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# The Effect of Ursodeoxycholic Acid on Parkinson's Disease: A Systematic and Meta-Analysis of Randomized Controlled trials

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## Abstract

Parkinson's disease (PD) is a progressive degenerative disorder involving dopaminergic neurons in the substantia nigra. Along with motor activity impairment, PD patients also have a range of neuropsychiatric, cognitive, and autonomic problems. Ursodeoxycholic acid (UDCA) has been used to treat a wide range of liver-related ailments, including gallstones, cholestatic diseases, and primary biliary cirrhosis (PBC). In addition to this, randomised control trials on the effects of Parkinson's disease have been conducted on UDCA. In the present study, we validate the effect of UDCA on Parkinson disease using meta-analysis. Various electronic databases such as Web of Science, PubMed/ Medline, Cochrane library and Scopus were used for search of articles. The randomized control trials (RCTs) for the effect of interventions of UDCA on Parkinson disease was evaluated using meta-analysis (Review Manager 5.4) software. A total of 304 articles were identified, of which 3 met the inclusion criteria. When compared to patients receiving the control medication, the UDCA-treated patients had higher concentrations of inorganic phosphate (Pi) and ATP. The z scores of UDCA on Pi and ATP concentration were determined to be 0.08 and 0.71 with p-values of 0.00001 and 0.0001, respectively. UDCA might increase brain mitochondrial activity and cellular ATP availability and could possibly have therapeutic disease-modifying effects. Ursodeoxycholic acid administrations in PD significantly increase the concentration of Pi and ATP and maintain ATP homeostasis by increasing ATPase activity and ATP production.

Keywords: Parkinson's disease, ursodeoxycholic acid, meta-analysis, ATP concentration.

## Introduction

Parkinson's disease (PD) is a neurological condition characterized by the premature death of dopaminergic neurons in substantia nigra pars compacta. The depletion of dopamine level in basal ganglia result in the movement disorder with symptoms similar to that of Parkinsonism. One third of the elderly population older than 75 is affect with Parkinson disease, still the causes of disease is unknow (1,2). Searching for novel treatment targets is expanding with the vast study being done on the molecular pathways underlying the cause and progression of Parkinson's disease (3). Mitochondrial dysfunction, particularly the selective suppression of complex I is another factor responsible for dopaminergic neuron depletion (4). Magnetic resonance spectroscopy is a powerful tool for non- invasively studying of metabolic alterations and bioenergetic changes in the brain of the patients with neurodegenerative condition. These techniques can directly measure the intracellular pH, free Magnesium and

phosphorus metabolites such as ATP, inorganic phosphate, phosphocreatine, glycerophosphocholine and phosphoethanolamine. As a result, in vivo 31P MRS provides essential insights into relationship between energy failure and neurodegenerative process (5-9).

Mitochondrial dysfunction can induce oxidative stress, as decrease ATP and increase in the production of 'reactive oxygen species (ROS)', further damaging dopaminergic neuron in the mitochondria (10). Various risk factors, including obesity, hypertension and dyslipidemia contribute to the rise in non-communicable disease (11). This causes the accumulation of misfolded α-synuclein, which binds to the electron transport chain (ETC) there by increase in the production of ROS, which promotesmitochondrial DNA damage, this decreases the ATP production. The damage of the ETC reduces Complex I activity, which includes opening of MPTP (Mitochondrial Permeability Transition Pore), releasing cytochrome c and Ca2+, increase inflammatory response through Succinate and Mitochondrial DAMP release, including apoptosis (12-14). Enhanced Drp1-mediated fission of mitochondria and its interactions with MFN1/2 and OPA1 proteins contribute to Parkinson's disease-related mitochondrial fragmentation. Moreover, Parkin and PINK1 mitophagy protein mutations cause defective mitophagy with autosomal recessive early-onset Parkinson's disease (15).

A naturally occurring hydrophilic bile acid called ursodeoxycholic acid (UDCA) has been demonstrated a neuroprotective agent for Parkinson's disease (16). For more than 30 years, UDCA has been approved to treat PBC (primary biliary cholangitis) at a dosage of 15mg/kg. Based on the choleretic actions and capacity to shield hepatocytes from hydrophobic bile acids, UDCA was first given FDA approval for the treatment of numerous cholestatic liver conditions. UDCA and TUDCA can inhibit the apoptosis, prevent mitochondrial dysfunction and reduces oxidative stress (17,18). Previous studies have demonstrated UDCA's ability to partially counteract the effects of the various agents on mitochondrial activity and reactive oxygen species formation. By controlling the PI3K- Akt/PKB pathways, UDCA can prevent the programmed cell death process from killing SH-SY5Y cells (19). UDCA can affect signaling pathway that causes the programmed cell death in neuronal cell lines. In order to further evaluate its neuroprotective potential in PD, the international Linked Clinical Trials (iLCT) designated UDCA as its most highly prioritized neuroprotective chemical for research in clinical studies in 2015 (20). In this study, we aim to validate UDCA effect on Parkinson's disease patients and healthy volunteers using statistical analysis.

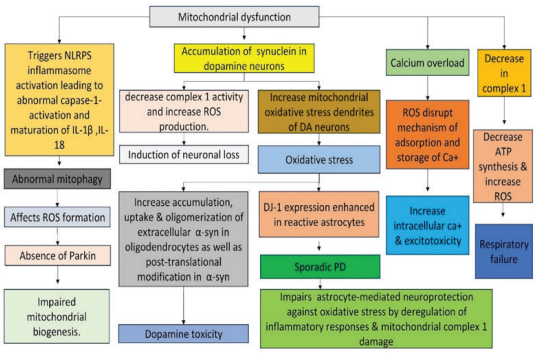


Fig. 1. Flowchart of Mitochondrial dysfunction on Parkinson's disease.

## Materials and Methods

### *Eligibility criteria*

We assess the PICO (Population, Intervention, Comparison, and Outcomes) framework: Population: Parkinson's disease-affected persons older than 60 (diagnosed by Pi concentration and ATP concentration using P-MRS); Intervention: Ursodeoxycholic acid (UDCA); Comparison: healthy volunteers, gender, severity, UDCA dosage, and Duration: 6 weeks; Outcomes: Increase in ATP concentration/ decreased dopaminergic neuron death and clinical signs.

### *Literature search*

Literature search systematically from the EMBASE (https://www.elsevier.com/en-in/products/embase), Medline (https://www.medline.com/), Drug Bank (https://go.drugbank.com/), Clinical Trial Gov (https://clinicaltrials.gov/), Google Scholar (https://scholar.google.com/), and Cochrane Central Register of Controlled Trials (CENTRAL) (https://www.cochranelibrary.com/central/about-central) was performed. Futhermore comprehensive survey for references was directed over 2 months, using querying and databases (PubChem, therapeutic target database, toxin target database) reviews, index searches of proceedings, backtracking references, conversations with colleagues, and internet searching. We screened clinical trials and published reviews to find appropriate studies. We searched using the keywords Parkinson Disease, UDCA on PD, Randomized control trials for Parkinsonism, Treatment of PD using UDCA, UDCA for Mental illness, ATP concentration in PD, ROS on mitochondria in PD. There was only English language studies included.

### *Screening and collection of data*

Certainly, potentially eligible RCTs was screened, with disagreements fixed by consensus. For study inclusion, we screened data concerning study characteristics, baseline characteristics, people with unstable circumstances, people with other neurological illnesses, people who were unable to undergo a 7-Tesla P MRS scan (21,22), Multiple systems atrophy (MSA) (23), drug-induced parkinsonism (24), progressive supranuclear palsy (PSP) (25), dystonic or essential tremor (26), intervention and outcomes of interest. We combined all of the data from a trial that was presented in several journals and discrepancies were resolved over discussion.

### *Homogeneity and transitivity assessment*

The trail characteristics and study examination across all qualified studies was evaluated through methodological and clinical heterogeneity. So then methods utilized for classifying disease severity, baseline disease severity and duration of interventions are considered as the chief outcome modifiers across the assessments and measured via distribution following this that any participant comprised in the network could be randomized to any of the accessible interventions are adopted through NMA rationality.

### *Data synthesis and analysis*

We analyzed observational studies and randomized controlled trials individually. For obtaining a continuous variable (Population, Age, Sex, UDCA dose), modification from baseline in UDCA vs. control groups, we measured the standard mean differences (SMDs) or efficacy mean differences (MDs) and 95% confidence intervals (CIs). Inverse variance method was adopted for pooling SMDs and MD. We calculated 95% confidence intervals and risk ratios (RR) using the Mantel-Haenszel method. Statistical heterogeneity was observed by Chi square test and I 2 statistic (27). Using random effects model regardless of heterogeneity all the meta-analyses were performed. We have intended 2 subgroup analysis to evaluate the effect of UDCA on PD patient. Subgroup 1; Effect of UDCA on inorganic phosphate (Pi) concentration in P-MRS (UDCA vs Placebo); Subgroup 2; Effect of UDCA on ATP concentration in P-MRS (UDCA vs Placebo). Sensitivity analyses was carried out, by using alternative effect which subsequently measures (OR vs. RR), alternative pooling methods, and statistical models regarding heterogeneity (random vs. fixed effects). Publication bias was noticed by visually inspecting symmetry of forest plot and funnel plots. The calculations were done using RevMan 5.4 software (28).

### *Risk of bias*

Using Cochrane tool the risk of bias was evaluated, to calculate the included studies for bias. Five areas of bias such as selection bias, reporting bias, detection bias, attrition bias, and

performance bias were used to evaluate the total risk of bias for each of the included studies (29,30). The risk of the decisions was categorised as high, low, or uncertain. Two reviewers completed the assessment independently. A third reviewer was consulted in the case that the options varied.

### *Confidence in the evidence*

Using the web application and Confidence in Network Meta-Analysis (CINeMA) (31,32) framework the confidence was assessed. CINeMA is a version of GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) for NMA. Each domain was categorized by uniting the direct evidence with statistical contributions to the network to obtain a confidence. Considering the completeness of the study search publication bias was evaluated. However, assessment of funnel plot symmetry was not resolved due to small-study effects and add to uncertainty.

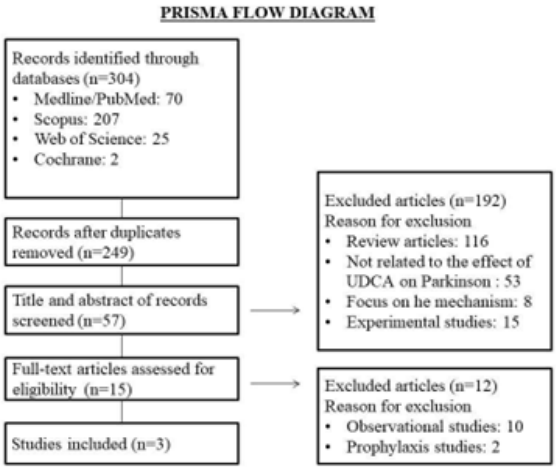


Fig. 2. PRISMA flowdiagram of the included articles.

## Results and Discussion

Overall, we recognized 304 references through electronic databases. After rejecting duplicates and references that did not satisfied our inclusion criteria, 15 references were qualified for the qualitative data synthesis; 3 references fulfilled inclusion criteria for the meta-analysis (Tables 1 and 2). The treatment duration is 6 weeks and the subjects provided with ~50mg/kg/day (based on the usage of 250 and 500mg capsules) of UDCA to be allocated into 3 equal daily doses and titrated up over ~3 weeks to a stable dose for 6 weeks. UDCA and the control group's ATP and Pi concentrations were measured using 31-Phosphorus Magnetic Resonance Spectroscopy, clinically which has the potential for neurological practice due to its safe in-vivo evaluation of energy metabolism in cells and the indirect analysis of intracellular pH, Mg 2+, ATP concentration, and phospholipid composition of the cell membrane.

### *Risk of bias assessment*

One study out of the three evaluated ones, as shown in Table 1, was determined to have a high RoB due to missing exclusion criteria (33). Due to bias resulting from the randomization method, deviations from the intended volunteers, incomplete outcome data, and bias in the selection of the reported result, the remaining two studies were identified as having & quot;certain concerns & quot; (Tables 1 and 2).

### *Assessment of clinical transitivity and heterogeneity*

Certainly, we are not able to analyze and assess transitivity and heterogeneity by considering only one research per comparison. Variability in clinical parameters was not detected from the data provided within any of the included trials. It was determined that there was substantial heterogeneity for pairwise comparisons of any intervention vs control (I 2 = 94 and 97%); However, this assessment should not be taken too seriously because there were not enough trials to carry out a more thorough heterogeneity estimation and therefore it may be erroneous.

### *Pairwise and network meta-analysis*

To examine the variations in intervention (UDCA) for each outcome measure, a me-

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ta-analysis was conducted. The forest plot (Fig 3 and 4) was created to make the similarities between the ATP and Pi concentration in UDCA and control more clearly. We examined the impact of UDCA on ATP concentration using two trials (Abishek G. Sathe et al. and Xiao-Hong Zhu et al) and Pi concentration using two trials (Bruno Barbiroli et al. and Xiao-Hong Zhu et al) (Table 1 and 2).

Table-1: Characteristics of the Included Studies

| Title | First Author's Name | Year of Publication | Country | Type of Study Design | References |
|---|---|---|---|---|---|
| Phosphorus Magnetic Resonance in Multiple System Atrophy and Parkinson's Disease | Bruno Barbiroli | 1999 | Italy | Clinical trail | [34] |
| Pharmacokinetics, Safety, and Tolerability of Orally Administered Ursodeoxycholic Acid in Patients With Parkinson's Disease- A Pilot Study | Abhishek G | 2020 | United States | Clinical trail | [14] |
| Quantitative Assessment of Occipital Metabolic and Energetic Changes in Parkinson's Patients, Using *In-vivo* 31P MRS-Based Metabolic Imaging at 7T | Xiao-Hong Zhu | 2021 | United States and United Kingdom | Clinical trail | [35] |

Table-2: Detailed characteristics of the studies

| Author | Population | Sex | | Eligibility | Exclusion | Severity | Primary Outcome | Secondary Outcome | Intervention | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Male | Female | | | | | | Case (UDCA Dose/ Duration) | Control |
| Abhishek G Sathe et.al.., | 5 | 4 | 1 | 18 years and older (adult, older adult) with Parkinson's disease | Pregnant and lactating women, people with unstable circumstances , people with other neurological illness. People who unable to undergo a 7- Telsa P-MRS scan. | Mild to moderate | Change in the ATP concentration | UDCA pharmacokinetics | 50mg/ kg/ day/ Orally for 6weeks | Healthy volunteers |
| Bruno Barbiroli et.al.., | 29 | 17 | 12 | 42-85 years | Multiple system atrophy (MSA), olivopontocerebellar atrophy (OPCA) and straitonigral degeneration variant (SND) | Mild to moderate | Estimation of Pi concentration using P-MRS | Estimation of ATP concentration | UDCA | Healthy volunteers |
| Xiao-Hong Zhu et.al.., | 38 | 18 | 20 | 60-64 years | - | Mild to moderate | Determination of ATP,PCr, Pi, PE and GPC concentration | Cerebral Phosphorus Metabolite | 50mg/ kg/ day/ Orally for 6weeks | Healthy volunteers |

### *Inorganic phosphate concentration (Pi)*

16 healthy participants and 13 people with Parkinson's disease were recruited by Bruno Barbiroli et al. Brain Pi level was considerably (1.63 mM 0.21 vs. 1.29 mM 0.13; p 0.0001) greater in PD patients than in controls (34). Pi has changed, according to research by Xiao-Hong Zhu et al. ([Pi]PD = 0.90 0.12 mM, [Pi] CT = 1.01 0.11 mM, n = 19, p = 0.007) (35). The UDCA, as compared to the control, favours a rise in the inorganic phosphate concentration (Pi), by statistical analysis with the z score = 0.08 (Fig 3).

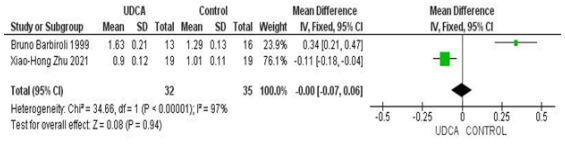


Fig. 3. Effect of UDCA on Pi concentration.

### *The outcome of ATP concentration*

Parkinson's disease patients had lower brain adenosine triphosphate (ATP) levels than age-matched, healthy controls, according to preliminary findings. Totally 5 individuals were taken into the study and P- MRS data were collected from the occipital lobes of three research subjects. The data from the other 2 individuals was either not captured or was useless due to the scanner's technical issue. In subjects 1, 2, and 4, the ATP concentrations were tested under pre-UDCA (2.68, 2.76, and 2.72 ) and post-UDCA(2.73, 2.79 and 2.75) circumstances. In the first two patients, we also saw a decrease in the metabolic rate of the ATPase reaction, followed by a rise in the metabolic rate of the creatine kinase reaction. The corrective effect of the UDCA therapy may be responsible for these observations. Statistically significant differences were detected in concentrations of ATP ([ATP] PD = 2.62 ± 0.17 mM, [ATP]CT = 2.82 ± 0.14 mM, n = 19, p = 0.0004) (20). The UDCA, as compared to the control it favours a rise in the ATP concentration, by statistical analysis with z score=0.71 (Fig 4).

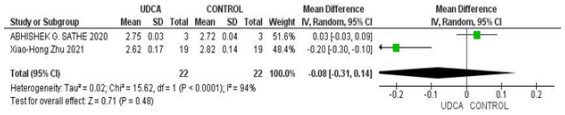


Fig. 4. Effect of UDCA on ATP concentration.

### *Confidence in the evidence*

Due to research limitations, heterogeneity, uncertain, oblique, and publication bias (Tables 1 and 2), confidence in estimates for changes in mean Pi and ATP concentration is regarded as minimal to extremely low (Tables 1 and 2). Due to the short sample size and lack of mixed data, the prediction interval estimate and inconsistency assessment could not be completed, and inconsistency was reduced as a result. The fundamental idea of transitivity may have been weakened by the lowering of inconsistency to account for variance in one impact modification discovered. Because of bias in the choice of the reported outcome, publication bias has been lowered. The evaluation of small-study impacts was not successful.

## Discussion

As Parkinson's disease is an entire brain disease, extranigral parts of the brain includes cerebral cortex, show evidence of neuro degeneration as progresses (36, 37). UDCA demonstrated to prevent rotenone-induced apoptosis by increasing mitochondrial action by increasing ATP levels. UDCA altered Bcl-2 and Bax mutations, and decreasing the activities of caspase-3, 8, 9 and modifying the intrinsic and extrinsic pathways. These effects are most likely associated with dopamine production and mitochondrial control. UDCA not only retained its membrane around the mitochondria integrity but also retained its energy production, as UDCA-treated rats had higher levels of ATP in the striatum (38-41). High dosages of UDCA (upto 50mg/kg/day) have been shown to be safe and tolerable in individuals with ALS (amyotrophic lateral sclerosis), and established that UDCA capable of crossing the BBB, with attainable levels in the CSF that correlate with serum levels (42). UDCA is a hydrophilic bile acid and has

been given FDA approval to treat primary biliary cholangitis. Several investigations employing PD cell lines and pre-clinical animal studies revealed its mitochondria-protective and anti-apoptotic properties. It is commonly acknowledged that NAD+ not only controls ATP energy production via NAD+/NADH reactions, also acts as the primary substrate for several NAD+-dependent enzymes responsible for diverse cellular signaling pathways. These enzymes activity is influenced by NAD+, and NAD+ deficiency linked to a variety of neurological diseases (43-45).

Mortiboys et al demonstrated that UDCA restores mitochondrial dysfunction in parkin-mutant fibroblasts derived from Parkinson's disease patients (46). According to the 'UP Study' of phase 2, a two-centered, double blind, randomized, placebo-controlled trial an increase in mean midbrain Pi by +0.02 in the UDCA group and a decrease by 0.006 in the placebo group is consistent with higher ATP hydrolysis in the UDCA treatment group. This Study proved that UDCA at 30 mg/kg is safe and well tolerated in Parkinson's disease, with no SAEs and only minor, temporary side effects recorded in the UDCA treatment group (20). 3 patients were found to have increased ATP levels in occipital cortical region, who had baseline and post UDCA P-MRS assessments. As a result, outcomes support that UDCA enhance the mitochondrial action in Parkinson's disease, and the metabolic rate was decreased in ATPase reaction in the first two participants, while the metabolic rate was increased in creatine kinase reaction in the similar brains. UDCA proved to be quite safe and approved, and this is the first report on UDCA pharmacokinetics in patients with Parkinson's disease (14). Xiao-Hong Zhu et al anticipated that the patients with Parkinson's disease, probably cause DNA damage or cellular abnormalities which change enzyme activities and decrease intracellular NAD+ content, thereby causing a drop in ATP content. As a result, activation of mitochondrial ATP synthase is anticipated to occur in order to increase ATP generation and energy requirements of brain cells (43). A recent clinical study had provided an understanding about the dopaminergic neurons in the substantial nigra are particularly vulnerable to the cellular dysfunctions observed in Parkinson's disease. The findings suggested that the greater susceptibility of nigral dopamine neurons can be directly related to their unique structural and bioenergetic properties leading to a greater basal energy necessity and reduced energy storing capacity. Consequently, they are more vulnerable to cellular stressors that affect energy production in mitochondria (47,48). Clinical trials in large population are required to confirm these discoveries and in contrast to examine the UDCA effect on Parkinson's disease (49). Investigating UDCA in combination with existing PD treatments, such as levodopa or other neuroprotective agents could provide synergistic benefits or enhanced therapeutic effects. We compared the effect of UDCA with the control (healthy volunteers) using P-MRS of the ATP and inorganic phosphate (Pi) concentrations using the meta-analysis software Review Manager 5.4. The ATP and Pi concentrations increased in the UDCA group as compared to the control. Considering its efficacy in animal models and human safety profile, UDCA appears to be a promising treatment for Parkinson's disease (50).

## Conclusion

UDCA at the higher doses is safe and endorse in early stage of PD patients. It has the excellent safety profile at 30 mg/kg, combined with the 31P-MRS-based evidence. The meta-analysis highlights promising preliminary findings regarding UDCA's effects on ATP concentration and mitochondrial activity in PD, future research should focus on expanding these findings through rigorous clinical trials, mechanistic investigations, and personalized medicine approaches. This comprehensive approach will be crucial for advancing UDCA from experimental evidence to clinically validated therapeutical intervention for Parkinson's disease and potentially on other neurological conditions.

**Author Contributions:**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Aswin Krishnamurthy], [Nandhini Sundaresan], [Vivekananthan G], [Sanjay R], and [Monish S]. All authors read and approved the final manuscript.

**Ethics Approval and Consent to Participate:** Not Applicable.

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**Conflict of Interest:** The authors declare no conflicts of interest.

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