

**TRENDS IN RESEARCH ON PARAQUAT-INDUCED PARKINSONISM**

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**Paraquat, a herbicide widely used in agriculture for better crop production, is an environmental toxin and causes oxidative stress-induced systemic damages in plants, animals and humans. Epidemiological studies report that paraquat toxicity is related to the onset of parkinsonism in humans. Animal experimentations indicate that paraquat toxicity causes the cellular and molecular changes associated with parkinsonism. Experimental evidences show that blood-brain-barrier limits the paraquat entry in brain of primates and humans and therefore, the doubts remain for a direct paraquat-induced parkinsonism in human. To define a remedial measure, extensive studies are required on the cause and prognosis of Parkinson's Disease induced by such environmental toxicant.**

Paraquat is a non-selective acutely toxic herbicide and most commonly used in the world because of its rapid action, relatively low cost and broad spectrum of its activity. Paraquat controls weeds and grasses in many agricultural and non-agricultural areas. This herbicide is now banned in 32 countries, including the 27 countries of the European Union due to its toxic effects on plant, animal and human. Recently, the geo-eco-friendly natural plant products are being suggested for use as herbicides, as an alternative approach of paraquat use. Ingestion of paraquat causes deleterious toxic effects in different systems of our body. There is no antidote of paraquat toxicity (Srinivasan 2003, Watts 2011, Neumeister and Isenring 2011, Dileep Kumar 2015). Paraquat induces oxidative stress and alters mitochondrial function and, thus causes cellular death. Animal studies (Mitra *et al.*, 2011) support the fact that slow paraquat poisoning for longer period is supposed to be associated with "Parkinsonism", a syndrome closely related to the clinical/symptomatic evidences of Parkinson's disease in human.

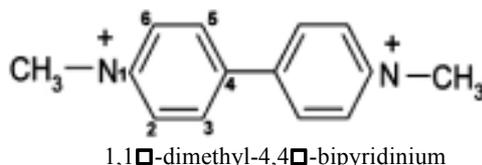
China is reported to be the world's largest manufacturer of paraquat (Watts 2011). In India, the Government authorities of agricultural departments have still approved the use of paraquat for better crops production (Dileep Kumar 2015). Paraquat is inactivated by absorption of the clay materials in the soil and leaves a minimum chance of ecological effects affecting human health. However, a proper protection in use of paraquat with implication of laws and regulations and prevention of unauthorized production are necessary for appropriate use of paraquat in agriculture without disturbances in freshwater ecosystems and human health. The alarming issue is that the paraquat is being sprayed directly on mature food crops and the chances of residual of paraquat in food staff used in our daily life may cause epidemic issues (Zeneca Agrochemicals, 1993; Selisker *et al.*, 1995). Therefore, the screening of paraquat residues in food staff and measurement of availability of paraquat in animals and humans is an important issue to prevent ecological imbalance and minimize

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the risk of paraquat toxicity in human health. In addition, the rise of prevalence of Parkinson's Disease in population, particularly in young adult humans, raise the question of the slow poisoning of paraquat in human health. Our research findings with mice model indicate that paraquat toxicity with sub-lethal dose, for longer period causes cellular and molecular changes in brain areas in association with changes in behavioural and motor activity in animals similar to the symptoms of Parkinson's Disease (Mitra *et al.*, 2011). Extensive research is being focused to find out the exact cause(s) of environmental toxins-induced Parkinson's Disease (sporadic Parkinson's Disease), evaluation of its suitable biomarker(s) for early detection and development of its better treatment strategy with multi-targeted drugs. Although there are several case studies in support of paraquat induced parkinsonism in human beings, the experimental evidences are not sufficient to explain the fact how paraquat crosses the blood-brain-barrier and affects human brain.

#### A. Chemical Nature of Paraquat and Trade names

Paraquat (molecular formula:  $C_{12}H_{14}N_2$ ) is a water soluble quaternary nitrogen compound (ammonium derivative) with chemical name as 1,1-dimethyl-4,4'-bipyridinium. Structurally, paraquat is very similar to the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a heroin analog. The related compounds of paraquat are paraquat dichloride, paraquat dichloride trihydrate, paraquat bis-methyl sulfate, and paraquat bistrifluoromethanesulfonate. Paraquat is available as white crystalline solid or granules and aqueous solution. The common trade name is Gramoxone and is available in market as 10-30% concentrated aqueous solutions with dark blue-green colour as alkaline sodium dithionite is added for colouring. Originally the aqueous solution of paraquat was formulated as reddish-brown colour which led them to be mistaken for drinks (tea, cocacola, red wine) followed by accidental usage. Paraquat is sold under numerous trade names and also found in compounds with other herbicides ([www.pan-uk.org](http://www.pan-uk.org), [www.paraquat.com](http://www.paraquat.com), [www.inchem.org](http://www.inchem.org), [www.fao.org](http://www.fao.org)).



#### B. Limelight of Global use of Paraquat

Paraquat was first synthesized in 1882 by two German scientists Weidel and Russo (Haley 1979). The redox property of paraquat was discovered by Michaelis and Hills in 1933 and, the compound was named as methyl vilogen. The herbicidal nature of Paraquat was reported in 1953-1955 [Imperial Chemical Industries (ICI) laboratories, now called Zeneca group, UK] and commercially produced in 1962. The chemist (Roger Jeater) from ICI found paraquat as good quality herbicide among other chemicals having weed management property for better cultivation of rubber and oil plantation in Malaysia. Since then, the paraquat had been used in over 130 countries around the world for agricultural growth and economical

development (Srinivasan 2003, Neumeister and Isenring 2011, [www.paraquat.com](http://www.paraquat.com)).

### C. Paraquat use in India

In India, the Central Insecticide Board and Registration Committee (CIBRC), the pesticide body under the Department of Agriculture, Government of India has approved the use of paraquat for weed controls on development of nine crops. In addition, the agricultural departments of State authorities and Universities and, manufacturing companies of paraquat in India have recommend the use of paraquat for better development of other crops (Dileep Kumar 2015). Paraquates are used for better production of following crops in India mentioned bellow. The asterisks (\*) indicate the crops approved by CIBRC, Government of India for better production by using paraquat.

Fruits & others	: Apple *, Banana, Cherry, Grapes *, Pineapple, Orange, Sugar cane.
Vegetables	: Bottle gourd, Brianjal, Chilli, Kakrol, Maize *, Okra (ladies' finger), Onion, Potato *, Pumpkin, Parble, Tomato.
Nuts	: Areca nut, Cashew, Ground nut.
Oil/Seeds	: Mustard, Oil palm, Sesame, Sunflower.
Cereals	: Jowar, Rice*, Wheat*.
Pulses	: Soya beans.
Beverage	: Coffee, Tea *.
Flowers	: Jasmine, Marigold.
Textile fibers & others	: Cotton*, Jute, Rubber *.

### D. Controversy of Paraquat use : Paraquat poisoning

The incidence of death due to paraquat poisoning was first reported in Singapore on 1966 (Bullivant, 1966). After that, the enormous reports on death due to paraquat poisoning have been documented in developed countries and developing countries (Fock 1987, Wesseling *et al.*, 2001, Watts 2011). Several incidences of paraquate poisoning in human are also reported in India (Sandhu *et al.*, 2003; Agarwal *et al.*, 2006, Raina *et al.*, 2008). Paraquat poisoning is mostly due to occupational hazards to farmers and workers through inhalation, skin exposures, eye contacts and ingestion. The non-occupational poisonings is intentional self-poisoning, i.e. suicide. Accidental ingestion occurs when paraquat is stored in refreshment, liquor, or medicine bottles. Severe and fatal poisonings have occurred in children playing with rinsed spray jets and bottle tops. The ecological impacts of paraquat poisoning occurs through aquatic toxicity (fish, amphibian, larvae of crustaceans, plants, plankton), terrestrial toxicity (mammals maximally affected, birds less affected), non-target terrestrial plants, micro-organisms (soil fungi and bacteria like nitrogen-fixing bacteria, nitrogen-fixing blue-green alga) found in rice/paddy (Elise 1990, Watts 2011).

Paraquat is used as a desiccant and sprayed directly on mature food crops. The field trials have shown that residues occur in fruits, tea, vegetables, legume, pulse, barley, wheat, rice, sorghum, banana, cabbage, potato, carrot, tomato, maize, cotton-seed and sunflower seed (IPCS 1984; JMPR 2004). The residues of paraquat found in potatoes can not be eliminated through boiling. Such residues also have been found in onions (IPCS 1984;

Wigfield *et al.*, 1993). Residues of paraquat in meat, milk and eggs do not decrease under storage up to 28 months (JMPR, 2004). WHO reported that the short-term dietary intake of paraquat for children up to 6 years might be as high as 50% of the Acute Reference Dose of paraquat (JMPR 2004). The intake of paraquat in food has been found to be 3 times higher than the Acceptable Daily Intake in certain area of South Africa (Raschke and Burger 1997).

Mostly in animal studies paraquat shows toxic effects in different systems. Evidences show that paraquat causes oxidative stress, diabetes and cancer (breast cancer). Paraquat toxicity is reported to be associated with hypothyroidism in women (Goldner *et al.*, 2011). The toxic effects of paraquat found in different physiological systems (US EPA. 1993, Watts 2011) are described below.

**Eye** : Cataracts.

**Lungs** : Chronic inflammation, thickened alveolar walls, fibrosis, oedema, and alveolar haemorrhage in rodents (Kimbrough and Gaines 1970).

**Liver** : Cell proliferation and fibrosis of the bile duct in rodents (Cagen *et al.*, 1976).

**Kidneys** : Nephritis, and renal tubular degeneration in rodents (Lock and Ishmale, 1979).

**Cardiac and haematolymphatic system** : Myocardium and haemolytic anaemia, inhibits the synthesis, and accelerates breakdown of haeme, swelling of the spleen, swelling and inflammation of the mesenteric lymph node, and leukaemia in rodents (Chan *et al.*, 2007).

**Immune system** : Decrease in macrophages, suppression of the T lymphocytes in rodents (Riahi *et al.*, 2011).

**Reproductive & developmental effects** : Necrosis and atrophy of the testis and ovary, uterine cysts and polyps, foetal mortality in rats, increased percentage of abnormal eggs in hens, and increased resorption and postnatal mortality rate in mice respectively.

**Birth defects (teratogenicity)**: Paraquat crosses the placenta and can cause acute poisoning including death of the foetus or chronic effects that can persist for the lifetime.

**Endocrine disruption** : Decreased levels of testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin in male rats. Thyroid adenomas have been observed in rats, adrenal cysts and atrophy of the thymus gland in rodents.

**In central nervous system**, paraquat causes dopaminergic cell death, the details of which have been explained below.

#### **E. Mode of Paraquat toxicity at cellular level**

Paraquat produces reactive oxygen species (ROS) in cytoplasm and mitochondria separately. In cytoplasm, paraquat itself is reduced in presence of NADPH then a single electron is transferred from reduced paraquat to oxygen forming free radical (Bus *et al.* 1974, Bus and Gibson, 1984). Secondly, paraquat ion (PQ<sup>+</sup>) alters the mitochondrial trans-membrane potential which in turn helps to enter PQ<sup>+</sup> in mitochondria. It is evident that mitochondria with abolished trans-membrane potential are failed to produce any reactive oxygen species after *in vitro* paraquat treatment (Castello *et al.*, 2007, Cocheme and Murphy 2008). After entering into the mitochondrial matrix, PQ<sup>+</sup> directly reacts with O<sub>2</sub> to produce O<sub>2</sub><sup>-</sup> (Castello *et al.*, 2007, Cocheme and Murphy 2008) with uncoupling of oxidative phosphorylation (Fukushima *et al.*, 2002). After reacting with molecular oxygen the PQ<sup>+</sup> is changed to PQ<sup>2+</sup> form which is again converted to the PQ<sup>+</sup> after accepting an electron from NADH with the

help of complex-1, present in inner membrane of mitochondria (Castello *et al.*, 2007, Cocheme and Murphy 2008, Fukushima *et al.*, 2002). The mode of cellular action of paraquat is designed in Fig 1.

Fig-01 (A)

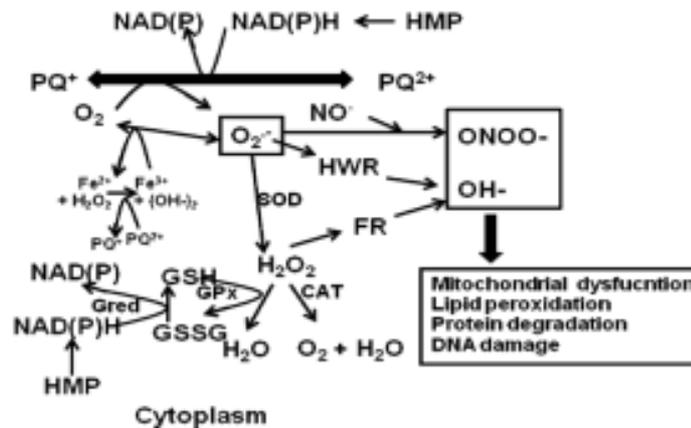
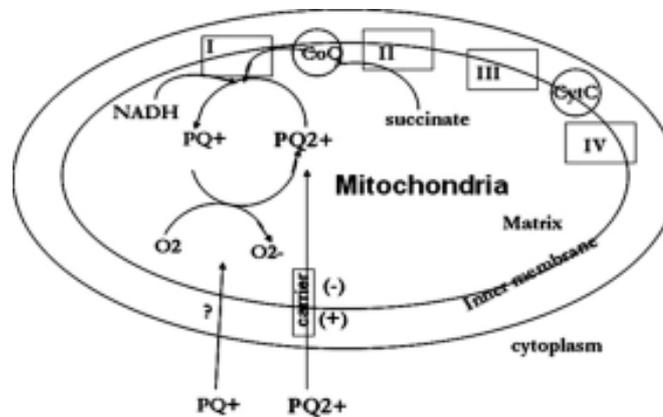


Fig-01-B



**Fig 1 : Mode of cellular action of paraquat. (A) Paraquat-induced oxidative stress in cytoplasm and related metabolic interactions.** The paraquat-induced oxidative stress causes mitochondrial dysfunction and damages of other biomolecules like lipids, proteins and DNA within the cell. [SOD: Superoxide dismutase, CAT: Catalase, GPx: Glutathione peroxidase, Gred: Glutathione reductase, HMP: Hexose monophosphate pathway, FR: Fenton reaction, HWR: Haber-Weiss Reaction]. **(B) Paraquat-induced oxidative stress in mitochondria is also related to mitochondrial dysfunction.** [CoQ : Coenzyme Q, CytC : cytochrome C]. (Adopted from Bus *et al.* 1974, Bus and Gibson, 1984, Castello *et al.* 2007, Cocheme and Murphy 2008)

Paraquat also causes the formation of nitric oxide. Paraquat exposure causes the activation of IK $\beta$  (a transcription factor) which again activates NFK $\beta$  in the mitochondria. This activated NFK $\beta$  causes the over-expression of NOS (Nitric Oxide Synthase) which in-turn causes the formation nitric oxide at cellular level (Ranjbar 2013). Oxidative stress produced by paraquat causes several adverse affect such as oxidation of membrane lipids and proteins, excitotoxicity such as excess activation of NMDA receptor and calcium entry, production of peroxyxynitrite after reaction with superoxide and nitric oxide. All these effect synergistically causes apoptosis and tissue injury in organisms (Fukushima 2002). Paraquat also causes the injury to the mitochondrial DNA, causing defects in the function of respiratory chain (Fukushima 2002). The herbicide has been found to be a mutagenic agent that causes inhibition of DNA synthesis (Carmine *et al.*, 1981) and can be associated with chromosomal aberration (Rios *et al.* 1995).

#### **F. Paraquat measurement in Environmental and Biological samples**

Identification and quantification of paraquat in environment and biological samples are necessary for forensic toxicology and therapeutic drug monitoring. The concentration of paraquat in serum plays an important role in prognosis of paraquat toxicity. Several high-throughput techniques are being use for determination of paraquat like, High Pressure Liquid Chromatography (HPLC), Gas Chromatography (GC), Capillary Zone Electrophoresis, Mass Spectroscopy (MS), Electrospray ionization-Mass Spectrometry (ESI-MS), Radioimmunoassay, time-resolved fluoroimmunoassay. The Spectrophotometry including common spectrophotometry (Khaton *et al.*, 2013), derivative spectrophotometry (Li *et al.* 2011) and spectrofluorimetry (Yao *et al.*, 2013) are commonly used to detect paraquat in primary hospitals. The derivative spectroscopic detection has been found to be more sensitive than simple spectroscopic detection with low economic cost for its determination in biological sample. The quenching of fluorescence of a probe like cucurbit[7]uril-coptisine (CB[7]-COP) is supposed to be low cost detection method of paraquat.

#### **G. Paraquat as the cause of Parkinson's Disease**

Epidemiological studies indicate that paraquat increases the risk of Parkinson's Disease. There are several case studies in different countries including Canada (Barbeau *et al.*, 1985, 1986), Hong Kong (Ho *et al.*, 1989), Israel (Goldsmith *et al.*, 1990), Taiwan (Liou *et al.*, 1997), USA (Firestone *et al.*, 2005, Dhillon *et al.*, 2008, Tanner *et al.*, 2009, Costello *et al.*, 2009) which reflect that paraquat toxicity is related to parkinsonism.

Parkinson's Disease, the second most common neurodegenerative disorder, is a multi-factorial disease caused by age, genetic and environmental factors. Several efforts are being used for better understanding of the Parkinson's Disease, its etiology, pathology, cellular/molecular mechanisms and development of neuro-protective/neuro-restorative treatment strategies. Studies with animal model and human subjects indicate that environmental toxins including paraquat might be the cause of Parkinson's Disease itself rather with the onset and progression of the disease, and behavioral changes associated with Parkinson's Disease (Spivey 2011, Tanner *et al.*, 2011, Blesa 2012). Apart from the motor problems, Parkinson's Disease has been found to be associated with several non-motor systems particularly, neuropsychiatric disorder and cognitive impairment (Weintraub and Burn 2011, Lee and

Weintraub 2012, Poletti *et al.*, 2012, Palavra *et al.*, 2013). Microscopic and Magnetic Resonance Spectroscopic (MRS) studies with 6-hydroxydopamine-induced rat model of Parkinson's Disease indicate the loss of neuronal and synaptic structure as well as function in the frontal cortex of brain (Hou *et al.*, 2010).

Several animal studies indicate that paraquat-induced dopaminergic neurodegeneration at substantia nigra (mid brain) are accompanied with changes of several parameters associated with oxidative stress, neuroinflammation and tropic factor (Miller 2007, Mangano *et al.*, 2009). Lethal dose of paraquat in rat model causes neuronal reactive oxygen species (ROS) formation, microglial activation and astrocytic oedema in area specific manner at substantia nigra, striatum and hippocampus (Wu *et al.*, 2013). Experiments with lipopolysaccharides (LPS) indicate that paraquat acts indirectly on microglial activation and microglial activation primed by lipopolysaccharides influences paraquat-induced dopaminergic neuronal death (Purisai *et al.*, 2007, Klintworth *et al.*, 2009, Mangano and Hayley 2009, Kim 2013). Other studies propose that paraquat activates microglial through enhancement of the NADPH-oxidase 2 (NOX2) activity. Paraquat-induced dopaminergic neurotoxicity is related to production of monovalent cation of paraquat (PQ<sup>+</sup>) by either a reducing agent or NADPH-oxidase on microglial and accumulation of it in dopaminergic neurons through dopamine transporter (DAT) and deficiency of organic cation transporter 3 in non-dopaminergic cells (Rappold 2011, Taetzsch and Block 2013).

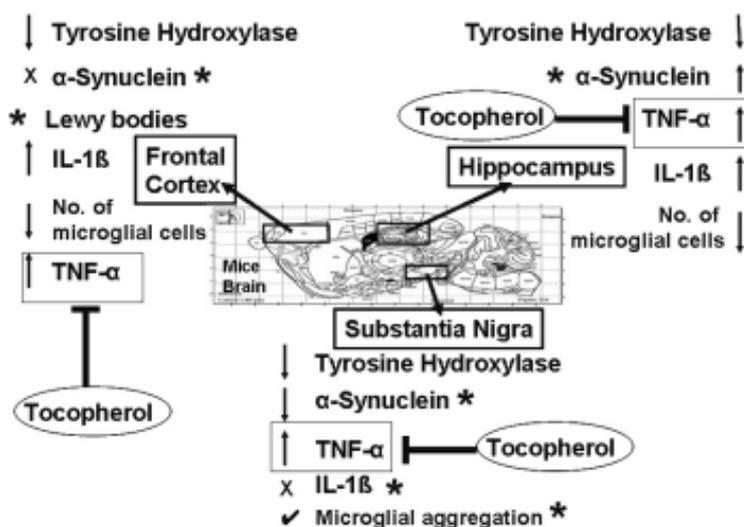
#### **H. Evidences of paraquat toxicity and parkinsonism in Indian scenario**

The case studies of paraquat poisoning in human subjects have been reported in Indian population (Singh *et al.*, 1999, Sandhu *et al.*, 2003, Ghosh *et al.*, 2012). Several animal studies have been conducted using biochemical analysis, molecular expression and gene array methods to find that paraquat induces oxidative stress, produces several molecules related to oxidative stress and causes neurotoxicity in mouse striatum. These studies reported that paraquat causes increase in catalase, glutathione-s-transferase, cytochrome, NADP-oxidase, nitric oxide production, iNOS expression through p38 and MAPK/ NF- $\kappa$ B signaling, lipid peroxidation, alpha-enolase activity and depletion of reduced glutathione (GSH) in the brain areas. Paraquat treatment causes differential expression pattern of complexin-I, a presynaptic protein, that expresses in axosomatic (inhibitory) synapses in mouse striatum (Patel *et al.*, 2006, Patel *et al.*, 2007, Patel *et al.*, 2008, Gupta *et al.*, 2010). It has been reported that paraquat and Zn intoxication follows similar oxidative stress induced dopaminergic neurodegeneration in rat (Kumar *et al.*, 2012). However, there is no report in Indian scenario, related to the structural and functional changes in hippocampus and cerebral cortex linked to alteration of cognitive function during Parkinson's Disease.

In ancient India, the treatment recommended in Ayurveda for Parkinson's Disease is the seeds of *Mucuna Pruriens* whose extract contains levodopa (Damodaran and Ramaswamy 1937, Kavitha and Thangamani 2014). In modern scenario, several neuroprotective agents are being tested for prevention of paraquat-induced neurotoxicity like plant products (resveratrol, silymarin, caffeine, nicotine) and endogenous (water-soluble coenzyme Q10, cytochrome P450) compounds (Somayajulu-Nitu *et al.*, 2009, Singhal *et al.*, 2011, Yadav *et al.* 2012, Srivastava *et al.* 2012). Recently a detailed study has been conducted with mitochondrial proteome analysis of the nigrostriatal tissues in presence and absence of

several pharmacological drugs like minocyclin (antibiotic as microglial inhibitor), levodopa (anti-PD drug) and manganese (III) tetrakis (1-methyl-4-pyridyl) porphyrin (superoxide scavenging). The study indicates differential expression pattern of mitochondrial proteins that cause mitochondrial dysfunction and microglial activation leading to the nigrostriatal dopaminergic neurodegeneration. The pharmacological drugs variably offset scores of such changes (Dixit *et al.*, 2013).

Our recent report on paraquat-induced animal (mice) model of Parkinson's Disease indicates, for the first time, brain regional basis of differential pattern of dopaminergic neurotoxicity and microglial activation. The cytokines are elevated in three regions (substantia nigra, hippocampus and frontal cortex) of brain, where tocopherol (antioxidant) supplementation after paraquat treatment attenuates the increase in TNF-alpha status without any effect on changes in other parameters (Mitra *et al.*, 2011). Therefore the further studies are required to find the importance of multi-targeted (antioxidant+anti-inflammatory) drugs for beneficial treatment of Parkinson's Disease. The details of our recent findings with paraquat induced mice model of parkinsonism are given in Fig 2.



**Fig 2 : Paraquat-induced Parkinsonism in mice model.** Differential pattern of molecular changes in three different regions of mice brain i.e. substantia nigra (positive site of parkinsonism), frontal cortex and hippocampus. The frontal cortex and hippocampus are considered to be sites for cognitive activity. It is reported that Parkinsonism is associated with cognitive alterations. Tocopherol supplementation after paraquat toxicity attenuates the paraquat-induced elevation of TNF $\alpha$  in brain areas without any impact on other parametric changes. Asterisks (\*) indicate that the concern parameters differentially express in brain regions during paraquat-induced toxicity. The upward arrow (?) and downward arrow (?) represent the increase and decrease, respectively, in value of parameter. (X) and (v) represent absence and presence of change in parameter respectively. (Adopted from our reports in Mitra *et al.* 2011)

### **I. Contradictory evidences of paraquat induced Parkinsonism in Human: Blood-Brain-Barrier limits paraquat availability in brain of primates and human**

In rodents, paraquat can cross the blood-brain barrier (Shimizu *et al.*, 2001) and can persist with a half-life of 28 days (Prasad *et al.*, 2007). The uptake of paraquat into the brain is age-dependent, with higher concentrations found in very young and very old in animal studies (Thiruchelvam *et al.*, 2002). However, other studies raised a doubt that the di-cation form of paraquat in blood limits the cross of blood brain barrier (Koller 1986, Miller 2007). The PET (Positron Emission Tomography) imaging study using [ $^{11}\text{C}$ ]-paraquat indicates that the brain of adult male rhesus macaques minimally uptake [ $^{11}\text{C}$ ]-paraquat after its supplementation. The highest concentrations of paraquat have been seen in the pineal gland and the lateral ventricles in monkey brain (Bartlett *et al.*, 2009). Therefore, this monkey study does not support the etiologic role of paraquat exposure in idiopathic Parkinson's Disease. Since there is no evidential proof regarding the crossing of blood-brain-barrier by paraquat, further studies are required to substantiate the *in vivo* effect of paraquat on development of Parkinson's Disease in higher mammals like human.

### **COMMENTS AND CONCLUSION**

Epidemiological reports demands that paraquat is the cause of Parkinsonism having neurological/neuropathological features including movement disorder and behavioural alterations. The facts claim the screening of paraquat residual in daily food and survey of blood/urine content of paraquat in human population. Furthermore, the extensive studies with brain imaging (CT/MRI/MRS/PET) and blood molecular arrays of patients can only substantiate the reality of paraquat induced parkinsonism in population.

Paraquat induced Parkinson-like symptoms and biochemical as well as molecular features in animal (rodents) experimentations demand that paraquat is the cause of the Parkinson Diseases. However, the etio-pathology of Parkinson's Disease is not clear. It is now experimentally proved that Parkinson's Diseases is related to dopaminergic neurodegeneration with integrated multi-factorial cause including metabolic insults, immuno-inflammation, alterations of neurotropic factors and disruption of endocrine milieu. In addition, our recent reports indicate that cellular and molecular networking of different brain regions including substantia nigra, cerebral cortex and hippocampus may imply important role on paraquat-induced Parkinson's pathogenesis. Recent molecular approaches of genomics, proteomics, and metabolomics studies with high-throughput techniques and the statistically meta-analysis of omics data will provide the clues to assess the involvement of multiple genes, proteins and metabolic molecules in paraquat-induced parkinsonism.

The effective clinical studies with patients and modern translational research with animal model will discover the exact cause of sporadic (environmental induced) Parkinson's Disease, its biomarkers for proper prognosis and development of drugs for better treatment strategy in near future.

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