



Recent Studies on the Therapeutic and Prophylactic Effect of Some Agents on Experimental Induced Parkinson Disease Models Review

I. M. Hassan^{1*} and A. M. Abdullahi²

¹Department of Veterinary Physiology and Biochemistry Usmanu Danfodiyo University Sokoto, Nigeria.

²Department of Veterinary Teaching Hospital University of Maiduguri, Nigeria.

Authors' contributions

This work was carried out in collaboration between both authors. Author IMH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AMA managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Neurodegeneration include disease of the central nervous system (CNS) such as Parkinson's disease (PD). The sign of this disease include destruction of dopaminergic neuronal cells. Main causes of this disease are unknown, but several studies reported polygenic causes. These include free radicals, malfunction of mitochondria, protein oxidation and DNA denaturation. Several reports implicated the involvement of oxygen species and stresses cause by over accumulation of reactive oxygen species in the contribution to the cascade that resulted in diminishing of dopamine cells destruction in this disease. Generally, natural defensive substances such as bio-cartelized (proteineous and non proteineous) from natural or synthetic sources played a unique role in protecting the susceptible neuronal cells from the adverse effects of the reactive oxygen species. In most cases antioxidant enzyme production by the body system diminished with advance age. Hence, treatment with antioxidant potential agent or administration of antioxidant substance with the

*Corresponding author: E-mail: ibrahim.hassan@udusok.edu.ng;

common drugs used in the treatment of PD may yield positive result in protecting neurons from degenerative changes caused by reactive oxygen species. Recent studies on the therapeutic and prophylactic effect of some agents on experimental induced PD summarized in this review paper.

Keywords: Parkinson's disease; oxidative stress; free radicals; antioxidants; neuroprotection; neurodegenerative.

1. INTRODUCTION

Neurodegenerative disorders are chronically progressive group of diseases involving nerve cells death. Majority of these disorders comprises diseases characterized with dementia and cerebral ischemia result from oxidative stress [1]. The Brain is a very active organ of human body weighing only 2% of the body weight but it consumes 20% of body oxygen and 25% of body glucose at rest [2]. ROS produced in any tissue is directly proportional to its oxygen consumption which further increases with intellectual process like thinking planning and reasoning [3], the brain is continuously under oxidation/antioxidation process which makes it prone to oxidative damage. Several antioxidant mechanisms are available within brain to combat ROS. Brain cells have catalase and glutathione peroxidase in their cytosol which hydrolyzes H_2O_2 and reduces organic hydroperoxides respectively. Neuronal mitochondria have superoxide dismutase for converting $\cdot O_2^-$ to H_2O_2 which is further metabolized by catalase and thus preventing the formation of neurotoxic and inflammatory cytokine-inducing $\cdot ONOO^-$ from $\cdot O_2^-$ and $\cdot NO$ [4]. Although, brain cells have defense mechanisms for dealing with ROS, yet it has been practically found that when level of ROS goes unusually high or antioxidant defense goes low, cells bear oxidative damage ultimately leading to neurodegenerative disorders [5]. Exogenous H_2O_2 may also produce ROS beyond the capacity of cellular defence system leading to apoptotic cell death [6]. So far, there are no effective drugs in conventional system which can effectively combat or check the onset or progression of neurodegenerative diseases [7]. But, Ayurveda has used many herbs for centuries to successfully treat and prevent neurodegenerative diseases [8]. There is very few scientific studies available showing neuroprotective effect of these plants [9]. Therefore search for novel therapies with little or no side effects is increasing day by day. Medhya rasayana are Ayurvedic drugs known to improve physical and mental health and immunity of the body [10].

Agent that neutralizes free radicals explained extensively in both online literature and conference press as protective agents that protect the body from several disease causes by free radicals [11]. These substances are molecules exogenous or endogenous sources that inhibit pathogenesis of cumulative free radical and its related disorders on neuronal cells [12]. The imbalance of antioxidant compound and free radical in neurodegenerative diseases is predisposed by several factors which include advance in brain age, genetic, inherent, mitochondrial diseases, increased ROS production and environmental toxicants [13]. To find a lasting solution to the effect of diseases caused by ROS accumulation, stress of treatment with multiple synthetic drugs and prolong treatment period the search for antioxidants agent or antioxidants lead compounds that work as single dose or synergistically as combing therapy become necessary [14]. Therefore, the aim of this study is to review the recent study on the neuro-protective potential of antioxidants agents in experimentally induced Parkinson Disease models.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Immunocyto-fluorescence used in western blotting, primary antibodies were monoclonal anti- HSP70 (Clone BRM-22, Sigma-Aldrich) and anti-Grp 75 (Mortalin) (Abcam), and anti- α -tubulin (Clone AA13, Sigma-Aldrich). Anti-mouse IgG:HRP (Bangalore genei) and antimouse Alexa Fluor 568 (Invitrogen) were used as secondary antibodies. The 3-[4,5- dimethylthiazol-2-yl]- 2,5-diphenyl tetrazolium bromide (MTT), Quercetin and 1'-1" Diphenyl- 2'-picrylhydrazyl (DPPH) were procured from Sigma-Aldrich. The PCR reagents including dNTP Mix, Random Hexamer Primer, 100bp ladder, Reverse Transcriptase and Taq DNA Polymerase were purchased from Fermentas, Thermo Fisher Scientific. Primers for synthesis of cDNA for α -tubulin, HSP and Mortalin were prepared from Biolink, India. All other chemicals and reagents were procured in their purest form available commercially from Indian companies [15].

2.2 Preparation of CP-MEx, CP-EEx and CP-WEx

Dried whole plants of *C. pluricaulis* were procured from local Ayurvedic Merchants and got identified from The Department of Botanical and Environmental Sciences, Guru Nanak Dev University, Amritsar, India. These were then powdered and 10 g of dry rhizome powder each was suspended separately in 100 ml of methanol/ethanol/ distilled water and kept stirring for 48 hours at $30 \pm 5^\circ\text{C}$ followed by filtration under sterile conditions. The filtrates thus obtained were concentrated with a vacuum rotary evaporator (Buchi, Switzerland) at temperature of 35°C and pressures 280, 170 and 60 mbar for methanolic, ethanolic, water extracts respectively. The concentrated extracts thus obtained are air dried to make powder. These were further diluted in respective solvent to give final concentration of 50 $\mu\text{g/ml}$ each for CPMEx, CP-EEx and CP-WEx [16].

2.3 Effect of Curcumin on Rotenone Toxicity, the LC_{50}

To test effect of curcumin on rotenone toxicity, the LC_{50} (the concentration causing 80% cell death) of rotenone was used. Pretreatment cells with curcumin at 0, 0.1, 0.5, 1 and 5 μM concentrations for 1 h, and then exposed them to LC_{80} of rotenone for 24 h was done. A pan caspase inhibitor, z-VAD (100 μM) as a positive control for curcumin protective experiments was used. Trypan blue exclusion was used to measure cell death by counting the number of dead (blue) and live cells in the cultures after rotenone exposure and/or curcumin treatment.

In Experiment I, cells were incubated with different concentrations of rotenone (2.5, 5, 50, 100, and 200 nM) for 24 h, and MTT assay was performed to detect IC_{50} value of rotenone. In Experiment II, cells were pretreated with different concentrations of hesperidin (2.5, 5, 10, 20, and 40 μg) for 4 h and then incubated with rotenone (effective dose) for 24 h. The effective dose of hesperidin was used to identify potential neuroprotective effects against rotenone toxicity [17].

2.4 Cell Culture and Treatments

Human Neuroblastoma cell line was obtained from NCCS, Pune, India and maintained on Dulbecco's Modified Eagle's Medium (DMEM) supplemented with streptomycin (100 U/ml),

gentamycin (100 $\mu\text{g/ml}$), 10% FCS (Life Technologies) at 37°C and humid environment containing 5% CO_2 . The H_2O_2 dose (IC_{50}) for neuroprotection studies was calculated by treating cells with H_2O_2 (7.5 μM to 1000 μM diluted in medium) at 50% confluency for 24 hours in serum free medium. To obtain the cytotoxicity profile and nontoxic dose of *C. pluricaulis* extracts were tested at higher doses from 25 to 2000 $\mu\text{g/ml}$. The Human Neuroblastoma cells were treated with CP-MEx, CP-EEx, CP-WEx and quercetin at concentration from 1.5 $\mu\text{g/ml}$ to 50 $\mu\text{g/ml}$ diluted in medium for 24 hours at 30- 40% confluency and then subjected to H_2O_2 (IC_{50} concentration i.e 250 μM) treatment for 24 hours in serum free medium. The medium of control culture without H_2O_2 and without extract was replaced with a fresh one [18].

2.5 Cell Viability Assay

MTT was used to assess cell integrity and potential cytotoxicity of the plant extract by monitoring the uptake of the vital mitochondrial dye, 3-[4,5-dimethylthiazol-2-yl]- 2,5-diphenyl tetrazolium bromide (MTT) by cell mitochondria [19].

2.6 Chemical Standardization of CP-MEX and Nature of Active Components

CP-MEx was subjected to preliminary phytochemical screening for alkaloids, amino acids, anthroquinones, flavonoids, phytosterols, saponins, steroids, tannins, triterpenoids and reducing sugars following the methods of Harborne. It was further subjected to thin-layer chromatography (TLC) using chloroform: methanol (19:1) as solvent front. TLC plate was subjected to iodine vapours for observation [20].

2.7 Estimation of Activities of Antioxidant Enzymes and Levels of Antioxidants

2.7.1 Catalase

Catalase activity was measured according to the method of Aebi. The rate of decomposition of H_2O_2 by catalase was measured spectrophotometrically at 240 nm. The reaction mixture (1 ml) contained 0.8 ml phosphate buffer (0.2 M, pH 7.0) containing 12 mM H_2O_2 as substrate, 100 μl enzyme sample and distilled water to make up the volume. The decrease in absorbance/minute at 240 nm was recorded against H_2O_2 -phosphate buffer as blank [21].

2.7.2 Superoxide dismutase (SOD)

Superoxide dismutase was estimated according to the method of Kono. This method is based on the principle of the inhibitory effects of SOD on the reduction of nitroblue tetrazolium (NBT) dye by superoxide radicals, which are generated by the autoxidation of hydroxylamine hydrochloride. The reduction of NBT was followed by an absorbance increase at 540 nm. In the test cuvette, the reaction mixture contained the following: 1.3 ml sodium carbonate buffer (50 mM), pH 10.0, 500 μ l NBT (96 μ M) and 100 μ l triton X-100 (0.6%). The reaction was initiated by addition of 100 μ l of hydroxylamine hydrochloride (20 mM), pH 6.0. After 2 min, 50 μ l enzyme samples were added and the percentage inhibition in the rate of NBT reduction was recorded [22].

2.7.3 Reduced glutathione (GSH) and glutathione peroxidase (GPx)

Total glutathione was measured as described by Sedlak and Lindsay. In brief, 100 μ l samples were mixed with 4.4 ml of 10 mM EDTA and 500 μ l of trichloroacetic acid (50% w/v). Contents were centrifuged at 3000 \times g for 15 min. The supernatant so obtained was mixed with 50 μ l of 5,5-dithiobis(2-nitrobenzoic acid) (10 mM) and absorbance was measured at 540 nm. Standard curve was prepared using pure glutathione. Glutathione peroxidase activity was measured indirectly by monitoring the oxidation of NADPH. The reaction mixture (1 ml) containing 100 mM GSH, 15nM NADPH and 15nM H₂O₂ in potassium phosphate buffer (50 mM, pH 7.5) was mixed with sample (50 μ l) and the change in absorbance was monitored at 340 nm. Glutathione peroxidase activity is defined as 1 μ mol of NADPH oxidized per min at pH 7.5 at 25°C using purified GPx enzyme [23].

2.7.4 Lipid peroxidation (LPx)

Method of Beuge and Aust was followed to measure the lipid peroxidation level. Lipid peroxides are unstable and decompose to form a complex series of compounds including reactive carbonyl compounds. Polyunsaturated fatty acid peroxides generate melonaldehyde (MDA) upon decomposition. MDA forms a 1:2 adduct with thiobarbituric acid (TBA) that gives a red colored product having absorption maximum at 532 nm. 100 μ l sample was incubated with 100 μ l each of FeSO₄ (1 mM), ascorbic acid (1.5 mM) and Tris- HCl Buffer (150 mM, pH 7.1) in a

final volume made of 1 ml, made up by DDW, for 15 minutes at 37°C. The reaction was stopped by adding 1 ml of trichloroacetic acid (10% w/v). This was followed by addition of 2 ml thiobarbituric acid (0.375% w/v). After keeping in boiling water-bath for 15 min, contents were cooled off and then centrifuged. The absorbance of supernatant so obtained was measured at 532 nm [24].

2.7.5 Immunocytochemistry

All cells, control and treated, were rinsed three times with ice cold 0.1M PBS and fixed with Paraformaldehyde (4%) for 30 minutes. Permeabilization was carried out with 0.32% PBST for 15 minutes. Coverslips were washed thrice with 0.1%PBST followed by blocking with 5% NGS (Normal Goat Serum) prepared in 0.1% PBST for 1 hour at room temperature. Cells were incubated with mouse anti-NF-200, mouse anti-HSP70 and mouse anti-Mortalin and, diluted in 0.1% PBST, for 24h at 4°C in humid chamber. Coverslips were then washed with 0.1% PBST thrice. Secondary antibody (anti-mouse Alexa Fluor 488, anti-mouse Alexa Fluor 568 and anti-rabbit Alexa Fluor 488) was applied diluted (1:200) in 0.32% PBST for 2h at room temperature. Coverslips were washed three times with 0.1% PBST and final washing was given with 0.1 M PBS. These were on the slides with anti-fading mounting media (Sigma) and were observed under fluorescent microscope Nikon E600. Images were captured using Cool Snap CCD camera and the pictures were analyzed using ImageJ 1.44p, NIH, USA [25].

2.7.6 Reverse transcription-PCR

Human Neuroblastoma cell line cells from 25 cm² culture flask were homogenized in TRI Reagent (Sigma). Total RNA was extracted and reverse transcriptized according to the manufacturer's instruction [26].

3. RESULTS AND DISCUSSION

3.1 Some Secondary Metabolite with Antioxidant Effect Use PD Study

Curcumin, is a bioactive compound present abundantly in *Curcuma longa* leaf and rhizome (Fig. 1A and B) is commonly used as a spice in curries, food additive and also, as a dietary pigment. It has also been used to treat various illnesses in the Indian subcontinent from the ancient times [27]. Currently, *in vivo* study on rat

model revealed its abilities to protect the brain tissues against MPTP-induced [28]. In vitro study on SH-SY5Y cells also shows this compound to be effective in protecting neuronal cells from damages induced by rotenone. Administration of 1 mM curcumin protect the cells against induced cell death by rotenone in a dose-dependent manner by protecting the free radical formation, mitochondrial destruction and caspase-9 and caspase-3 activation [29].

Fig. 2A and B *Convolvulus pluricaulis*, is among the frequently prescribed rasayanas for improvement of learning and memory and also treatment of mental health problem. CP-MEX, CP-EEX and CP-WEX have been reported to protect the IMR32 neuroblastoma cell from

induce toxic effect of H_2O_2 at dose dependent manner (Kshitija et al., 2012). The authors shows that CP-MEX 25 μM yield better result compare to CP-EEX and CP-WEX.

Hesperidin (Fig. 1), a naturally occurring flavanone major flavanone that exist in citrus and other plants and can isolated in large amount from peels of *Citrus aurantium* (bitter orange) [30]. It has been reported that, this plant exert wide range of Pharmacological effects such as antioxidant, anti-inflammatory, anti-hypercholesterolemic and anticarcinogenic [31]. Antioxidant activity of Hesperidin have been tested and reported to protect SK-N-SH human neuroblastoma cells against cytotoxicity induce by rotenone at the dose of 20 μg [32].

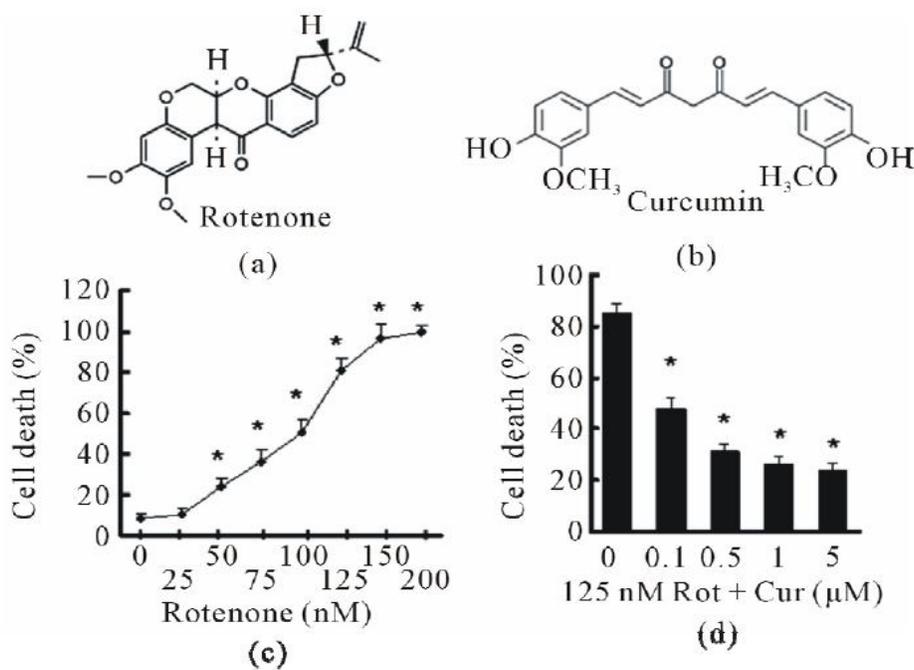


Fig. 1A. Curcumin protect *in vitro* cell death induced by rotenone exposure. (a) Biochemical form of rotenone; (b) SH-SY5Y cells death in dose dependent manner after exposure to rotenone. SH-SY5Y cells were treated with Rotenone for 24 h in 2% FBS OPTI-1 media. Cell death was measured with Trypan blue assay. Values are expressed as means \pm SEM. Ratio of cell death in multiple groups were significantly higher than that of control group with no Rotenone exposure ($*p < 0.05$); (c) Chemical structure of curcumin; (d) SH-SY5Y cells were pre-treated with curcumin at the indicated concentrations for 1 h, then either left untreated (control) or treated with 125 nM rotenone for 24 h. Cell death was measured with Trypan blue exclusion assay. Curcumin treated cells showed significant lower cell death rate when compared to those cells with rotenone exposure but no curcumin treatment ($*p < 0.05$)

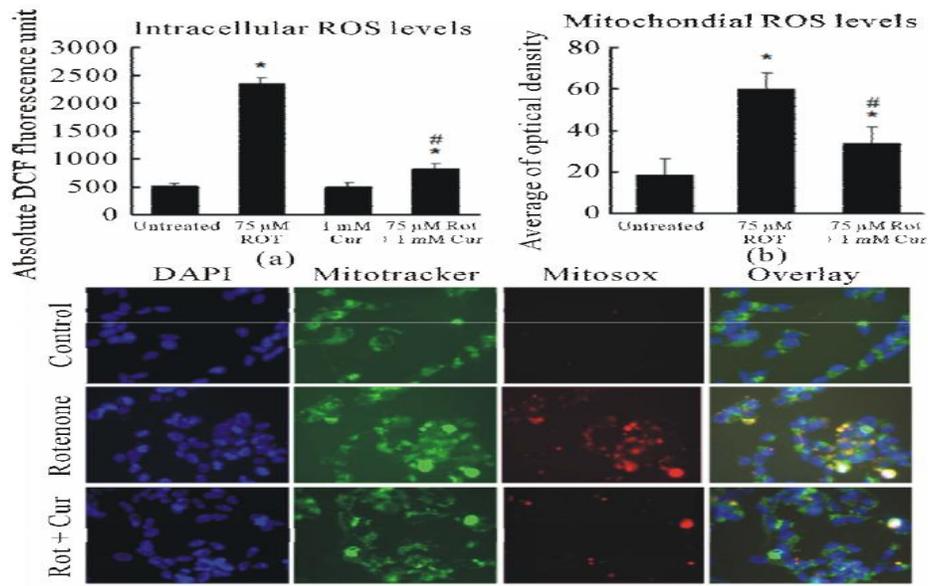


Fig. 1B. Curcumin reduced intracellular and mitochondrial ROS levels. (a) SH- SY5Y cells quantification with DCF fluorescence. Curcumin significantly reduced rotenone-induced intracellular ROS increase; (b) and (c) Curcumin significantly reduced rotenone-induced ROS in mitochondria. Digital photomicrograph under fluorescent illumination showing mitochondrial superoxide signal is shown in (c) and the average optical density of MitoSOX is summarized in (b). The ROS level is indicated by the average value of cellular MitoSOX optical density in 10 random fields in each condition. Data are shown as the mean \pm SEM for three separate experiments. (* $p < 0.05$, ROS level was significantly different when compared with the cells with no rotenone and no curcumin treatment. # $p < 0.05$, ROS level was significantly different when compared to cells with rotenone exposure)

Quercetin (Fig. 1B), is one of the unique antioxidant that need to be considered due to its efficiency as observed in several researches that involved induced neuronal damages in both *in vitro* and *in vivo* models. Recently, studies on neuroprotective potential of this compound on PC12 cells and in a zebrafish model were reported [33]. This flavonoid at 25-100 μ M protect PC12 cell from induced 6-OHDA cell apoptosis. Pretreatment of zebrafish with 6 and 12 μ M quercetin significantly prevent 6-OHDA induced DAergic neuron death resulting to its efficacy as drug used in the management of PD [34]. Additionally, recent uses of quercetin in inducing hypoxia on experimentally induced ischemic disease protect the neuron by neutralizing the free radicals, disappearance of abnormal behavior, decreases in the quantity of infarct, reduction in neuronal tissue swelling, and cellular injury in both *in vivo* and *in vitro*

models based on its free radical inhibitory effect [35].

Coenzyme A key component of the electron transport chain, Q10 (CoQ10 Fig. 1C) plays an important role in the production of ATP. The therapeutic effect of CoQ10 and decreased CoQ10 in the MPTP model of Parkinson's mice was studied in a recent review [36]. CoQ10 given at 1600 mg/kg/day resulted in substantial defense against MPTP-induced loss of DA (10 mg/kg, i.p., per 2 h x 3 doses), followed by a marked increase in plasma CoQ10.0 concentrations. CoQ10 therapy at 1600 mg/kg/day in the diet also demonstrated excellent therapeutic efficacy in a chronic MPTP model (40 mg/kg per day for 1 month) by greatly inhibiting striatal DA degradation, loss of dopaminergic neurons in the SNpc and the development of SNCA aggregates in the dopaminergic neurons of mice.

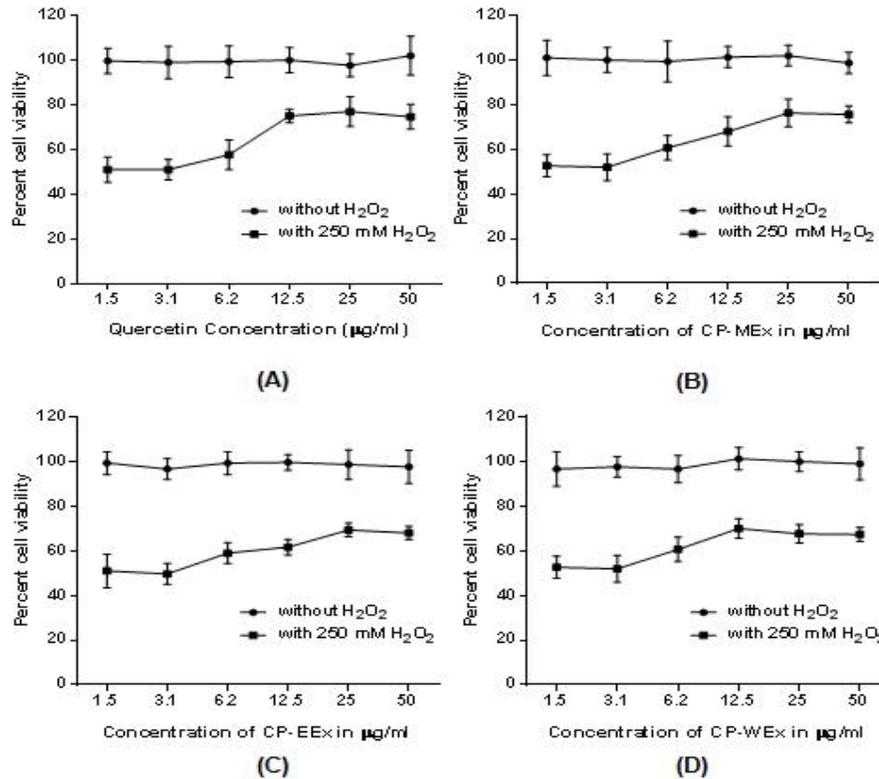


Fig. 2A. The effects of quercetin on IMR32 neuroblastoma cell viability in the absence or presence of H₂O₂. (A) Incubation of quercetin with IMR32 cells for 24 h protected against the cytotoxicity elicited by H₂O₂ in a concentration-dependent manner. No cytotoxicity was observed in the cells after incubation with quercetin alone for 24 h in the concentration range 1.5 to 50 µg/ml. (B) The effects of CP-MEX on IMR32 cell viability in the absence or presence of H₂O₂. Incubation of the extract with HepG2 cells for 24 h protected against the cytotoxicity elicited by H₂O₂ in a concentration-dependent manner. No cytotoxicity was observed in the cells after incubation with the extract alone for 24 h in the concentration range 1.5 to 50 µg/ml. (C) The effects of CP-EEx on IMR32 cell viability in the absence or presence of H₂O₂. Incubation of the extract with HepG2 cells for 24 h protected against the cytotoxicity elicited by H₂O₂ in a concentration-dependent manner. No cytotoxicity was observed in the cells after incubation with the extract alone for 24 h in the concentration range 1.5 to 50 µg/ml. (D) The effects of CP-WEx on IMR32 cell viability in the absence or presence of H₂O₂. Incubation of the extract with HepG2 cells for 24 h protected against the cytotoxicity elicited by H₂O₂ in a concentration dependent manner. No cytotoxicity was observed in the cells after incubation with the extract alone for 24 h in the concentration range 1.5 to 50 µg/ml

The combination therapy of CoQ10 and creatine (Fig. 1D) was studied in a PD mouse model of MPTP [37]. The researchers show that dietary supplementation with these combination agents in mice with 2% creatine and 1% CoQ10 for one week prior to treatment with MPTP (40 mg/kg body weight daily for 28 days through osmotic pumps) induced additive neuroprotective effects against dopamine deficiency in the striatum and loss of tyrosine hydroxylase (TH) neurons in the SNpc, reduced lipid peroxylase neurons in the SNpc.

Resveratrol (Fig. 1E) is a common antioxidant with extensive therapeutic effects, including the regulating roles of anti-inflammatory, anti-mutation, anti-tumor and blood fat [38]. DAergic neurons in PD rats were preserved by oral therapy with resveratrol or resveratrol liposomes (20 mg/kg per day for 14 days). Complete ROS levels decreased drastically and the overall antioxidant potential of the nigral tissues increased significantly. The researchers concluded that resveratrol's radical scavenging ability and antioxidant properties may lead to its

effective neuroprotection in PD. In addition, a single dose of up to 5 g of resveratrol, leading to its effective use for neuroprotection, did not cause significant side effects in healthy participants in clinical trials [39].

A polyphenolic compound present in many ingredients, including peanut shells, parsley, artichoke leaves, celery, peppers, olive oil, rosemary, lemons, sage, peppermint, and thyme, is luteolin (Fig. 2A). Luteolin (5, 10, and 20 μM) greatly attenuated the rise in output of ROS and prevented reductions in mitochondrial, CAT, and GSH function in primary neurons insulated by ROS. The study showed that luteolin neuroprotection in ROS-insulted primary neurons could occur through a rebalancing of the status of pro-oxidant-antioxidant [40].

Brassinosteroids (BRs) (Fig. 2) are strongly oxygenated steroids, including *Vicia faba* seeds and spores, isolated from many vegetables [41]. Two natural BRs and five synthetic analogs were synthesized and tested for their neuroprotective activities against neuronal PC12 cells induced by MPP+ in a recent report. The researchers proposed that neuronal PC12 cells were shielded against MPP+ toxicity by selected BRs and analogs and exerted neuroprotective effects resulting from their antioxidative properties. In addition, they stated that a significant antioxidant role in neuroprotective action is played by the steroid B-ring and lateral chain and further study should be carried out on in vivo animal PD models [42].

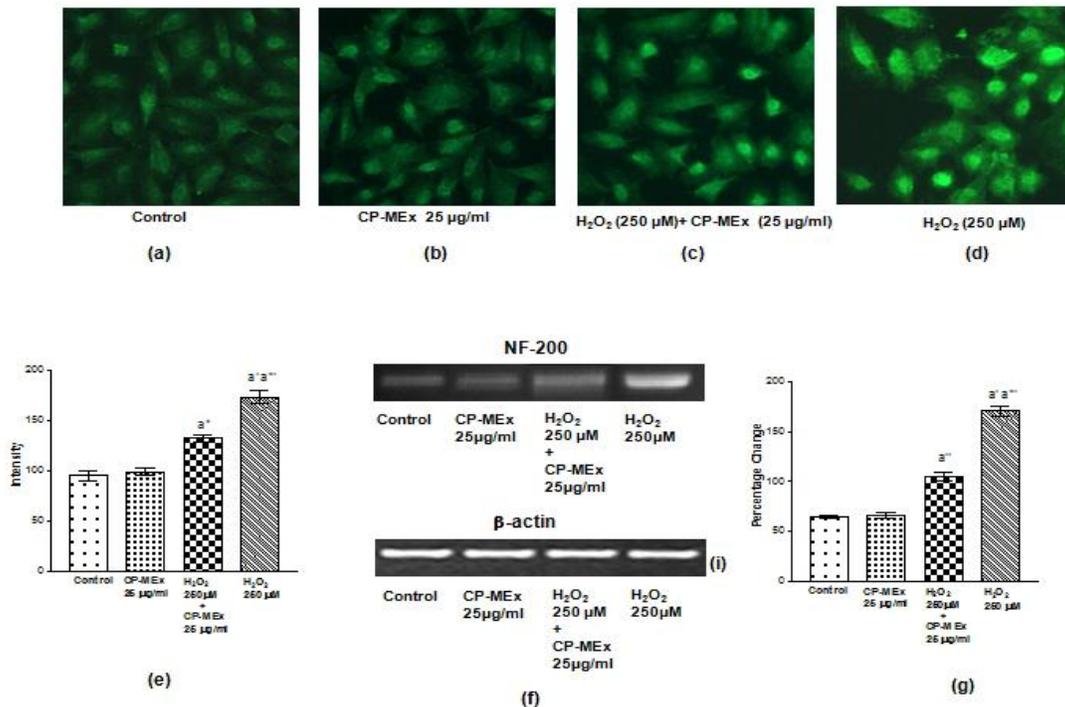


Fig. 2B. Localization of NF-200 in IMR 32 neuroblastoma cells (a), untreated control (b), CP-MEx treated (c) CP-MEx+ H_2O_2 treated (d) H_2O_2 treated. Cells grown on coverslips ($n = 5$) for 4 days were fixed and stained for NF-200 (Alexa Fluor 488) immunoreactivity. (e) Relative intensity measurement of NF-200 immunofluorescence performed by ImageJ 1.44p. (f) Representative reverse transcription-polymerase chain reaction (RT-PCR) showing NF-200 and β -actin expression in untreated control, CPMEx treated, CP-MEx+ H_2O_2 treated, H_2O_2 treated IMR 32 neuroblastoma cells. (g) Relative optical density measurement of mean values of NF-200 expression in RT-PCR for each group expressed as percentage of β -actin. The values having $P < .05$ are considered significant. a^* , there is statistically significant change in H_2O_2 treated cultures with respect to the control cultures; a'' , statistical different in CP-MEx + H_2O_2 treated cultures compared to the CP-MEx treated cultures; a''' , statistically significant change in H_2O_2 treated cultures with respect to the CP-MEx + H_2O_2 treated cultures

The compound idebenone (Fig. 2B) has been tested to increase the lifetime and enhance motor control in HtrA2 knockout mice [43]. Feeding idebenone (500 mg/kg body weight/day orally) to HtrA2 knockout mice extended lifetime and postponed motor phenotype degradation. Experiments carried out in mice's cell culture and brain tissue showed that idebenone works by controlling the combined stress reaction downwards. The researchers stated that in HtrA2 knockout mice, idebenone enhances disease symptoms, suggesting that antioxidants in the striata of these mice could postpone neuronal degeneration. This discovery indicates idebenone's promise for the treatment of neurodegenerative disorders, including PD [44].

3 alpha-acetoxyeudesma-1,4(15),11(13)-trien-12,6a-olide (AETO, Fig. 2C) is a secondary metabolite isolated leaf of *Laurus nobilis* L. AETO (0.4, 2, and 10 μ M) reduces the active form of caspase-3 and p53 levels, followed by dose-dependent rises in Bcl-2 levels. Flow cytometry and Western blot analysis revealed that AETO greatly inhibits apoptosis caused by DA and suppresses the function of intracellular tyrosinase, the generation of ROS, quinoprotein, and the development of SNCA. These findings suggest that AETO prevents apoptosis caused by DA, which is closely linked to the suppression of activity of intracellular tyrosinase and the production of alpha-syn, ROS, and quinoprotein in the cells of SH-SY5Y [45].

S-allylcysteine (SAC, Fig. 2D) is a sulphur-containing compound extracted from garlic with different biological processes. The most abundant organosulfur compound in aged garlic extracts has been tested in the striatum of C57BL/6J mice for its defensive activities against oxidative stress caused by MPP+. SAC pretreatment (125 mg/kg i.p.) every day for 17 days, accompanied by MPP+ administration (0.72 mg/kg i.c.v.), greatly decreases the loss of striatal DA levels caused by MPP+ (32 percent). SAC dramatically prevents (100% protection) lipid peroxidation and decreases the development of superoxide radicals shown by up-regulation of the activity of Cu-Zn-superoxide dismutase in mice induced by MPP+. Behavioral analyses have demonstrated that SAC increases locomotion deficiency caused by MPP+ (35 percent). These results indicate that SAC attenuates the neurotoxicity caused by MPP+ in the striatum of mice through its strong antioxidant effect induced by MPP+ toward oxidative stress [46].

Organoselenides ebselen and diphenyl diselenide (Fig. 2 E&F) was studied for neuroprotective effects on SH-SY5Y cell-line exposed to 6-OHDA [47]. Screening of many organoselenides to explore their antioxidant ability at 3 μ M concentrations revealed neuroprotective potential in differentiated SH-SY5Y human neuroblastoma cells with 6-OHDA challenge. Researchers suggested that these chosen organoselenium molecules could be further evolved as possible pharmacological and therapeutic drugs for the treatment of PD [48].

Deprenyl is a selective MAO-B inhibitor (Fig. 3A) used in hospitals to delay the development of symptoms in PD patients. In a recent report, up-regulated NQO1 expression and behavior of deprenyl (10, 20, 50 and 100 μ M) attenuated the rise in quinoprotein levels in MPP+-treated PC12 cells and defended against oxidative damage by the Nof2/ARE pathway [49]. In addition, its effect on NQO1 upregulation has been substantially attenuated in the Nof2 siRNA transfected cells. Regulation of Nof2/ARE signaling by deprenyl in PC12 cells is independent of inhibition of MAO-B [50].

SCM198 is a chemically synthesized compound which exhibits cardioprotective effects in models for myocardial infarct as well as neuroprotective impacts in mid-cerebra artery occluded rats (4-guanidino-n-butyl syringate Fig. 3B) [51]. SCM198 (0.1, 1 and 10 mM) pretreatment dramatically increased SOD activity, enhanced intracellular ROS generation, prevented dissipation of mitochondrial membrane potential, decreased apoptotic cell death, down-regulated Bax, and up-regulated Bcl-2 mRNA and protein levels relative to 6-OHDA impaired cells [52]. Intragastric administration of SCM198 at 18 or 60 mg/kg/day for four weeks greatly increased apomorphine-induced contralateral rotations in 6-OHDA-induced rats. The study suggested that the underlying mechanisms of SCM198 for providing powerful neuroprotective effects against in vivo and in vitro 6-OHDA-induced toxicity may be inhibiting oxidative stress and apoptosis [53,54].

The chemical compound of phenothiazine (Fig. 3C) is used with various anti-psychotic and antihistamine medications. 500 nM phenothiazine was confirmed to have good cell neuroprotective effects and improved results in conduct research. Thus in vivo rescue of DAergic toxicity to Nano-molar concentrations, based on strong antioxidant properties, Chain Breakers like phenothiazine can be produced as therapeutics

for PD [55]. While in vitro and in vivo doses in PD models are far below the toxic threshold, side effects, including acathisia and tardive dyskinesia, hyperprolactinemia, malignant neuroleptic syndrome, and significant growth in weight, should be treated [56].

The therapeutic potential was tested by dl-3n-butylphthalide (NBP, Fig. 3D) in the treatment of clinically ill patients. MPP+ cytotoxicity is minimized with NBP (0.1, 1.0 and 10 μ M) to inhibit the mitochondrial permeability transition, to lower the rush and improve the cellular GSH content of MPP+ treated PC12 cells. In addition, NBP also decreases the concentration of the Lewy corps, SNCA [57].

SUN N8075 (Fig. 3E), another novel antioxidant, currently undergoes clinical trials on stroke patients [58]. Previous studies have found a potent neuroprotective effect of this compound in the mid-cerebral occlusion in vivo model. This research shows that part of the underlying neuroprotective function may provide oxidative stress defense [59]. The same scientist studied the in vitro neurological effects of SUNN8075 in human neuroblastoma SH-SY5Y cells for H₂O₂-induced ROS development and 6-OHDA cell death.

Another novel antioxidant, SUN N8075 (Fig. 3E), is currently in clinical trials for patients suffering from stroke [60]. Previous studies have revealed a potent neuroprotective activity of this agent in an in vivo transient middle cerebral artery occlusion model. This study suggested that the underlying neuroprotective mechanism might partly involve protection against oxidative stress [61]. The same scientist investigated the neuroprotective effects of SUNN8075 in vitro on both H₂O₂-induced ROS production and 6-OHDA-induced cell death in human neuroblastoma SH-SY5Y cells. The neuroprotective effects were also tested in an in vivo mouse model of PD for MPTP-induced neurotoxicity. SUNN8075 micromolar therapy decreased dramatically ROS production caused by H₂O₂ and shielded from cell death by 6-OHDA. Intraperitoneal SUNN8075 injections (30 mg/kg twice over five hours interval) blocked in vivo forebrain mouse lipid peroxidation. Subsequently, the preventive effects of SUN N8075 (10 and 30 mg/kg i.p. double) against the TH positively mediated decreasing in meaningful nigra is significant. The researchers concluded that SUN N8075's shielding effects were at least in part by an anti-oxidation process in experimental PD models [62] Fig. 3.

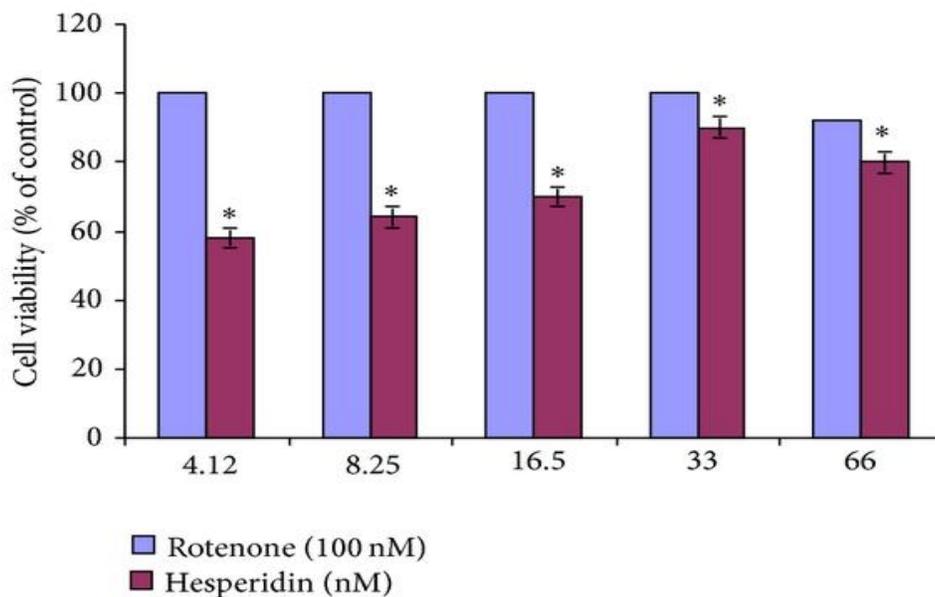


Fig. 3. Effect of hesperidin on rotenone-induced reduction in cell proliferation in SK-N-SH neuroblastoma cells. Treatment with hesperidin alone (blue column) (2.5-40 μ g) did not affect cell proliferation. The same compound (2.5-20 μ g) pretreatment dose dependently enhanced cell proliferation against rotenone toxicity

The pharmacopoeitic drug and dietary supplement N-acetyl-cysteine (NAC, Fig. 4A) was mostly used as mucolytic agent for treatment and overdose of paracetamol. Recently, NAC supplements in potable water (40 mM) have been speculated to shield against SNCA [63]. Oxidative stress can increase DA-dependent aggregation of toxic SNCA types [64]. Transgenic mouse with wild-type SNCA drink water introduced to NAC between 6 weeks and 1 year. Consequently, within five to seven weeks of therapy, the NAC increased GSH's SN amounts. The loss of DAergic terminals in one year with SNCA over-expression was stated to be substantially attenuated by the addition of NAC by researchers [65]. In the brains of PDGFB-SNCA transgenic mice compare to controls NAC there is substantially decreased in the amount of Human SNCA [66]. The scientist indicated that growing oxidative stress in the DAergic SN neurons due to early GSH defects in the SN may

result in better SNCA toxicity, indicating techniques for GSH raise or blocking NAC oxidative strain can help avoid SNCA from occurring in the PD [67].

Oleanolic acid, because of its antiinflammatory function, is a triterpenoid used in Asian medicine for decades. Any workers studied CDDO-methyl amide, a Synthetic Triterpenoid (Fig. 3B), at least 200.000 times more strong than its naturally occurring remote parent. CDDO-MA (Fig. 3B) was researched. It is called CDDO-MA. NQO-1 caused oleanolic acid [68]. The deeply profound neuroprotective benefits of a CDDO-MA diet at 800 mg/kg of total diet against MP and neurotoxicity have been reported. The neuroprotective effects have been shown to be caused by their antioxidant influence and by activation of pathways, which are known to be regulated through Nrf2/ANI, such as the synthesis of GSH [69] Fig. 4.

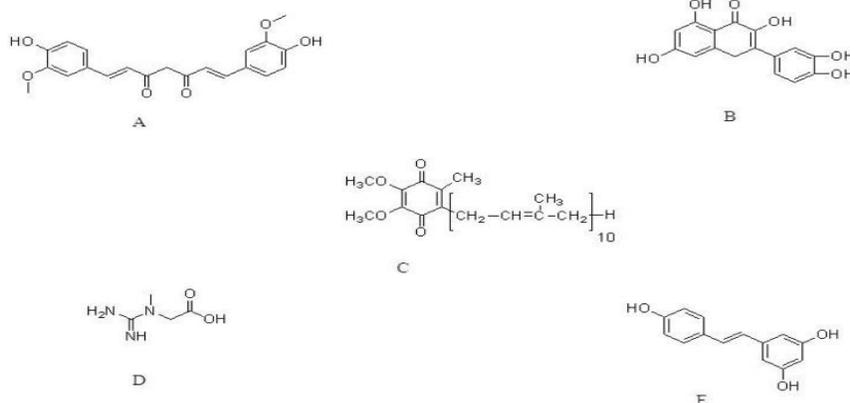


Fig. 4. Curcumin structure (A); Quercetin (B); Coenzyme Q10 (C); Creatine (D) and Resveratrol (E)

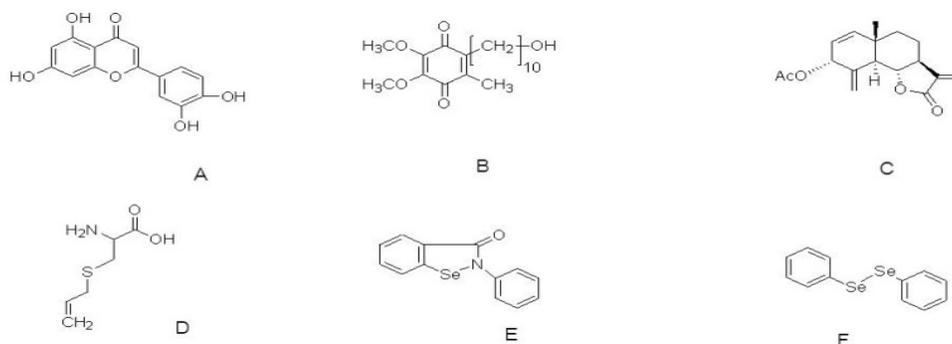


Fig. 5. Luteolin (A); Idebenone (B); 3α-acetoxyeudesma-1,4(15),11(13)-trien-12,6a-olide (C); S-Allylcysteine (D); Ebselen (E) and Diphenyl diselenide (F)

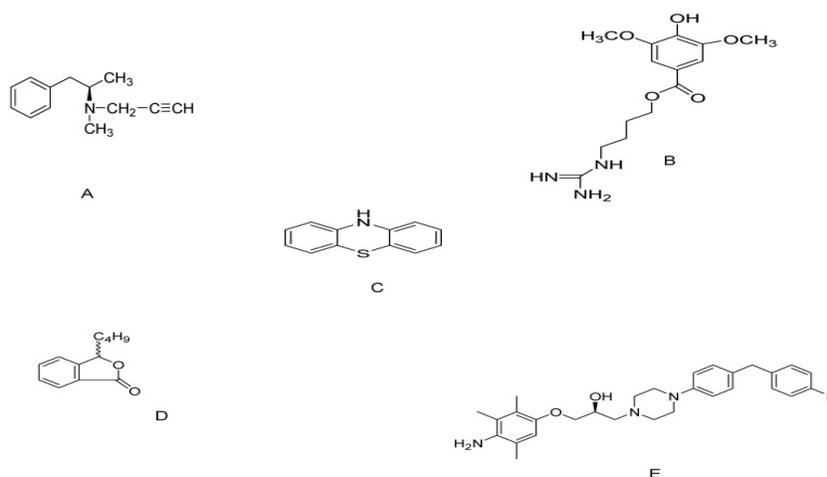


Fig. 6. Deprenyl (A); SCM198 (B); Phenothiazine (C); dl-3n-Butylphthalide (D) and SUN N8075 (E)

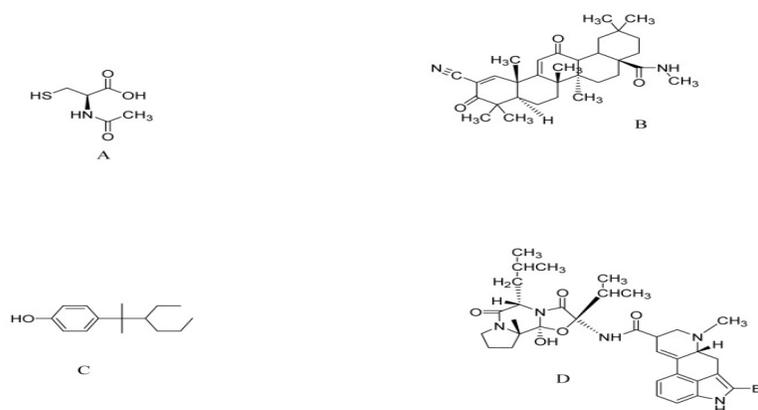


Fig. 7. N-acetyl-l-cysteine (A); CDDO-methyl amide (B); NP7 (C); Bromocriptine (D)

NP7 (Fig. 4C) is a modern marine antioxidant originating from *Streptomyces* spp., with a chemical composition that is distinct from that of classic phytochemicals. Study demonstrated the beneficial impact of nP7 in neuronal and glial midbrain cultures of null mouse parkin (PK-KO) on cell death due to oxidative stress [70]. Application of H₂O₂ and necrosis on neuronal and Glial midbrain crops of wild type and PK-KO mouse (NP7 5-10 μM) were prevented. The H₂O₂-induced dropout of DA neurons was observed in the NP7. NP7 was deleted. Result has shown that NP7 can be a potential oxidative stress defense agent for PD [71].

DA agonist (Fig. 4D) Bromocriptine has since 1974 been commonly used in PD clinics for delaying and minimizing deleterious motor fluctuations in long-term l-dopy therapy [72]. The

latest findings show that bromocriptine is a free radical spray which inhibits radical free forming by sprouting hydroxyl and superoxide radicals in vitro. Based on those properties, bromocriptine's cytoprotective function for oxidative damage in PC12 cells treated with H₂O₂ has been recorded. The expression and activity of the antioxidant enzyme NQO1, up-regulated with bromocriptine (5 μM) decreased the increased amount of protein-bound quinone in PC 12 cells treated with H₂O₂. PC12 cells have been secured from oxidative damage and Nrf2 expression and nuclear translocation has improved. bromocriptine's [73].

The result in PD models based on their antioxidant properties of synthetic compounds, such as selenium [74], R-alpha-lipoic acid [75], rosmanic acid [76], eugenol [77], isoborneol [78],

melatonin [79], metalsystem compounds and ion-metal chelator [80] has also been reported. Synthetic compounds such as **Luteolin** (Fig 5A-F), Deprenyl (Fig6 A-E) and N-acetyl-l-cysteine (Fig 7A-D) were also evaluated and show positive result on currying neurodegenerative diseases including PD.

4. CONCLUSION

Despite the existence of various types of drugs, like l-dopa, DA agonists, monoamin oxidase inhibitors, catechol-O-methyltransferase inhibitors and anticholinergic agents, a remedy remains elusive. Although the precise essence of the neurodegeneration pathway in PD is not well known, oxidative stress is one of the main risk factors for triggering and/or fostering DA neuron degeneration. The rate of progression of this disease may either be stopped or decreased by antioxidant therapy. Antioxidant compounds have been shown to protect neuronal cells by breaking free radicals or by activating antioxidant pathways. In the last five years, various experiments on in vitro and in vivo animals have been based on oxidative stress and ROS controlled processes such as ethnic scavenging, chelating metals and/or the activation of antioxidant enzymes. Nevertheless, experimental evidence has shown that oxidative stress is not the only destructive force involved in the death of DAergic neurons, and other modulated processes can also play key roles in the neuroprotection of progressive PD on signal transduction pathways and on gene expression. The compounds mentioned in this study can also be used to control the antioxidant processes along these pathways, which may be synergistic for beneficial effects in PD. Moreover, combined treatment with antioxidants and current medications may also support and improve the effectiveness of traditional PD therapy. A number of free radicals are generated and antioxidants are diverse in their capacity to quench these numerous free radicals. Therefore the supplementation of several antioxidants with the use of a cocktail of agents will yield improved effects, each directly aimed at one part of the degenerative process during its appropriate dosage and timing. However it is also important to analyze the vital factors, including ideal concentrations, which types of biological action are required and the blood brain barrier of these agents to exert possible therapeutic benefits. To validate these results for beneficial effects in treating PD, it is desperately important to thoroughly understand ROS' molecular pathways

and wider trials, epidemiologic as well as spontaneous clinical studies in humans, as well as animal studies.

COMPETING INTERESTS

Authors have declared there are no competing interests.

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