https://doi.org/ 10.33472/AFJBS.6.9.2024.2055-2074

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Spirulina as neuroprotective supplement in parkinsonism; A review

Authors' name

Moin Khan, Shivani Srivastava, Jai Gopal Sharma*

Affiliations

Dept. of Biotechnology, Delhi technological university.

Corresponding authors' details;

Name: Prof. Jai Gopal Sharma

Affiliation: Dept. of Biotechnology, Delhi technological university.

Article History

Volume 6,Issue 9, 2024

Received: 26-03-2024

Accepted : 30-04-2024

doi: 10.33472/AFJBS.6.9.2024.2055-2074

ABSTRACT

Parkinson disease is a progressive disorder that impacts the central nervous system and the component that are controlled by nerves. Major pathological hallmark of Parkinsonism is the presence of anomalous aggregates of α-Synuclein protein. Several experimental and pathological studies explain the other key involvement in PD pathogenesis like; loss of dopaminergic neurons is mid brain, Chronic microglial and astrocyte's activation, mitochondrial dysfunction, brain inflammation and oxidative stress. Parkinsonism indicates the several motor and non-motor symptoms like bradykinesia (slowness and stiffness in movement), tremor and resting tremor. There is no known permanent treatment of Parkinson disease, yet certain drugs are effective on symptoms. Blue green algae such as spirulina is a unicellular species and economically distributed as nutritive food supplements. Spirulina is one the influential source of natural nutrient and many experimental studies informed about the antioxidant and anti-inflammatory properties of spirulina in parkinsonism. Spirulina contain multiple nutrients like vitamins, protein and essential fatty acid. Phycocyanin; colour pigment protein of spirulina algae which is playing a crucial role in brain inflammation and certain PD related pathogenesis oxidative stress, microglial cell activation, cytotoxicity.

KEYWORDS: Parkinson's disease, Oxidative stress, Microglial cell activation, Mitochondrial dysfunction, Spirulina plantensis.

1. INTRODUCTION

Parkinson is one of the most challenging progressive neurodegenerative disorders and it's characterized by bradykinesia, tremor, resting tremor, motor and non-motor symptoms. Several reports of PD explained about the non-motor symptoms like; Depression and anxiety. Interestingly few reports revealed that non motor symptoms are more pronounced in PD patient (Leite Silva et al., 2023). Lewy bodies which are the pathological hallmark of PD contain α-Synuclein (α-Syn) aggregates, play a determining role in Parkinsonism (Wakabayashi et al., 2007a). Alongside, as per the neurohistological and neuroimaging studies, PD effects peripheral organs and central nervous system as well which plays a crucial role in brain inflammation (Çınar et al., 2022). Also, microglial cell activation leads to brain inflammation. This activation is controlled and expressed by CX3CL1 (Fractalkine, FKN) and belongs to chemokine family is expressed by neurons in CNS (central nervous system) and its receptor CX3CR1 abundantly expressed by microglial cell. Evidently disruption of CX3CL1-CX3CR1 signalling leads to inflammatory response in human brain. (Helmke et al., 2019) Similarly, 6-OHDA neurotoxicity leads to production of Oxidative species and brain inflammation into the CNS are the dominant features of PD (Simola et al., 2007). Parkinson disease protein 7, also known as DJ1 (PARK7) is potent biomarker for Parkinson and also serve the essential function for neurons like neutralization of reactive oxygen species (Bonifati et al., 2003). Mutation in DJ1(PARK7), leads to the deleterious effect on brain health. DJ-1 protein is playing crucial role in the oxidative stress as well mitochondrial functional protein (Ariga et al., 2013). Spirulina plantensis serves as nutrition aid in most of the countries from last few decades and also spirulina used as supplement food for the astronaut by NASA. Because it delivers high protein and vitamin rich supplement without any adverse effect on the health, this alga is considered one of the valuable foods for human diet (Karkos et al., 2011a). Certain important biochemicals component includes carbohydrates polymer unit (polysaccharides), Provitamins (b-carotene), Fatty acid (Linolenic acid), colour pigment protein (Phycocyanin). Phycocyanin is a most valuable biochemical compound is widely used in cosmetics industry for colouring and it has certain neuroprotective property like; Anti-inflammatory, antioxidant and hepatoprotective as well (Su et al., 2014). From last few years, several experimental research revealed that the intake of spirulina manifest positive effect and outcomes on human brain health. Spirulina is known as a valuable source in supplements and therapeutic medicine and shows the neuroprotective activity in PD and increase the expression of Fractalkine receptor (cx3cr1) to generate positive effect in rat model and 6-OHDA model of PD (Pabon et al., 2012) (Lima et al., 2017a). Experimental studies also support that Spirulina alga reduce the apomorphine induced rotation behaviour in rat model, although the response of recovery of DA neurons is not well understood but the partial recovery of DA and DOPAC depletion is observed. Similarly, Loss of DA neurons in the substantia nigra compacta is the major hallmark of parkinsonism but for Parkinson patient, the partial reversal of DA depletion in SPI may support some neuroprotection. Spirulina plantensis also support the blockade of oxidative stress as well as ROS (Reactive oxygen species) production in PD (Lima et al., 2017b).

Hence the aim of this review is to provide a brief explanation of therapeutic role of spirulina in Parkinson disease.

2. PARKINSON: A NUERODEGENERATIVE DISORDER

Parkinson is a progressive degeneration of dopaminergic neuron in mid brain. This progressive loss of dopaminergic neuron in substantia nigra which is portion of midbrain, is manifested by symptoms like; tremor, bradykinesia, and other motor and non-motor symptoms (Hayes, 2019). Tremor is the most common indication of Parkinson disease and progressive loss of the dopaminergic neuron in the dorsal and posterior region of substantia nigra (SN) supported into certain PD pathophysiology studies. Although certain dopamine precursor drugs and synergy drugs are employed in tremor symptoms as a first line of defence but none of these are completely effective in dopaminergic loss in CNS (Abusrair et al., 2022). Bradykinesia is combination of two words i.e. akinesia (Failure in movement of muscle voluntarily) and hypokinesia (Motor control disability). Bradykinesia could be the connecting link of creating the instruction (programming) and their execution. Muscle weakness, Rigidity, Rest and action tremor, movement variability can be secondary root cause of bradykinesia (Berardelli et al., 2001). PD is the secondary quotidian neurodegenerative disease after Alzheimer. The key neuropathological diagnostic features of Parkinson disease are modest to severe degeneration or loss of neurons in the substantia nigra which is the portion of midbrain (Kim et al., 2018). Lewy body which is the major hallmark of Parkinson is discovered by Friedrich Heinrich Lewy in 1912 in the brain of a patient who had suffered from parkinsonism and initially they found neuronal inclusion in the brain of patient but later they named Lewy body after the discovery (Rodrigues E Silva et al., 2010). Cellular events like inclusion body formation and the aggregation of protein (α-Synuclein) are related to Parkinson disease. Protein aggregation of α-Synuclein is the main pathological hallmark or characteristics of parkinsonism's. Lewy bodies broadly distributed in the most of the part of CNS like; substantia nigra. This broad distribution of Lewy body pathology might help to understand the array of motor and non-motor symptoms of Parkinson disease. Researchers explain the α-Synuclein oligomers and protofibrils are possibly cytotoxic but on the other hand fibrillar α-Synuclein may serve as the certain neuroprotective mechanism in Parkinson's disease. Another possibility if host cell continues create toxic protein and in response LB continuously degrade those protein, leading to the excessive build-up of protein aggregation into the host cell and eventually cell will die (Wakabayashi et al., 2007b).

Postmortem studies addressed early postural instability and inability or freezing in walk (Gait), the motor symptoms and similarly other motor and cognitive studies are addressed (Barbosa et al., 2016). Other motor symptoms like slowness in voluntary movement and speech (bradykinesia) with muscular rigidity, shaking or trembling in movement (tremor or postural inability, sleeping disturbance and dementia (Sveinbjornsdottir, 2016). Neuropathological studies also revealed that prolonged activation of microglial cell play a detrimental role in Parkinson disease (Béraud et al., 2012).

3. C- PHYCOCYANIN; A PIGMENTED PROTIEN

Prokaryotic, photosynthesis-dependent microorganisms called algae are able to adapt a wide range of external circumstances. Spirulina is a string and spiral algae with soft membranes that is easy to digest and rich in essential amino acids, vitamin B12 and GLA (Izadi & Fazilati, 2018). Spirulina species provide vitamins, minerals, and Carotenoids that are beneficial

against hypercholesterolemia, oxidative stress, and hyperglycaemia and have antihypertensive qualities. They also boost probiotic development and demonstrate antibacterial activity (Grover et al., 2021). Both people and animal ingest Spirulina, a nutritional supplement, which is a biomass of Cyanobacteria (blue-green algae)(Karkos et al., 2011b). The Phycobiliprotein, a key fluorescent protein involved in light acquisition and categorized based on pigment, is found in Spirulina and it is divided into Allophycocyanin, Phycocyanin and Phycoerythrin. Spirulina was primarily concerned in producing high- value proteins, such as Phycocyanin (blue pigment). The pale blue substances known as Phycocyanin, which are present in Cyanobacteria and blue-green algae, occupy orange and red light at 620nm and emits illumination at 650nm (Ratha & Prasanna, 2012). Phycobilisomes are the specific location of Phycocyanin(Fernandes et al., 2023). Food products and cosmetics are colored using C-Phycocyanin, a vivid blue protein derived from Spirulina (Liu et al., 2016). Like biliverdin, Phycocyanin is a naturally occurring peptide inhibitor that effectively inhibits NADPH oxidized, a key component in oxidative stress-related illnesses, affecting organ development, inflammatory processes, and immunological responses (Izadi & Fazilati, 2018). Cyanobacteria may produce C-PC through cell wall disruption and water - soluble phycobiliprotein extraction, with factors like solvent type, biomass ratio, and biomass type influencing extraction methods (Pan-utai & Iamtham, 2019). The C-PC amino acid composition of S.Platensis reveals that a majority of strains share similar compositions, consisting of alpha and beta subunits with 162 and 172 amino acids, respectively (Liu et al., 2016). Additionally, C- Phycocyanin has been used as a food additive, fluorescent dye, medication, and colorant. It has been demonstrated to have antioxidation, inflammatory, anticancer and immunity-boosting properties and can also be processed to create fluorescent reagents, probes, and traces for use in medical research and diagnosis (Liu et al., 2016). When coupled with He-Ne light, C-Phycocyanin functions as a photosensitive agent in photodynamic treatment, which enhances tumor treatment. Its particular propensity towards macrophages linked to tumors (TAMs) boots the drug's efficacy as a cancer treatment. It also contains anti-inflammatory properties that support leukocyte function or the regenerating of mammalian blood cells (Jiang et al., 2017). Assay level C-Phycocyanin at 3.9, or exceedingly pure C-Phycocyanin at above 4.0, is equivalent to meal quality C-PC with a quality of 7.0. The authenticity of C-PC is crucial for both industrial and medical applications (El-Mohsnawy & Abu-Khudir, 2020). The latest nanotechnology assures the stability of C-PC, a naturally occurring anti-inflammatory drug with antioxidant properties that has potential use in cancer therapy because of its ability to decrease the production of COX-2, reduce epidermal ageing, and activate pro-apoptotic pathways (Dranseikienė et al., 2022). The effect of C-PC on MCF-7 cells from breast cancer patients and people's basic fibers revealed that C-PC had a comparatively low 24-hour death rate, with more than 90% of basic cell types of fibroblasts being viable (Safaei et al., 2019).

Table 1. Various method of cell disruption techniques used in Spirulina extraction.

S. No.	Types	Details
1.	Freeze and thaw process	By repeating Freezing and thaw cycles leads to the cell lysis and membrane disruptions.

2.	Mixing and homogenization	Squeezing of cell by physically, like using of mortar and pestle.
3.	Bead milling	Mechanical cell disruption technique which leads to direct damage to cell wall.
4.	High pressure homogenization	Using pressurized homogeneity with lysosomal treatment.
5.	Ultrasonic method	Ultrasonic waves are used to disrupt the biological membrane.
6.	Electric field	Electric pulse is used to remove Phycocyanin from Spirulina.
7.	Enzyme assisted method	Used of various enzyme with the required conditions and PH.
8.	Microwave	Environment friendly method, used of little input of energy

- Chemical assays show C-PC inhibits α-synulein fibril nucleation and elongation, potentially preventing toxicity in the Parkinson's disease yeast model, reducing inclusions and cytotoxicity, and mitigating oxidative stress and proteostasis deregulation (Pentón-Rol et al., 2021).

4. EFFECT OF MICROGLIAL CELL ACTIVATION IN BRAIN HEALTH

Microglial cells are the main resident cell of the mid brain, which is derived from the myeloid lineage by hematopoietic cytokines expression. Microglial cell is the main cellular network of CNS which maintain the neuronal network and response rapidly in the brain injury repair mechanism. Microglial response against the toxin, free radicals and soluble antigens are extremely controlled regulated, because over activation or prolonged activation of microglial cell leads to the deleterious for the CNS.

The main job role of microglial cell is elimination of pathogen and bacteria, response against protein aggregation and other soluble antigen in the CNS. Additionally microglial cell is the main cell which support the apoptosis during the brain injury and secrets numerous chemoattracts and cytokines, which contribute the influential immune response against the soluble antigen and tissue repair in CNS (Colonna & Butovsky, 2017a). These cells are the key component of immune cells and abundantly found in the CNS (Central nervous system). Microglial cells are said to be resting (Ramified morphology) in a healthy brain but once they

disturbed by any signalling event, they become activated. Activated microglial (ameboid morphology) rapidly migrate to the site of Lewy bodies in PD, where they proliferate and release of multiple cytokines and pro-inflammatory (Färber & Kettenmann, 2005).

4.1. Cross talks of CX3CL1/CX3CL1 in microglial cell activation; As we know that the immune response is a pivotal role of homeostasis because it provides the boundary against the outer pathogen as well as internal tissue/cellular damage, however prolonged activation of immune cell leads to unfavourable rather than defensive (Lotz et al., 2021). Microglial cell, which contribute the 10% of CNS resident cell are mononuclear and quite dynamic in structure (Colonna & Butovsky, 2017b). Fractalkine (FKN, CX3CL1) is a chemokine which is expressed copiously in neurons. Chemokines are the small proteins which are help in recruit the inflammatory cell on the site of action. Chemokines having four subclassed C, CC, CXC, CX3C .CX3C are followed by its receptor "R" and a specific number (e.g., CX3CR1) and "L" for ligand (e.g., CX3CL1). This expression induces microglial cell by its specific receptor (CX3CR1) (Jones et al., 2010),(Pawelec et al., 2020). CX3CL1 could found in membrane bound glycoprotein which serve as cell adhesion either they can be found in soluble form after proteolytic cleavage. Proteolytic cleavage can proceed by metalloproteinases (protease whose catalytic mechanism involves a metal) ADAM10 and ADAM17 (Hundhausen et al., 2003). The CX3CL1 and its receptor present on the microglial cell (CX3CR1) allows the bridge of communication between neurons and microglial cell, also the study of substantia nigra compacta (SNc) suggest that abundantly expression of CX3CL1 which is inhibits the activation of activation of microglial cell (Pawelec et al., 2020).

4.2. Role of Spirulina in Microglial activation: Microglial activation against the neurotoxicity is the main protective unit or first line of defence in the CNS. However prolonged activation of microglial cell is not favourable for the neuron's survival in the Parkinson disease. In the review we explain that the α-Synuclein aggregates are the main cause of PD and serves as the major hallmark in the patient of parkinsonism. Scientific studies suggest that the there is an increase in activated microglial cell population where the expression of the α-Synuclein aggregates are seen. Various approaches like; α-Synuclein rat model for Parkinson is used to investigate that how α-Synuclein effects the activation of microglial cell (Joers et al., 2017). Spirulina rich diet on rat model of α-Synuclein demonstrate spirulina is play a neuroprotective role against the α-Synuclein which is directly linked to the reduced the number of microglial MHC-II activation. Proinflammatory cytokines and microglial MHC-II activation are the potent biomarkers for the m1 microglial cell activation. Another aspect of microglial cell activation is Fractalkine (CX3CL1) An inherent signal to aimed the reduce microglial activity is expressed by neurons and their receptor (CX3CR1; GPCRs) which is present on the microglial cell. The study indicates that spirulina significantly enhanced the expression of CX3CR1, irrespective of the treatment of theα-Synuclein (Pabon et al., 2012). As descried above that microglial cell is the main cellular network which has been involved by the production of certain proinflammatory cytokines. Several studies suggest that synergically effect of spirulina with other antioxidants like; blueberry induce a brief rise in 0X-6 positive microglial cell the area of CNS injury or inflammation area. Certain animal model of PD demonstrated that animal fed with

antioxidant diet such as spirulina and blueberry normalized the level of OX-6 positive microglial cell but on the other hand control diet fed animal are indicate increase/spike in the level of microglial cell. Although effect of spirulina and blueberry are not completely effective for the dopaminergic neuron recovery in the area of mid brain but certain marker and studies support that the spirulina rich diet are shoeing the beneficial result in the patient of PD and rat model (Strömberg et al., 2005). Experimental studies also explain the Spirulina plantensis also reduce the microglia cell activation and toxicity, induced by LPS- induced treatment (Chen et al., 2012).

5. 6-OHDA-AN OXIDATIVE NUEROTOXIN

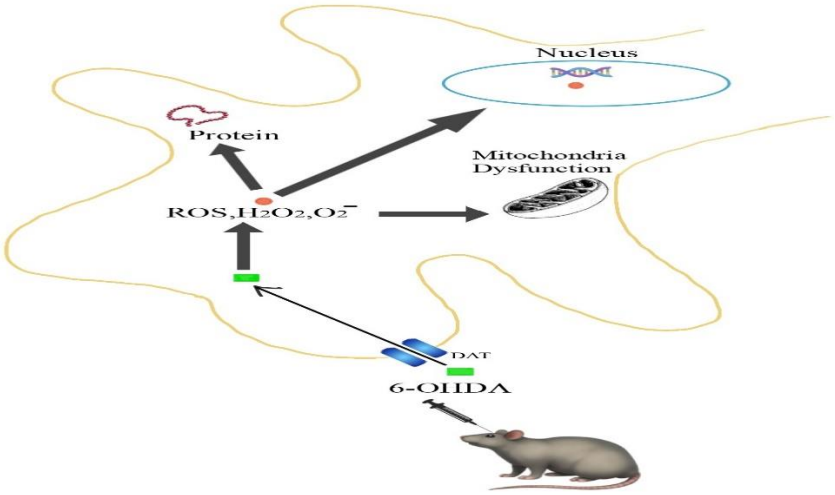
There are several facts that the 6-OHDA has been significantly used as Parkinson In-Vivo model.

- Production of Reactive oxygen species (ROS) that can cause neuronal damage.
- When 6-OHDA breaks it can generate the Free radicals that can react with oxygen species and produce hydrogen peroxide, super oxide and, Hydroxyl radicals and many more.
- An exceedingly reason of mitochondrial dysfunction.
- Oxidative stress.
- Modified essential functional of protein (Varešlija et al., 2020).

6-OHDA a potent oxidative neurotoxin, serves as a valuable tool in the Parkinson model of rat. 6-Hydroxydopamine is showing the structural resemblance of dopaminergic and catecholaminergic neurons that's why widely used in the neuropathological and substantial studies of neurodegeneration. (Simola et al., 2007). 6-OHDA and LPS are the neurotoxins which induce chronic microglial activation by changing their morphology and 6-OHDA is also the primary factor for inflammatory process in PD model(Parra et al., 2020). 6-OHDA direct administration couldn't cross the blood brain barrier, Therefore Neurotoxin like 6-OHDA is directly delivered to CNS by directly injection (Stereotaxic surgery)(Glinka et al., 1997). Although 6-OHDA couldn't mimic the all aspect and hallmark of PD but it can reduce almost 60% dopaminergic neurons. It can enter into the neurons and accumulate there, Entry of 6-OHDA is permitted by transporter of catecholamines which is present in membrane (Salari & Bagheri, 2019). Hypothetically studies explains that administration of 6-OHDA produces delayed Production of Oxidant species (after 1 hour) under the physiological PH, however some studies also revealed that ROS production is rapid (within minute) to 6-OHDA by using the other assay. As per the time-based study, ROS production is depending on the aconitase activity, which is an iron-sulphur complex (Prominently found in mitochondria as well as cytosol) and its activity is a potent indicator and involve in the production of oxidant. B65 cell with 6-OHDA treatment also revealed that 6-OHDA persuade the mitochondrial ERK activation, which can lead to the reason of protein dysfunction as mentioned above(Kulich et al., 2007). Catalase enzyme, which is majorly found in the peroxisomes of mammals which is known as the removing hydrogen peroxide decomposition which is generated by 6-OHDA. MTT and LDH release assay confirmed that the H202 decomposition which is generated by 6-OHDA is partially abolished by catalase not completely. 6-Hydroxydopamine is can also trigger the programmed cell death which is known as

Apoptosis mechanism by activating the Endo proteases protein. Such apoptosis is regulated by the cascade protein caspase3/7 in mammalian cell line. This caspase is activated by the cytochrome c, which is present in intermembrane/intercristae space of mitochondrion cell (Hanrott et al., 2006; Saito et al., 2007). Additionally, SOD2 (superoxide dismutase); an enzyme which change superoxide form into the hydrogen peroxide (H202). Hydrogen peroxide is a less reactive form which may travel easily out to the mitochondrial membrane. Several studies suggested that mutation loss of functionality of SOD2 may trigger the neurodegenerative disorder like PD (Flynn & Melovn, 2013).

5.1. Role of Spirulina in 6-OHDA; Microscopic cyanobacterium spirulina is rich source of multiple beneficial biomolecules and considered as a safe diet food. Microalga spirulina gained deep attention by people and researcher because of protein rich pigmented protein. In cosmetics and food industries Widley used phycocyanin, a blue colour natural pigment protein which is significantly used as antioxidants, anti-inflammatory and anti-cancer therapy source (Lupatini et al., 2017). In most of the neurodegenerative disease like Parkinson, marked by neuroinflammation and mitochondrial dysfunction may result in increase in oxidative stress. This oxidative stress might release the reactive oxygen (ROS) and nitrogen species. Similarly, iron is the most important transient metal elements in our physiological system because it involves in multiple pathways of growth and development of cell. Adverse effect of iron interaction with certain chemical and biological processes can leads to detrimental. This may trigger the oxidative stress and reactive oxygen species production which can cause the membrane alteration and cytotoxicity. In addition, iron cytotoxicity induced LDH release, which catastrophically harms the neuroblastoma cellular network (Bermejo-Bescós et al., 2008).



ROS, 6-OHDA.

Figure 1. 6-OHDA mimics natural pattern of neurotoxicity. 6-OHDA (into green) directly inserted into the host and then it enters into dopaminergic neurons via DAT (Dopamine transporter). Inside the neurons oxidation of 6-OHDA produces several cytotoxic species like oxygen and nitrate. Such Reactive cytotoxic species may impact to nucleus, protein inactivation (PDI), mitochondrial dysfunction and activation of glial cell.

The 6-OHDA model of Parkinson or hemi Parkinsonism is help to understand the neuroprotective quality of spirulina platensis (SPI). Spirulina platensis appreciably lowered the nitrate and lipid peroxidation content with in the right striatum of 6-OHDA group indication the role of oxidative stress in Parkinson and other neurodegenerative disease. Several studies are also supported the spirulina play's a beneficial role in KA mediated oxidative stress, which are the reason of neuronal death in neurodegenerative disorder. Degradation or Disruption of mitochondrial function may occur through KA release of lactate dehydrogenase (LDH) in MTT toxicity assay of neurovegetative disorder, so spirulina play a key role in mitochondrial stability and help of maintenance the cellular network (Zhang & Zhu, 2011)(Lima et al., 2017b). Experimental studies of synergic effect of spirulina fusiform with Amantadine (antidyskinetic medicine, used in the treatment of Parkinson) manifested the valuable result in the 6-OHDA rat model of Parkinson. Positive response of spirulina with amantadine like; locomotor activity, muscle coordination and distance travelled are also seen (Chattopadhyaya et al., 2015). As mentioned above down regulation of SOD2 leads to deleterious is PD, however spirulina polysaccharides complex enhances the expression of SOD2 enzyme, which can restore the normal function of mitochondria (Machihara et al., 2023).

6. MUTANT DJ1 PROTIEN FORM; A POTENT BIOMARKER OF PARKINSON DISEASE

DJ-1 protein superfamily, which is marked or known as the Parkinson disorder protein 7 is a potent biomarker. In 2003, physiological role and its studies suggest that the mutation in DJ-1 gene linked with the oxidative stress response of Parkinsonism (Bonifati et al., 2003). DJ-1 Parkinson model is the widely accepted model, which can describe the genetic studies of Parkinson disease. Several monogenic gene for parkinsonism is SNCA (PARK1-4), LRRK2 (PARK8), Parkin (PARK2), DJ-1 (PARK7). Mutation of these gene leads to autosomal-dominant parkinsonism (Klein & Westenberger, 2012). DJ-1 (PARK7) is present in most of the mammals and bacteria too. Human DJ-1 superfamily of protein is extensively studies model because of its principal role in multiple disease including neurodegeneration. Researcher Explanation suggest over last few years DJ-1 superfamily homologues are significantly reduced the production of ROS (Reactive oxygen species) (Smith & Wilson, 2017). DJ-1 activity regulates multiple functions like; Regulates transcription, mitochondrial function, neutralization of reactive species and free radicals. Cell growth and regulation have several pathways, one of best known is phosphoinositide-3 kinase pathway that minimize cellular death and increase cellular development when encounter stimulus of epidermal growth factor (EGF). PTEN which is present on chromosome 10 is deleted is a oncogene and act as a negative regulator for PI3 K/Akt pathway by limiting PI3 K. PTEN's activity is directly hindered by DJ-1 protein through binding. In DJ-1 model of PD, after inducing oxidative stress in rat Akt pathway is switched on simultaneously PTEN is inactivated and DJ-1 knockout mice, exhibit decrease level of Akt phosphorylation, which is the major reason of neuronal death. In mitochondria DJ-1 protein binds to mitochondria complex I and control the activity of mitochondria. Rat and flies model studies of PD demonstrated that fragmented mitochondria are found in neurodegenerative condition, however there is a controversy on DJ-1's autophagy function (Ariga et al., 2013).

6.1. Role of Spirulina in DJ-1 mutation; Drosophila melanogaster, a key model to understand the physiopathology of neurodegenerative disease like PD. For understanding the role of DJ-1 in PD chemical induced and genetic mutation-based model are developed in Drosophila. DJ-1$\beta^{\Delta 93}$ is flies model of parkinsonism (Solana-Manrique et al., 2022). DJ-1$\beta^{\Delta 93}$ is used in survival and ageing studies in neurodegenerative disorder. Spirulina and its compound C-phycocyanin and certain vitamin derivatives are works as defence system in Neurodegeneration. In DJ-1$\beta^{\Delta 93}$ model survival assay studies explained that intake of spirulina in drosophila PD model improve life span of organism. This improve may the reason of antioxidant and antiaging properties of super food spirulina. Spirulina is also reduced the Hsp70 and JNK signalling in PD model of drosophila. In several other model like C. elegans, yeast, rats and flies JNK signalling effect life span and on the other hand Hsp70 serves as cellular stress marker. Spirulina intake in several model studies revealed the benefits effect on brain health (Kumar et al., 2017).

7. CONCLUSION

Spirulina serves as the revolutionary role in the malnutrition (Nutrition deficiencies) burden. Spirulina is microscopic, multicellular algae which is rich in nutrition. Spirulina used as dietary supplement because of its unique biochemical properties such as significant amount of protein component, vitamins precursor and derivatives like beta-carotene, minerals and most importantly low-cost dietary food. Because of it contain natural colour compound, spirulina serves as important role in the cosmetics industry too. Spirulina are also used as the placental developmental because it contains rich protein source food during the pregnancy of women's. SPI and its synergic effects with other drugs such as amantadine, blueberry source as employ the neuroprotective role in the certain neurodegenerative disease like PD (Sinha et al., 2018). Parkison disease is a neurodegenerative disorder, which is characterized by the gradual or progressive loss of neurons in the substantia nigra compacta (a portion of mid brain). Parkinsonism is identified by various symptoms like; irregularities or slowness in movement including Bradykinesia, resting tremor, dementia and muscle stiffness. Pathophysiological studies of Parkinson disorder demonstrated that, continues depletion of dopaminergic neurons in the CNS is the major hallmark of PD. Another aspect of PD like α-Synuclein misfolded, chronic or prolonged activation of microglial, Lewy bodies, oxidative stress and mitochondrial dysfunction may involve in the PD neurodegenerations (Haider et al., 2023). Prolonged activation of microglial cells is the marker of neuroinflammation in PD because when they activated, they release nitrogen and oxygen reactive species. Proinflammatory cytokines like; TNF-α, IL-1β, and IL-6 they further lead to activation of astrocytes. Spirulina's biomolecules phycocyanin protects microglial cell from the different pro-inflammatory cytokines and LPS induced cytotoxicity (Chen et al., 2012). CX3CL1 Fractalkine signals, which is induces by neurons continuously and its receptor present on microglial cell as CX3CR1 (G-protein coupled receptor). This pathway of fractalkine mediates the cell development communication between neurons and microglial cell. This pathway flows normally in health individual but during the neurovegetative disease it may decreases. Surprisingly spirulina enhance the level of CX3CR1 in Several rat model of PD and play a beneficial role between the cross talk to neurons and microglial cell (Pabon et al., 2012). 6-OHDA is widely accepted tools used to investigate the neuron degeneration and motor symptoms of Parkinson model. 6-OHDA enters into the neurons through DAT; which

is dopamine transporters into the dopaminergic neurons and mimic natural pattern of Parkinson disease. Spirulina alone and with the combination of other neuroprotective drugs like amantadine are showed protective effect into several PD model. In rat brain damaged which is caused by 6-OHDA, Spirulina with the combination of amantadine improve neuroprotective activity and restoration of dopamine level in striatum portion (Chattopadhyaya et al., 2015). Another cause of cell damaged and neurodegeneration is increase in ROS (Reactive oxygen species) production within the cellular compartment. Iron toxicity may induce the oxidative stress and ROS production in the neuroblastoma cell (SH-SY5Y cell). Spirulina imputed the strong antioxidant activity because of certain active component like phycocyanin, b-carotene and vitamins (Bermejo-Bescós et al., 2008). According to the pathogenic mechanism in Parkinson disease, Mitochondrial dysfunction and oxidative stress are the main factors in pathogenesis of PD. Spirulina polysaccharides complex restore the function of mitochondria by upregulating the expression of SOD2 enzyme. SOD2 is an enzyme which covert superoxide into the less reactive form which can easily diffuse to the mitochondrial membrane. Hence, by reviewing the role of spirulina in certain neuroprotective parameters, we may state that the spirulina and its bioactive components acting beneficial role in Parkinson disorder.

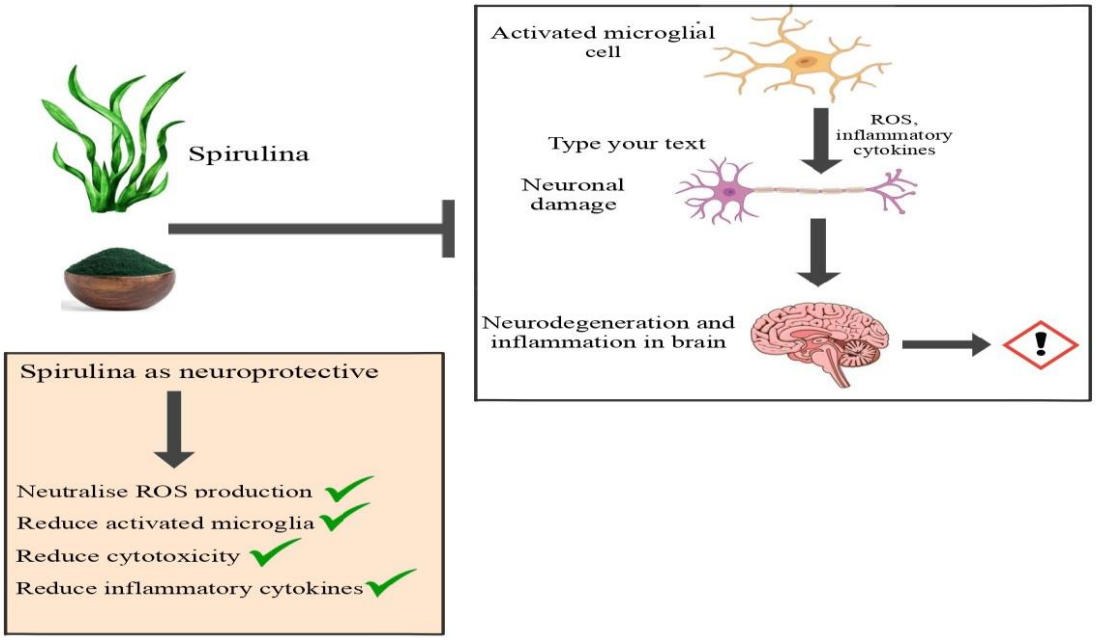


Figure 2. Spirulina role as neuroprotective agent. Spirulina has been determined anti-inflammatory/ neuroprotective properties in neurodegeneration. Intake of spirulina employ neutralise the reactive oxygen species, reduced activated microglial cell, reduce cellular toxicity and inflammatory cytokines.

9. AUTHOR CONTRIBUTION

M.K, S.S; analysis, writing, drafting, review and editing.

J.G.S; Supervision, resources and formal analysis.

10.FUNDING

This work isn't supported by any funding source.

11. CONFLICT OF INTEREST

We have declared that no competing interests exist.

12. ETHICAL APPROVALS

This study doesn't include any experiment on animal or human subject.

13. DATA AVAILABILITY

All the data are available within the review article.

REFERENCES:

Abusrair, A. H., Elsekaily, W., & Bohlega, S. (2022). Tremor in Parkinson's Disease: From Pathophysiology to Advanced Therapies. *Tremor and Other Hyperkinetic Movements*, *12*(1), 1–19. https://doi.org/10.5334/TOHM.712

Ariga, H., Takahashi-Niki, K., Kato, I., Maita, H., Niki, T., & Iguchi-Ariga, S. M. M. (2013). Neuroprotective Function of DJ-1 in Parkinson's Disease. *Oxidative Medicine and Cellular Longevity*, *2013*. https://doi.org/10.1155/2013/683920

Barbosa, A. F., Chen, J., Freitag, F., Valente, D., Souza, C. D. O., Voos, M. C., & Chien, H. F. (2016). Gait, posture and cognition in Parkinson's disease. *Dementia & Neuropsychologia*, *10*(4), 280. https://doi.org/10.1590/S1980-5764-2016DN1004005

Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain : A Journal of Neurology*, *124*(Pt 11), 2131–2146. https://doi.org/10.1093/BRAIN/124.11.2131

Béraud, D., Hathaway, H. A., Trecki, J., Chasovskikh, S., Johnson, D. A., Johnson, J. A., Federoff, H. J., Shimoji, M., Mhyre, T. R., Maguire-Zeiss, K. A., Maguire-Zeiss, K. A., Béraud, D., Federoff, H. J., Mhyre, T. R., Hathaway, H. A., Chasovskikh, S., Johnson, D. A., & Johnson, J. A. (2012). Microglial Activation and Antioxidant Responses Induced by the Parkinson's Disease Protein α-Synuclein. *Journal of Neuroimmune Pharmacology 2012 8:1*, *8*(1), 94–117. https://doi.org/10.1007/S11481-012-9401-0

Bermejo-Bescós, P., Piñero-Estrada, E., & Villar del Fresno, Á. M. (2008). Neuroprotection by Spirulina platensis protean extract and phycocyanin against iron-induced toxicity in SH-SY5Y neuroblastoma cells. *Toxicology in Vitro*, *22*(6), 1496–1502. https://doi.org/10.1016/J.TIV.2008.05.004

Bonifati, V., Rizzu, P., Van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., Dekker, M. C. J., Squitieri, F., Ibanez, P., Joosse, M., Van Dongen, J. W., Vanacore, N., Van Swieten, J. C., Brice, A., Meco, G., Van Duijn, C. M., Oostra, B. A., & Heutink, P. (2003). Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science (New York, N.Y.)*, *299*(5604), 256–259. https://doi.org/10.1126/SCIENCE.1077209

Chattopadhyaya, I., Gupta, S., Mohammed, A., Mushtaq, N., Chauhan, S., & Ghosh, S. (2015). Neuroprotective effect of Spirulina fusiform and amantadine in the 6-OHDA induced Parkinsonism in rats. *BMC Complementary and Alternative Medicine*, *15*(1). https://doi.org/10.1186/S12906-015-0815-0

Chen, J. C., Liu, K. S., Yang, T. J., Hwang, J. H., Chan, Y. C., & Lee, I. Te. (2012). Spirulina and C-phycocyanin reduce cytotoxicity and inflammation-related genes expression of microglial cells. *Nutritional Neuroscience*, *15*(6), 252–256. https://doi.org/10.1179/1476830512Y.0000000020

Çınar, E., Tel, B. C., & Şahin, G. (2022). Neuroinflammation in Parkinson's Disease and its Treatment Opportunities. *Balkan Medical Journal*, *39*(5), 318–333. https://doi.org/10.4274/BALKANMEDJ.GALENOS.2022.2022-7-100

Colonna, M., & Butovsky, O. (2017a). Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annual Review of Immunology*, *35*, 441. https://doi.org/10.1146/ANNUREV-IMMUNOL-051116-052358

Colonna, M., & Butovsky, O. (2017b). Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annual Review of Immunology*, *35*, 441. https://doi.org/10.1146/ANNUREV-IMMUNOL-051116-052358

Dranseikienė, D., Balčiūnaitė-Murzienė, G., Karosienė, J., Morudov, D., Juodžiukynienė, N., Hudz, N., Gerbutavičienė, R. J., & Savickienė, N. (2022). Cyano-Phycocyanin: Mechanisms of Action on Human Skin and Future Perspectives in Medicine. In *Plants* (Vol. 11, Issue 9). MDPI. https://doi.org/10.3390/plants11091249

El-Mohsnawy, E., & Abu-Khudir, R. (2020). A highly purified C-phycocyanin from thermophilic cyanobacterium Thermosynechococcus elongatus and its cytotoxic activity assessment using an in vitro cell-based approach. *Journal of Taibah University for Science*, *14*(1), 1218–1225. https://doi.org/10.1080/16583655.2020.1812287

Färber, K., & Kettenmann, H. (2005). Physiology of microglial cells. *Brain Research. Brain Research Reviews*, *48*(2), 133–143. https://doi.org/10.1016/J.BRAINRESREV.2004.12.003

Fernandes, R., Campos, J., Serra, M., Fidalgo, J., Almeida, H., Casas, A., Toubarro, D., & Barros, A. I. R. N. A. (2023). Exploring the Benefits of Phycocyanin: From Spirulina Cultivation to Its Widespread Applications. *Pharmaceuticals (Basel, Switzerland)*, *16*(4). https://doi.org/10.3390/PH16040592

Flynn, J. M., & Melovn, S. (2013). SOD2 in Mitochondrial Dysfunction and Neurodegeneration. *Free Radical Biology & Medicine*, *62*, 4–12. https://doi.org/10.1016/J.FREERADBIOMED.2013.05.027

Glinka, Y., Gassen, M., & Youdim, M. B. H. (1997). Mechanism of 6-hydroxydopamine neurotoxicity. *Journal of Neural Transmission. Supplementum*, *50*(50), 55–66. https://doi.org/10.1007/978-3-7091-6842-4_7

Grover, P., Bhatnagar, A., Kumari, N., Narayan Bhatt, A., Kumar Nishad, D., & Purkayastha, J. (2021). C-Phycocyanin-a novel protein from Spirulina platensis- In vivo toxicity, antioxidant and immunomodulatory studies. *Saudi Journal of Biological Sciences*, *28*(3), 1853–1859. https://doi.org/10.1016/j.sjbs.2020.12.037

Haider, A., Elghazawy, N. H., Dawood, A., Gebhard, C., Wichmann, T., Sippl, W., Hoener, M., Arenas, E., & Liang, S. H. (2023). Translational molecular imaging and drug development in Parkinson's disease. *Molecular Neurodegeneration*, *18*(1). https://doi.org/10.1186/S13024-023-00600-Z

Hanrott, K., Gudmunsen, L., O'Neill, M. J., & Wonnacott, S. (2006). 6-hydroxydopamine-induced apoptosis is mediated via extracellular auto-oxidation and caspase 3-dependent

activation of protein kinase Cdelta. *The Journal of Biological Chemistry*, *281*(9), 5373–5382. https://doi.org/10.1074/JBC.M511560200

Hayes, M. T. (2019). Parkinson's Disease and Parkinsonism. *The American Journal of Medicine*, *132*(7), 802–807. https://doi.org/10.1016/J.AMJMED.2019.03.001

Helmke, A., Nordlohne, J., Balzer, M. S., Dong, L., Rong, S., Hiss, M., Shushakova, N., Haller, H., & von Vietinghoff, S. (2019). CX3CL1–CX3CR1 interaction mediates macrophage-mesothelial cross talk and promotes peritoneal fibrosis. *Kidney International*, *95*(6), 1405–1417. https://doi.org/10.1016/J.KINT.2018.12.030

Hundhausen, C., Misztela, D., Berkhout, T. A., Broadway, N., Saftig, P., Reiss, K., Hartmann, D., Fahrenholz, F., Postina, R., Matthews, V., Kallen, K. J., Rose-John, S., & Ludwig, A. (2003). The disintegrin-like metalloproteinase ADAM10 is involved in constitutive cleavage of CX3CL1 (fractalkine) and regulates CX3CL1-mediated cell-cell adhesion. *Blood*, *102*(4), 1186–1195. https://doi.org/10.1182/BLOOD-2002-12-3775

Izadi, M., & Fazilati, M. (2018). *Asian Journal of Green Chemistry Orginal Research Article Extraction and purification of phycocyanin from spirulina platensis and evaluating its antioxidant and anti- inflammatory activity*. *2*, 364–379. https://doi.org/10.22034/AJGC.2018.63597

Jiang, L., Wang, Y., Yin, Q., Liu, G., Liu, H., Huang, Y., & Li, B. (2017). Phycocyanin: A potential drug for cancer treatment. *Journal of Cancer*, *8*(17), 3416–3429. https://doi.org/10.7150/jca.21058

Joers, V., Tansey, M. G., Mulas, G., & Carta, A. R. (2017). Microglial phenotypes in Parkinson's disease and animal models of the disease. *Progress in Neurobiology*, *155*, 57. https://doi.org/10.1016/J.PNEUROBIO.2016.04.006

Jones, B. A., Beamer, M., & Ahmed, S. (2010). Fractalkine/CX3CL1: A Potential New Target for Inflammatory Diseases. *Molecular Interventions*, *10*(5), 263. https://doi.org/10.1124/MI.10.5.3

Karkos, P. D., Leong, S. C., Karkos, C. D., Sivaji, N., & Assimakopoulos, D. A. (2011a). Spirulina in Clinical Practice: Evidence-Based Human Applications. *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2011*. https://doi.org/10.1093/ECAM/NEN058

Kim, S. D., Allen, N. E., Canning, C. G., & Fung, V. S. C. (2018). Parkinson disease. *Handbook of Clinical Neurology*, *159*, 173–193. https://doi.org/10.1016/B978-0-444-63916-5.00011-2

Klein, C., & Westenberger, A. (2012). Genetics of Parkinson's Disease. *Cold Spring Harbor Perspectives in Medicine*, *2*(1). https://doi.org/10.1101/CSHPERSPECT.A008888

Kulich, S. M., Horbinski, C., Patel, M., & Chu, C. T. (2007). 6-HYDROXYDOPAMINE INDUCES MITOCHONDRIAL ERK ACTIVATION. *Free Radical Biology & Medicine*, *43*(3), 372. https://doi.org/10.1016/J.FREERADBIOMED.2007.04.028

Kumar, A., Christian, P. K., Panchal, K., Guruprasad, B. R., & Tiwari, A. K. (2017). Supplementation of Spirulina (Arthrospira platensis) Improves Lifespan and Locomotor Activity in Paraquat-Sensitive DJ-1βΔ93 Flies, a Parkinson's Disease Model in Drosophila melanogaster. *Journal of Dietary Supplements*, *14*(5), 573–588. https://doi.org/10.1080/19390211.2016.1275917

Leite Silva, A. B. R., Gonçalves de Oliveira, R. W., Diógenes, G. P., de Castro Aguiar, M. F., Sallem, C. C., Lima, M. P. P., de Albuquerque Filho, L. B., Peixoto de Medeiros, S. D., Penido de Mendonça, L. L., de Santiago Filho, P. C., Nones, D. P., da Silva Cardoso, P. M. M., Ribas, M. Z., Galvão, S. L., Gomes, G. F., Bezerra de Menezes, A. R., dos Santos, N. L., Mororó, V. M., Duarte, F. S., & dos Santos, J. C. C. (2023). Premotor, nonmotor and motor symptoms of Parkinson's Disease: A new clinical state of the art. *Ageing Research Reviews*, *84*. https://doi.org/10.1016/J.ARR.2022.101834

Lima, F. A. V., Joventino, I. P., Joventino, F. P., de Almeida, A. C., Neves, K. R. T., do Carmo, M. R., Leal, L. K. A. M., de Andrade, G. M., & de Barros Viana, G. S. (2017a). Neuroprotective Activities of Spirulina platensis in the 6-OHDA Model of Parkinson's Disease Are Related to Its Anti-Inflammatory Effects. *Neurochemical Research*, *42*(12), 3390–3400. https://doi.org/10.1007/S11064-017-2379-5

Liu, Q., Huang, Y., Zhang, R., Cai, T., & Cai, Y. (2016). Medical Application of Spirulina platensis Derived C-Phycocyanin. In *Evidence-based Complementary and Alternative Medicine* (Vol. 2016). Hindawi Limited. https://doi.org/10.1155/2016/7803846

Lotz, S. K., Blackhurst, B. M., Reagin, K. L., & Funk, K. E. (2021). Microbial Infections Are a Risk Factor for Neurodegenerative Diseases. *Frontiers in Cellular Neuroscience*, *15*. https://doi.org/10.3389/FNCEL.2021.691136

Lupatini, A. L., Colla, L. M., Canan, C., & Colla, E. (2017). Potential application of microalga Spirulina platensis as a protein source. *Journal of the Science of Food and Agriculture*, *97*(3), 724–732. https://doi.org/10.1002/JSFA.7987

Machihara, K., Oki, S., Maejima, Y., Kageyama, S., Onda, A., Koseki, Y., Imai, Y., & Namba, T. (2023). Restoration of mitochondrial function by Spirulina polysaccharide via upregulated SOD2 in aging fibroblasts. *IScience*, *26*(7). https://doi.org/10.1016/J.ISCI.2023.107113

Pabon, M. M., Jernberg, J. N., Morganti, J., Contreras, J., Hudson, C. E., Klein, R. L., & Bickford, P. C. (2012). A spirulina-enhanced diet provides neuroprotection in an α-synuclein model of Parkinson's disease. *PloS One*, *7*(9). https://doi.org/10.1371/JOURNAL.PONE.0045256

Pan-utai, W., & Iamtham, S. (2019). Physical extraction and extrusion entrapment of C-phycocyanin from Arthrospira platensis. *Journal of King Saud University - Science*, *31*(4), 1535–1542. https://doi.org/10.1016/J.JKSUS.2018.05.026

Parra, I., Martínez, I., Ramírez-García, G., Tizabi, Y., & Mendieta, L. (2020). Differential Effects of LPS and 6-OHDA on Microglia's Morphology in Rats: Implications for Inflammatory Model of Parkinson's Disease. *Neurotoxicity Research*, *37*(1), 1–11. https://doi.org/10.1007/S12640-019-00104-Z

Pawelec, P., Ziemka-Nalecz, M., Sypecka, J., & Zalewska, T. (2020). The Impact of the CX3CL1/CX3CR1 Axis in Neurological Disorders. *Cells*, *9*(10). https://doi.org/10.3390/CELLS9102277

Pentón-Rol, G., Marín-Prida, J., & McCarty, M. F. (2021). C-Phycocyanin-derived Phycocyanobilin as a Potential Nutraceutical Approach for Major Neurodegenerative Disorders and COVID-19- induced Damage to the Nervous System. *Current Neuropharmacology*, *19*(12), 2250–2275. https://doi.org/10.2174/1570159x19666210408123807

Ratha, S. K., & Prasanna, R. (2012). Bioprospecting microalgae as potential sources of "Green Energy"—challenges and perspectives (Review). *Applied Biochemistry and Microbiology 2012 48:2*, *48*(2), 109–125. https://doi.org/10.1134/S000368381202010X

Rodrigues E Silva, A. M., Geldsetzer, F., Holdorff, B., Kielhorn, F. W., Balzer-Geldsetzer, M., Oertel, W. H., Hurtig, H., & Dodel, R. (2010). Who was the man who discovered the 'Lewy bodies'? *Movement Disorders : Official Journal of the Movement Disorder Society*, *25*(12), 1765–1773. https://doi.org/10.1002/MDS.22956

Safaei, M., Maleki, H., Soleimanpour, H., Norouzy, A., Zahiri, H. S., Vali, H., & Noghabi, K. A. (2019). Development of a novel method for the purification of C-phycocyanin pigment from a local cyanobacterial strain Limnothrix sp. NS01 and evaluation of its anticancer properties. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-45905-6

Saito, Y., Nishio, K., Ogawa, Y., Kinumi, T., Yoshida, Y., Masuo, Y., & Niki, E. (2007). Molecular mechanisms of 6-hydroxydopamine-induced cytotoxicity in PC12 cells: involvement of hydrogen peroxide-dependent and -independent action. *Free Radical Biology & Medicine*, *42*(5), 675–685. https://doi.org/10.1016/J.FREERADBIOMED.2006.12.004

Salari, S., & Bagheri, M. (2019). In vivo, in vitro and pharmacologic models of Parkinson's disease. *Physiological Research*, *68*(1), 17–24. https://doi.org/10.33549/PHYSIOLRES.933895

Simola, N., Morelli, M., & Carta, A. R. (2007). The 6-hydroxydopamine model of Parkinson's disease. *Neurotoxicity Research*, *11*(3–4), 151–167. https://doi.org/10.1007/BF03033565

Sinha, S., Patro, N., & Patro, I. K. (2018). Maternal protein malnutrition: Current and future perspectives of spirulina supplementation in neuroprotection. *Frontiers in Neuroscience*, *12*, 1–18. https://doi.org/10.3389/FNINS.2018.00966/BIBTEX

Smith, N., & Wilson, M. A. (2017). Structural Biology of the DJ-1 Superfamily. *Advances in Experimental Medicine and Biology*, *1037*, 5–24. https://doi.org/10.1007/978-981-10-6583-5_2

Solana-Manrique, C., Sanz, F. J., Torregrosa, I., Palomino-Schätzlein, M., Hernández-Oliver, C., Pineda-Lucena, A., & Paricio, N. (2022). Metabolic Alterations in a Drosophila Model of Parkinson's Disease Based on DJ-1 Deficiency. *Cells*, *11*(3). https://doi.org/10.3390/CELLS11030331/S1

Strömberg, I., Gemma, C., Vila, J., & Bickford, P. C. (2005). Blueberry- and spirulina-enriched diets enhance striatal dopamine recovery and induce a rapid, transient microglia activation after injury of the rat nigrostriatal dopamine system. *Experimental Neurology*, *196*(2), 298–307. https://doi.org/10.1016/J.EXPNEUROL.2005.08.013

Su, C. H., Liu, C. S., Yang, P. C., Syu, K. S., & Chiuh, C. C. (2014). Solid-liquid extraction of phycocyanin from Spirulina platensis: Kinetic modeling of influential factors. *Separation and Purification Technology*, *123*, 64–68. https://doi.org/10.1016/j.seppur.2013.12.026

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*, *139 Suppl 1*, 318–324. https://doi.org/10.1111/JNC.13691

Varešlija, D., Tipton, K. F., Davey, G. P., & McDonald, A. G. (2020). 6-Hydroxydopamine: a far from simple neurotoxin. *Journal of Neural Transmission 2020 127:2*, *127*(2), 213–230. https://doi.org/10.1007/S00702-019-02133-6

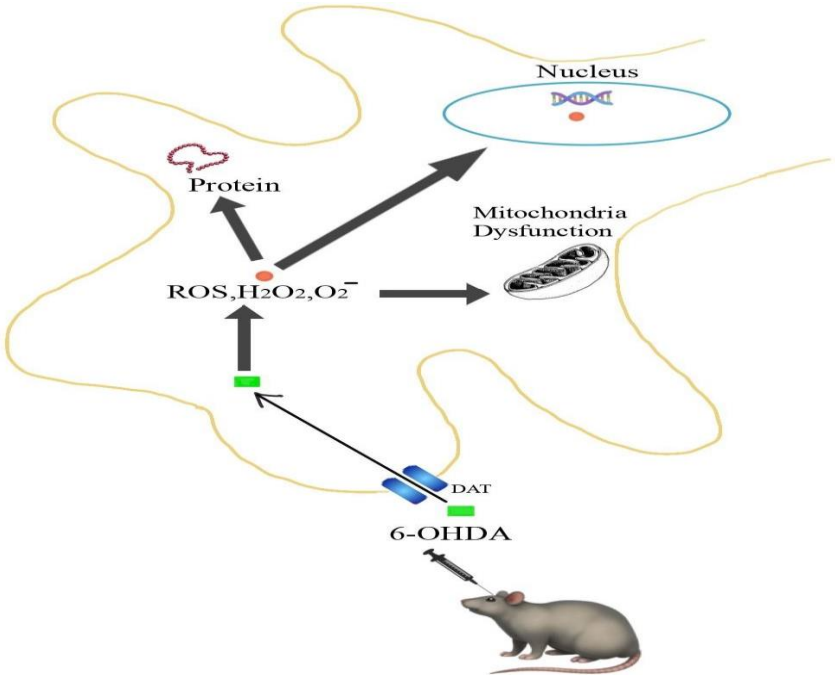
Wakabayashi, K., Tanji, K., Mori, F., & Takahashi, H. (2007a). The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of alpha-synuclein aggregates. *Neuropathology : Official Journal of the Japanese Society of Neuropathology*, *27*(5), 494–506. https://doi.org/10.1111/J.1440-1789.2007.00803.X

Wakabayashi, K., Tanji, K., Mori, F., & Takahashi, H. (2007b). The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of alpha-synuclein aggregates. *Neuropathology : Official Journal of the Japanese Society of Neuropathology*, *27*(5), 494–506. https://doi.org/10.1111/J.1440-1789.2007.00803.X

Zhang, X.-M., & Zhu, J. (2011). Kainic Acid-Induced Neurotoxicity: Targeting Glial Responses and Glia-Derived Cytokines. *Current Neuropharmacology*, *9*(2), 388. https://doi.org/10.2174/157015911795596540

Table 1. Various method of cell disruption techniques used in Spirulina extraction.

S. No.	Types	Details
1.	Freeze and thaw process	By repeating Freezing and thaw cycles leads to the cell lysis and membrane disruptions.
2.	Mixing and homogenization	Squeezing of cell by physically, like using of mortar and pestle.
3.	Bead milling	Mechanical cell disruption technique which leads to direct damage to cell wall.
4.	High pressure homogenization	Using pressurized homogeneity with lysosomal treatment.
5.	Ultrasonic method	Ultrasonic waves are used to disrupt the biological membrane.
6.	Electric field	Electric pulse is used to remove Phycocyanin from Spirulina.
7.	Enzyme assisted method	Used of various enzyme with the required conditions and PH.
8.	Microwave	Environment friendly method, used of little input of energy



ROS, 6-OHDA.

Figure 1. 6-OHDA mimics natural pattern of neurotoxicity. 6-OHDA (into green) directly inserted into the host and then it enters into dopaminergic neurons via DAT (Dopamine transporter). Inside the neurons oxidation of 6-OHDA produces several cytotoxic species like oxygen and nitrate. Such Reactive cytotoxic species may impact to nucleus, protein inactivation (PDI), mitochondrial dysfunction and activation of glial cell.

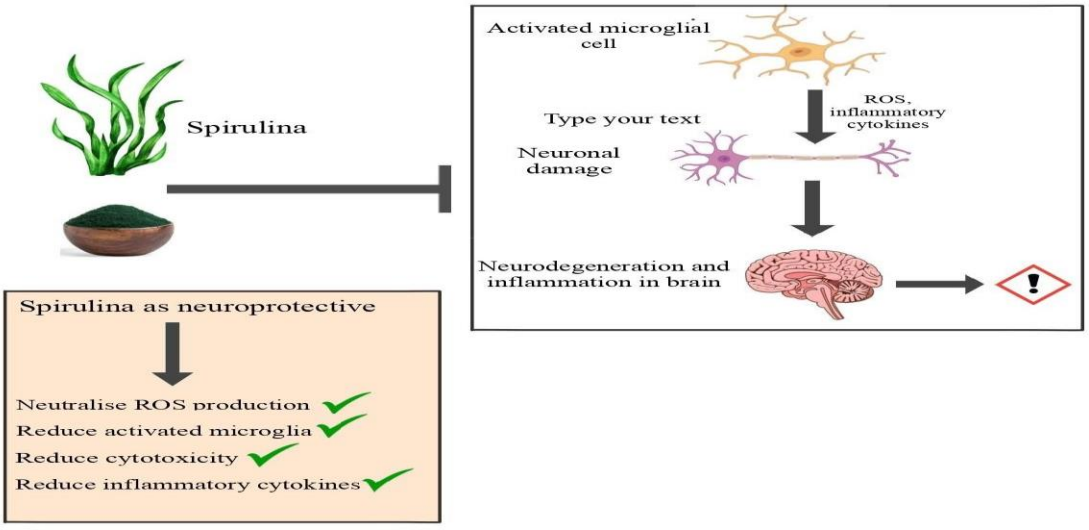
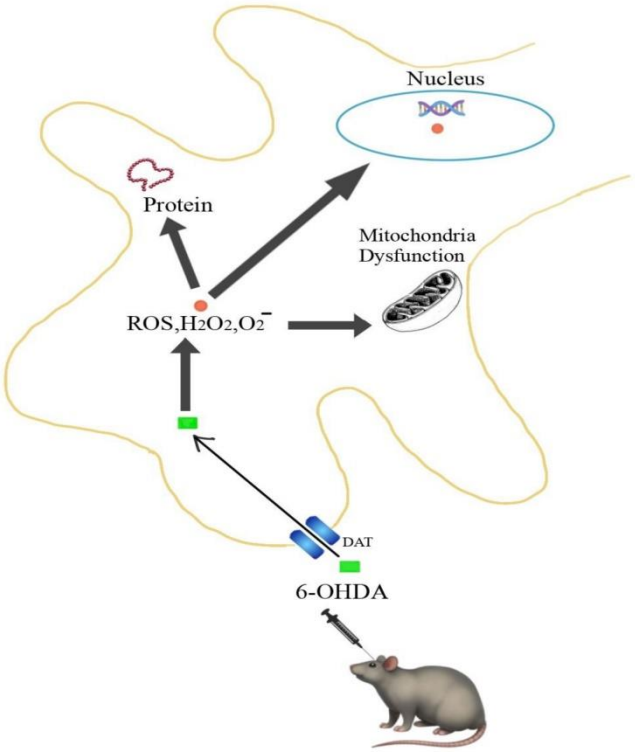
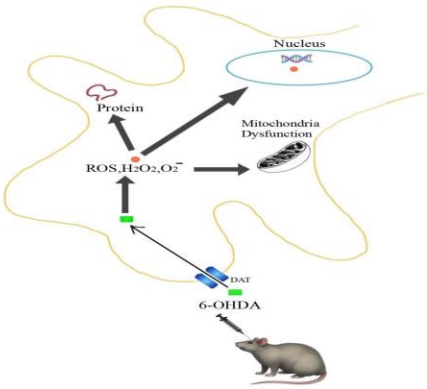


Figure 2. Spirulina role as neuroprotective agent. Spirulina has been determined anti- inflammatory/ neuroprotective properties in neurodegeneration. Intake of spirulina employ neutralise the reactive oxygen species, reduced activated microglial cell,
reduce cellular toxicity and inflammatory cytokines.



ROS, 6-OHDA.

Figure 1. 6-OHDA mimics natural pattern of neurotoxicity. 6-OHDA (into green) directly inserted into the host and then it enters into dopaminergic neurons via DAT (Dopamine transporter). Inside the neurons oxidation of 6-OHDA produces several cytotoxic species like oxygen and nitrate. Such Reactive cytotoxic species may impact to nucleus, protein inactivation (PDI), mitochondrial dysfunction and activation of glial cell.



ROS, 6-OHDA.

Figure 1. 6-OHDA mimics natural pattern of neurotoxicity. 6-OHDA (into green) directly inserted into the host and then it enters into dopaminergic neurons via DAT (Dopamine transporter). Inside the neurons oxidation of 6-OHDA produces several cytotoxic species like oxygen and nitrate. Such Reactive cytotoxic species may impact to nucleus, protein inactivation (PDI), mitochondrial dysfunction and activation of glial cell.

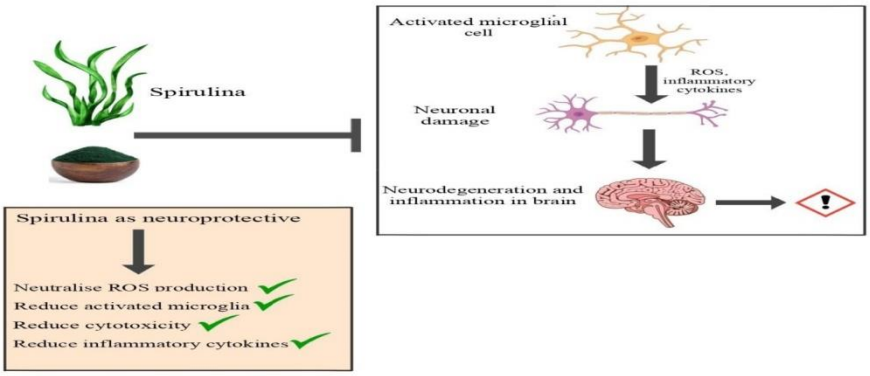


Figure 2. Spirulina role as neuroprotective agent. Spirulina has been determined anti-inflammatory/ neuroprotective properties in neurodegeneration. Intake of spirulina employ neutralise the reactive oxygen species, reduced activated microglial cell, reduce cellular toxicity and inflammatory cytokines.