

# Rotenone Effects on the Human Body with Reference to Neurological Disorder

Shreya Singh<sup>1,\*</sup>, Ruchi Yadav<sup>2</sup>

## Abstract

*It has been claimed that the well-known neurotoxic pesticide rotenone, which is known to block the mitochondrial complex I, is strongly linked to the pathophysiology and etiology of Parkinson's disease (PD) in humans. There have been numerous analyses in the past and are still being conducted to establish a relationship between the two in order to completely comprehend the level of harm brought on by rotenone. Numerous laboratory studies shown that rotenone exposure results in vivo substantia nigra dopaminergic cell death, which is a hallmark of PD neuropathology. Rotenone also causes  $\alpha$ -synuclein to aggregate in vivo, which is another characteristic of the neuropathology associated with PD. Patients with Parkinson's disease have Lewy bodies and Lewy neurons in their brains. In addition, some in vivo models of rotenone mimic the symptoms of Parkinson's disease (PD), including inclusions. Peripheral synuclein and intestinal motility disorders are thought to precede typical PD symptoms, including bradykinesia. Resting Tremor and hardness of the tooth plate. It is thus very important to tackle rotenone toxicity in humans utilizing the available advanced technologies and approaches. Through this study, we are trying to highlight the havoc that rotenone causes as an attempt to attract the attention of the scientific community.*

**Keywords:** Exposure, neurotoxic pesticide, Parkinson's disease, rotenone, toxicity

## INTRODUCTION

Rotenone is an odorless, colorless, broad-spectrum pesticide. Found in the roots of this plant and belongs to the family Leguminosae. The now-known rotenone-containing plants that were used to kill leaf-eating caterpillars were first mentioned in writing in 1848; these same plants had been used for ages to poison fish. While travelling through French Guiana in 1895, Emmanuel Geoffroy, a French botanist, discovered the active chemical component—then known as nicouline—from a specimen of *Robinia nicou*, which is today known as *Deguelia utilis* [1]. His thesis, which was published in 1895 following his death from a parasite illness, included an analysis of this research. It occurs naturally in the seeds and stems of many plants, including the jicama vine plant. In Papua New Guinea, poisoning incidents involving intentional consumption of these plant roots are not uncommon (Figure 1). However, there has only ever been one recorded incidence of human poisoning from commercially available rotenone, which occurred after a 3.5-year-old child inadvertently consumed it.

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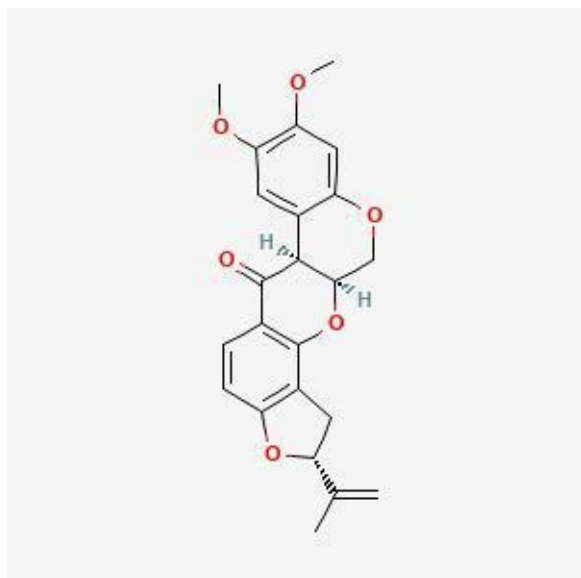
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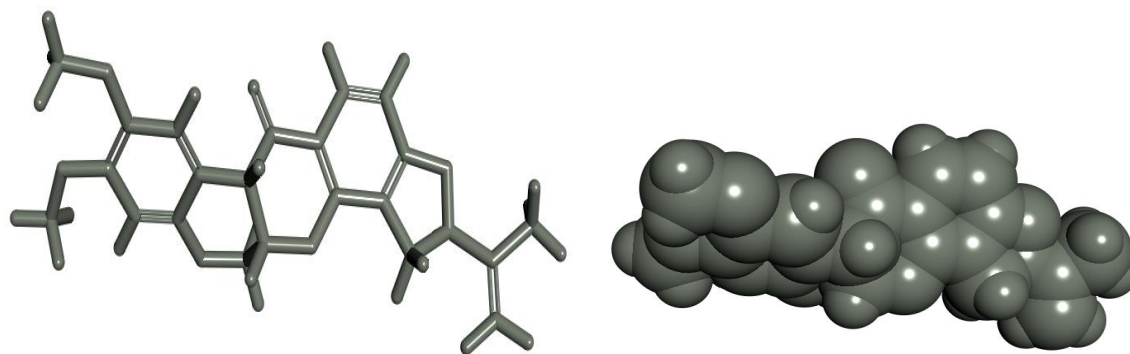
## ROTENONE EFFECT ON HUMAN BRAIN

Rotenone affects central nervous system and developing brain likely through inclusion of organ system that triggers neuronal cell death and alteration of  $Ca^{++}$  pathway. Rotenone increases the amount of intracellular free calcium ions ( $[Ca^{2+}]_i$ ) and activates CaMKII, which in turn causes apoptosis in neurons and inhibits mTOR signaling. Using BAPTA/AM to chelate  $[Ca^{2+}]_i$ , EGTA to block extracellular  $Ca^{2+}$  influx, KN93 to inhibit CaMKII, or CaMKII silencing, all greatly reduced the amount of  $H_2O_2$  produced, mTOR inhibition, and cell death when rotenone was present (Figure 2).

This pesticide inhibits axogenesis by affecting microtubule dynamics, actin cytoskeleton and its regular pathway and affects small RhoGTPase RhoA. Rotenone also affects catecholaminergic neurons. Rotenone reduces feeding behavior. Reduce spontaneous movement and causes the death of dopamine neurons in the substantia nigra pars compacta, which is the brain area of fish. It induces neuronal oxidative stress through the activation of microglia and aggregation of misfolded alpha synuclein (P129) is also seen [2].



**Figure 1.** 2D Chemical Structure of Rotenone.



**Figure 2.** Representation of 2D Structure of Rotenone in Stick and CPK format. Images Generate using Biovia Discovery Studio.

### A Case Study on Rotenone

As Parkinson's disease is also a rotenone induced disorder (not a main cause), so in recent studies it has been concluded that fecal microbiota transplantation can protect rotenone induced Parkinson's disease. To assess the preventive benefits of FMT treatment on Parkinson's disease to investigating the underlying processes scientists constructed a chronic rotenone induced PD mouse model in their study. It attests to the pathophysiology of PD being influenced by gut microbiota dysbiosis via the gut – brain axis microbiome. The key finding of the study is that FMT treatment can restore gut microbial dysfunction and can be used for future research in this area [3].

### Rotenone is a Cause of Mitochondrial Dysfunction

Rotenone also Causes mitochondrial dysfunction. As rotenone increases oxidative stress in mitochondria, it is possible that due to rotenone there must be an increase in ROS (Reactive Oxygen Species) in the mitochondria.

### **Exposure of Rotenone to Mitochondria Leads to**

- Release of ROS.
- NLRP3 and Inflammasomes release.
- Disruption in the membrane potential.
- Cytochrome – C release.
- Mutation in mtDNA.
- Low ATP synthesis.
- Decrease in GSH (glutathione) level.

### **What if Pregnant Ladies Are Exposed to This Pesticide?**

Due to exposure to pesticide in pregnant ladies the effect can be seen on babies too.

#### ***Acute Exposure***

In case of bit of exposure to this pesticide the baby may or may not get affected because the fetus and the mother are connected by umbilical cord, via blood and food and nutrition transportation. This type of pesticide may affect the child and lead to physical or mental disorders.

#### ***Chronic Exposure***

In case of chronic or large exposure of the mother to this pesticide the baby must get affected by this pesticide. There are several studies and news about the exposure of pregnant ladies to pesticide which leads to various disorders in children as well as in mothers. Rotenone is also a type of pesticide which is even more toxic than other pesticides [4].

### **Exposure to This Pesticide Can Lead to:**

- Mental retardness in children.
- Retarded growth.
- Genetic variations.
- weak bones and uneven body posture.
- eyesight issues.
- may lead to genetic disorders.
- sometimes leads to death.
- Rotenone can enter the body of pregnant women by oral supplements (like insulin).

## **NEURODEGENERATIVE DISORDERS**

The term “neurodegenerative disorders” refers to a set of illnesses in which neurons or we can say nerve cells in the brain or peripheral nervous system gradually lose their structure or function. The ability of the nervous system to efficiently send impulses and communicate is predominantly impacted by these illnesses.

Although the etiology of these neurodegenerative diseases differs, many of them share a genetic, environmental, and behavioral component.

Currently, most neurodegenerative diseases have no cure. Instead, treatment is aimed at relieving symptoms and slowing the progression of the disease. The main objective of ongoing research is to better understand the root causes. Develop new treatment methods and improve the quality of life of patients with Parkinson's and Alzheimer's diseases. Two examples are given:

### **1. Alzheimer’s Disease**

The neurodegenerative disease known as Alzheimer's disease primarily affects the brain and results in cognitive impairment and memory loss. Alzheimer is found to be the cause of dementia for between 60 and 80 percent, making it the most frequent cause of neurological issues. As per the most recent

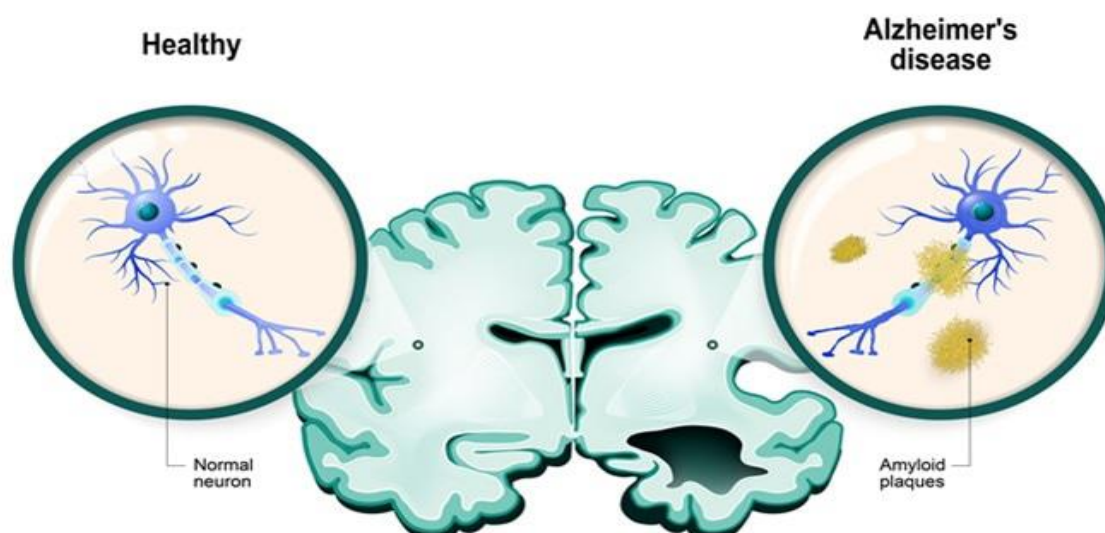
knowledge update it is said that Alzheimer is a very dangerous disorder. It could be genetic if detected in pregnant mother or father is a carrier or diseased.

### Rotenone Effect on Alzheimer's Disease

Rotenone is one of the cell-death inducing stimuli that has been linked to both Parkinson's disease and Alzheimer's disease. Rotenone functions as a traditional, highly affine inhibitor of electron transport through complex 1 (Figure 3).

It is unclear how rotenone affects cholinergic neurons [5].

It has been a hypothesis that long term cumulative exposure to pesticides could result in a negative effect on the central nervous system. Late onset of AD begin to manifest at most at the age of 60. It leads to an increase in loss of memory and cognitive impairment and dysfunction in both work and daily activities. Amyloid plaques and neurofibrillary tangles, two pathologically significant protein aggregates associated with AD, are composed of tightly packed filamentous networks of hyper phosphorylated tau protein helical filaments [6].



**Figure 3.** Difference between Normal Brain Condition and Alzheimer's Disease Brain Condition [7].

## 2. Parkinson's Disease

Parkinson's disease is a brain disorder (caused due to neurological abnormalities in the body due to various aspects and one of which is Rotenone, a pesticide) that causes unintended or uncontrollable movement of the body, such as shaking, stiffness and difficulty in balancing and coordination of the body [8].

In the early stages of Parkinson's disease your face may be expressionless soft or soft sound and the arms do not swing when walking. As your disease progresses over time, your PD symptoms may worsen [9].

### SYMPTOMS

#### *Cogwheel Rigidity*

Cogwheel rigidity is a form of stiffness in which an attempted movement causes a limb to react with jerks resembling cogwheels. One crucial physical examination characteristic for the diagnosis of Parkinson's disease is cogwheel rigidity. Any limb may feel it in a person. Sometimes stiffness goes unnoticed by a person in their daily lives.

### ***Bradykinesia***

Parkinson's disease is characterized by bradykinesia, or slow movement. Bradykinesia is characterized by weakness, tremors, or rigidity. Although these may not be the only causes.

### ***Resting Tremor***

Resting tremor is a characteristic feature of Parkinson's disease. The cause of the remaining tremor is currently unknown. The cause of the remaining tremor is currently unknown. Recent positron emission tomography studies. This study of these patients with isolated resting tremor reveals markedly reduced fluoro-dopa uptake at the periphery of Parkinson's disease.

### **Rotenone as Cause of Parkinsonism**

Rotenone is said to be a cause of Parkinson's disease, but it is still not proven that rotenone is the actual cause of Parkinson's disease. Rotenone affects the neural cells which leads to neurological changes which are like PD. Lewy neuroalgia is caused by low doses of rotenone, however, it is not caused by Lewy body aggregation. It has been shown that giving Lewis rats rotenone subcutaneously at a dose of 2–4 mg/kg per day for seven days causes the pathology of Parkinson's diseases [10].

Pesticide enters the body via inhalation, dermal absorption, and ingestion of fish collected from areas where rotenone has been put in. It is identified that the dosage of oral dose that is 300–500 mg/kg can be toxic to the human body, but the actual dose cannot be detected because of various factors (age, sex, immune level etc.) in humans [11].

### **MICROBIOTA ANALYSIS**

Parkinson's disease (PD) is a common neurodegenerative disease which shows abnormalities of the digestive system. In addition to the well-known motor malfunctions. As time passes, the gut microbiome influences the microbiota–gut–brain axis which is the relationship between the intestines and brain in the development of Parkinson's disease. Recent research suggests that fecal microbial transplantation (FMT) is a method for restoring normal microbial populations. It has a positive effect on Parkinson's disease. To evaluate the preventive benefits of FMT treatment in PD and explore the underlying processes, we created chronic Rotenone. The PD mouse model in this study via the microbiota–gut–brain axis the role of gut microbial diversity in the pathogenesis of PD has also been demonstrated.

### **RESULTS**

In addition to demonstrating rotenone-induced gut microbial diversity results in impaired gastrointestinal function and poor behavioral performance in PD mice, 16S RNA sequencing revealed bacterial strains. Akkermansia and Desulfovibrio varieties increase in fecal samples from rats caused by rotenone. On the other hand, FMT treatment significantly improved the gut microbial ecosystem. It helped PD rats with motor dysfunction and gastrointestinal dysfunction.

Later research showed that FMT administration reduced intestinal inflammation and barrier breakdown which reduces inflammation levels throughout the body FMT therapy then induced substantia nigra, reduced neuroinflammation in the SN, reduced blood–brain barrier (BBB) dysfunction and reduced damage to dopaminergic neurons. Further mechanistic research suggests that FMT treatment reduces lipopolysaccharide (LPS) levels in colon, serum, and SN TLR4/MyD88/NF- $\kappa$ B. The signaling cascade and downstream anti-inflammatory products are suppressed in the colon and SN.

You cannot eat Akkermansia because there are no foods that contain it. Eat foods that contain apples, nuts, berries, grapes, flax seeds, green tea, almonds, olives, asparagus, onions, oats, etc., which increase the risk of developing Akkermansia. Akker. Romancea helps maintain a healthy weight. Strengthen the mucosa of the intestines and digestive health is increased Up to 4% of intestinal bacteria in a healthy gut contain Akkermansia.

The human gastrointestinal and vaginal flora is made up of anaerobic Gram-negative bacteria called strains Desulfovibrio.

A key feature of the pathogenesis of Parkinson's disease (PD) is the aggregation of a protein in neurons, alpha-synuclein, or alpha-synuclein. It has been suggested that pathogenic intestinal microorganisms such as *Desulfovibrio* bacteria which is related to Parkinson's disease causes alpha-synuclein to accumulate in intestinal cells.

## NEURODEVELOPMENTAL DISORDERS

The illness known as a neurodevelopmental disorder affects how your brain functions. They might be minor, allowing people who are affected to lead relatively normal lives, or severe, requiring lifelong care. Children with neurodevelopmental problems may have issues with their motor abilities, behavior, learning, memory or other processes. The whole neurodevelopmental impairments symptoms often vary or evolve as a child gets older certain disabilities are irreversible. It might be challenging to diagnose certain illnesses and treat them.

Examples of Neurodevelopmental Disorders

- Attention deficit hyperactivity disorder (ADHD).
- Autism spectrum disorder (ASD).

### Autism Spectrum Disorder (ASD)

ASD is a neurodevelopmental disorder that affects learning, behavior, and communication. This is because symptoms usually appear within the first two years of life. Autism is therefore called. It is considered a “developmental disorder” even though it can be diagnosed at any age [12].

Two neurodevelopmental illnesses that lack clear limits in their clinical description, epidemiology, genetics and protein-protein interactions are intellectual disability and autism spectrum disorder (ASD) [13].

### Rotenone Effect on ASD

In various studies it has been proved that pesticides are one of the causes of autism spectrum disorder. Regarding neurotoxic substances, several pesticides families have lately been connected to ASD. The most studied compounds include carbamates (CM), pyrethroids (PT), neonicotinoids (NN), and organochlorines (OC). OC compounds are pesticides. Synthetics are used throughout the world and have important applications in industry and agriculture. Their toxicity is mainly due to axonal sodium gate (DDT type) and GABAergic regulation of the influx of chlorine ions (chlorinated alicyclic type) aldrin, dieldrin, endosulfan, DDT, and DDD are some of the most important OC [14]. Rotenone will also have the same effect as an insecticide.

### Attention Deficit Hyperactivity Disorder (ADHD)

ADHD or attention deficit hyperactivity disorder is one of the most common mental health conditions affecting children today. Symptoms of ADHD include impulsivity, hyperactivity, and attention.

In many facets of a person's life, including interpersonal connections, daily functioning, academic and professional success, ADHD is seen as a chronic and disabling disorder (Harping, 2005). When this disease is left untreated in youngsters and children's this can lead to various issues in them like low self-esteem and low confidence as their social functioning will get poor.

### Rotenone Effect on (ADHD) attention deficit hyperactivity disorder

In a study it has been proved that pesticides do have effect on ADHD and the result was – ADHD symptoms were more prevalent in pesticides applicators than in non – applicators. A dose response relationship between urinary TCPy concentration and symptoms was found. In comparison to participants without ADHD, applicators with ADHD claimed to have used pesticides for a greater number of hours during the application season and to have higher cumulative TCPy levels. A diagnosis of ADHD was made for one-fourth of all applicants who reported six or more symptoms.

## CONCLUSIONS

The examination of the pesticide rotenone highlights its substantial toxicity and the intricate impact it has on the human body, notably affecting vital organs such as the brain and mitochondria. Recognized as a potent inhibitor of complex 1, its harmful effects extend to various facets of health, presenting a particularly concerning link to the onset of Parkinson's disease. Despite extensive research, pinpointing the exact harmful dose of rotenone remains challenging due to individual variabilities influenced by factors like age, sex, and immunity.

The absence of a definitive cure for Parkinson's disease, closely associated with rotenone exposure, underscores the pressing need for alternative agricultural practices. The findings strongly advocate a shift towards natural fertilizers and manures in agricultural fields as a proactive measure to alleviate the risks posed by toxic pesticides. As we navigate the intricate relationship between environmental toxins and human health, embracing sustainable and eco-friendly farming practices emerges as a crucial step in safeguarding both our well-being and the ecosystems we inhabit.

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