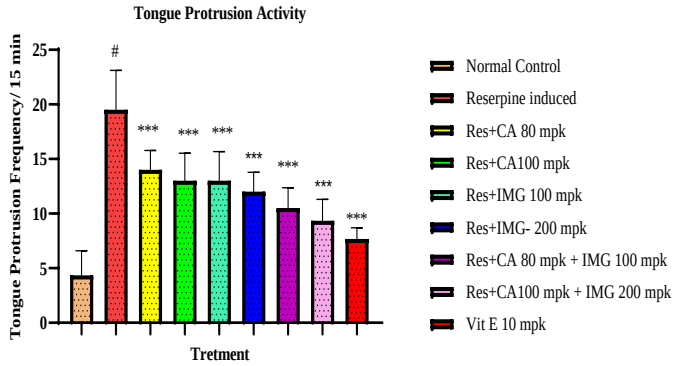

Figure 1B: Effects of imeglimin and coumaric acid, both separately and together, on tongue protrusion in rats given reserpine. Tukey's test and one-way ANOVA are used to analyse the data, which are shown as mean ± SEM (n = 6). $p < 0.05 vs. Coumaric acid (80 mg/kg) plus Imeglimin (100 mg/kg); @p < 0.05 vs. Coumaric acid (100 mg/kg) + Imeglimin (200 mg/kg); *p < 0.05, **p < 0.01, ***p < 0.001 vs. Reserpine; #p < 0.05 vs. Control.

Reserpine-treated rats exhibited severe **orofacial dyskinesia**, reflected by a high frequency of tongue protrusions (TPs) and vacuous chewing motions (VCMs) ($p < 0.001$), indicative of dopaminergic dysfunction and extrapyramidal disturbances. Treatment with coumaric acid (80 and 100 mg/kg) and imeglimin (100 and 200 mg/kg), either alone or in combination, significantly decreased VCM and TP frequencies in a dose-dependent manner ($p < 0.001$). The combined higher-dose regimen showed the greatest improvement, restoring behavior to near-normal levels comparable to those of the standard antioxidant, vitamin E (Figures 1A & 1B).

2. Locomotor activity

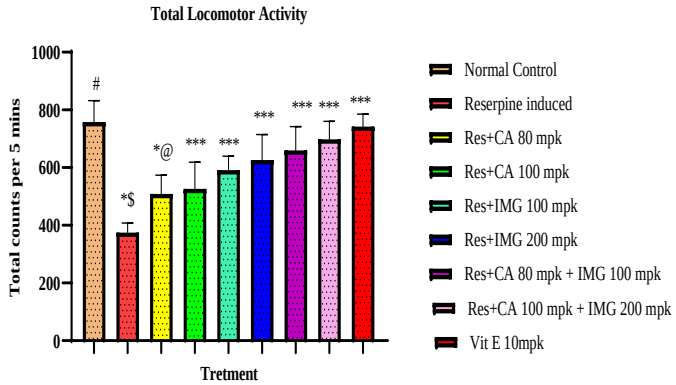

Figure 2: Effect of coumaric acid, imeglimin, and their combination on locomotor activity. A one-way ANOVA using Tukey's multiple comparison test was used to analyze the data, which were presented as mean ± SEM (n = 6). **p < 0.01, ***p < 0.001 vs. reserpine; #p < 0.05 vs. control; $p < 0.05 vs. imeglimin (100 mg/kg) + coumaric acid (80 mg/kg); @p < 0.05 vs. imeglimin (200 mg/kg) + coumaric acid (100 mg/kg)

In the **actophotometer test**, reserpine caused a marked reduction in locomotor counts ($p < 0.001$), confirming bradykinesia and hypokinesia. Pretreatment with coumaric acid and imeglimin significantly improved the dose-dependent pattern of locomotor activity ($p < 0.001$), whereas their combination produced an additive effect approaching control levels (Figure 2).

3. Rota Rod Test

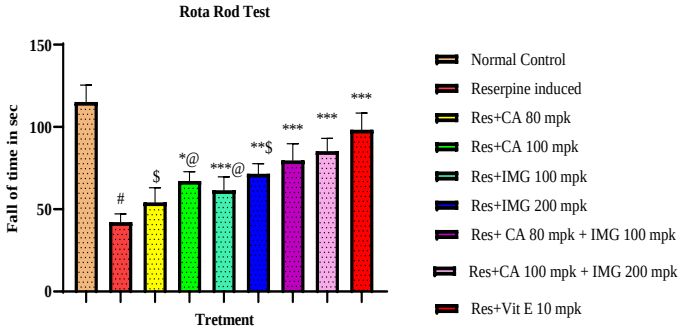

Figure 3: Effect of Imeglimin and coumaric acid on rota-rod performance, both separately and together. Tukey's test and one-way ANOVA were used to analyse the data, which were presented as mean ± SEM (n = 6). **p < 0.01, ***p < 0.001 vs. reserpine; #p < 0.05 vs. control; $p < 0.05 vs. imeglimin (100 mg/kg) + coumaric acid (80 mg/kg); @p < 0.05 vs. imeglimin (200 mg/kg) + coumaric acid (100 mg/kg).

Reserpine significantly reduced the latency to fall ($p < 0.05$) in the rotarod test, indicating impaired motor coordination. Both coumaric acid and imeglimin improved performance individually, whereas their combination, particularly at higher doses, showed greater effects ($p < 0.001$), indicating robust protection of neuromuscular coordination. Collectively, behavioral outcomes demonstrate that the combination of coumaric acid and imeglimin effectively mitigated reserpine-induced motor deficits and dyskinetic behaviors, reflecting pronounced functional improvement (Figure 3).

4. Hole Board Test

In the hole-board test, reserpine markedly reduced head-dipping activity ($p < 0.001$), suggesting decreased exploratory behavior and increased anxiety. Administration of coumaric acid and

imeglimin, individually and in combination, significantly increased head-dipping frequency ($p < 0.001$), indicating normalization of exploratory drive. The combined treatment produced the greatest restoration, which was nearly equivalent to that of vitamin E (Figure 4).

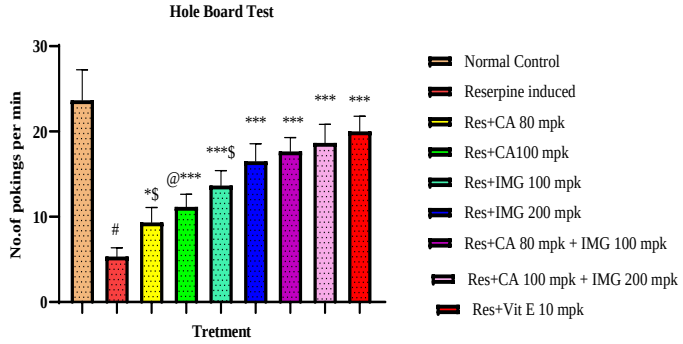

Figure 4: Effect of Imeglimin and coumaric acid on the number of pokings, both separately and together. The data (n = 6) are shown as mean ± SEM. One way ANOVA, followed by Tukey's test; $\$p < 0.05$ vs. coumaric acid (80 mg/kg) plus imeglimin (100 mg/kg); $@p < 0.05$ vs. coumaric acid (100 mg/kg) + imeglimin (200 mg/kg); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. reserpine; $\#p < 0.05$ vs. control

Biochemical assessment

Reserpine administration significantly diminished catalase activity, reduced glutathione (GSH) and superoxide dismutase (SOD) levels, and elevated lipid peroxide (LPO) levels, indicating pronounced oxidative stress. Treatment with coumaric acid and imeglimin markedly decreased LPO in a dose-dependent manner and increased levels of antioxidant enzymes; their combination produced greater improvement than individual therapies, demonstrating additive antioxidant effects. Vitamin E showed the strongest normalization of oxidative parameters (Table 1).

Table 1: Effect of Coumaric acid and Imeglimin alone and in combination on Biochemical parameters- Catalase, GSH, SOD, and LPO activity

Treatment	Catalase activity (µMole of H_2O_2 decomposed/mg protein)	GSH Level (µMole/mg protein)	SOD Level (% inhibition of reduction of NBT)	LPO activity (nMole of MDA/ mg protein)
Control	53.83±2.1	9.25±1.5	89.22±2.5	21.71±3.4
Reserpine 1mg/kg; s.c.	17.98±1.4#	3.18±0.7#	20.38±1.1#	81.03±6.1#
Coumaric acid 80 mg/kg p. o	23.14±2.3*$	5.57±0.9**	28.53±2.9**$	66.41±5.5*$
Coumaric acid 100 mg/kg p. o	23.67±1.5**@	5.81±0.6*@	30.69±4.7*@	61.39±6.2***@
Imeglimin 100 mg/kg p. o	24.17±3.5*$	5.30±1.1***$	28.34±2.5***$	64.24±9.6**$
Imeglimin 200 mg/kg p. o	32.57±3.3**@	6.49±1.0***	31.02±2.5***@	57.73±9.1***
Coumaric acid 80 mg/kg p.o + Imeglimin 100 mg/kg p. o	37.03±3.1***	7.56±1.6***	40.36±4.5***	49.91±7.0***
Coumaric acid 100 mg/kg p.o + Imeglimin 200 mg/kg p. o	42.63±2.6***	8.04±1.4***	51.88±6.5***	45.50±6.3***
Vit E - 10 mg/kg p. o	49.25±2.1***	8.29±1.0***	71.09±5.1***	29.96±5.6***

Table 2: Effect of Coumaric acid and Imeglimin alone and in combination on Biochemical parameters- Dopamine and soluble alpha synuclein level.

Treatment	Dopamine Level (ng/g of tissue)	Soluble Alpha Synuclein Level (ng/mL)
Control	421.50±25.0	5.49±1.7
Reserpine 1mg/kg; s.c.	120.33±11.5#	11.42±0.9#
Coumaric acid 80 mg/kg p. o	204.17±37.3***$	8.62±1.6*$
Coumaric acid 100 mg/kg p. o	271.50±47.2***@	6.95±0.7***
Imeglimin 100 mg/kg p. o	260.17±22.3***$	8.30±1.3**
Imeglimin 200 mg/kg p. o	309.17±17.1***	7.38±0.7***
Coumaric acid 80 mg/kg p.o + Imeglimin 100 mg/kg p. o	316.83±16.0***	5.83±1.6***
Coumaric acid 100 mg/kg p.o + Imeglimin 200 mg/kg p. o	329.17±33.2***	5.38±2.1***
Vit E - 10 mg/kg p. o	374.67±36.9***	4.44±0.9***

Reserpine also increased soluble alpha-synuclein levels and significantly decreased striatal dopamine levels, reflecting early dopaminergic impairment [29]. Both coumaric acid and imeglimin treatments significantly increased dopamine and reduced alpha-synuclein upregulation, whereas their combined administration achieved near-control levels, comparable to vitamin E ($p < 0.001$). These findings show that the combination therapy successfully prevented oxidative damage and restores functional integrity (Table 2)

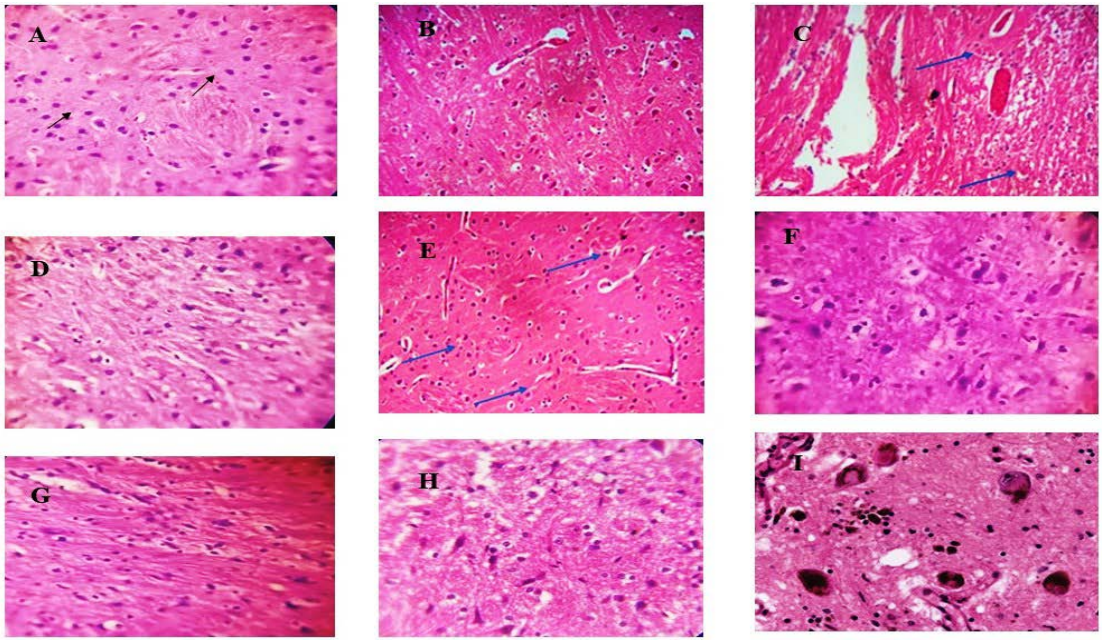

Figure 5: Rat's midbrain histopathological alterations in haematoxylin and eosin-stained sections: (A) Normal histoarchitecture was observed in the control area. (B) Reserpine-treated rats exhibited alterations in neuronal morphology and cytoarchitecture. (C) Rats were given 80 mg/kg of CA plus Reserpine. (D) Rats treated with Reserpine and CA 100 mg/kg. (E) Rats treated with Reserpine and Imeglimin 100mg/kg. (F) Rats treated with Reserpine and imeglimin 200mg/kg. (G) Rats treated with Reserpine and Combinations of lower doses of CA and Imeglimin. (H) Rats treated with Reserpine and Combinations of higher doses of CA and Imeglimin. (I) Rats given vitamin E and reserpine. Haematoxylin and eosin-stained sections ×400 magnification.

Histopathological Evaluation

Histological examination of the substantia nigra revealed subtle changes, including cell shrinkage and loss of normal architecture, in reserpine-treated rats. Treatment with coumaric acid and imeglimin, individually, partially restored neuronal morphology. In contrast, combination therapy restored near-normal cytoarchitecture with minimal neuronal morphological alterations, surpassing the protective effect of vitamin E. The observed additive beneficial effects are attributed to the complementary antioxidant and anti-inflammatory actions of coumaric acid and the mitochondrial-supportive mechanisms of imeglimin (Figure 5)

DISCUSSION

The current investigation showed that coumaric acid and imeglimin have a beneficial effect on neuronal integrity, administered alone and in combination, against reserpine-induced Parkinsonism in rats. Reserpine administration significantly reduced dopamine levels, suppressed endogenous antioxidant enzymes, and elevated oxidative stress markers, thereby mimicking the biochemical, behavioral, and neuropathological features of Parkinson's disease [30,31]. These alterations were accompanied by increased alpha-synuclein levels, indicating abnormal protein expression that further contributes to dopaminergic impairment [32]. Histopathological analysis confirmed substantial neuronal damage in the substantia nigra of reserpine-treated animals, consistent with the observed motor impairments. However, the changes cannot be interpreted as dopaminergic neuron–specific damage. Coumaric acid treatment significantly restored antioxidant enzyme activities, including catalase, SOD, and GSH, while reducing LPO levels in a dose-dependent manner. Its ability to scavenge free radicals may explain its beneficial effects and its capacity to stabilize cell membranes against oxidative insult [33,34,35]. Similarly, imeglimin treatment improved antioxidant status and reduced

lipid peroxidation, most likely through its specific action on mitochondrial function, where it enhances bioenergetics and reduces ROS generation at the site of production [36]. These results are consistent with earlier findings that implicate both oxidative stress and mitochondrial dysfunction as central mechanisms driving neurodegeneration in Parkinson's disease.

Beyond antioxidant restoration, both coumaric acid and imeglimin significantly improved dopamine levels depleted by reserpine. The increase in dopamine observed at higher doses highlights their capacity to restore neuronal integrity [37,38]. This dopaminergic restoration was further supported by improvements in locomotor activity and coordination, and by a reduction in dyskinetic movements, suggesting that biochemical protection translated into functional recovery. Importantly, the combination therapy of coumaric acid with imeglimin produced greater improvements in dopamine content than either treatment alone, with values approaching those of the control group.

A significant increase in total (soluble) α-synuclein levels was observed in reserpine-treated animals, consistent with upregulated expression rather than protein aggregation. Both coumaric acid and imeglimin reduced alpha-synuclein expression in a dose-dependent manner, with the combination treatment showing the most pronounced suppression, nearly normalizing protein levels. This is of considerable importance, as current therapies largely provide symptomatic relief without addressing abnormal protein expression, which contributes to progressive neuronal loss [39,40]. The histopathological findings corroborated the biochemical and behavioral outcomes, revealing that coumaric acid and imeglimin preserved neuronal density and integrity in the substantia nigra, with combination therapy producing nearly complete restoration of normal architecture. These additive benefits likely arise from their complementary mechanisms of action: coumaric acid primarily targets oxidative stress via radical scavenging, whereas imeglimin acts by improving mitochondrial function and energy metabolism [41]. Together, these agents provide a dual line of defense that appears more effective than focusing on a single pathological pathway.

While vitamin E, a well-established antioxidant, demonstrated the strongest overall ameliorative effects in this study, the combination of coumaric acid and imeglimin showed comparable efficacy, highlighting the therapeutic potential of natural antioxidant–drug repurposing strategies. The fact that imeglimin is already clinically approved for type 2 diabetes enhances the translational value of this approach, as repurposing may shorten the timeline for clinical application in Parkinson's disease. As a dietary phytochemical, coumaric acid also offers the advantages of safety and accessibility [42,43].

Collectively, the findings from this study indicated that simultaneously addressing oxidative stress, mitochondrial dysfunction, dopamine depletion, and protein expression may provide comprehensive recovery. The combination of coumaric acid and imeglimin was particularly effective in mitigating reserpine-induced behavioral deficits, restoring antioxidant balance, enhancing dopamine content, reducing alpha-synuclein expression, and preserving neuronal integrity. These results support the concept that multimodal therapy may be superior to single-agent interventions in complex neurodegenerative disorders such as Parkinson's disease [44]. Nevertheless, further studies employing chronic PD models, dose optimization, and clinical research will be required to confirm the long-term safety and effectiveness of this intriguing treatment combination.

CONCLUSION

This study demonstrated that coumaric acid and imeglimin enhanced the protection against reserpine-induced Parkinsonism by alleviating oxidative stress, restoring mitochondrial function, and attenuating neuronal damage, thereby highlighting the therapeutic promise of combined antioxidant and mitochondrial-targeted interventions in Parkinson's disease management.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Yogita Bagul conducted the laboratory experiments, collected, analysed, and interpreted the data, and drafted the manuscript. Vandana Nade guided the studies, designed the protocol, and helped to shape the final manuscript. L.A. Kawale analysed data and constructed the manuscript.

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