NeuroImage: Clinical 41 (2024) 103555

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Relationship of irisin with disease severity and dopamine uptake in Parkinson's disease patients

Xiaoxue Shi [a,b,c,1], Qi Gu [a,b,c,1], Chang Fu [d], Jianjun Ma [a,b,c,*], Dongsheng Li [a,b,c], Jinhua Zheng [a,b,c], Siyuan Chen [a,b,c], Zonghan She [a,b], Xuelin Qi [a,b], Xue Li [a,b,c], Shaopu Wu [a,b,c], Li Wang [a,b,c]

[a] Department of Neurology, Henan Provincial People's Hospital, Zhengzhou, China
[b] Department of Neurology, Zhengzhou University People's Hospital, Zhengzhou, China
[c] Department of Neurology, Henan University People's Hospital, Zhengzhou, China
[d] Department of Nuclear Medicine, Henan Provincial People's Hospital, Zhengzhou, China

ARTICLE INFO

Keywords:
Parkinson's disease
α-syn
Irisin
Dopamine uptake
Striatum

ABSTRACT

Background: This study was designed to investigate the relationship of irisin with the severity of Parkinson's disease (PD) and dopamine (DOPA) uptake in patients with PD and to understand the role of irisin in PD.
Methods: The plasma levels of irisin and α-syn were measured by enzyme-linked immunosorbent assay (ELISA). Motor and nonmotor symptoms were assessed with the relevant scales. DOPA uptake was measured with DOPA positron emission tomography (PET)/magnetic resonance imaging (MRI).
Results: The plasma levels of α-syn and irisin in patients with PD gradually increased and decreased, respectively, with the progression of the disease. There was a negative correlation between plasma α-syn and irisin levels in patients with PD. The level of irisin in plasma was negatively correlated with Unified Parkinson's Disease Rating Scale (UPDRS)-III scores and positively correlated with Montreal Cognitive Assessment (MoCA) scores. The striatal/occipital lobe uptake ratios (SORs) of the ipsilateral and contralateral caudate nucleus and anterior and posterior putamen in the high-irisin group were significantly higher than those in the low-irisin group, and irisin levels in the caudate nucleus and anterior and posterior putamen contralateral to the affected limb were lower than those on the ipsilateral side. The level of irisin was positively correlated with the SORs of the ipsilateral and contralateral caudate nucleus and putamen in PD patients.
Conclusions: Irisin plays a neuroprotective role by decreasing the level of α-syn. Irisin is negatively correlated with the severity of motor symptoms and cognitive impairment. More importantly, irisin can improve DOPA uptake in the striatum of patients with PD, especially on the side contralateral to the affected limb.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease and is characterized by both motor and nonmotor dysfunction (Kalia and Lang, 2015). The main pathological characteristics of PD consist of the loss of dopaminergic neurons and the formation of Lewy body pathology [mainly α-synuclein (α-syn)] in the substantia nigra (Giguere et al., 2018; Mehra et al., 2019). Clinically, there are two types of treatments for PD: surgical therapy (deep brain stimulation) and medication (levodopa and other dopamine receptor agonists) (Armstrong and Okun, 2020). While these treatments are very effective initially, their effectiveness diminishes over time, and a range of side effects emerges (Galna et al., 2015). The currently available medication treatments provide only symptomatic relief and do not control or prevent disease progression (Fahn et al., 2004; Tarazi et al., 2014). As such, treatments that slow the progression or inhibit the underlying drivers of PD pathogenesis are urgently needed.

Irisin is an exfoliated extracellular domain of the transmembrane protein FNDC5, which is secreted from skeletal muscle and other organs and increases with exercise (Huh et al., 2012; Jedrychowski et al.,

* Corresponding author at: at: Department of Neurology, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Henan University People's Hospital, Zhengzhou 450003, Henan Province, China.
E-mail address: majj1124@163.com (J. Ma).
[1] These authors contributed to the work equally and should be regarded as co-first authors.

https://doi.org/10.1016/j.nicl.2023.103555
Received 25 July 2023; Received in revised form 14 December 2023; Accepted 14 December 2023
Available online 15 December 2023

2015). Exercise enhances the activity and expression of some receptors, such as peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) (Raefsky and Mattson, 2017). This increased expression results in the production of the FNDC5 protein (Baghi et al., 2021). Splitting this protein leads to the production of irisin (Bostrom et al., 2012). Some studies have reported that factors such as irisin have a neuroprotective effect and can improve the functioning of the nervous system after central nervous system (CNS) injury (Dun et al., 2013; Lourenco et al., 2019). Irisin has been observed to prevent the loss of dopamine neurons and the reduction of striatal dopamine levels and to improve motor dysfunction (Kam et al., 2022; Zhang et al., 2022).

To better explore the relationship between irisin and PD, we investigated the correlation between irisin and α-syn. We used correlation analysis to further evaluate the relationship between irisin and PD motor and nonmotor symptom scale scores. Finally, the relationship between irisin and DOPA uptake in the striatum of PD patients was further clarified by DOPA PET/MRI.

2. Methods

2.1. Participant inclusion criteria

A total of 100 PD patients were recruited from the Department of Neurology, Henan Provincial People's Hospital, between March 2020 and October 2022. Patients were diagnosed by two experienced neurologists according to the 2015 MDS clinical diagnostic criteria for Parkinson's disease (Postuma et al., 2015). Patients with (1) atypical or secondary PD, (2) cardiovascular or cerebrovascular diseases, such as myocardial infarction or cerebral infarction, and (3) acute or chronic infections or surgical procedures within the previous 3 months were excluded. A total of 70 healthy volunteers participated in this study. All subjects signed written informed consent before participation.

2.2. Clinical characteristics

General clinical data, such as sex, age, education levels and body mass index (BMI), were recorded. The levodopa equivalent daily dose (LEDD) was assessed according to the levodopa conversion formula (Tomlinson et al., 2010). In brief, 100 mg levodopa = 133 mg entacapone = 1 mg pramipexole = 5 mg ropinirole = 10 mg selegiline = 1 mg rasagiline = 100 mg amantadine. Disease duration was defined as the time between presentation with initial motor symptoms and the present study. Hoehn and Yahr (H-Y) staging was used to divide PD into stages 0 ~ 5 (Goetz et al., 2004) (stages 1 ~ 2 are the early stages, and stages 2.5 ~ 5 are the middle and late stages). Motor symptoms were evaluated by Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) (Gallagher et al., 2012). Both the H-Y classification and the UPDRS-III were used to evaluate disease severity. Cognition was examined by the Montreal Cognitive Assessment (MoCA) (Schrag et al., 2017). All of the assessments were completed once during a patient's "on" period.

2.3. Sample collection

Between 07:30 and 08:30 am, after overnight fasting and before breakfast, peripheral blood from each subject was collected into EDTA-containing test tubes. Immediately after collection, blood was centrifuged (3000 rpm, 10 min) and preserved at −80 °C until measurement. Participants were instructed to refrain from smoking, alcohol consumption, and vigorous activity for 24 h before the study.

2.4. Measurement of plasma irisin and α–syn levels

Plasma irisin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (catalog number: E-EL-H5735c; Wuhan Elabscience Biotechnology Co., Ltd., Wuhan, China). The detection range of this kit was 78.13–5000 pg/mL, with a sensitivity of 46.88 pg/mL, and the intra- and interassay variability was < 10 %. Plasma α-syn levels were measured using an ELISA kit (catalog number: ZC-32191; Shanghai Zhuocai Biotechnology Co., Ltd., Shanghai, China). The detection range of this kit is 1.25–40 ng/mL, with a sensitivity of 0.1 ng/mL, and the intra- and interassay variability were < 10 %. Samples were analyzed in duplicate on the same plate in accordance with the manufacturers' instructions.

2.5. ^{18}F-DOPA PET/MRI imaging

^{18}F-DOPA was prepared by the PET Center of Henan Provincial People's Hospital and was synthesized using a medical cyclotron (GE Minitrace, USA) and an automatic synthesis device (AllinOne, Belgium); the radiochemical purity of the product was > 95 %. Subjects received an intravenous injection of ^{18}F-DOPA (370 MBq). After approximately 90 min of quiet rest, PET/MRI was performed on the brain. The PET acquisition time was 30 min.

The following 3D-mode PET and MRI sequences were acquired: 3D T1-weighted imaging (repetition time (TR)/echo time (TE) = 7.2/3; matrix = 256 × 230; bandwidth = 250; layer thickness/interval = 1 mm/1.5 mm), 3D T2-weighted imaging (TR/TE = 2000/288.6; matrix = 256 × 230; bandwidth = 650; layer thickness/interval = 1 mm/1.5 mm), and 3D T2 fluid-attenuated inversion recovery (FLAIR; TR/TE = 6500/403.92; matrix = 256 × 230; layer thickness/interval = 1 mm/1.5 mm). The total collection time was approximately 20 min.

2.6. Image processing and analysis

Semiquantitative analysis of the striatal ^{18}F-DOPA uptake index was conducted by an experienced deputy chief physician, who read the films while blinded to the patients' diagnoses. The region of interest (ROI) was drawn on the fusion image on the PET workstation. First, MR images from the level of the striatum were selected and displayed, and the bilateral putamen and caudate nucleus were traced on each image. Next, these tracings were copied to the corresponding PET images to calculate the average radioactivity of the putamen and caudate nucleus on each side. In this study, the occipital lobe was selected as the reference area; three consecutive layers of the occipital lobe were selected. The ROI of the corresponding occipital lobe was drawn on each layer, and its average radioactivity was calculated. The striatal/occipital lobe uptake ratio (SOR) was used as the index of striatal 18F DOPA uptake (Jokinen et al., 2009).

2.7. Statistical analysis

The Kolmogorov–Smirnov test and Levene's test were used to check the data for normality and homogeneity of variance. Numerical variables that followed a normal distribution are expressed as the mean ± SD; those that did not follow a normal distribution are expressed as medians (interquartile ranges). Nominal variables are expressed as percentages. To compare two groups of normally distributed data, an independent-sample Student's *t* test was used. Multiple groups of data consistent with a normal distribution and homogeneity of variance were compared by one-way analysis of variance, and a post hoc least significant difference (LSD) test was used to further assess the differences through pairwise comparisons between groups. For variables that violated the assumption of normality or homoscedasticity, the groups were compared using the nonparametric Mann–Whitney *U* test (for 2 groups) or Kruskal–Wallis test (for > 2 groups). Pearson's (or Spearman's) correlation analysis was conducted according to whether the variables were normally distributed. Statistical analysis was performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, United States) and GraphPad Prism 7 (GraphPad Software, Inc., San Diego, CA, United States). A P value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics

No differences were found between the PD and control groups in age (60.80 ± 9.94 vs. 62.89 ± 6.98, P = 0.132), sex (64.0 % vs. 36.0 %, P = 0.147), BMI (24.55 ± 3.20 vs. 23.78 ± 3.21, P = 0.128) or education (9 (6,12) vs. 9 (6,12), P = 0.669). Plasma α-syn levels were significantly higher in the PD patients than in the healthy controls (3.25 ± 0.56 ng/ml vs. 2.62 ± 0.51 ng/ml, P < 0.001), and plasma irisin levels were significantly lower in the PD patients than in the healthy controls (238.61 ± 39.08 pg/ml vs. 251.77 ± 31.77 pg/ml, P = 0.021).

3.2. Plasma α-syn and irisin levels in controls and PD patients at different H-Y stages

Plasma α-syn levels were significantly higher in PD patients than in healthy controls. When the PD patients were divided into early-stage (n = 58) and middle-to-late-stage PD patients (n = 42) based on the H-Y classification, plasma α-syn levels in early-stage PD patients were higher than those in healthy controls (P < 0.001), and plasma α-syn levels in middle-to-late-stage PD patients were higher than those in early-stage PD patients (P = 0.017) (Fig. 1A).

Plasma irisin levels were significantly lower in PD patients than in healthy controls. When the PD patients were divided into early-stage (n = 58) and middle-to-late-stage PD patients (n = 42) based on the H-Y classification, plasma irisin levels in early-stage PD patients were found to be lower than those in healthy controls (P = 0.037), and plasma irisin levels in middle-to-late-stage PD patients were lower than those in early-stage PD patients (P = 0.016) (Fig. 1B).

3.3. Correlation of plasma α-syn and irisin levels in PD patients

We found a negative correlation between plasma α-syn and irisin levels in PD patients (r = −0.605, P < 0.001) (Fig. 2).

3.4. Correlation of plasma irisin levels and clinical characteristics in PD patients

Correlation analysis showed that plasma irisin levels were negatively correlated with disease duration (r = −0.309, P = 0.002) and UPDRS-III scores (r = -0.524, P < 0.001) and positively correlated with MoCA scores (r = 0.327, P = 0.001). The LEDD was not related to plasma irisin levels (P > 0.05).

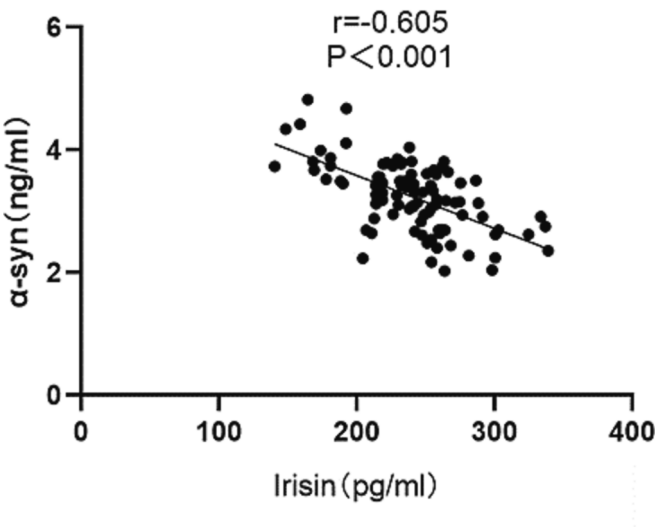

Fig. 2. Correlations between plasma α-syn and irisin levels in PD patients.

3.5. Relationship between irisin levels and striatal DOPA uptake in patients with PD

Using the mean irisin concentration of all PD patients as the cutoff point (238.61 pg/ml), PD patients were divided into a high-irisin group and a low-irisin group.

We obtained corresponding DOPA PET/MRI scans for all 100 of the enrolled PD patients; however, corresponding DOPA PET/MRI scans could be obtained for only 28 of the healthy controls.

3.5.1. Visual analysis

^{18}F-DOPA PET images of typical cases in the healthy control group, the high-irisin group and the low-irisin group are shown in Fig. 3. We found that the concentrations of ^{18}F-DOPA in the caudate nucleus, the anterior putamen and the posterior putamen were higher in the healthy controls than in the PD group. Compared with the high-irisin group, the low-irisin group had reduced concentrations of ^{18}F-DOPA in the caudate nucleus, anterior putamen and posterior putamen bilaterally.

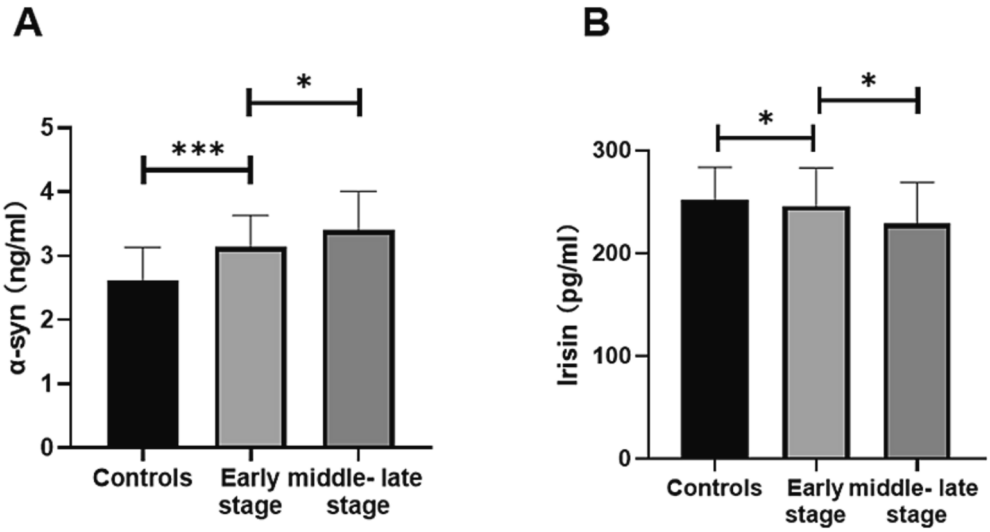

Fig. 1. Distribution of plasma α-syn and irisin levels in PD patients classified by H-Y stages. (A) Distribution of plasma α-syn levels in different H-Y stages. (B) Distribution of plasma irisin levels in different H-Y stages.

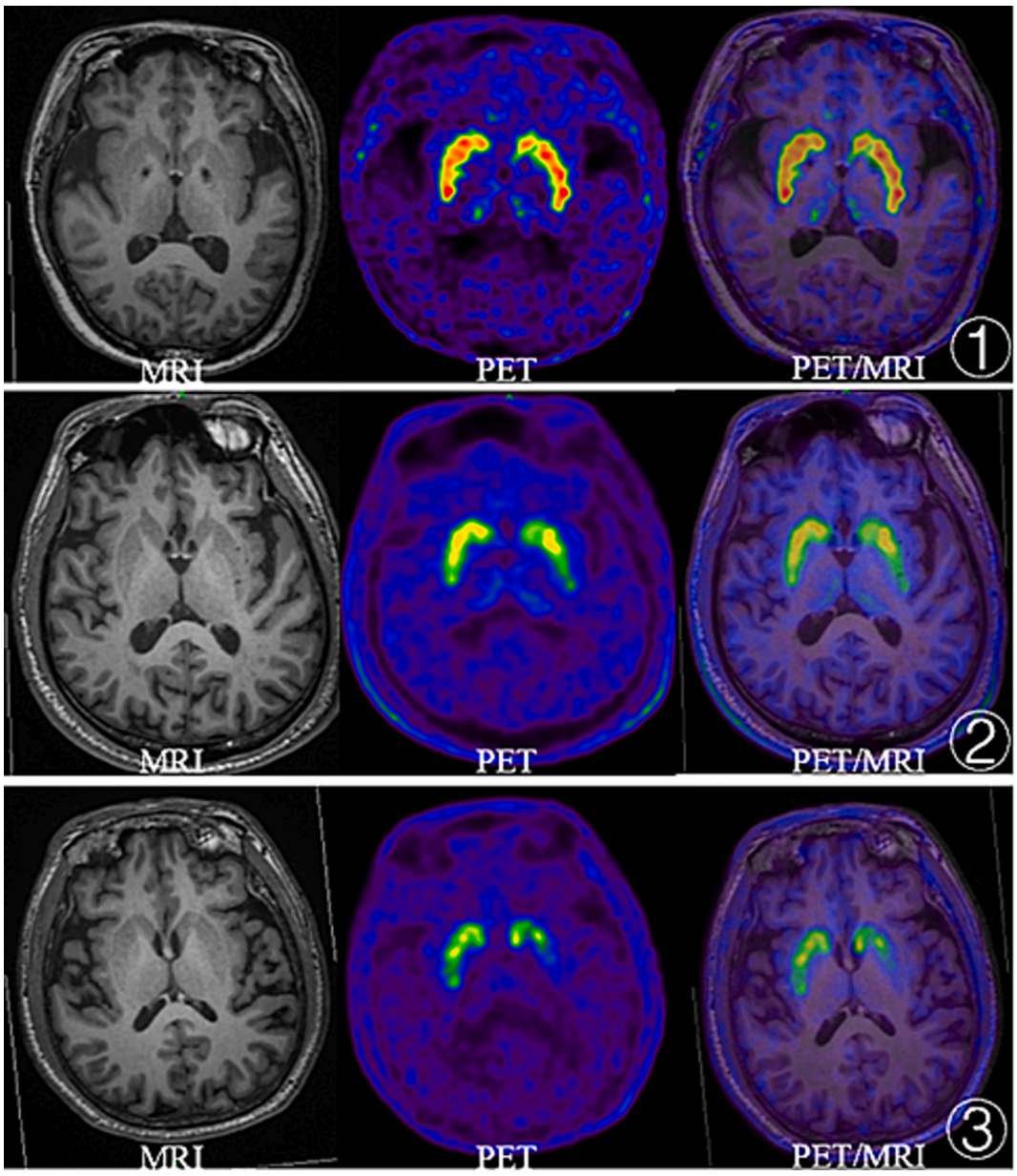

Fig. 3. ①: ^{18}F-DOPA PET images of healthy volunteers in the control group; ②: ^{18}F-DOPA PET images of patients with PD in the high-irisin group; ③: ^{18}F-DOPA PET images of patients with PD in the low-irisin group.

3.5.2. Semiquantitative analysis

The SORs of the contralateral caudate nucleus, anterior putamen and posterior putamen in the healthy control group were significantly higher than those in the PD group (3.44 ± 0.60 vs. 2.68 ± 0.47, t = −7.080, P < 0.001; 3.62 ± 0.74 vs. 2.42 ± 0.40, t = −11.465, P < 0.001; 3.30 ± 0.81 vs. 1.90 ± 0.29, t = −14.409, P < 0.001, respectively). The SORs of the ipsilateral caudate nucleus, anterior putamen and posterior putamen in the healthy control group were significantly higher than those in the PD group (3.29 ± 0.63 vs. 2.84 ± 0.40, t = −4.597, P < 0.001; 3.51 ± 0.74 vs. 2.54 ± 0.36, t = -9.790, P < 0.001; 3.29 ± 0.84 vs. 2.06 ± 0.28, t = −12.374, P < 0.001, respectively). Additionally, the SORs of the contralateral caudate nucleus, anterior putamen and posterior putamen in the high-irisin group were significantly higher than those in the low-irisin group (2.91 ± 0.43 vs. 2.43 ± 0.39, t = −5.919, P < 0.001; 2.59 ± 0.32 vs. 2.23 ± 0.38, t = -5.140, P < 0.001; 2.00 ± 0.30 vs. 1.79 ± 0.24, t = −3.923, P < 0.001, respectively). On the ipsilateral side, the SORs of the caudate nucleus, anterior putamen and posterior putamen in the high-irisin group were significantly higher than those in the low-irisin group (2.96 ± 0.40 vs. 2.71 ± 0.37, t = −3.250, P = 0.002; 2.64 ± 0.35 vs. 2.42 ± 0.36, t = −3.277, P = 0.001; 2.13 ± 0.26 vs. 2.00 ± 0.28 t = −2.495, P = 0.014, respectively) (Fig. 4).

We also found that the levels of irisin in the contralateral caudate nucleus, anterior putamen and posterior putamen of the affected limb were lower than those in the ipsilateral side of the affected limb, and the difference was statistically significant (2.68 ± 0.47 vs. 2.84 ± 0.40, t = −2.558, P = 0.011; 2.42 ± 0.40 vs. 2.54 ± 0.36, t = −2.197, P = 0.029; 1.90 ± 0.29 vs. 2.07 ± 0.28, t = −4.063, P < 0.001, respectively).

3.5.3. Correlation analysis

We found a positive correlation between plasma irisin levels and the SORs of the contralateral caudate nucleus, anterior putamen and posterior putamen in PD patients; the same was true for the ipsilateral side (Fig. 5).

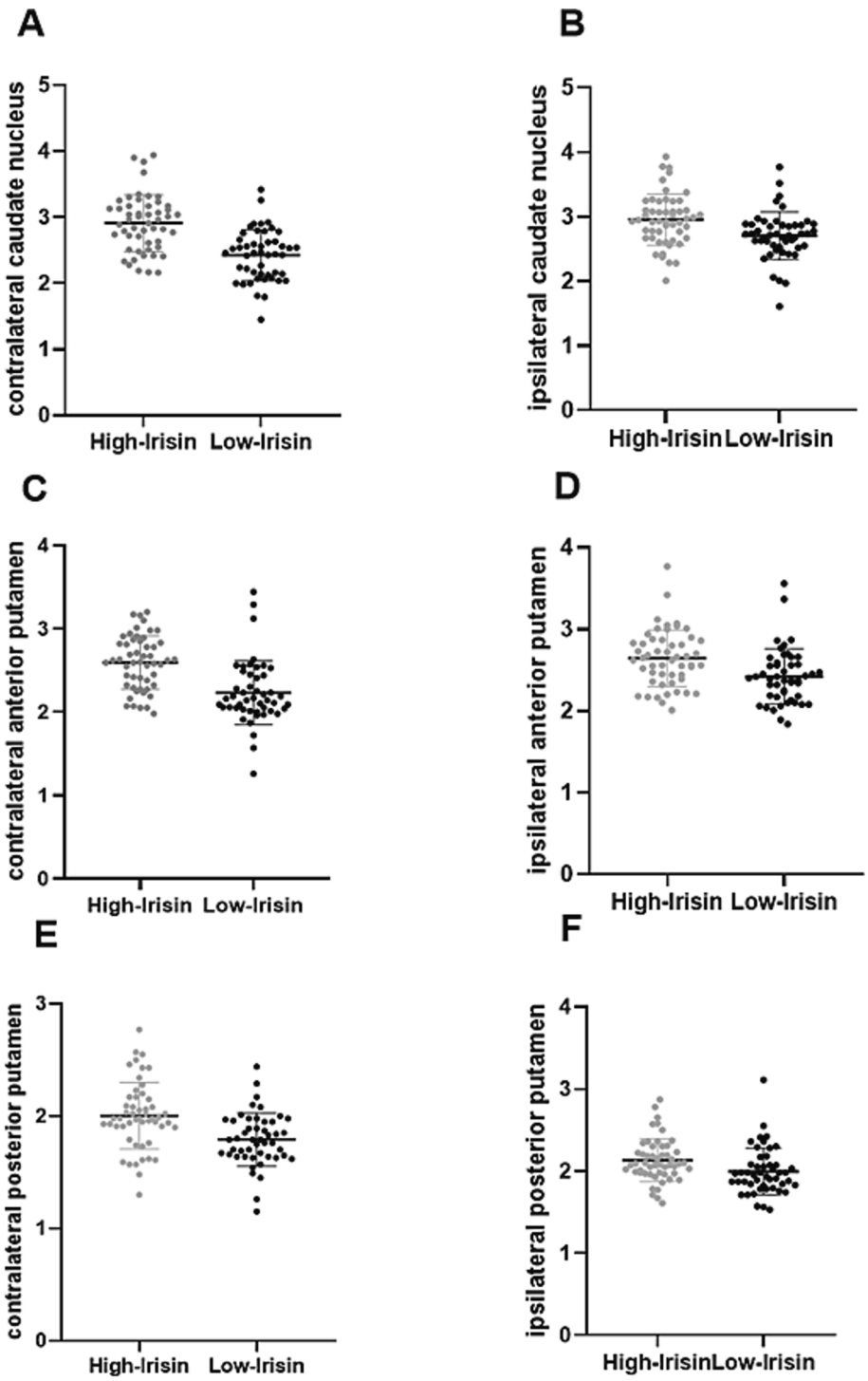

Fig. 4. (A) The SORs of the contralateral caudate nucleus in PD patients with high irisin and low irisin levels. (B) The SORs of the ipsilateral caudate nucleus in PD patients with high irisin and low irisin levels. (C) The SORs of the contralateral anterior putamen in PD patients with high irisin and low irisin levels. (D) The SORs of the ipsilateral anterior putamen in PD patients with high irisin and low irisin levels. (E) The SORs of the contralateral posterior putamen in PD patients with high irisin and low irisin levels. (F) The SORs of the ipsilateral posterior putamen in PD patients with high irisin and low irisin levels.

4. Discussion

The main finding of this study is the relationship of plasma irisin levels with disease severity and dopamine uptake in patients with PD. Kim et al. (Kam et al., 2022) showed that irisin prevented pathological α-*syn*-induced neurodegeneration, loss of dopamine neurons and reduction in striatal dopamine in a mouse model of PD. These findings highlight the potential of irisin in the treatment of PD.

We found that the plasma irisin level in patients with PD was significantly lower than that in healthy controls and gradually decreased with the progression of the disease. Upon exploring the neuroprotective role of irisin in PD, we further concluded that irisin had a significant negative correlation with α-syn. Accumulation of misfolded pathological α-syn is involved in the pathogenesis of PD, and available evidence suggests that in a mouse model, irisin can prevent the formation of pathological α-syn and protect neurons from its toxic effects (Kam et al.,

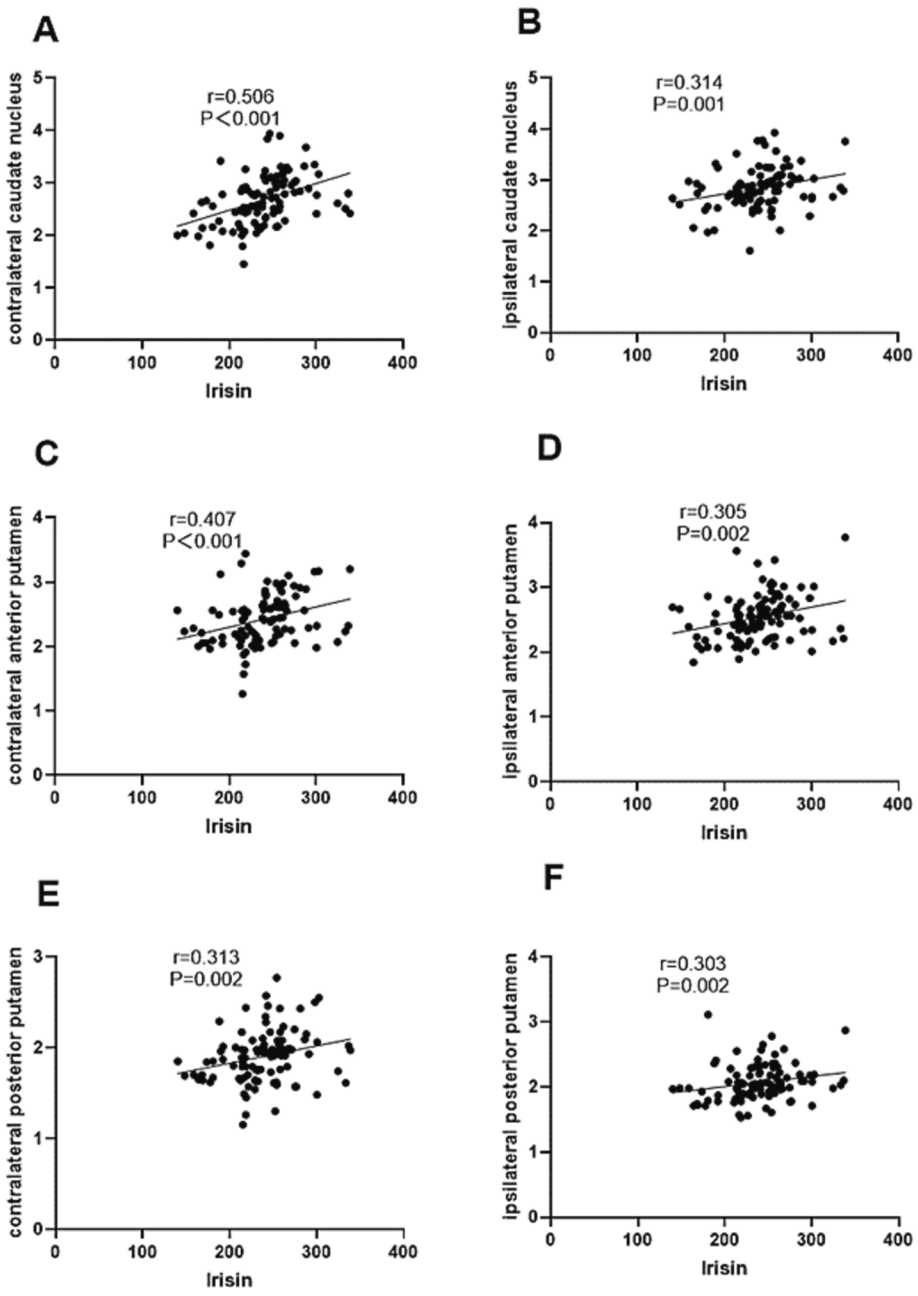

Fig. 5. (A) Correlations between the SORs of the contralateral caudate nucleus and plasma irisin levels in PD patients. (B) Correlations between the SORs of the ipsilateral caudate nucleus and plasma irisin levels in PD patients. (C) Correlations between the SORs of the contralateral anterior putamen and plasma irisin levels in PD patients. (D) Correlations between the SORs of the ipsilateral anterior putamen and plasma irisin levels in PD patients. (E) Correlations between the SORs of the contralateral posterior putamen and plasma irisin levels in PD patients. (F) Correlations between the SORs of the ipsilateral posterior putamen and plasma irisin levels in PD patients.

2022; Mehra et al., 2019). This study offers mechanistic evidence that the amelioration of α-syn pathology by irisin occurs via at least three pathways: 1. Irisin prevents the formation of pathologic α-syn and protects neurons against α-syn neurotoxicity. 2. Irisin can prevent the accumulation of pathological α-syn by reducing its internalization and aggregation. 3. Irisin prevents the pathological transmission of α-syn by promoting its endolysosomal degradation. Irisin is highly conserved between species and has 100 % sequence identity between mice and humans (Bostrom et al., 2012). In our study, we found that α-syn increased as irisin decreased in patients with PD. On the basis of our findings, we hypothesized that irisin may act on α-syn and thus exert neuroprotective effects in patients with PD.

In the present study, we showed that plasma irisin levels were negatively correlated with disease duration and UPDRS-III scores. Irisin largely prevented the behavioral deficits induced by α-syn preformed fibrils, as determined by the pole test and the grip strength test (Kam et al., 2022). Higher plasma α-syn levels were significantly associated with worse UPDRS Part III motor scores and more advanced stages according to the modified H-Y classification (Ren et al., 2022). We suggest that irisin plays a neuroprotective role by reducing α-syn levels. In patients with PD, the level of irisin decreased gradually with the development of the disease and throughout the disease course. The weaker the neuroprotective effect of irisin was, the higher the UPDRS-III scores were.

Cognitive dysfunction is common in patients with PD (Emre et al., 2014; Roheger et al., 2018). In our study, the correlation analysis

showed that the level of plasma irisin was positively correlated with the MoCA cognitive scale score. Recent studies have shown that irisin helps to preserve cognitive function through various mechanisms. Irisin is processed from the type I membrane protein encoded by the FNDC5 gene and is then secreted into the blood, where it circulates to several systems and passes through the blood–brain barrier (BBB) (Bostrom et al., 2012). FNDC5 and irisin are expressed in many tissues, especially in the hippocampus and hypothalamus, and are important for memory and cognition (Dun et al., 2013; Varela-Rodriguez et al., 2016). FNDC5 gene expression is elevated following the increase in PGC-1α expression induced by exercise in both central and peripheral organs, which stimulates the expression of BDNF in the brain (Bostrom et al., 2012). Irisin, a myokine derived from FNDC5, also acts through PGC-1α and passes through the BBB to increase BDNF expression and enhance learning, memory, and mood (Bostrom et al., 2012). FNDC5/irisin acts as a messenger of muscle–brain crosstalk, influencing neurogenesis in people with cognitive impairment, particularly through the neuroprotective effects of BDNF (Peng and Wu, 2022). In the CNS, irisin causes neurogenesis and particularly the differentiation of stem cells into neurons in the hippocampus (Grygiel-Gorniak and Puszczewicz, 2017). Furthermore, our study confirms that irisin is negatively associated with cognitive severity in patients with PD. Whether by stimulating BDNF expression or promoting neuronal differentiation in the hippocampus, plasma irisin can improve cognitive function to some extent in PD patients.

In this study, we found for the first time that the SOR of the ipsilateral and contralateral caudate, anterior putamen, and posterior putamen was significantly higher in patients with PD in the high-irisin group than those in the low-irisin group. The irisin levels in the caudate nucleus, anterior putamen and posterior putamen contralateral to the affected limb were lower than those on the ipsilateral side. In PD patients, the plasma irisin levels were positively correlated with the SORs in the ipsilateral and contralateral caudate nucleus, anterior putamen and posterior putamen. 18F-DOPA, a radioactive marker similar to levodopa, binds specifically to presynaptic receptors when it enters the brain, and 18F-DOPA PET imaging is used to assess the function of central dopaminergic neurons as presynaptic cells (Brooks et al., 1990). The 18F-DOPA used in this study was produced by fully automatic synthesis, which made the process easy to carry out. Additionally, 18F-DOPA has the advantages of a long physical half-life, ease of use and good imaging performance. In a mouse model of PD, irisin injection reduced the loss of DA neurons in the striatum, and irisin was found to rescue both dopamine transporter (DAT)-positive and tyrosine hydroxylase (TH)-positive fibers as determined by immunoblotting. At the same time, irisin successfully prevented the accumulation of pathological α-syn (Kam et al., 2022). Interestingly, administration of irisin over 7 days may increase PGC-1α expression in different areas of the brain, especially in the striatum and substantia nigra pars compacta, to protect dopaminergic neurons from degeneration (Zarbakhsh et al., 2019). In patients with PD, a positive correlation between irisin and intracranial DOPA uptake was suggested by the quantitative detection of DOPA uptake in the striatum, which suggests that the ability of intracranial DOPA uptake may be indirectly reflected by plasma irisin levels.

Our study has some limitations. First, the number of enrolled subjects was small, and the small sample size limits the generalization of the results to all PD patients. Second, the design of this study is only cross-sectional. In the future, we will conduct a longitudinal follow-up study to further explore the relationship between irisin levels and PD. Finally, at present, DOPA PET MRI is available only in tertiary hospitals and research institutions, which currently limits the scale of its use for PD diagnosis.

However, this study is noteworthy because it establishes a previously unreported relationship of irisin with disease severity and dopamine uptake in PD. The basis of this association is still unclear, but irisin plays an important role in the occurrence and development of PD and has great potential for its treatment.

5. Conclusions

This study was designed to investigate the relationship of irisin with the severity of PD and DOPA uptake in patients with PD and to understand the role of irisin in PD and its potential value as a drug therapy. Our study showed that irisin plays a neuroprotective role by decreasing the level of α-syn. Irisin was negatively correlated with the severity of motor symptoms and cognitive impairment. More importantly, irisin can improve DOPA uptake in the striatum of patients with PD, especially on the side contralateral to the affected limb. Irisin plays an important role in the occurrence and development of PD and has great potential for its treatment.

Funding

This work was supported by the Science and Technology Department of Henan Province (192102310085) and the Henan Provincial Commission of Health and Family Planning (SBGJ202102035).

Ethics approval and consent to participate

This research was approved by the Ethics Committee of Henan Provincial People's Hospital (2019 in No. 76). All subjects agreed to participate and signed a written informed consent form.

Consent to participate and publish

Informed consent was obtained from all individual participants included in the study.

CRediT authorship contribution statement

Xiaoxue Shi: Conceptualization, Writing – original draft. **Qi Gu:** Writing – review & editing. **Chang Fu:** Writing – review & editing. **Jianjun Ma:** Conceptualization, Resources, Supervision, Project administration, Writing – review & editing. **Dongsheng Li:** Writing – review & editing. **Jinhua Zheng:** Investigation. **Siyuan Chen:** Validation. **Zonghan She:** Investigation. **Xuelin Qi:** Investigation. **Xue Li:** Investigation. **Shaopu Wu:** Investigation. **Li Wang:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

We gratefully acknowledge the cooperation of all research staff and participants.

References

Armstrong, M.J., Okun, M.S., 2020. Diagnosis and treatment of parkinson disease: a review. J. Am. Med. Assoc. 323, 548–560.

Baghi, M., Yadegari, E., Rostamian Delavar, M., Peymani, M., Ganjalikhani-Hakemi, M., Salari, M., Nasr-Esfahani, M.H., Megraw, T.L., Ghaedi, K., 2021. MiR-193b deregulation is associated with Parkinson's disease. J. Cell Mol. Med. 25, 6348–6360.

Bostrom, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Bostrom, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Hojlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463–468.

Brooks, D.J., Salmon, E.P., Mathias, C.J., Quinn, N., Leenders, K.L., Bannister, R., Marsden, C.D., Frackowiak, R.S., 1990. The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure, and Parkinson's disease, studied with PET. Brain 113 (Pt 5), 1539–1552.

Dun, S.L., Lyu, R.M., Chen, Y.H., Chang, J.K., Luo, J.J., Dun, N.J., 2013. Irisin-immunoreactivity in neural and non-neural cells of the rodent. Neuroscience 240, 155–162.

Emre, M., Ford, P.J., Bilgic, B., Uc, E.Y., 2014. Cognitive impairment and dementia in Parkinson's disease: practical issues and management. Mov. Disord. 29, 663–672.

Fahn, S., Oakes, D., Shoulson, I., Kieburtz, K., Rudolph, A., Lang, A., Olanow, C.W., Tanner, C., Marek, K., 2004. Parkinson Study, G., 2004. Levodopa and the progression of Parkinson's disease. N. Engl. J. Med. 351, 2498–2508.

Gallagher, D.A., Goetz, C.G., Stebbins, G., Lees, A.J., Schrag, A., 2012. Validation of the MDS-UPDRS Part I for nonmotor symptoms in Parkinson's disease. Mov. Disord. 27, 79–83.

Galna, B., Lord, S., Burn, D.J., Rochester, L., 2015. Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. Mov. Disord. 30, 359–367.

Giguere, N., Burke Nanni, S., Trudeau, L.E., 2018. On Cell Loss and Selective Vulnerability of Neuronal Populations in Parkinson's Disease. Front. Neurol. 9, 455.

Goetz, C.G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T., Counsell, C., Giladi, N., Holloway, R.G., Moore, C.G., Wenning, G.K., Yahr, M.D., Seidl, L., 2004. Movement disorder society task force on rating scales for parkinson's, d., 2004. movement disorder society task force report on the hoehn and yahr staging scale: status and recommendations. Mov. Disord. 19, 1020–1028.

Grygiel-Gorniak, B., Puszczewicz, M., 2017. A review on irisin, a new protagonist that mediates muscle-adipose-bone-neuron connectivity. Eur. Rev. Med. Pharmacol. Sci. 21, 4687–4693.

Huh, J.Y., Panagiotou, G., Mougios, V., Brinkoetter, M., Vamvini, M.T., Schneider, B.E., Mantzoros, C.S., 2012. FNDC5 and irisin in humans: I. Predictors of circulating concentrations in serum and plasma and II. mRNA expression and circulating concentrations in response to weight loss and exercise. Metabolism 61, 1725–1738.

Jedrychowski, M.P., Wrann, C.D., Paulo, J.A., Gerber, K.K., Szpyt, J., Robinson, M.M., Nair, K.S., Gygi, S.P., Spiegelman, B.M., 2015. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell Metab. 22, 734–740.

Jokinen, P., Helenius, H., Rauhala, E., Bruck, A., Eskola, O., Rinne, J.O., 2009. Simple ratio analysis of 18F-fluorodopa uptake in striatal subregions separates patients with early Parkinson disease from healthy controls. J. Nucl. Med. 50, 893–899.

Kalia, L.V., Lang, A.E., 2015. Parkinson's disease. Lancet 386, 896–912.

Kam, T.I., Park, H., Chou, S.C., Van Vranken, J.G., Mittenbuhler, M.J., Kim, H., Mu, A., Choi, Y.R., Biswas, D., Wang, J., Shin, Y., Loder, A., Karuppagounder, S.S., Wrann, C. D., Dawson, V.L., Spiegelman, B.M., Dawson, T.M., 2022. Amelioration of pathologic alpha-synuclein-induced Parkinson's disease by irisin. PNAS 119.

Lourenco, M.V., Frozza, R.L., de Freitas, G.B., Zhang, H., Kincheski, G.C., Ribeiro, F.C., Goncalves, R.A., Clarke, J.R., Beckman, D., Staniszewski, A., Berman, H., Guerra, L. A., Forny-Germano, L., Meier, S., Wilcock, D.M., de Souza, J.M., Alves-Leon, S., Prado, V.F., Prado, M.A.M., Abisambra, J.F., Tovar-Moll, F., Mattos, P., Arancio, O., Ferreira, S.T., De Felice, F.G., 2019. Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. Nat. Med. 25, 165–175.

Mehra, S., Sahay, S., Maji, S.K., 2019. alpha-Synuclein misfolding and aggregation: Implications in Parkinson's disease pathogenesis. Biochim Biophys Acta Proteins Proteom 1867, 890–908.

Peng, J., Wu, J., 2022. Effects of the FNDC5/Irisin on Elderly Dementia and Cognitive Impairment. Front. Aging Neurosci. 14, 863901.

Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30, 1591–1601.

Raefsky, S.M., Mattson, M.P., 2017. Adaptive responses of neuronal mitochondria to bioenergetic challenges: Roles in neuroplasticity and disease resistance. Free Radic. Biol. Med. 102, 203–216.

Ren, J., Pan, C., Wang, Y., Xue, C., Lin, H., Xu, J., Wang, H., Zhang, W., Xu, P., Chen, Y., Liu, W., 2022. Plasma alpha-synuclein and phosphorylated tau 181 as a diagnostic biomarker panel for de novo Parkinson's disease. J. Neurochem. 161, 506–515.

Roheger, M., Kalbe, E., Liepelt-Scarfone, I., 2018. Progression of cognitive decline in parkinson's disease. J. Parkinsons Dis. 8, 183–193.

Schrag, A., Siddiqui, U.F., Anastasiou, Z., Weintraub, D., Schott, J.M., 2017. Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study. Lancet Neurol. 16, 66–75.

Tarazi, F.I., Sahli, Z.T., Wolny, M., Mousa, S.A., 2014. Emerging therapies for Parkinson's disease: from bench to bedside. Pharmacol. Ther. 144, 123–133.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25, 2649–2653.

Varela-Rodriguez, B.M., Pena-Bello, L., Juiz-Valina, P., Vidal-Bretal, B., Cordido, F., Sangiao-Alvarellos, S., 2016. FNDC5 expression and circulating irisin levels are modified by diet and hormonal conditions in hypothalamus, adipose tissue and muscle. Sci. Rep. 6, 29898.

Zarbakhsh, S., Safari, M., Aldaghi, M.R., Sameni, H.R., Ghahari, L., Khaleghi Lagmouj, Y., Rahimi Jaberi, K., Parsaie, H., 2019. Irisin protects the substantia nigra dopaminergic neurons in the rat model of Parkinson's disease. Iran. J. Basic Med. Sci. 22, 722–728.

Zhang, H., Wu, X., Liang, J., Kirberger, M., Chen, N., 2022. Irisin, an exercise-induced bioactive peptide beneficial for health promotion during aging process. Ageing Res. Rev. 80, 101680.