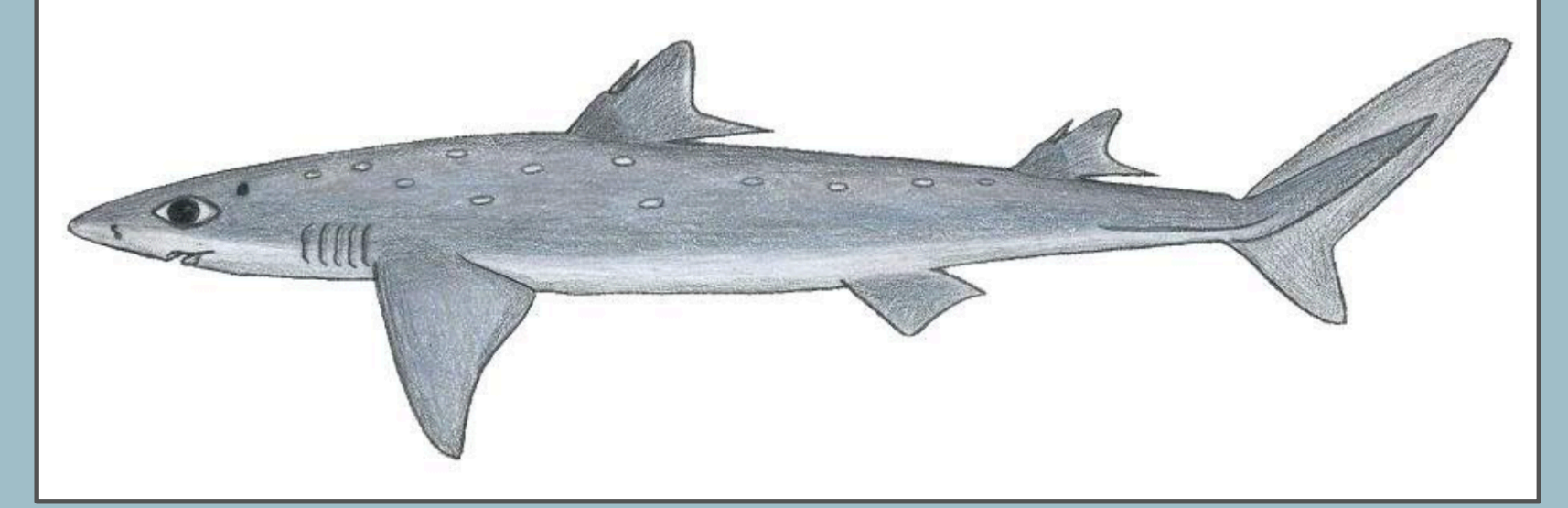


# Sustainable biomedical applications of Elasmobranchs: Synthesized Squalamine derived from Spiny Dogfish and inhibiting aggregation of $\alpha$ -synuclein.

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Sofia Sierra & Dr. Emily Lemmon

Department of Biological Sciences, Florida State University



## Abstract

Research on the Elasmobranch immune system has shown promising evidence of antibacterial activity in some immunocomponents. This paper will investigate the current research behind Squalamine (SQ) and its application to the aggregation of  $\alpha$ -synuclein in human neurons. Derived from the stomach tissue of the Spiny Dogfish (*Squalus acanthias*), SQ is an aminosterol that exhibits microbicidal activity against Gram-positive and Gram-negative bacteria. Additionally, it serves as an anti-tumor compound against certain cancers. Aggregation (protein folding) of  $\alpha$ -synuclein is associated with a variety of neurodegenerative disorders like Parkinson's. SQ has been found to inhibit growth factor-dependent pathways indicating its potential in inhibiting the aggregation of  $\alpha$ -synuclein. *In-vitro* studies and in-cell human neuroblastoma cultures show modulation of aggregation of  $\alpha$ -synuclein through displacement of the protein from the lipid membranes. The application of synthetic Squalamine in inhibiting aggregation of  $\alpha$ -synuclein demonstrates promise as a therapeutic agent.

## Background

- Elasmobranchii are a subdivision of the cartilaginous fish species, stemming from the species Chondrichthyes, which include sharks.
  - The lack of "sick" sharks found in the world's seas can be attributed to their evolved immune systems.
- Squalamine (SQ) was extracted from the stomach of the Spiny Dogfish, showing activity as an antibiotic aminosterol (Fig.1).
  - The compound, a steroid with similar structure to that of Cholesterol, acts as an antibiotic exhibiting microbicidal activity against Gram-positive and Gram-negative bacteria.
- It is important to note that the aminosterol can be synthetically reproduced through a nine step process.
- Spiny Dogfish species are considered vulnerable by the IUCN Red List and endangered in the Northeast Atlantic.
  - It is vital to consider their conservation as a species when evaluating the potential efficacy of SQ.
- SQ has been found to displace proteins that are bound to the cytoplasmic face of phospholipid membranes.
  - This has created interest in SQ's role in acting as a competitor of fibril accelerating phospholipid binding.
- $\alpha$ -synuclein proteins can bind to lipids, resulting in disordered folding, or amyloid fibrillation (Fig.2).
  - The accumulation of disordered proteins stems from neurodegenerative disorders, like Parkinson's and Alzheimer's.
- The inhibition of  $\alpha$ -synuclein aggregation has the potential to reduce neurological and gut-related symptoms of Parkinson's.

## Research Objectives

- Objective 1:** Explore the current research behind the synthesis of Squalamine
- Objective 2:** Evaluate the efficacy of Squalamine as an inhibitor in the aggregation of  $\alpha$ -synuclein

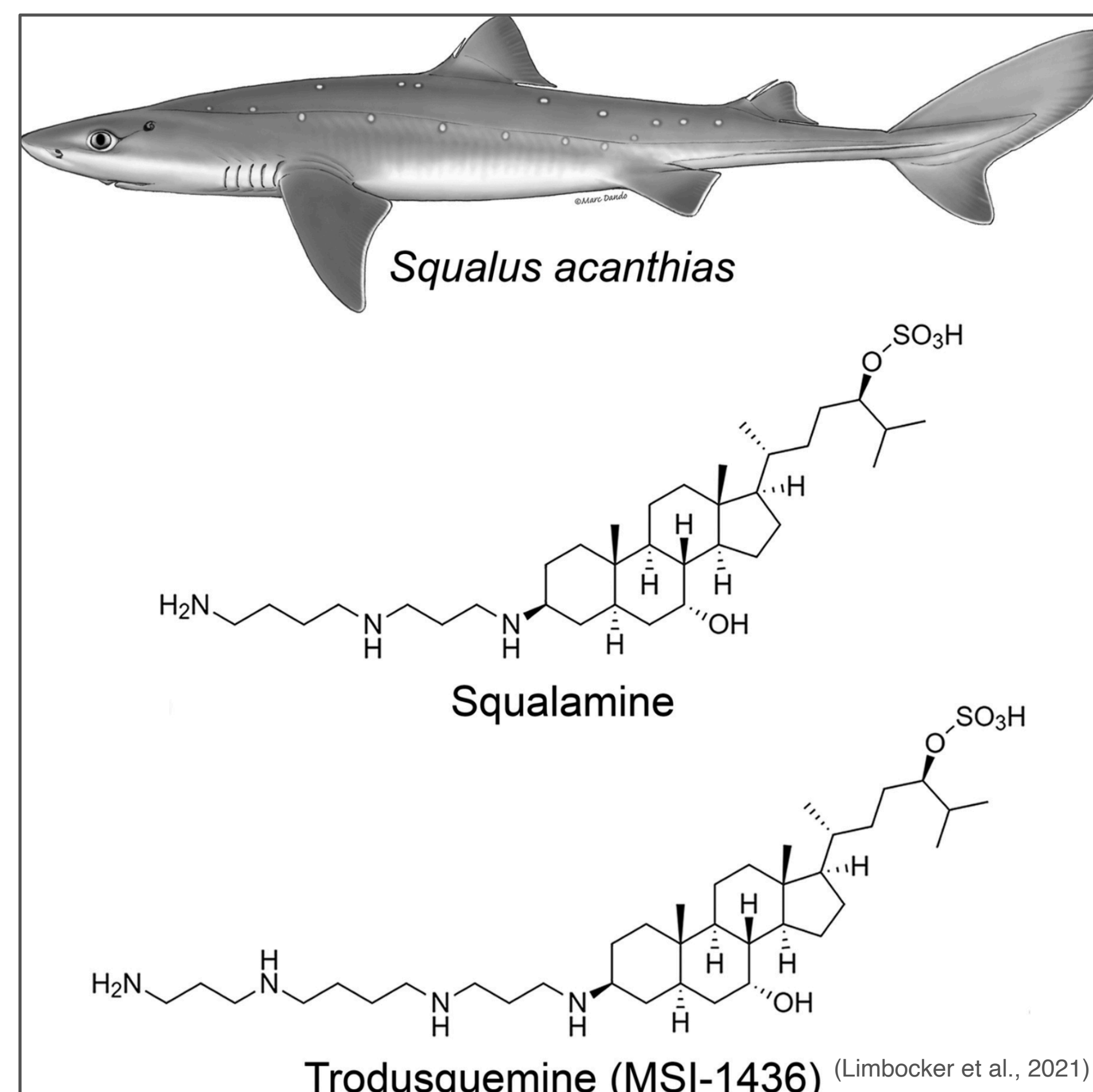


Figure 1. Chemical structure of Squalamine and Trodusquemine, found in Spiny Dogfish (*Squalus acanthias*). Figure taken from Limbocker et al., 2021.

## Methods

- All existing literature regarding Squalamine and the relation between the amyloid fibril of  $\alpha$ -synuclein was reviewed.
- Literature was retrieved through four databases: Pubmed, MEDLINE, Web of Science, and ScienceDirect.
- Literature was searched for based on the keywords: "Squalamine" and " $\alpha$ -synuclein", "Squalamine" and "Parkinson's", "Protein aggregation", "Amyloid formation", "Synthesized".
- All research was reviewed to meet the inclusion criteria: English-language, Peer-reviewed.

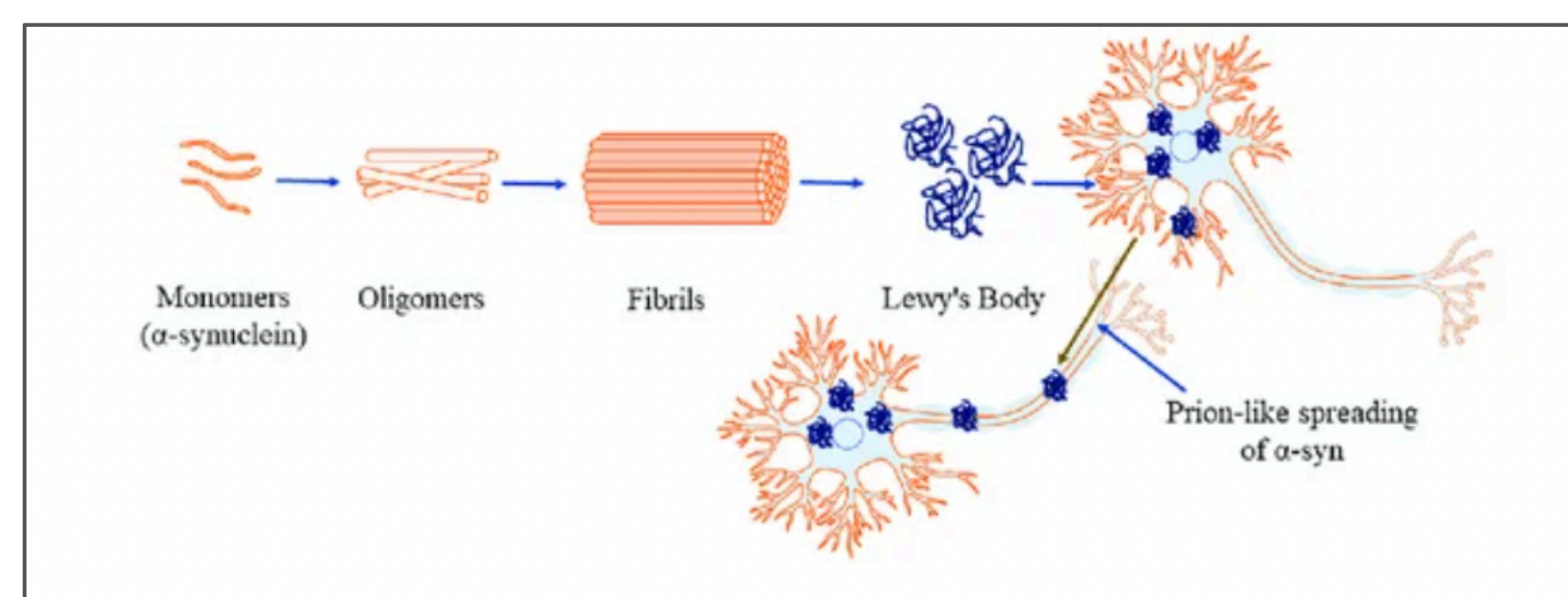


Figure 2. Pathway of aggregation of  $\alpha$ -synuclein and its relation to the neuron. Taken from Ray et al., 2021.

## Results

- Thirty-nine studies were reviewed initially. 16 studies met the criteria (Fig.3) (Fig.4).
- Squalamine is shown to inhibit amyloid fibrils of  $\alpha$ -synuclein in:
  - In vivo* and *in vitro* models of *C. elegans* with Parkinson's disease & *In vitro* human neuroblastoma cells.
  - Phase 1 and 2 clinical trials through the Human Enteric System.
- SQ can displace the protein from binding to the lipid bilayer, decreasing pace of protein aggregation.
  - Alpha-synuclein aggregate increases with lipid count.
- Trodusquemine, which has a greater charge than SQ, has a higher efficacy than SQ in *In vivo* trials of *C.elegans*.
  - Includes alpha-synuclein and amyloid-beta plaques.

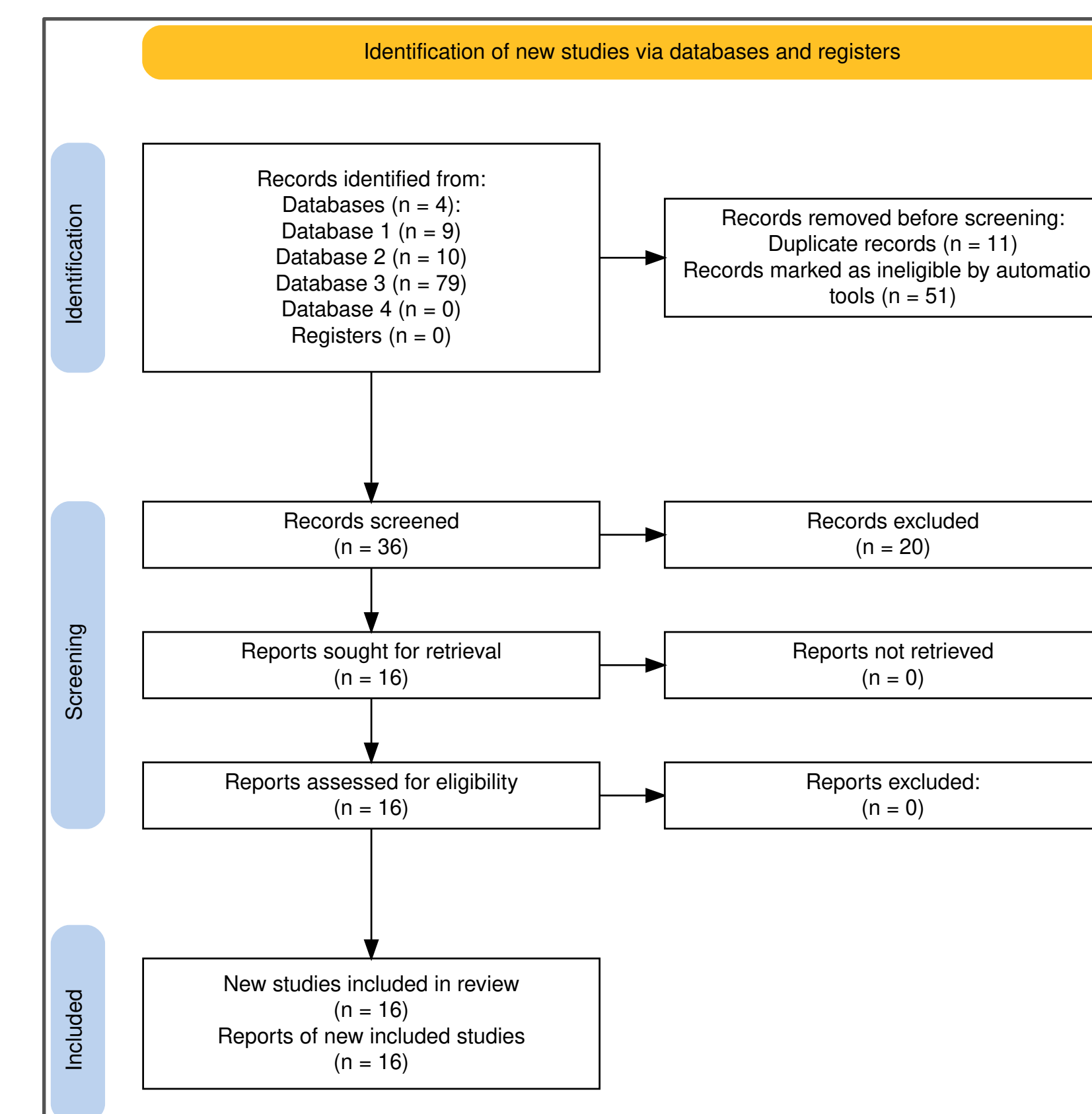


Figure 3. PRISMA flow chart of literature review. Accessed database on March 8th, 2026.

## Discussion

- There is a strong negative relationship between SQ concentration and  $\alpha$ -synuclein aggregation.
- SQ suppress initial aggregation by displacing  $\alpha$ -synuclein from the lipid membrane as shown in *in vitro* cultures.
- The results of a genetically modified *C.elegans* with SQ showed improved survival (motility and swimming speed).
- SQ improved gut dysmotility and constipation in Parkinson's patients through two phases of clinical trials.
- Trodusquemine, an aminosterol, is more effective in reducing  $\alpha$ -synuclein than SQ.
  - TQ exhibited a greater effect than SQ in *C.elegans* models of Parkinson's.
- TQ is able to cross the blood-brain barrier, suggesting it is promising for a brain-targeted therapy.

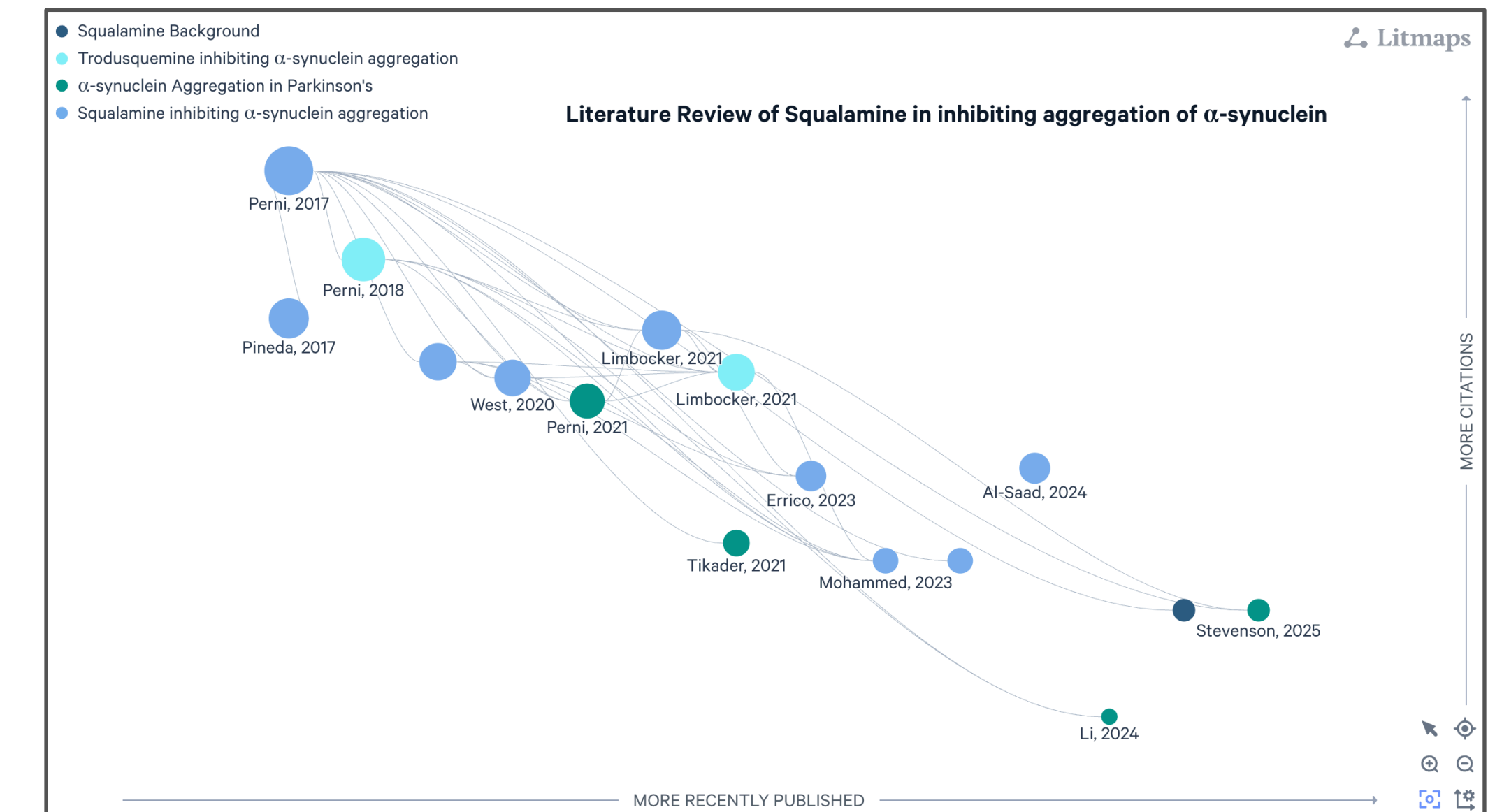


Figure 4. Literature Review of Squalamine in inhibiting aggregation of  $\alpha$ -synuclein. Created March 7th, 2026.

## Conclusions

- Squalamine (SQ) is able to effectively inhibit aggregation of amyloid fibrils.
- SQ is effective in decreasing gut-related symptoms of Parkinson's
- Trodusquemine (TQ) has similar yet stronger effects than SQ.

## Future Directions

- Clinical studies focusing on efficacy and safety need to be done on SQ.
- Mechanism research and clinical trials regarding Trodusquemine could provide insight to a mechanism used to localize a derived medication through the blood-brain barrier.

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