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ORIGINAL ARTICLE

A hypothesis: MiRNA-124 mediated regulation of sirtuin 1 and vitamin D receptor gene expression accelerates aging

Poulami Dhar[1] | Shailaja Moodithaya[1] | Prakash Patil[2] | Kellarai Adithi[3]

[1]Department of Physiology, K. S. Hegde Medical Academy, Nitte (Deemed to be University), Mangalore, Karnataka, India

[2]Central Research Laboratory, K. S. Hegde Medical Academy, Nitte (Deemed to be University), Mangalore, Karnataka, India

[3]Department of General Medicine, Justice K. S. Hegde Charitable Hospital, Nitte (Deemed to be University), Mangalore, Karnataka, India

Correspondence
Shailaja Moodithaya, Department of Physiology
K. S. Hegde Medical Academy, Nitte (Deemed to be University)
Mangalore, Karnataka, India.
Email: shailaja.moodithaya@nitte.edu.in

Abstract

Objectives: Specific miRNAs are evident to be overexpressed with age, lifestyle, and environmental changes. Previous studies reported miR-124 overexpression in different scenarios in aged skin, age-related cognitive impairment, ischemic heart disease, muscle atrophy, and fractures. Thus miR-124 was considered to be a reliable miRNA target to establish a hypothesis on aging epigenome. Parallelly the hypothesis focuses on the expression of SIRT1 and VDR genes as a target for this specific miRNA expression as these genes were believed to be related to aging. This study aims to derive facts and evidence from past studies on aging. The objective was to establish a hypothetical linkage between miR-124 with age-related genes like SIRT1 and VDR.

Methods: An in silico search was performed in the TargetScan and miRbase databases to analyze the aging-associated miRNAs and their gene targets, the Python seaborn library was used, and the results were represented in terms of a bar plot.

Results: Based on an in silico analysis and studies available in the literature, we identified that miR-124-3p.1 and miR-124-3p.2 targets 3′ UTR of VDR and SIRT1 genes, and hence thereby indicates that the miR-124 can regulate the expression of these genes. Further, few in vitro research studies have observed that miR-124 overexpression leads to the downregulation of VDR and SIRT1 gene expression. These results indicate that the suppression of these target genes accelerates early aging and age-related disorders.

Conclusions: Overall, this study hypothesizes that the overexpression of miR-124 diminishes the expression of VDR and SIRT1 genes, and thereby advances the process of aging, resulting in the development of age-associated complications.

KEYWORDS
aging, epigenetics, microRNA, SIRT1, VDR

1 | INTRODUCTION

Aging is the underlying cause of the majority of health risks. The elderly population is increasing rapidly, in 2019 CDC reports 54.1 million US adults were 65 which is 16% of the population.[1] Population Reference Bureau (PRB) gave us whole statistical data where China held to be the first followed by India, the United States, Japan, and so on.[2] An increasingly aged population doesn't imply a healthy population. It becomes

a global threat to maintaining a healthy nation with a rapidly aging population. Indeed, aging is a subjective gradual change that occurs at different rates among individuals in an unpredictable manner. Though it is an unpredictable process, lifestyle, exposure to stress, diet, and environment can all influence the rate of aging. All these factors can contribute to epigenetic alteration where gene expression changes without changing the DNA sequences. This is an omni potential of epigenetic changes because it can be modulated, and on the other hand, its effect is reversible. In the past decade, mainstream gerontologists have accepted this reversible nature of epigenetic changes in the aging process.[3] Epigenetic changes are mediated by three fundamental modifications namely, DNA methylation, histone protein modification, and microRNA (miRNA) biosynthesis. The production of miRNAs, small non-coding RNAs that potentially cause epigenetic alteration without changing the primitive DNA sequences, is one emerging viewpoint in the process of aging. It mainly acts through post-transcriptional modification, as evidenced by several experimental studies that show miRNAs can actively regulate cellular mechanisms including apoptosis, cellular differentiation, proliferation, and migration.[4] Identification of age-associated miRNAs and the introduction of therapeutic targets can potentially reduce age-related health risks.[5]

Recent gerontological studies are vigorously focusing on anti-aging as well as reversing aging. The aim is not to cease the aging process, rather is to progress through healthy aging with minimal health issues. Sirtuins, a promising target from SIRT1, act in slowing down the aging process. It is perpetual to longevity as slow-aging individuals show longer life expectancy and are less likely to have major health consequences.[6] It can be explained by the mechanism involved in LMNA gene mutation in HGPS (Hutchinson–Gilford progeria syndrome) where children show senescence due to accelerated aging processes. Here vitamin D plays a huge role in slowing down the faster rate of aging in HGPS. Vitamin D supplementation increases human SIRT1 expression which in turn increases sirtuins action.[7] Sirtuins is one of the class III histone deacetylase enzymes which mainly depends on NAD+. Along with histones, sirtuins also deacetylate other transcription factors as well as cytoplasmic proteins. These actions of sirtuins are indispensable for reducing oxidative stress, controlling inflammation in aging cells, DNA repair, and indicating apoptosis. Thus, cumulatively sirtuins protect cellular senescence and become an anti-aging target.[4] Additionally, the vitamin D receptor gene (VDR) has been found to have autophagic, apoptotic, and immune properties and thus related to the anti-aging targets.[8] With this background and an in silico analysis, we derived a hypothesis that the overexpression of gene-specific miRNA downregulates the expression of VDR and SIRT1 genes, and thereby accelerates the process of aging, leading to the occurrence of age-associated disorders.

2 | HYPOTHESIS

Discovery of circulating miRNAs added a new dimension to the research field. MiRNAs can be easily isolated from plasma and determined their expression levels by the qRT-PCR technique,[9] and this made it a more acceptable probe for researchers. Over time, around 2000 miRNAs have been found in the human genome and a database has been made out of it.[10] While working on miRNA related to senescent cells, Harada et al. have found miR-124 to be upregulated with increasing cell senescence.[9] They have confirmed their finding by miRNA PCR array where there is a significant increase in miR-124 levels found in aged facial skin than the young skin cells. On the extended side of their finding, they showed suppression of the proportion of malignant cells upon overexpression of miR-124.[11] Using Targetscan v26, miR-124-3p.1, and miR-124-3p.2 were localized, and are cohesively related to SIRT1 and VDR gene expression (Figure 1). It has already been seen that the SIRT1 gene is a potent modulator for aging.[6,12,13] Also, the deficiency of vitamin D or dysregulation of the VDR gene can induce early aging.[14] Henceforth, in silico approach, we can hypothesize that the overexpression of miR-124-3p.1, and miR-124-3p.2 are indicators of downregulated SIRT1 and VDR gene expression and potential predictors of accelerated aging.

3 | METHODS

An in silico search was performed using bioinformatics tools, and TargetScan, the database for human miRNA searches through mRNA sequences from targeted 3′ UTRs human genes.[15] The search was made by the key gene names SIRT1 and VDR for human mRNA and found that for both genes, miR-124.3p.1 and miR-124.3p.2 were located simultaneously. Next, the miRNA database called miRbase was used to retrieve the data for those targeted miRNAs[16] and it shows that miR-124.3p.1 and miR-124.3p.2 were found for their potential role in diseases. The data in the CSV file were downloaded and analyzed using Python to obtain the most likely diseases related to miR-124.3p.1 and miR-124.3p.2. A bar plot was made, and the 20 most likely diseases were plotted out of 550 and 560 entities for miR-124.3p.1 and miR-124.3p.2, respectively (Figures 2 and 3). In both cases, carcinoma remains the first position followed by Alzheimer's, Parkinson's, psychological depression, ischemic heart disease, arthritis, etc. These diseases are proven to be related to aging and henceforth these miRNAs were specified and targeted.

Furthermore, a vigorous literature search was performed through the Scopus and Web of Science search. The keyword, miR-124 was used for searching and 871 articles were found, out of which 28 articles were found to be relatable. Further, a thorough analysis of these studies showed that 19 articles were relevant for supporting this hypothesis (Table 1).

4 | EXPLANATIONS FOR HYPOTHESIS

4.1 | SIRT1 and aging

Aging is a wholesome process that can be modulated or possibly delayed preventing some age-associated pathologies. Experiments and interventions on animals and humans supported the fact that some

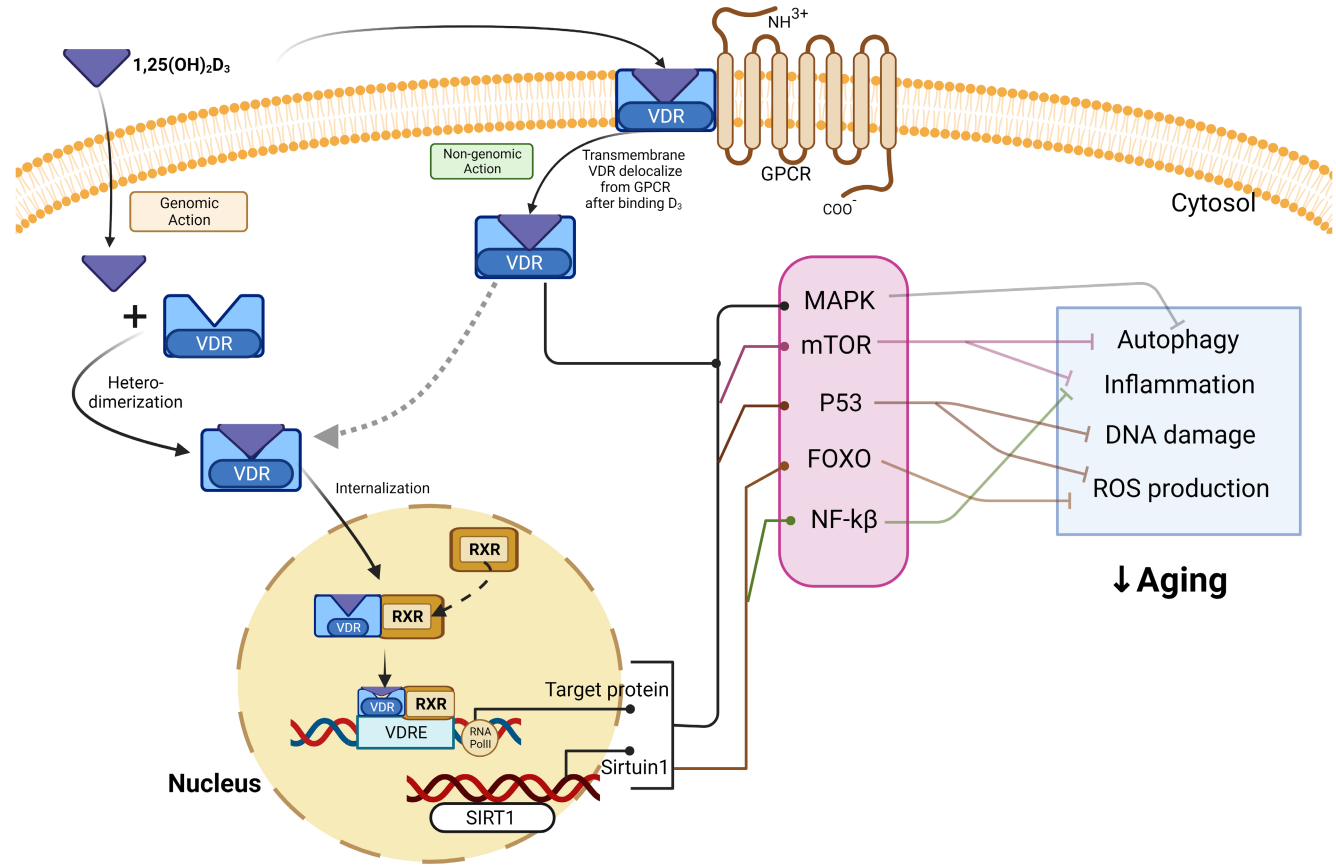

FIGURE 1 Interaction of miRNA with VDR and SIRT1 gene expression on early onset of aging. The hypothetical diagram represents the conventional action of VDR and SIRT1 gene expression being altered and ceased by the mediation of miR-124.3p.1 and miR-124.3p.2 and the acceleration of aging. Created by BioRender.com.

biomedical or pharmaceutical approaches can successfully control aging and thus they termed it a plastic process. Proteins belonging to the sirtuin family are one of the most promising anti-aging targets. Seven different isoforms of sirtuin (SIRT1 to 7) are evident in humans. These are mostly deacetylase and mono-ADP ribosyltransferase in enzymatic activity.[4] SIRT1 is the most profound in different tissues including the brain, retina, adipose tissue, kidneys, heart, liver, skeletal muscles, blood vessels, and uterus.[35] Studies reported that if mouse zygotes are deprived of both the copies of SIRT1 gene, then there is a 50% chance of survival, and out of these only 20% would attain maturity and sterility can be seen with developmental delay.[36,37] Shreds of evidence suggest the involvement of SIRT1 activity in decision-making over cellular senescence or apoptosis. SIRT1 is also involved in the activation of the salvage pathway in vascular smooth muscle cells, which increases the replicative lifespan of cells. Tissue-specific SIRT1 overexpression in cardiomyocytes reduces the MI-affected area and improves recovery. With the inclination of age NAD+ activity and availability are reduced, along with simultaneous DNA damage, which causes low SIRT1 levels in the liver, brain, and other tissues. These lead to age-related diseases like atherosclerosis, neurocognitive disorders, skin aging, and others. Due to the pleiotropic activity of SIRT1 in senescence, it has become a critical biomarker for aging and age-associated diseases[12,13] (Figure 4).

4.2 | VDR and aging

Aging and its association with vitamin D have always been a pivotal point of research. Vitamin D deficiency is one of the most occurring hypovitaminosis. Several studies support the fact that vitamin D deficiency can be a risk for aging and age-related diseases.[38,39] The ability of the body to produce calcitriol and the ability of the skin to synthesize vitamin D are both reduced by 50% by the age of 70 whereas the absorption rate by the intestine remains unaffected.[40] The deficiency is often marked by a decrease in vitamin D receptors (VDR) gene expression in different cells. It is reported that the level of VDR is found to be lesser in human skeletal myocytes and parathyroid glands with aging.[41] This might be the cause of the dysregulation of the vitamin D receptor gene. Traditionally, VDR mediates vitamin D action, where calcitriol (active vitamin D) binds with VDR, and VDR in turn heterodimerizes with RXR (Retinoid X receptor) inside the nucleus and binds to its cognate receptor element, VDRE (vitamin D responsive element) to accentuate transcription of specific target genes. This event activates RNA Pol II which in turn translates target protein. These target proteins in turn regulate pathways including MAPK, mTOR, and p53, to modulate autophagy, inflammation, and DNA damage, respectively.[8,42,43] Apart from this classical action, VDR also acts as a transcription factor and potentially

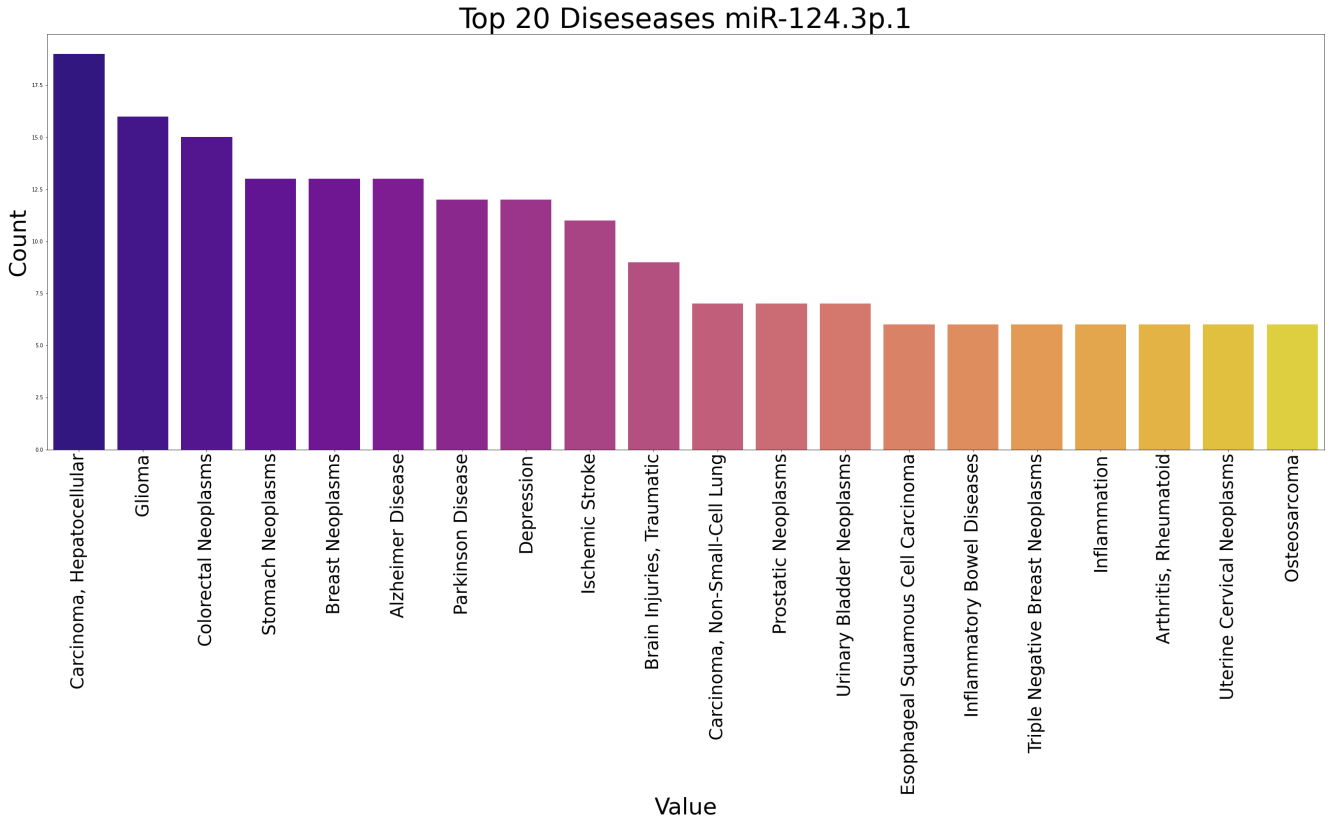

FIGURE 2 Bar plot representing the occurrence of diseases in miR-124.3p.1 expression.

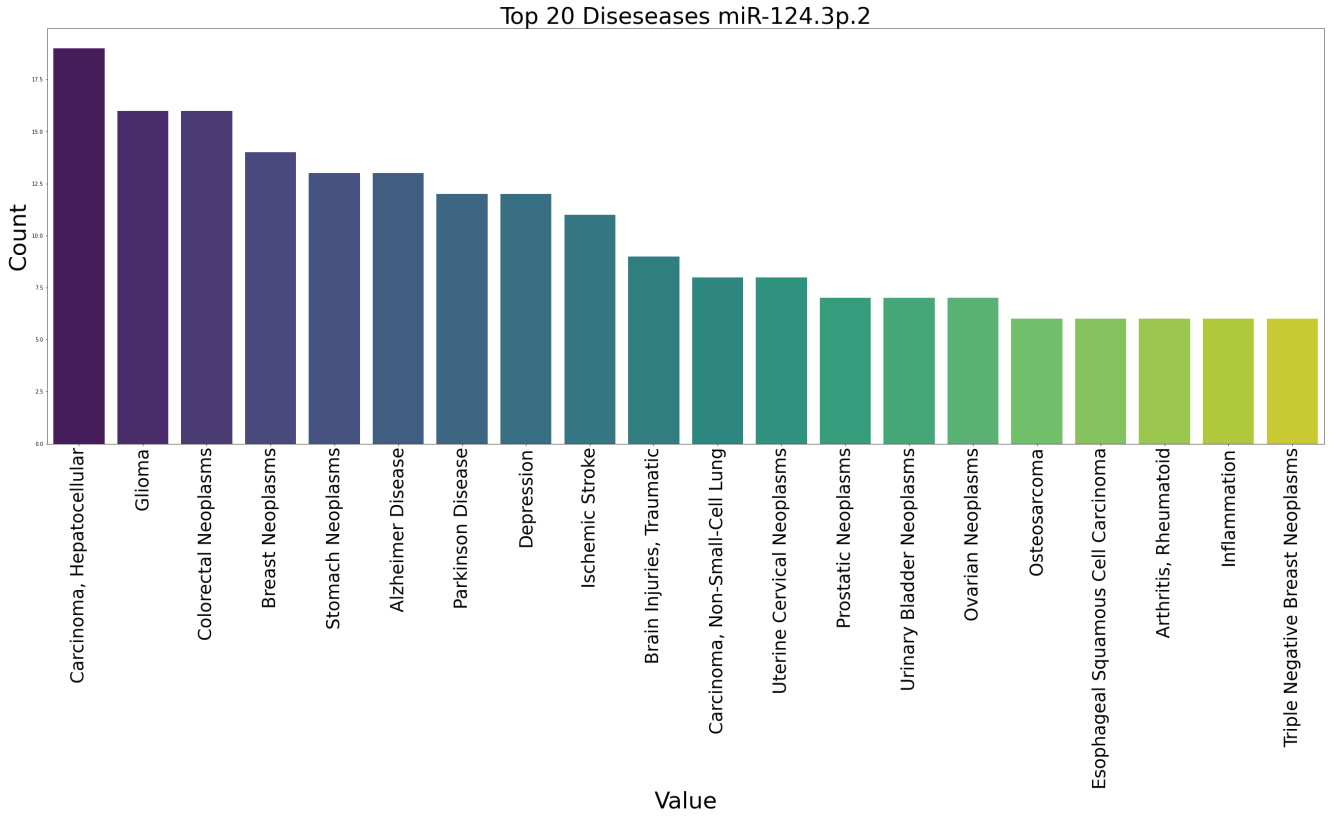

FIGURE 3 Bar plot representing the occurrence of diseases in miR-124.3p.2 expression.

TABLE 1 MicroRNAs implicated in aging mechanism and biomarker.

Sr. no.	MicroRNAs	Functional role	Site of action	Target genes	References
Downregulated					
1.	miR-124-3p	Biomarker	Hippocampal neuronal cell	Caveolin-1, PI3K, Akt, GSK3β	Li et al. (2023)[17]
2.	miR-124-3p, miR-137-5p, miR-138-5p, miR-219a-2-3p, miR-135a-5p, miR-541-5p, and miR-770-3p	Biomarker	Blood	Not identified	Robles et al. (2023)[18]
3.	hsa-let-7e-5p, hsa-miR-124-3p, hsa-miR-17-5p, hsa-miR-185-5p	Biomarker	Blood	Not identified	Wang et al. (2023)[19]
Upregulated					
4.	miR-124	Age-related cognitive decline	Brain, neuronal cell	RyR3	Liu et al. (2022)[20]
5.	miR-let-7c, miR-let-7b, miR-181a, and miR-124	Senescence-and atrophy-related miRNAs	Myocytes	Not Identified	Parker et al. (2022)[21]
6.	miR-1-3p and miR-124-3p	Age-related gut dysfunction and inflammatory bowel disease	Colonic tissues from humans and mice	C1GALT1	Sun et al. (2022)[22]
7.	miR-124-3p	Age-related cataract (ARC)	Human lens epithelial cells (SRA01/04 cells)	KCNQ1OT1	Xu et al. (2022)[23]
8.	miR-637, miR-148a-3p, miR-125b-5p, miR-124-3p, miR-122-5p, miR-100-5p, miR-93-5p, miR-21-5p, miR-23a-3p, and miR-24-3p	Biomarkers in elderly with sarcopenia and non-sarcopenia	Blood	Not Identified	He et al. (2021)[24]
9.	miR-124 and miR-39	Longevity markers	LPS-treated human umbilical vein endothelial cells, *C. elegans*	IRAK-1, IL-6	Coppari et al. (2021)[25]
10.	hsa-miR-124-5p and hsa-miR-6507-5p	Biomarker	Cardiomyocyte lines (AC16 cells), blood	Not Identified	Zhao et al. (2021)[26]
11.	miR-124-3p	Biomarker	Colon mucus layer in 2-, 16-, and 24-month-old mice and aged humans	C1GALT1	Huang et al. (2020)[27]
12.	hsa-miR-21-5p, hsa-miR-34a-5p, hsa-miR-124-5p, hsa-miR-132-3p, and hsa-miR-144-3p	Biomarkers	Blood	Not identified	Sessa et al. (2020)[28]
13.	miR-9-5p, miR-130a-3p, miR-92a-3p, miR-20a-5p, miR-93-5p, miR-9-3p, miR-709 and miR-124	Retinal development	Mouse retina	PI3K, AKT, mTOR, FOXO, MAPK	Wang et al. (2020)[29]
14.	miR-124	Heal during aging	Cutaneous tissue	MALAT1	He et al. (2020)[30]
15.	miR-124 and miR-29	Cellular senescence	Kidney, heart, liver, brain, and lung tissue	Ccna2, p53	Xu et al. (2019)[31]
16.	miR-200b, miR-21, and miR-124	Biomarkers	Blood, tissue	Bcl-2, Bcl-xL, REST	Sessa et al. (2019)[32]
17.	miR-124	Senile osteoporosis	Bone marrow monocytes (BMMs) of osteoporotic mice	Rab27a	Tang et al. (2017)[33]
18.	miR-124	Skin senescence	Human epidermal keratinocytes (NHEKs) and cutaneous squamous cell carcinoma (SCC)	Not Identified	Harada et al. (2016)[9]
19.	↓miR-9,-19a,-135a,-15b,-16,-195,-29c,-214; ↑miR-124	Senile plaque formation in the brain, age-related cognitive decline	Forebrain cortex and hippocampus	APP, BACE1	Che et al. (2014)[34]

controls several physiological actions including Ca2+ homeostasis, cellular differentiation-proliferation, and immunomodulatory action. However, target proteins from VDR also induce sirtuin production from the SIRT1 gene, which has similar regulatory mechanisms along with FOXO and NF-κβ, and it can modulate ROS production. On the other hand, calcitriol carries out non-genomic

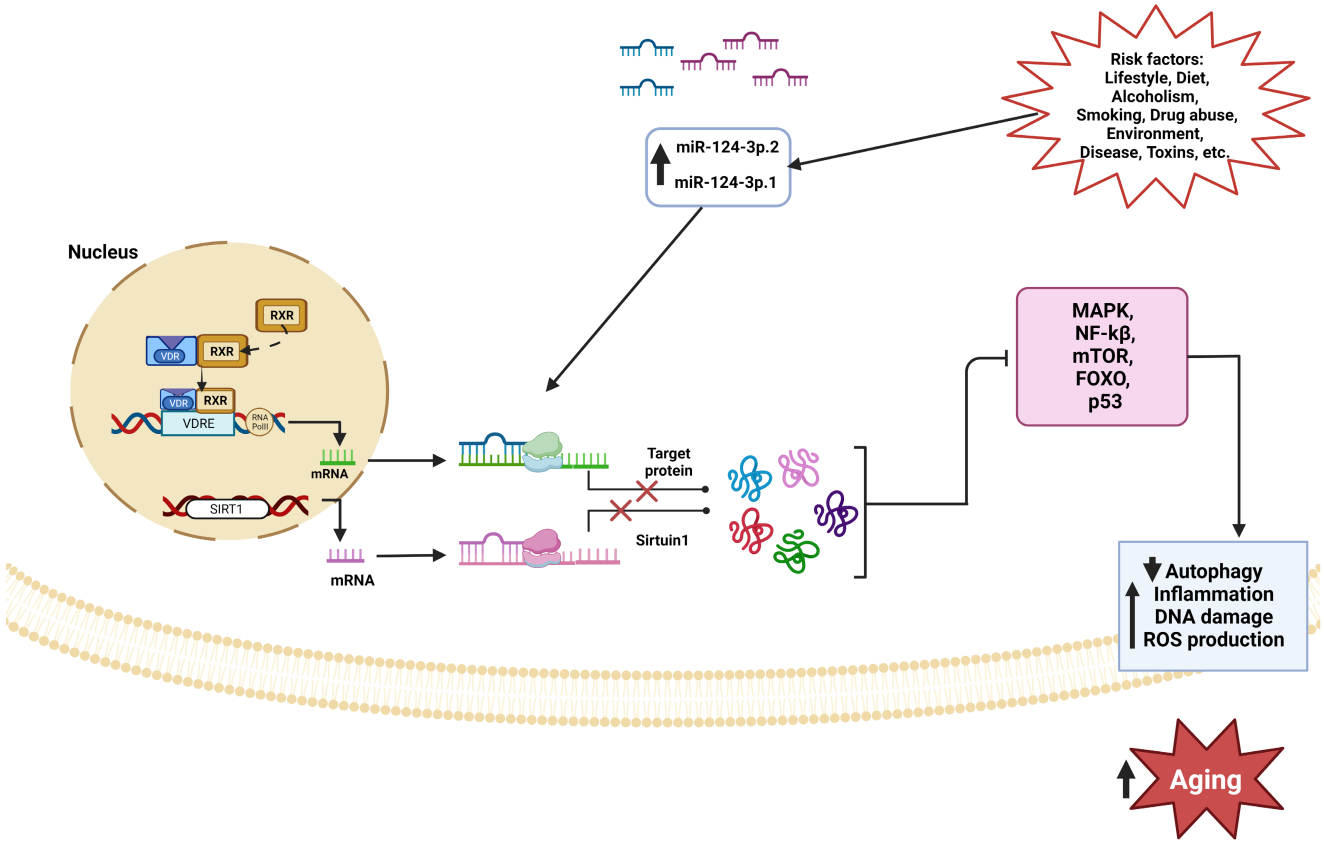

FIGURE 4 Molecular interactions among VDR and SIRT1 gene expression in conventional aging pathways namely MAPK (mitogen-activated protein kinase), mTOR (mammalian target of rapamycin), p53, FOXO, and NF-κβ to regulate aging. Created with BioRender.com.

actions through the dimerized unit and it similarly induces MAPK, mTOR, P53, FOXO, and NF-κβ to modulate autophagy, inflammation, DNA damage, and ROS production.[40,44,45] All these regulatory pathways coherently slow down the rate of aging and help in attaining successful aging. Several studies stated the fact that dysregulation of VDR activity can cause chronic diseases including cancer, early aging, age-related diseases like cardio-metabolic diseases, and cognitive disorders.[46] (Figure 4).

Studies showed that VDR KO and mutant mice show all the signs and symptoms of aging like skin thinning, wrinkling, calcification, alopecia, and others. People with prolonged vitamin D deficiency often show these signs earlier than usual.[13] Vitamin D controls aging by regulating several cellular mechanisms such as autophagy, that helps in removing toxic waste like dead cells, dysfunctional mitochondria, cellular proliferation, and others. These mechanisms proportionately maintain cellular health and aging. Vitamin D also reduces oxidative stress, ROS production, inflammation, epigenetic changes, DNA disorders, and telomere shortening.[47] Hence, it can be justified to say that VDR and its ligand vitamin D are intimately related to all biological processes that help in ameliorating age-related pathologies. In the silico approach, the VDR gene has been found to interact with miR-124-3p.1 and miR-124-3p.2. Concurrently SIRT1 gene also interacts with the aforementioned microRNAs.

4.3 | MicroRNAs, an epigenetic regulator of aging

The rate of aging and longevity of humans are believed to be controlled by insulin/IGF-1 signaling, mTOR, AMPK, and sirtuins pathway.[15,16] MicroRNAs are one of the small single-stranded non-coding RNAs that were first isolated in *C. elegans* and are found to regulate lifespan negatively or positively by influencing these pathways. A mature miRNA contains 18–22 nucleotides and is presumably transcribed from DNA. MiRNAs mediate gene silencing or down-regulation of gene expression post-transcriptionally binding at 3′UTR either by induction of mRNA degradation or by blocking translation machinery. One miRNA has the potential to target more than one mRNA and likewise, one mRNA can be targeted by more than one miRNA. The changes occurred due to miRNA action often called epigenetic modulation without changing the underlying DNA sequences.[48,49]

In the past decades, the discovery of miRNA has supported so many physiological and pathological enigmas, and one of those is senescence. miRNAs that were discovered in *C. elegans* are shown to regulate lifespan by functioning through the IIS pathway and a similar mechanism has also been established in humans. Studies showed that miRNA lin-4 and its target lin-14 influence controlling lifespan through the IIS pathway in humans. There are reports to show that miRNA also regulates components of the IIS pathway

namely miR-1, miR-320, and miR-206 by targeting IGF-1, while miR-216a, miR-217, and miR-21 mainly target PTEN. Evidence is there to link between mTOR and miRNA, like miR-100 known to inhibit the mTOR pathway.[16] Another miRNA called miR-124 was identified in 2016 which seemed to be upregulated in aged skin as compared to young skin. Overexpression of miR-124 results in an increase in senescence associated with beta-galactosidase and that accentuates skin keratinocyte aging. On the contrary, its level goes down in squamous cell carcinoma.[11,50] Among known miRNAs, the expression of miR-217 is progressively increased during aging in the endothelial cells which can also regulate SIRT1 expression via binding at 3′UTR of SIRT1 mRNA. Similarly, miR-34a, miR-199a, and miR-132 also target SIRT1 with different components. These all regulate the sirtuin pathway of aging. Identifying miRNAs can also be an indication of diseases like miR-1 downregulation associated with hypertrophic growth of the heart, while miR-122 and miR-375 are seen to decrease among myocardial infarction patients. Hence, the estimation of specific circulatory miRNAs can be a key indicator for future health status including aging and age-associated diseases.[16]

5 | CONCLUSION

With time, the physiological properties of the human body start deteriorating. The deterioration is often an outcome of genetic and epigenetic interference. This is an in silico search-derived hypothesis, on which further evidence can be proved, and based on the protocol an intervention model can be programmed in the future. Early detection of specific miRNAs and modulation of their expression by therapeutic intervention or using antisense oligonucleotide targeting miRNAs[3,17,51] can be an analeptic target to decrease the probability of age-associated diseases. Altogether, this hypothesis provides a notion that circulating miRNAs as one of the epigenetic gene expression modulators and impede it can be an effective restorative target in the successful aging process.

AUTHOR CONTRIBUTIONS

Ms. Poulami Dhar: Writing, designing, and illustration. Dr. Shailaja Moodithaya: Drafting, interpretation, and revision. Dr. Prakash Patil: Conceptualization, interpretation, and revision. Dr. Adithi K.: Drafting and revision.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

ORCID

Shailaja Moodithaya https://orcid.org/0000-0001-9602-9171

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