World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Therapeutic Potential of miR-34b/miR-23a Modulation in Parkinson's Disease via Keap1-Nrf2 and ULK1 Pathways

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World Journal of Biology Pharmacy and Health Sciences, 2026, 25(02), 352-361

Publication history: Received on 19 January 2026; revised on 24 February 2026; accepted on 27 February 2026

Article DOI: https://doi.org/10.30574/wjbphs.2026.25.2.0127

Abstract

The role of PD as a disorder characterised by interrelated disruptions of oxidative stress regulation and autophagy, which are two pathways that play a central role in the vulnerability of dopaminergic neurons, is increasingly recognised. This systematic review was an investigation of therapeutic potential of miR-34b and miR-23a (microRNAs) that can influence the Keap1 Nrf2 antioxidant axis and ULK1-mediated autophagy pathway. The peer-reviewed articles that were synthesised included five articles published between 2021 and 2024 and synthesised with the use of structured data extraction, CASP appraisal, and thematic analysis. Results show that there is strong conceptual evidence that microRNA plays a role in oxidative stress and autophagy, but direct evidence that miR-34b or miR-23a is involved in Keap1 -Nrf2 regulation or ULK1 activation in PD-specific models is very weak. Although combinatorial targeting of autophagy and oxidative stress is a concept with potential, there are many limitations, such as pleiotropic miRNA effects, barriers to delivery, and the absence of PD-specific mechanistic research, which considerably restricts translational potential at the moment. Critical research gap that is found in this review: There is no primary experimental literature that directly manipulates miR-34b and miR-23a in verifiable models of PD to corroborate pathway-specific effects. It is crucial that this evidence base should be strengthened before dual-miRNA therapeutic approaches can advance to clinical use.

Keywords: MicroRNAs Therapy; Parkinson's disease; Oxidative stress therapy; Autophagy; Keap1–Nrf2 / ULK1 pathways

1. Introduction

Recent reports indicate that Parkinson disease (PD) is one of the rapidly expanding neurological conditions across the world. The prevalence of PD in 2021 was 11.8m with an age standardised of 138.6 per 100,000. The incidence has been on the increase in the past decades (DeMaagd et al., 2024). Data on meta-analyses of data between 1980 and 2023 show that the upward trend is undeniable and more pronounced since the beginning of 2000s (Yang et al., 2024). It is estimated that the inarable population count of people with PD may go up to 25.2 millennium by 2050, which can be primarily due to ageing of the population (Su et al., 2025). The role played by China is disproportionate. It was the country with the highest age standardised incidence (24.3 per 100,000) and prevalence (245.7 per 100,000) in 2021 with increases of 89.7 per cent and 167.8 per cent since 1990 respectively (Xu et al., 2024). A national survey identified a 1.86% prevalence in adults aged 65 years and older, with more males and people in large cities, indicating that ageing and increased case detection are some of the causes of the increase (Song et al., 2022). These reports highlight the fact

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that the burden of PD is increasing very quickly worldwide, that China is an emerging epicentre and that there is inconsistency between model-based estimates and empirical survey estimates.

Although there have been improvements in the pathology of PD, there is no curative treatment. The existing therapies primarily alleviate symptoms as opposed to modifying the process of neurodegeneration. New evidence implicates the dysregulated microRNAs, in particular, miR -34b and miR -23a, in PD pathways. They modulate oxidative stress through the Keap1 -Nrf2 pathway and cause autophagy by transmitting ULK1 signals. Nevertheless, research results are inconsistent: various models are found, as well as the lack of consistent expression patterns and various mechanistic explanations. In addition, Chinese studies will provide useful mechanistic and preclinical information, although they are diffused throughout numerous databases, and often not incorporated into global reviews.

To pool existing evidence, make comparisons of mechanistic results, in cellular, animal, and human studies, and identify areas of convergence and disparity in therapeutic modulation of miR -34b and miR -23a, a systematic literature review is required. An SLR also frames analysis of quality of studies, methodology, and translation gaps and offers reliable evidence base as compared to narrative reviews.

This review identifies whether the potential effects of targeting these miRNAs on oxidative stress reduction, autophagy dysfunction correction and protection of dopaminergic neurons are meaningful by synthesising both global and Chinese studies. The aim is to help to elucidate their potential of therapeutic use and inform future experimental and clinical efforts.

2. Methodology

The systematic literature review was conducted according to Booth et al. (2021), Garcia-Peñalvo (2022), and Bettany-Saltikov and McSherry (2024) guidelines on systematic literature reviews. Keywords were directly extracted in the title of the research, and narrowed down with the use of directions on constructing transparent and reproducible search strategies (Mohamed Shaffril et al., 2021). Chinese scholarship and international scholarship were searched in 5 major academic databases, including CNKI, WanFang, PubMed, Embase, and Web of Science. Search terms were in combination of microRNAs, miR -34b, miR -23a, Parkinson disease, Keap1 -Nrf2, and ULK1. Only peer-reviewed journal articles were searched and no grey literature was taken into account according to the best-practise guidelines of SLR in management and biomedical research (Sauer, & Seuring, 2023).

Systematic inclusion and exclusion criteria were used to assure the rigour of the method. The inclusion criteria were as follows: (1) peer-reviewed journal articles; (2) studies devoted to the therapy prospects of microRNAs; (3) and studies devoted to Parkinson disease. The part of the exclusion criteria was based on recommendations of relevance and quality (Booth et al., 2021): publications prior to 2021, non-English articles, and all grey literature including theses, conference proceedings, or non-indexed reports. The first search in the five databases has retrieved a number of hundreds of records. All of the results were exported into a reference manager, then duplicate entries were eliminated by standard SLR staging practises defined by Bettany-Saltikov and 2024 McSherry.

After removing the duplicates, the review was conducted in successive screening phases based on the stepwise methods advocated in the literature on SLR (Sauer, 2023; Mohamed Shaffril et al., 2021). First, inclusion criteria were used to eliminate studies that failed to satisfy the language, date and publication-type criteria. Secondly, the other studies were screened manually: the titles and abstracts were read to determine whether they were in line with the therapeutic and mechanistic preoccupation of the review. Only those that directly test microRNA modulation, in the case of miR -34b or miR -23a, and their mechanism of action during the pathology of PD were retained. Five articles were eligible and after being screened successfully, data extraction and synthesis were done (see Appendix A for data extraction table). The PRISMA flow diagram summarises the whole process and is based on the standards of transparency and reproducibility of SLR.

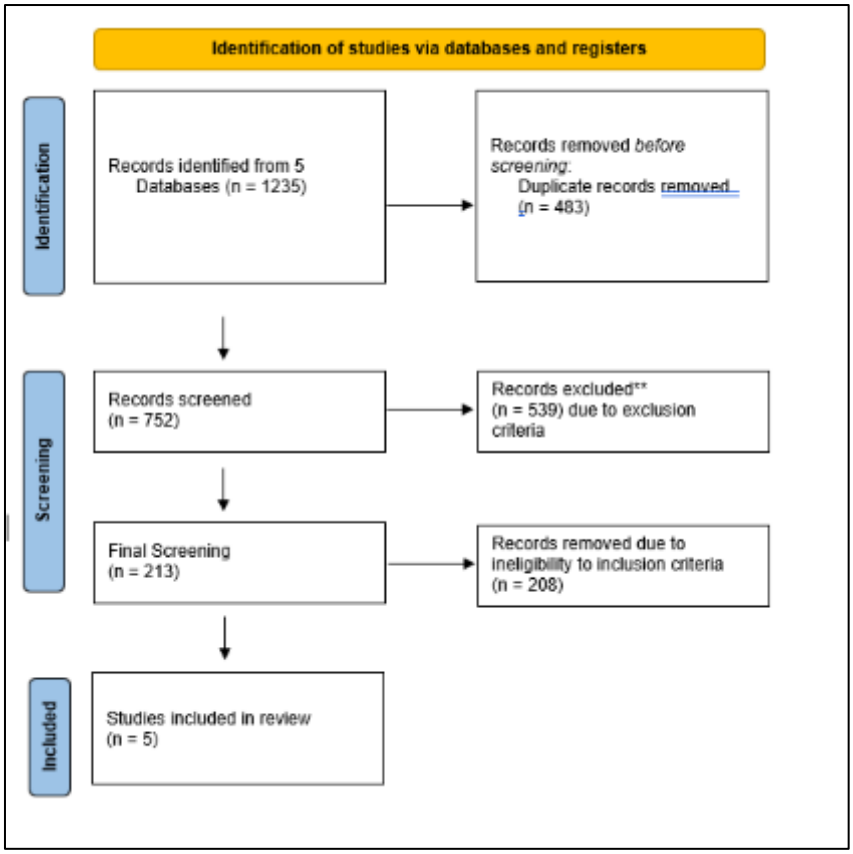

Figure 1 Data extraction and critical appraisal para.

3. Results

3.1. miR-34b in Parkinson's Disease – Regulation of the Keap1-Nrf2 Pathway

The evidence in the chosen articles all points consistently to the Keap1-Nrf2 axis as their primary antioxidant defence, but the strength with which they place miR-34b as a mediator of this pathway varies widely. Xu et al. (2021) suggest that multiple miRNAs regulate the Keap1-Nrf2 activity, but point out the regulation networks, as opposed to miR-34b. This makes their conclusions on Parkinson disease (PD) weak. A similar finding is the association of miR -34 family members with redox regulation of cardiac and pulmonary systems by Climent et al. (2020). Their evidence, however, is based on extrapolation of non-neuronal tissue, thus restricting the application on the degeneration of dopamine neurons. Conversely, the miR-34b dysregulation demonstrated by Shaheen et al. (2024) helps to impair the mitochondria and promote the oxidative stress in the PD. They fail to form a direct mechanistic contact with Keap1-Nrf2. Wang et al. (2020) and Neag et al. (2022) also support miRNA-mediated Nrf2 activation as one of the neuroprotective interventions; however, they note that the existing evidence is based on associative data instead of anti-PD miR-34b causal modulation.

A trend is observed in all these reviews: the researchers concur that increasing Nrf2 signalling decreases oxidative load, but they differ on whether miR34b is a useful tool to accomplish this. As one of a host of regulators, Xu et al. (2021) and Climent et al. (2020) introduce miR-34b and imply that the effect of inhibiting a single miRNA might be insufficient to have a therapeutic effect. In contrast, Shaheen et al. (2024) suggest a greater therapeutic prospects by establishing a connexion between miR -34b deficiency and the pathology of early PD; the existence of direct experimental evidence substantially weakens this argument. Wang et al. (2020) express a positive view on the Nrf2 activation by miRNAs and warn that the majority of the evidence is preclinical and does not correspond to PD. Neag et al. (2022) also indirectly prove the therapeutic importance of the pathway by ischemia-reperfusion injury studies but not by PD-specific data.

Possible advantages of miR-34b-mediated Keap1-Nrf2 regulation are increased antioxidant potential, minimised neuronal damage caused by ROS, and potential dopaminergic neuron preservation (Xu et al., 2021; Wang et al., 2020; Shaheen et al., 2024). Nevertheless, none of the authors avoid mentioning risks and side-effects, mainly because miRNAs are pleiotropic. By manipulating miR -34b, there is a risk of interfering with various other unrelated networks of genes

(Climent et al., 2020; Shaheen et al., 2024). Additional difficulties in therapeutic translation include ensuring a steady uptake of CNS, eliminating immune responses and off-target tissue effects, making delivery issues (Shaheen et al., 2024). In general, whereas the Keap1 2 Nrf2 pathway is generally considered neuroprotective, the data throughout the chosen articles show that miR -34b is a promising but not convincingly proven therapeutic option against PD. It needs closer mechanistic and translational studies prior to clinical viability being determined.

3.2. miR-23a in Parkinson's Disease – Regulation of the ULK1/Autophagy Pathway

These articles support the idea that dysregulated autophagy is part of neurodegeneration, but they provide indirect and partial evidence of a particular miR -23a -ULK1 pathway in Parkinson's disease. Xu et al. (2021) demonstrate that a number of microRNAs may influence the oxidative stress and corresponding pathways, but do not mark miR 23a or ULK1, undermining the argument that this two is mechanistically defined in PD. Shaheen et al. (2024) comment on autophagy dysregulation and the role of miRNAs in PD in which the miRNAs are treated as a general group with effects on protein clearance and the health of mitochondria without direct evidence suggesting miR 23a to act on ULK1. Wang et al. (2020) show that exosomal microRNAs are able to modulate neurodegenerative events, such as autophagy, yet they do not develop a specific miR 23a ULK1 therapeutic axis in PD models. The articles by Neag et al. (2022) and Climent et al. (2020) also associate microRNAs with stress responses and cell survival, but their work either refers to non-PD or non-autophagy models, which is not relevant to translational studies.

Cumulating these reviews, they end up on the conceptual attractiveness of microRNA-mediated autophagy regulation but differ on the realism and specificity of miR 23a ULK1 targeting as a PD treatment. Shaheen et al. (2024) consider autophagy-related miRNAs as a potentially therapeutic intervention in PD, but their findings cannot be considered practical since there is no miR-23a-specific experimental evidence. Wang et al. (2020) have a more conservative approach with an emphasis on exosomal miRNAs as the potential regulators of neurodegeneration despite the presence of translational challenges and the initial research phase. Xu et al. (2021) and Climent et al. (2020) also highlight that not only do individual miRNAs, like miR-23a, act within the framework of a complex regulatory system, but a reduction in the efficacy of therapeutic effects may be compensated over time. Neag et al. (2022) postulate that in acute brain injury, it is possible to protect the neurons with microRNA modulation, yet since their research is not based on chronic PD, it is not clear how the results can be applied to Parkinson.

The analysis of these reviews suggests that hypothetical miR-23a-ULK1/autophagy-based therapy might have the following potential benefits: increased toxic protein clearance, better control of mitochondrial quality, and decreased neuronal susceptibility in case of autophagy restoration to a physiological level (Wang et al., 2020; Shaheen et al., 2024; Xu et al., 2021). Nevertheless, the risks are also enormous according to the same sources because the autophagy is a two-sided process as a lack of it along with its excess may damage neurons (Shaheen et al., 2024; Xu et al., 2021). The pleiotropy of miR-23a implies that a therapeutic modulation may unwantedly change a large number of off-target transcripts, and has an unpredictable system-wide impact other than ULK1 (Xu et al., 2021; Climent et al., 2020). The delivery is one of the key issues as both Shaheen et al. (2024) and Wang et al. (2020) note that the CNS penetration, stability, immune activation, and targeted exposure to the affected brain areas are problematic (Shaheen et al., 2024; Wang et al., 2020). In general, the chosen articles do not offer empirical evidence to support the miR-23a regulation of ULK1/autophagy as a treatment option in PD, as they are conceptual, and do not have the characteristics of empirical evidence (Xu et al., 2021; Neag et al., 2022; Climent et al., 2020; Wang et al., 2020; Shaheen et al., 2024).

3.3. Combined Modulatory Effects

The chosen reviews will generally hold that oxidative stress and autophagy are no longer independent phenomena, but constitute a highly interdependent network in neurodegeneration. Xu et al. (2021) also define microRNAs as major regulators of the oxidative-stress signalling pathway, and its downstream pathways to cell survival that are well known to overlap with autophagic responses. (Xu et al., 2021) Climent et al. (2020) also state that microRNA-ROS crosstalk determines cellular fate choices, so that the secondary effect of chronic redox imbalance is deemed to perturb degradative pathways like autophagy. In Wang et al. (2020), exosomal microRNAs are explicitly presented as mediators that can promptly and concurrently regulate oxidative stress and neurodegenerative cascades which is implicitly encompassing any of the aforementioned processes like autophagy. Shaheen et al. (2024) combine all these ideas into Parkinson disease (PD) context and point out that miRNA dysregulation is what leads not only to the oxidative damage but also to impaired protein clearance yet falls short of mapping specific miRNA pairs to specific oxidative-stress autophagy pathways. All of these reviews give credence to the fact that mechanistic crosstalk exists, but little direct evidence of how it can be used in the context of PD precisely and safely is available. Therefore, they need to gain a deeper comprehension of the economic case, which would likely reduce the development of such issues in the future.<|human|>Thus, they must have a more in-depth understanding of the economic case, which is likely to mitigate the development of such concerns in the future.

The idea of a dual-miRNA approach to miR-34b-mediated Keap1-Nrf2 and miR-23a-mediated ULK1/autophagy regulation seems theoretically appealing within the context of this conceptualization framework but has not been empirically tested in the chosen literature. Xu et al. (2021) and Climent et al. (2020) note that individual microRNAs act in dense regulatory networks, which means that targeting two nodes may improve coverage of important pathways, at the cost of introducing greater possibilities of unpredictable compensatory responses. It is implied that exosomal delivery may allow the simultaneous modulation of several microRNAs, and Wang et al. (2020) advocate the concept of a dual-miRNA approach; however, they highlight the novelty of such strategies and the lack of disease-specific optimisation. Shaheen et al. (2024) are more optimistic about the multi-miRNA therapeutic opportunities in PD, introducing microRNA panels as a diagnostic and interventional tool, yet their point is mostly speculative because they do not provide data on mixed miR-34b/miR-23a manipulation. Neag et al. (2022) also demonstrates in ischemia-reperfusion injury that neuroprotection can be realised through the modulation of a number of microRNAs, but this acute injury paradigm is not comparable to chronic PD and, therefore, has limited direct applicability. (Neag et al., 2022)

The benefits of dual-miRNA therapy which are inferred encompass the potential to mitigate oxidative stress and normalise autophagy at the same time, as two interlocking agents of dopaminergic neuron death. In theory, sharing the therapeutic load between miR-34b and miR-23a could enable a lower dose to be delivered to each of the two miRNAs, potentially decreasing the toxicity of each specific miRNA, but resulting in network effects. Nevertheless, the issues and risks are great: all the authors emphasise on the pleiotropic properties of microRNAs, thus, simultaneous mutation of two regulators can increase the off-target effects and interfere with unrelated signalling. Wang et al. (2020) and Shaheen et al. (2024) also note other translational barriers such as accessibility to a particular brain area, chronic safety, inter-subject variability, and the inability to determine the benefit or harm of a particular component of a dual therapy. In a nutshell, the chosen articles confirm dual-miRNA modulation as an overly conceptually strong and experimentally unproven therapeutic approach, which requires strict experimental research before such combined approaches can be plausibly promoted to PD. Moreover, prioritising the medical aspects of the disease, which includes an individual's health and welfare, is acceptable.<|human|>In addition, the medical aspect of the disease, such as the health and well-being of an individual, should be given priority, which is acceptable.

4. Discussion

4.1. Methodological Rigour of Findings

In the sampled reviews, a number of common methodological strengths were observable. Each article had a well-defined research focus, detailing the relationship between microRNAs and oxidative stress, or autophagy, or neurodegeneration, which is expected of CASP in terms of clarity of purpose. The reviews all showed good conceptual synthesis; all incorporated mechanistic pathways and emphasised biological relevance; specifically in terms of redox regulation, mitochondrial dysfunction, and miRNA-mediated signalling. This thematic unity indicates the presence of a good interpretive profundity, which has been observed many times in better reviews. Also, the vast majority of articles utilised a general literature base that utilised multi-disciplinary evidence of molecular biology, neuroscience, and pathology that enabled authors to place microRNA regulation in a broader neurodegenerative paradigm. Moreover, some of the reviews, especially the most recent ones, included critical considerations of therapeutic translation, considering the efforts of delivery barriers, off-target effects, and the intricacy of miRNA network interactions, proving methodological maturity and the recognition of clinical applicability.

The reviews also had some significant limitations despite these strengths. All the articles did not meet the criteria of a rigorous systematic review, with the majority not having clear search strategies, pre-specified inclusion criteria, or explicit critical evaluation of included evidence, and this is a weakness present in their CASP ratings (see Appendix B). Most of them depended on a storey as opposed to a systematic synthesis, which makes them more vulnerable to selection bias and subjectivity. Some of the reviews made widespread recourse to the indirect data provided in other non-PD settings, in particular, cardiac, pulmonary, or ischemia-reperfusion models, which restricted the applicability of their results to Parkinson's disease. The other typical limitations were the lack of clear mechanistic mapping of particular microRNAs (miR-34b and miR-23a) and pathway of interest, which resulted in conceptual claims that were larger than the supporting evidence base. Lastly, none of the reviews included explicit quality evaluation of primary studies, which reduces the level of confidence in the strength of the conclusions and constrains their applicability to inform the process of therapeutic decision-making.

4.2. Comparison with Past Studies

Overall findings of this review are consistent with existing literature about the importance of oxidative stress and dysregulation of autophagy in the context of Parkinson disease (PD), but the degree of evidence level of specific

microRNAs including miR-34b and miR-23a differs significantly in this regard. The microRNAs and their direct and indirect mechanisms involved in the oxidative-stress pathways regulation by microRNAs are described in a much more comprehensible and straightforward manner by several authors, such as Saha (2024) and Xie and Chen (2016) in their models of PD. The previous works find explicit miRNA-target interactions, but the articles reviewed in your review are based mostly on general associations and non-PD evidence, developing a conceptual gap between already known molecular processes and the overall conclusions drawn by the chosen authors. In that regard, the current review adds a more sceptical understanding, which is more decisive in Saha (2024) and Xie and Chen (2016).

The dysregulation of microRNA in neurodegeneration, in general, and Dogra et al. (2025) as well, promote the overall finding that microRNAs are promising therapeutic targets and biomarkers. Nevertheless, Dogra et al. (2025) provide stronger evidence of linking particular miRNAs to neurodegenerative pathways than the reviews that are evaluated in this case because many of them omit the description of specific miRNA-gene interactions. Where Dogra et al. point to an accumulating body of evidence in favour of miRNA specificity, the current review notes that there is no direct experimental evidence of miR-34b and miR-23a in the pathways of interest and this indicates that the evidence strength rather than the overall direction of the concept is divergent.

In the same vein, Kinoshita and Aoyama (2021) also offer confirmation of non-coding RNA, such as microRNA, to influence glutathione-medicated neuroprotection- therefore supporting the use of redox signalling as a target. This is consistent with the fact that oxidative-stress pathways were found to be very relevant by your review, but is inconsistent with its conclusion that the choice of studies did not report a direct mechanistic mapping of miR-34b or miR-23a in PD. Comparatively, Kinoshita and Aoyama have better biochemical grounding than the analysed reviews.

Wang et al. (2021) adopt a pharmacological approach and show that the Nrf2/HO-1 activation produces neuroprotective effects in PD. Their results support the conclusion of your review that Keap1Nrf2 signalling is a viable treatment axis. Nevertheless, Pharmacological evidence is given by Wang et al., and the chosen reviews are founded on the regulation on a microRNA level without the direct causal evidence, revealing a major gap between mechanistic plausibility and experimental validation. In this way, the general direction is consistent, but the level of evidence is significantly different.

Finally, the findings in Wang et al. (2020) on exosomal microRNAs supplement your conclusions on a combined effect of such modulators, especially the concept of simultaneous modulation of oxidative stress and autophagy by microRNAs. Contrary to most of the works in your review sample, the work by Wang et al. (2020) directly covers the aspect of delivery systems, one of the most significant translational barriers that your review determines. Nevertheless, their work, too, does not eliminate the specificity problem that is associated with miR-34b and miR-23a, which supports the thesis that dual-miRNA modulation is still an empirically understudied concept that is still theoretically viable.

4.3. Implications

4.3.1. Clinical translation challenges

There is a set of challenges facing clinical translation of miR-34b/miR-23a-mediated regulation of Keap1-Nrf2 and ULK1/autophagy in Parkinson which the general miRNA literature already reveals. Evans et al. (2021) indicate that a large portion of the so-called promising miRNA effects in worms, flies or rodents are not only reduced but also eliminated once tested in human material, revealing a fundamental species-translation gap of miRNA targets and networks. Ma et al. (2013), also argue that despite the number of miRNAs have been reported to be involved in PD models, very few have gone past preclinical proof-of-concept due to the lack of full target validation in human neurons and brain tissue. This is strengthened by Nguyen et al. (2022) who state that miRNAs are now much more of a biomarker than a drug: miRNAs can differentiate human brains, but it is technically still immature and safe to manipulate those signatures.

Delivery and specificity are significant obstacles even in the event that target relevance is established. As Fioravanti et al. (2022) emphasise, miRNAs are positioned in the centre of the thick web of oxidative-stress networks thus any attempt to manipulate them therapeutically will rewire whole circuits of stress-responses instead of a single pathway. Important evidence-of-principle is given by Kabaria et al. (2015): miR-7 can activate Nrf2 through Keap1 and shows that Nrf2 can be controlled by miRNAs, however, they also show that a single miRNA can and does regulate a number of transcripts, making prediction of doses and off-target activities challenging. Nguyen et al. (2022) also point to the problems with the penetration of the blood to the brain, with cell-type-specific uptake, and the inability to evade immune response or genomic destabilization with further intake. Collectively, these investigations indicate that the conceptual enigma of dual miR-34b/miR-23a therapy is high, but the present translational environment is not ready to

provide accurate, lasting, and secure miRNA therapeutic interventions of Keap1-Nrf2 and ULK1/autophagy in clinical PD.

4.3.2. Future Therapeutic Directions

The next phase in the future of miR-34b/miR-23a-based therapy in the context of Parkinson is the transition to single-pathway modulation to more complex network-based interventions. Prasad (2017) demonstrates that dynamically changing microRNA profiles in PD are determined by oxidative stress and inflammation, and that treatment modalities need to respond to a dynamic molecular environment instead of addressing specific nodes. Jain et al. (2026) also suggest that the Nrf2 -Keap1 antioxidant axis and NLRP3-induced inflammation should be addressed simultaneously and not separately, which is why it is essential to use a multi-target approach in which redox and immune pathways are actively co-modulated.

The current literature provides convenient initial points of such strategies. Kabaria et al. (2015) show that it is possible to activate Nrf2 via miRNA and this model offers a mechanistic framework that can be expanded to miR-34b. Xie and Chen (2016) also emphasise the regulatory safety of miRNAs in the control of oxidative stress, which suggests that miRNA therapies or miRNA-drug conjugates can be more precise than any single miRNA. On the whole, multi-miRNA or multi-pathway modulation is expected to become a key component of the therapeutic development in the future due to the improvements in delivery technologies, biomarker monitoring, and systems modelling, to be able to deliver comprehensive and safe intervention.

5. Conclusions

This article review indicates the conceptual potential of targeting miR-34b and miR-23a to activate two key pathogenic pathways in PD, oxidative-stress control via the Keap1-Nrf2 axis and autophagy induction via ULK1. In the literature reviewed, oxidative stress and autophagy dysfunction have been consistently found as primary triggers of dopaminergic degeneration, and microRNAs are evidently upstream regulators of both. Nevertheless, the evidence directly implicating miR-34b with Keap1 Nrf2 or miR-23a with ULK1 in Parkinson specific contexts is still not complete in spite of this solid theoretical premise. Most of the available information stems out of wider neurodegeneration, ischemia or non-neural disease models, highlighting the deficiency of PD-specific mechanistic studies. Even though a joint miRNA approach, which would involve simultaneous oxidative stress and autophagy targets, seems to be biologically viable and could be highly effective, the existing evidence base is not yet smart enough to underpin clinical translation. In general, the review indicates that miRNA-based modulation is a new frontier, which has theoretical potential but is limited by lack of mechanistic understanding, dose-delivery, and dose-safety information.

The SLR demonstrate that one of the gaps in research that this review creates is the lack of primary experimental research that directly investigates the role of miR-34b and miR-23a in validated models of Parkinsonism, especially that examines their causal role in regulation of Keap1.Nrf2 and ULK1 signalling. There were no in vitro or in vivo studies of PD that control these microRNAs and measure downstream pathway outcomes, neuronal survival, or behaviour. Such a gap restricts the possibility of concluding whether these miRNAs are only associated with the pathology of PD or whether they are potentially useful candidates in therapeutic intervention. To bridge this gap, it will be necessary to implement specific mechanistic investigations, dual-miRNA modulation, and translational studies that unite delivery technologies that will provide the desired outcome of control over microRNAs in brain regions.

5.1. Limitations

The weakness of this review lies in the fact that all of the study materials included were review articles, so no primary experimental or clinical studies were obtained to obtain direct evidence on miR-34b or miR-23a in PD. The use of the secondary literature also presents the interpretive and selection bias, most of the reviews failed to mention the search strategies, inclusion criteria, and quality measures. The search restriction to journal articles and the exclusion of non-English and pre-2021 articles could have caused the omission of background evidence, whereas the exclusion of possible relevant grey literature. Lastly, due to the lack of mechanistic specifics of PD in the material under study available, the synthesis is also limited in its scope to dependent evidence, which restricts the possibility of making solid therapeutic statements.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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Appendix A – Data Extraction table

Study (In-text Citation)	Article Type / Model	miRNA(s) Investigated or Discussed	Pathway(s) / Biological Focus	Key Findings Relevant to Therapeutic Potential
Xu et al. (2021)	Review	Multiple oxidative-stress-related miRNAs	Oxidative stress mechanisms; Keap1–Nrf2 signalling	Shows various miRNAs regulate redox homeostasis and Keap1–Nrf2 activity, supporting miRNAs as therapeutic modulators of oxidative stress.
Neag et al. (2022)	Review	Numerous miRNAs linked to ischemia–reperfusion injury	Oxidative stress, neuroinflammation, apoptosis	Demonstrates miRNA modulation affects oxidative stress and neuronal survival pathways, providing parallels to PD mechanisms.
Climent et al. (2020)	Review	Multiple ROS-related miRNAs	ROS generation, inflammation, oxidative damage	Highlights miRNA control of ROS signalling across diseases, reinforcing the rationale for miRNA-based redox therapies in neurodegeneration.
Shaheen et al. (2024)	Review	Range of PD-associated miRNAs	α-synuclein aggregation, neuroinflammation, oxidative stress, mitochondrial function	Identifies dysregulated miRNAs in PD with diagnostic and therapeutic potential; discusses challenges in clinical translation.
Wang et al. (2020)	Review	Exosomal miRNAs involved in neurodegeneration	Oxidative stress pathways, intercellular miRNA communication	Suggests exosomal miRNAs as regulators of oxidative stress and potential therapeutic delivery systems for neuroprotection.

Appendix B – Appraisal of Methodological Rigour of the selected articles

Study (In-text citation)	Xu et al. (2021)	Neag et al. (2022)	Climent et al. (2020)	Shaheen et al. (2024)	Wang et al. (2020)
Clear Review Question	Yes	Yes	Yes	Yes	Yes
Appropriate Search Strategy	Partial	Yes	Partial	Yes	Partial
Explicit Inclusion Criteria	Partial	Partial	No	Yes	No
Quality Assessment Reported	No	No	No	Partial	No

Adequate Data Synthesis	Yes	Yes	Yes	Yes	Yes
Minimised Bias / Transparency	Partial	Partial	Partial	Yes	Partial
Overall CASP Rating	Moderate Quality	Moderate–High Quality	Moderate Quality	High Quality	Moderate Quality