

Ambroxol therapy for Parkinson's disease: Systematic literature review

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ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease. The accumulation of α -synuclein protein in the basal ganglia is the underlying pathogenesis of PD. Genetic abnormalities are one of the predisposing factors for PD. PDs with GBA gene mutations have abnormalities coding for β -glucocerebrosidase (GCase) enzymes in lysosomes, which lead to increased accumulation of α -synuclein. Ambroxol has long been known as a therapy for airway disorders which also has antioxidant benefits. However, recently, there have been many experimental studies examining the benefits of ambroxol in neurodegenerative diseases, including PD. This study aims to examine experimental studies of ambroxol administration in PD.

Keywords: Parkinson, ambroxol, therapy

INTRODUCTION

PD is a neurodegenerative disease of the brain associated with motor disturbances and other complications, including cognitive, mental, sleep, pain and sensory disturbances [1]. PD is the second most common neurodegenerative disease after Alzheimer's disease and is expected to increase by ~65% between 2010 and 2030 [2]. Accumulation of intraneuronal protein in the form of Lewy bodies (LB), which originates from alpha-synuclein in the gray matter pars compacta is a pathology of PD. The etiology that plays a role in PD is multifactorial, genetic and environmental factors contribute to the development of this disease, and age is the biggest factor. Another gene at risk is GBA1, the gene that encodes GCase in lysosomes [3,4].

PD with GBA gene mutation have a greater susceptibility to developing familial Parkinson's disease at an earlier age. GCase functions as a catalyze glycolipid glucocerebrosides into ceramides and glucose. Decreased GCase activity can increase the accumulation of α -synuclein protein in neurons. The buildup of these proteins can lead to worsening of PD [3]. In PD rat models, overexpression of GCase reduced α -syn and improved cognitive function [5,

6]. Decreased GCase activity will cause dysregulation of lysosomal-autophagy pathway and causes interference with lysosomes in degrading α -syn proteins in Gaucher disease (GD) and PD [4].

For three decades, Ambroxol served as a remedy for respiratory ailments. However, Ambroxol has other effects than drugs for respiration. Ambroxol at a dose of 10 – 90 mg/kg has antioxidant and anti-inflammatory effects in vivo [7]. Recent study with animal model of cynomolgus monkey found that Ambroxol can have a central effect, penetrating the blood-brain barrier and increasing 20% of GCase activity [8]. This study aims to conduct a systematic review of experimental studies that have been conducted previously regarding the role of Ambroxol in Parkinson's Disease.

METHOD

In this study, we use ScienceDirect, MEDLINE and Springer as search engines. The research time frame was in the past 10 years (2013 – 2023). The key word combinations in this study were Parkinson OR Parkinson's Disease AND Ambroxol. We reviewed only experimental research articles. Selection of research

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articles used inclusion and exclusion criteria. The inclusion criteria in this study used the Population, Intervention, Comparison, Outcome and Study Design (PICOS) format (Table 1).

TABLE 1. PICOS research criteria

Criteria	Participation	Exceptions
Population	Human or animal model with PD	PD that is difficult or cannot be distinguished from other diseases
Intervention	Ambroxol	
Comparison	Any	
Outcomes	Any	
Study design	Experimental research conducted by researchers	Case report, review, qualitative study and other research besides experimental research

RESULTS AND DISCUSSION

A total 343 studies were identified from databases (ScienceDirect, MEDLINE and Springer) based on the search keywords. The breakdown of the search results were ScienceDirect (n = 13); MEDLINE (n = 235); Springers (n = 95). The screening results excluded 308 articles that did not have the same theme as this research and 30 research articles did not meet the inclusion and exclusion criteria. A total 5 articles were included in this systematic literature review. The article screening process can be seen in Figure 1.

The majority of the studies used human tissue as sample, and only one study used animal mode. All human studies have the same characteristic, associated with GBA gene mutations and all studies have GCase as the outcome variable. The hypothesis of ambroxol as a neurorestorative found in all studies. We summarize the research outline in Table 2.

Ambroxol has the effect of increasing GCase activity in many studies [9-13]. Research with an animal model of Cynomolgus monkeys showed increased GCase activity in the striatum, cortex and midbrain with 100 mg/day of oral ambroxol for 28 days [8]. A possible potential binding site for ambroxol in the GCase N370s mutant was also discovered [12] in the previous study, which requires further exploration. ambroxol dosage *in vitro* study of Ambroxol administration in the range of 10 μM - 50 μM had effect on GCase activity [11,12], comparing the effectiveness of *in vitro* doses of ambroxol administration may need to conduct. Further exploration of effective oral ambroxol doses in human is needed.

The number of adverse effect (AE) incident in human subject studies were identified, from 176 identified AEs, 5 patients were probably related (AEs: nausea, vomiting, burning sensation, loose stools) and 3 patients were definitely related (AEs: acid reflux, nausea, conditions transitory skin on chest, back and hands) [9]. Nausea, vomiting and diarrhea are indeed side effects of ambroxol [14]. Ambroxol is fairly well tolerated. However, research on ambroxol therapy in human subjects with PD is still very limited and there

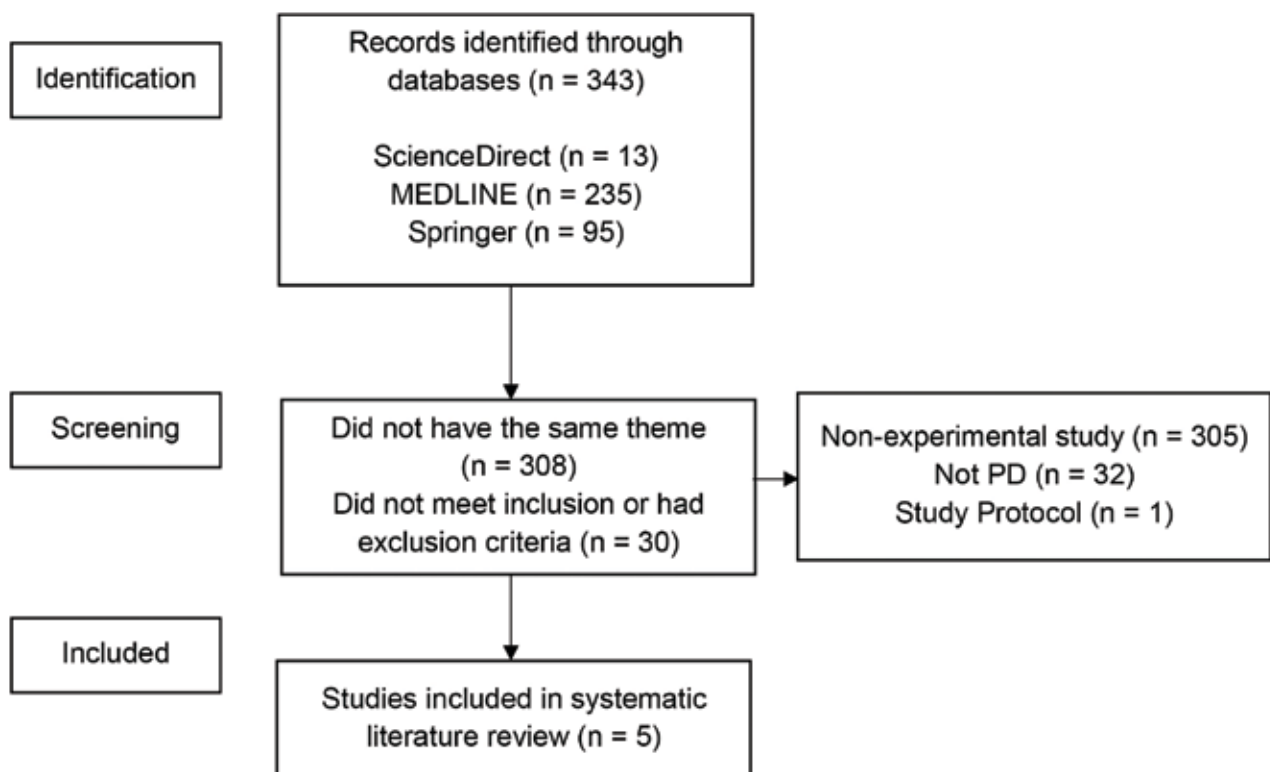


FIGURE 1. Article screening flow chart

TABLE 2. Results of article synthesis

Author (Year)	Population	Method	Result	Conclusion
McNeill, et al. (2014)	<ul style="list-style-type: none"> - 5 subjects with GD type 1 - 5 subjects with PD (4 heterozygous carrier patients, 1 patient with E326K GBA mutation homozygous gene) - 2 samples of PD carriers without neurological disorders - 3 control samples without neurological disorders and GBA mutations 	<p>Fibroblast cells from skin biopsy were taken from all subjects prior to the study and the activity of enzyme and protein GCase. Dihydroethidium oxidation rate were measured before and after the intervention of 10 μM, 30 μM and 60 μM ambroxol HCl culture media. kultur</p>	<p>Glucosylceramidase protein and enzyme activity of fibroblast in patient with GD and carrier heterozygous mutations with and without PD was lower and the dihydroethidium oxidation rate was significantly higher compared to controls. Ambroxol HCl treatment increased the activity of the GCase enzyme and decreased dihydroethidium oxidation rate.</p>	<p>Mutant GCase associated with decreased GCase activity and evidence of oxidative stress. Ambroxol treatment can increase GCase activity and reduce oxidative stress markers in mutant GCase cells.</p>
Mishra, et al. (2019)	60 rat animal models	<p>4 groups of rat models with each group consisting of 15 rats with the following treatments:</p> <p>K1: Control K2: Sham K3: unilateral intrastriatal 6-hydroxydopamine induction K4: unilateral intrastriatal 6-hydroxydopamine induction + Ambroxol 800 mg/kg/day day 28 - 70</p>	<p>The group of rats that received ambroxol had improved behavior and improved progressively. This group also had improvement in levels of tyrosine hydroxylase (TH), dopamine transporter (DAT), increases in soluble α-synuclein and GCase activity</p>	<p>Ambroxol demonstrated neurorestorative potential in hemiparkinsonian rats in this study</p>
Mullin, et al. (2020)	<ul style="list-style-type: none"> - 8 PD subjects with GBA1 mutations - 10 PD subjects without GBA1 mutation 	<p>Administration of Ambroxol for 186 days, with 28 days of increasing doses:</p> <ul style="list-style-type: none"> - 60 mg (days 1-7) - 120 mg (days 8-14) - 180 mg (days 15-21) - 300 mg (days 22-28) <p>After the exposure period, followed by 158 days at 1.26 g/day (420 mg three times per day) Cerebrospinal fluid (CSF) sampling was carried out on day 0 and day 186 and blood samples on day 0, 11, 93 and 186</p>	<p>There was a significant increase in Ambroxol levels in CSF in day 186. There was a significant increase in tau α-synuclein protein and GCase protein in both groups. Ambroxol therapy was well tolerated and there were no serious side effects</p>	<p>Ambroxol is well tolerated and has no serious side effects. This study is consistent with previous studies, ambroxol has an inhibitory effect on GCase activity in acellular CSF</p>
Kopytova, et al. (2021)	<ul style="list-style-type: none"> - 14 GD subjects - 6 PD with GBA mutations subjects - 30 healthy control subjects 	<p>Macrophage cultures derived from the patient's monocyte cells with medium containing 50 μM ambroxol hydrochloride for four</p>	<p>There was an increase in GCase activity and enzyme colonization in macrophage cells of GD and PD patients with GBA mutations compared to cells that had not been given ambroxol. The spatial structure of the N370s mutant GCase indicates the possible binding sites for ambroxol</p>	<p>Research using monocyte cells given ambroxol showed improvement in enzyme activity and colonization. The GCase N370s mutant was shown to possibly have an ambroxol binding site</p>
Yang, et al. (2022)	<ul style="list-style-type: none"> - 3 PD with heterozygous GBA1 mutations subjects - 3 healthy control subjects without GBA1 mutations 	<p>Neural crest stem cells that differentiate into cholinergic neuron cells were taken from skin biopsies of research samples, given 10 μM ambroxol for six days</p>	<ul style="list-style-type: none"> - Significant decrease in GCase activity and protein, together with cathepsin D levels in neurons with GBA1 mutations - Increased levels of tau and α-synuclein in GBA1 mutation nerve cells - Ambroxol significantly increased GCase enzyme activity and decreased levels of tau and α-synuclein in cholinergic nerve cells 	<p>The GCase gene mutation affects the metabolism of tau protein and α-synuclein in cholinergic neuron cells. Therapy on the GCase pathway can be a potential target of therapy in neurodegenerative diseases associated with pathological accumulation of tau and α-synuclein proteins.</p>

are no known long-term AEs for neurodegenerative diseases.

CONCLUSION

From this review, the benefit of ambroxol in increasing GCase activity was consistent in five exper-

imental studies, and demonstrated neurorestorative potential in PD especially with GCase mutants. However, further clinical studies need to be conducted to search the benefit and AE of ambroxol therapy in PD with and without GCase mutants considering that PD's therapy is for the long term period.

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