

UPDATE ON PESTICIDES EXPOSURE AND PARKINSON'S DISEASE. A REVIEW

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ABSTRACT

Parkinson's disease (PD) is one of the common neurodegenerative disability characterized by dopaminergic neuron loss in the substantia nigra. Number of genetic and environmental factors have been associated in the pathogenesis of PD. Single risk factors related to PD are likely to put forth relatively minor effects, whereas their mixed interaction may prove to be sufficient to cause PD. In the present review we summarize current knowledge from *in-vitro* cellular association studies regarding the interaction between expression of different proteins and different pesticides exposure in the risk of PD along with the reported neuroprotective agents considered for clinical trial to cure PD. A number of intra-cellular studies have investigated joint effects between manipulation of proteins and pesticides on PD risk. These studies have provided evidence that perturbation on the expression of proteins either in metabolism, elimination and transport of pesticides or in the extent of mitochondrial dysfunction, oxidative stress and neuronal loss *in-vitro* as well as *in-vivo* leads to PD. These findings confirm the importance of considering pesticide-protein interactions in future studies in order to gain a better understanding of the pathogenic mechanisms of PD.

KEYWORDS: Parkinson's Disease, Proteins, α -Synuclein, Cellular Interaction, Pesticides, *In-Vitro*, Risk, Toxins.

INTRODUCTION

Parkinson's disease (PD) is characterized by loss of dopamine (DA) secreting neurons in the substantia nigra pars compacta (SNpc) and DA levels in the corpus striatum of the nigrostriatal DA pathway in the brain.^[1] This loss of DA causes a deregulation in the basal ganglia pathways that leads to the manifestation of motor symptoms like resting tremor, bradykinesia, postural instability and rigidity as well as non-motor symptoms such as sleeping trouble, depression, and cognitive insufficiency.^[2] A presynaptic neuronal protein i.e. α -Synuclein is found to be linked genetically and neuropathologically to PD. α -Synuclein may contribute to the pathogenesis of PD in number of ways, but it is generally thought that its anomalous soluble oligomeric conformations (called protofibrils) are the toxic species that arbitrary disrupt the cellular balance and neuronal death, through effects on different intracellular targets, including synaptic function. In addition, secreted α -synuclein may exert deleterious effects on nearby cells, including seeding of accumulation, thus may contributing to disease propagation.^[3] The precise etiology of PD still remains mysterious and the exact mechanisms that cause PD remain to be the area of research.^[4,5]

At the cellular and sub-cellular level, PD is linked with oxidative stress via excess production of reactive oxygen species (ROS), alterations in the metabolism of

catecholamine, mitochondrial electron transporter chain (METC) function along with enhancement of iron deposition in the SNpc. Aging is also believed to add the increased vulnerability of DA neurons.^[6,7] While the familial forms of PD, that have been documented, involve number of factors like mutations in a number of genes^[8,9], disfunctioning of mitochondria, inflammation of neurons and environmental factors are progressively more appreciated as key determinants of dopaminergic neuronal susceptibility in PD, and are a characteristic of both familial and sporadic forms of the disease.^[10] In both cases, oxidative stress is found to be the common principal mechanism that leads to disfunctioning of cells and, eventual cell death. Mitochondrial dysfunction and oxidative stress occur in Parkinson's disease (PD), but the molecular mechanisms controlling these events are not completely understood.^[11]

Advantages of *in-vitro* studies

The key advantage of *in-vitro* cell culture models is that, experiments can be set according to need and time-efficient manner, quick screening of toxins, gene knockdown, easy assessment of gene/protein expression, cell signaling, transfection for over-expression proteins etc.^[12] Human dopaminergic neuronal cell lines that are in the stage of post mitotic phase can be ideal candidates for a PD model. To study the PD related proteins expression, primary neuronal cultures from transgenic

mice can be voluntarily immortalized by retroviral transduction to generate cell culture models.^[13]

SH-SY5Y, MN9D, PC12, and NB41 cell lines as well as primary midbrain cultures have been documented to study the toxicological studies related with neurons and PD^[14] but protein expression can vary from cell-type to cell-type. The catecholaminergic neuroblastoma cell lines, such as SH-SY5Y, have been used to elucidate the proposed mechanisms of 6-OHDA and MPTP neurodegeneration in PD, via oxidative stress and inflammation.^[15-17] The SH-SY5Y cells as compared to other cultured brain cells are less sensitive to pesticides since they are not neuronal cells. N27 cells are an immortalized line derived from the rat mesencephalon, physiologically similar to dopaminergic neurons. MN9D cell line is a fusion of embryonic ventral mesencephalic and neuroblastoma cells. N27 cells and MN9D can express both tyrosine hydroxylase and the DA transporter, after treatment with toxic chemicals; produce measurable amounts of DA.^[18] These cells are also used to understand the mechanisms of toxic exposure and reaction of different proteins and to develop potential therapeutics to prevent DA neuronal loss in PD research^[19], such as CHO-K1 and HEK293 are non-dopaminergic cell lines which are also used for studying PD.^[20,21] A rat pheochromocytoma cell line i.e. PC12, has been extensively used for studying the function of neurotrophic factors and neuronal differentiation. PC12 is also used as a model cell to study the environmental effects, oxidative stress, and genetic manipulation on PD progression. It is documented that 6-OHDA induced PC12 cell death by oxidative stress, cell apoptosis, and necrosis in a pro-inflammatory manner.^[22,23] There are still other cells, such as peripheral T-lymphocytes, that can be used to study the inflammatory and cell apoptotic pathways during PD progression.^[24,25]

Pesticides

Pesticides are implicated as an important environmental risk factor in the onset of sporadic PD.^[26] Pesticides can be defined as any substance or mixture meant for repelling, preventing, destroying or mitigating pests. Many commonly used pesticides cause mitochondrial dysfunction and oxidative damage, similar to that observed in idiopathic PD.^[27-29]

Toxin models of Parkinson's disease

To fill major gaps in the assessing cellular and molecular causes of PD, toxin models are found to be noteworthy in the field of PD study.^[31] These models provided invaluable information about the etiology and pathogenesis of PD as well as about the underlying biochemical processes in the cells. Most commonly and widely used toxins for the study of PD include 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), rotenone, 6-OHDA and paraquat. These all have different mode of actions, causing cytotoxic injury at cellular and sub-cellular level to the dopaminergic neurons.^[32] Almost all neurotoxin

induced models affect the mitochondria, alpha synuclein protein and some targeting specific proteins and complex I and III of mitochondria.^[32]

6-Hydroxydopamine (6-OHDA)

(6-OHDA) has been used as a catecholaminergic neurotoxin for more than 30 years. It is a hydroxylated analogue of the neurotransmitter dopamine^[33] and due to this structural similarity exhibits a high affinity for catecholaminergic membrane transporters like dopamine (DAT) and norepinephrine (NET) transporters. This allows it to damage both noradrenergic and dopaminergic neurons. Once inside the cell 6-OHDA can accumulate in the cytosol, damage catecholaminergic structures by causing oxidative stress or destroy adrenergic nerve terminals.^[34-35] It inhibits mitochondrial complex I and plays a part in the production of superoxide free radicals. It easily oxidizes producing para-quinone and hydrogen peroxide and can take part in reactions involving metabolic monoamine oxidation.^[36]

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

MPTP is chemically an organic molecule that causes selective degeneration of the dopaminergic neurons of the substantia nigra in a variety of mammalian species as well as in cell lines. MPTP administration successfully reproduces most PD symptoms like bradykinesia, tremor, rigidity and postural instability in rats^[37] and the manner of degeneration that occurs after MPTP exposure in animals produces pathologic conditions similar to those seen in humans.^[38]

It is the most frequently used toxin in animal and in-vitro cell culture models of PD and has been extensively used to reveal numerous mechanisms of dopaminergic cell-death.^[39] It is structurally related to number of commonly used herbicides (e.g. paraquat) and pesticides (rotenone) that have studied and shown evidence of dopaminergic cell degeneration.^[40]

After exposure of MPP+ *in-vitro*, it's get accumulated within the mitochondria and inhibits complex I, III and IV of the electron transport chain which results into decreases of ATP production lead to fractional depolarisation of cell membrane ionic gradients.^[41] MPP+ perturbs cytosolic calcium homeostasis balance and leads to cell death due to abnormally elevated calcium concentration in the cell.^[42] Vesicular monoamine transporter (VMAT) integrates MPP+ into 'dopamine containing synaptic vesicles' and can protect cells from toxic effects of MPP+^[43] while this translocation triggers excess release of cytosolic dopamine which, after undergoing auto-oxidation causes oxidative stress via ROS production.^[44] Inhibition of MAO (monoamine oxidase) activity and a decrease in DA and its metabolites have also been observed in SH-SY5Y neuroblastoma cells exposed to MPTP.^[45]

Rotenone

Rotenone is a commonly used cytotoxic retinoid extracted from some plants of Leguminosae family like *Derris elliptica*, *Derris mallaccensis*, *Lonchocarpus urucu* and *Lonchocarpus utilis*.^[46] It is an insecticide and widely used to kill fish.^[47] Like MPTP, it is highly lipophilic and can easily cross the Blood Brain Barrier (BBB) and other biological membranes without transporter. Rotenone is found to be a good candidate marker of Complex I inhibition, ROS production, acute ATP deficiency and oxidative stress both *in vivo* and *in vitro* models. Rotenone causes oxidative damage in a time and dose dependent manner with increased protein oxidation. Oxidative protein loss and DA loss is reported after exposure to rotenone. Chronic rotenone toxicity causes a delayed depletion of glutathione accompanied by oxidative damage to proteins and DNA.^[48,49]

It is also reported that after exposure of rotenone inhibits microtubule formation from tubulin and excess microtubules formation prove to be toxic to cells and may provide a link with neurodegeneration.^[50]

Excess tubulin monomers can be toxic to cells and may provide a link with neurodegeneration. Indeed, parkin (gene responsible for PD) can bind to tubulin, provoke degradation of misfolded tubulins.^[51] Rotenone also causes the formation of proteinaceous aggregates in live dopaminergic neurons. Its long time exposure has successfully produced Lewy's body like cytoplasmic aggregates that are ubiquitin and α -synuclein positive accompanied with DA neuron loss.^[52]

Paraquat

Paraquat (N, N'-Dimethyl-4,4'-bipyridinium dichloride) (PQ) is a commonly used cationic non-selective herbicide that is reported to be consistently linked with PD.^[53] It has shown a dose-dependent effect with the incidence of PD. It has a very similar structure to MPTP and MPP⁺ has prompted researchers to label it as a risk factor for PD and therefore it is increasingly being used in cell-culture and animal studies.^[54] The mode of action of PQ is the generation of toxic superoxide free radicals through redox cycle.

ORGANOCHLORINES AND PYRETHROIDS

Pesticides belong to organochlorine family are highly lipophilic that readily cross the BBB^[55] and steadily available in the environment, cause DA neurotoxicity and oxidative stress.^[56]

Pyrethroids are a newer class of insecticides often contained in household insecticides and mosquito repellants. Some of the animal studies have revealed the ability of pyrethroids to indirectly elevate the dopamine transporter-mediated dopamine uptake^[57] and thus cause indirect apoptosis of dopaminergic cells.^[58] However, this area requires further study, as there is little specific human data besides the general finding that pesticide exposure, including pyrethroids, is associated with

PD.^[59] Deltamethrin, one of the form pyrenoid causes apoptosis via Na⁺ channels followed by calcium overload and activation of the ER stress pathway which is one of the reasons of neurodegeneration in PD.^[60]

Metals

There are variety of mode by which human can exposed to metals like through diet, occupational exposure such as through effluent of industries and welding processes.^[61] Although many metals are proof to be essential for human health but too much exposed towards metals can be detrimental.^[62] For example iron and manganese are found to be associated with PD.

Iron

Excessive exposure to iron leads to neurodegeneration and oxidative damage via production of free radicals in substantia nigra neurons and *in-vitro* cells model. A study conducted by Oh *et al.*, demonstrated that through Hyper-spectral fluorescence imaging for cellular iron mapping, SHSY5Y cells exposed to iron with ferric ammonium citrate and found that iron particles concentrated on the cell membrane/edge of shrunken cells leads to apoptosis.^[63] Recent study conducted by Ortega *et al.*, revealed that *in-vitro* α -synuclein over-expression induces increased iron accumulation and redistribution from the cytoplasm to the perinuclear region in iron exposed PC12 cells.^[64]

Manganese (Mn)

Although Mn is an essential metal but excessive exposure through air or food may lead neurological sequelae and PD. Mitochondria is the target site of Mn where its toxicity leads to cellular dysfunction via inhibition of oxidative phosphorylation.^[65] Studies also reported that Mn get released in astrocytes by inhibiting glutamine synthesis process revealed failure of astrocytes mechanism that provide neurons with substrates for energy and neurotransmitter metabolism, leading to down regulation of neuronal glutathione levels and energy metabolism.^[66] *In-vitro* study conducted by Wegrzynowicz and Aschner 2013 in cultured astrocytes showed that Mn decreases glutamate uptake and down regulate the expression of the high-affinity glutamate transporter GLAST hence also play a role in the alteration of glucose metabolism.^[67]

Recent studies related to the exposure of above mentioned toxic agents with inferences are summarized under table no. 2.

Neuroprotective strategies and clinical trials

Neuro-protection is a form of therapy to slow the rate of progression of a neurodegenerative disease.^[68] Concepts of potential neuroprotective approaches for PD focused on mediator that reduce oxidative damage, enhance mitochondria function, counteract inflammation and slow down apoptosis. Alpha synuclein aggregation, cytosolic DA levels and slow down ubiquitin-proteasome system proof to be cause of PD but due to lack of

reasonable agents to test for trial, initiative have not been undertaken yet.^[69]

With the advancement of new knowledge on pathogenesis and genetic mechanisms have been studied in the last few years, there are now new ideas on naturalpathy as well as man- made drugs that could be tested in clinical trials. Number of studies has been done to test the different natural and chemical compounds as neuro-protective agents and evaluate their mechanisms. List of findings are summarized in table number 2.

Case control studies

Epidemiologic data supported the hypothesis that broadly defined pesticide exposure may increase risk of PD.^[70-72] Meta-analysis of case-control studies performed in the United States revealed that patient with PD are over two times as likely to report ever being exposed to pesticides as compared to unaffected individuals.^[73] Studies have assessed associations between specific classes of pesticides and PD as shown in table no 3. Further, farming residence and well-water consumption are considered to be risk factors for the development of PD.^[74]

Micro RNA and Parkinson's disease

Micro RNAs (miRNAs) are a group of small, single-stranded and non-coding RNAs which have been identified as post-transcriptional regulators of gene expression.^[75] Studies have confirmed that miRNAs expression perturbation is the cause for the progression

of neurodegenerative diseases.^[76] miRNA may be used as a specific diagnostic biomarker for PD. miR-339-5p found to be down-regulated whereas miR-223, miR-324-3p and miR-24 are found to be up-regulated in PD tissues, which may be considered as specific diagnosis biomarkers of PD.^[77] In-vitro study conducted by Researchers on MPTP treated SH-SY5Y cells and MES23 cells and confirmed the role of miR-144-3p and miR-590-3p in regulating mitochondrial functions, along with its target gene amyloid precursor protein (APP) respectively.^[78]

Furthermore, Researchers^[79] identified the key proteins and markers associated with the impairment of mitochondrial dysfunction. Studies revealed that that up-regulation of miR-590-3p and knockdown of JMJD1C (target gene for miR-590-3p) elevates the expression of peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α) simantaneously downstream targets of PGC-1 α , including nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (TFAM), which are the key genes responsible for the regulation of mitochondrial function.

Other miRNAs (miR-34b or miR-34c) were also indentified related to the viability of cells, alteration in mitochondrial dynamics and depletion of cellular adenosin triphosphate content in cultured SH-SY5Y dopaminergic neuronal cells. Downregulation of MiR-34b/c leads to the decrease in the expression of DJ1 and Parkin (proteins associated to familial forms of PD).^[80]

Table no 1: *In-vitro* Neuroprotective agent's treatment and findings.

Cell lines	Neurotoxic agent	Neuroprotective agent	Inference	References
SH-SY5Y cells	Rotenone	Lithium chloride	lithium able to attenuate cell apoptosis, inhibit ROS production and MMP decrease induced by rotenone via autophagy pathway	[81]
SH-SY5Y cells	Rotenone	Resveratrol (phytoalexin)	Resveratrol partially prevents rotenone-induced neurotoxicity in cultured SH-SY5Y cells via activation of heme oxygenase-1 dependent autophagy.	[82]
SH-SY5Y cells	MPP(+)-	Gastrodin (phenolic glucoside), a main constituent of a Chinese herbal medicine <i>Gastrodia elata</i> Blume	Gastrodin can induce heme oxygenase-1 (HO-1) expression through activation of p38 MAPK/Nrf2 signaling pathway (cell growth pathway), thus protecting the SH-SY5Y cells from MPP(+)-induced oxidative cell death	[83]
SH-SY5Y cells	beta-amyloid (cytotoxic to cultured neurons)	Astaxanthin (flavonoid)	Astaxanthin upregulates the expression of heme oxygenase-1 through ERK1/2 pathway and its protective effect against beta-amyloid-A β (25-35)-induced cytotoxicity in SH-SY5Y cells	[84]
MN9D	Rotenone	DJ-1 (protein)	DJ-1 protects MN9D cell after exposed to rotenone (induced apoptosis by enhancing ERK-dependent mitophagy)	[86]
Human Fibroblast cells	Rotenone	Resveratrol (phytoalexin)	resveratrol regulates energy homeostasis through activation of AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) and raise of mRNA expression of a number of PGC-1 α 's target genes resulting in enhanced mitochondrial oxidative function, likely related to a decrease of oxidative stress and to an	

			increase of mitochondrial biogenesis.	
Astrocytes monoculture cells	Hydrogen peroxide	ATP	adenosine 5'-triphosphate (ATP) protects hippocampal astrocytes from hydrogen peroxide (H ₂ O ₂)-evoked oxidative injury in astrocytes monocultures	[87]
HEK cells	Exogenous alpha synuclein	CLR01(molecular tweezer)	suppressed α -syn aggregation in neurons, and reduced α -syn-induced apoptosis. α -Syn expression was found to inhibit the ubiquitin proteasome system in α -syn-ZF neurons, resulting in further accumulation of α -syn. Treatment with CLR01 almost completely mitigated the proteasome inhibition. The data suggest that CLR01 is a promising therapeutic agent for the treatment of Parkinson's disease and other synucleinopathies.	[88]
PC12	GSK-3 β antagonists LiCl or SB216763	Rotenone	the data suggested that Wnt/ β -catenin and Nurr1 are crucial factors in the survival of DA neurons, and the activation of Wnt/ β -catenin pathway exerts protective effects on DA neurons partly by mean of a co-active pattern with Nurr1.	[89]
primary dopaminergic cultures from mouse mesencephala	Thymoquinone (TQ) is the main active constituent of Nigella sativa seeds	MPP(+)	The TQ protects dopaminergic neurons in primary mesencephalic culture by enhancing lysosomal degradation that clears damaged mitochondria and inhibits mitochondria-mediated apoptotic cell death	[90]
SH-SY5Y cells	MPP+	Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) (transcription factor)	The overexpression of PGC-1 α can inhibit MPP(+)-induced mitochondrial damage in SH-SY5Y cells, and PGC-1 α may realize the neuroprotective effects via the ERR α , PPAR γ , and NRF-1 pathway.	[91]
MN9D cells	MPP+	sphingosine kinases, Sphk2 and its metabolite sphingosine-1-phosphate (S1P)	sphingosine kinases, Sphk2 and its metabolite sphingosine-1-phosphate (S1P)	[92]
SH-SY5Y cells	MPP+	Pinocembrin (most abundant flavonoid in propolis)	Study revealed that Pinocembrin activated the HO-1 expression as a result MPP(+)-induced oxidative damage via ERK1/2 signaling pathways suppressed.	[93]

Table no 2: Studies on different cell lines exposed to pesticides.

Cell lines	Pesticides	Inference	References
PC12	MPP+	MPP+-induced oxidative damage via downregulation of PCNA (Proliferating cell nuclear antigen) protein through the p53 pathway	[94]
N27	PQ	Explored the role of PQ toxicity in N27 cells and found that glucose metabolism depletion is the cause of neurotoxicity	[95]
PC1	MPP+	Study demonstrated that NogoA (myelin-associated protein inhibits axonal fiber growth and regenerates after injury of the mammalian central nervous system) may regulate MPP+ induced neurotoxicity in cultured cells via the mTOR/STAT3 signaling pathway.	[96]
SH-SY5Y cells	MPP+	Results demonstrated that MTERF2 (mitochondrial transcription termination factor 2) is involved in MPP(+)-induced	[97]

		mitochondrial disruption and cell damage.	
Dopamenergic cells	Copper	α -synuclein stimulates Cu toxicity in cultured dopaminergic cells self-regulating from its aggregation via modulation of protein degradation pathways.	[98]
PD cell model	MPP+ and phenformin	silent information regulator 1 (SIRT1) and hypoxia inducible factor 1 signalling is involved in etiology of PD	[99]
Cultured ventral mesencephalic (VM) dopaminergic (DA) neurons cells	rotenone	at low nanomolar concentrations, rotenone induces ROS and caspase-3-mediated apoptosis higher in mature VM as compared to immature VM	[100]
Mesencephalic culture	annonacin, the major acetogenin of <i>Annona muricata</i> (soursop), a tropical plant	Study elucidates that annonacin enhance dopaminergic neuronal death in-vitro via impairment of energy production.	[101]
Primary cultures prepared from embryonic mouse mesencephalic cells	rotenone	Rotenone induces toxicity in cultured cells by down regulating the mitochondrial membrane potential, increasing reactive oxygen species production and move respiration cycle to a more anaerobic state	[90]
Nigrostriatal neurons	paraquat and rotenone	Results through NMR revealed that the effects of paraquat and rotenone cannot effect directly on the expression of aS, emphasize the concept that the role of these herbicides in PD is limited to the inhibition of mitochondrial complex I and/or the up-regulation of aS.	[102]

Table no 3: Case studies finding exposed to pesticides

Environmental Agent	Reference	Number of Cases/Controls	Inference
Rotenone	[103]	110/358	Rotenone exposure associated with PD
	[104]	102/84	Report of past rotenone use was associated with PD
	[105]	69/237	Protective glove use modified association of paraquat and permethrin with PD, paraquat OR 3.9 (95% CI 1.3, 11.7) * & permethrin OR 4.3 (95% CI 1.2, 15.6) * but did not modify the association with rotenone.
Paraquat	[106]	87/343	Men exposed to paraquat with functional glutathione S-transferase M1 (GSTT1) genotype had lower risk of PD compared to men exposed to paraquat lacking GSTT1
	[107]	357/754	Paraquat exposure and history of traumatic brain injury associated with PD risk
	[103]	110/358	Paraquat exposure associated with PD
	[108]	224/557	Paraquat exposure not associated with PD
Maneb	[109]	362/341	Combined exposure to all 3 pesticides associated with PD risk at workplaces and combined exposure to ziram and paraquat at workplaces associated with PD risk
Organochlorines	[110]	149/134	PD patients had higher serum levels of β -HCH than controls in higher exposure cohort, but in cohort with lower levels there was no significant difference
	[111]	225	Insignificant associations between Lewy Body pathology and presence of organochlorine compounds

	[112]	70/75	β Hexachlorocyclohexane (HCH) and Dieldrin levels were significantly higher in PD
	[113]	89	Dieldrin was associated with a nonsignificant higher risk of tremor at rest
Organophosphates	[114]	351/363	Increased risk of PD with exposure to ambient organophosphates and having common genetic variant in <i>PONI</i>
	[115]	357/752	Exposure to ambient organophosphates associated with increased odds of PD
	[116]	357/807	Frequent use of household pesticides containing organophosphates increased the odds of PD
Iron	[117]	50/50	Serum iron levels were not significantly different between PD and control subjects
	[118]	238/302	Iron and selenium concentrations were significantly increased in PD patients
	[119]	150/170	Plasma iron and copper levels were significantly elevated in PD subjects compared to controls, with no significant difference in manganese and lead
	Costa -Mallen <i>et al.</i> 2015	128/226	PD cases has lower serum iron levels than controls

CONCLUSIONS

This review summarized the role of number of pesticides exposure *in-vitro* leads to PD via creating dysregulation of proteins. Researchers are continuously looking for associated cellular pathways involved in PD. Today's world where individuals are daily exposed to pesticides as well as environmental pollutants directly or indirectly, so there is an urgent need to explore large number of compound which may cause PD along with the prominent neuro-protective agents to combat PD.

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