UNIVERSIDADE FEDERAL DO PARANÁ

LARYSA SABOYA CAVALOTTI PERDONSINI

EXPRESSÃO ENDÓGENA DE IRISINA NA PROGRESSÃO E REPARO DA PERIODONTITE E EM OUTRAS CONDIÇÕES CRÔNICAS NÃO TRANSMISSÍVEIS

CURITIBA

2025

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EXPRESSÃO ENDÓGENA DE IRISINA NA PROGRESSÃO E REPARO DA PERIODONTITE E EM OUTRAS CONDIÇÕES CRÔNICAS NÃO TRANSMISSÍVEIS

Dissertação apresentada ao Programa de Pós-Graduação em Odontologia, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Odontologia.

Orientador: Prof. Dr. João Paulo Steffens

CURITIBA

2025

Perdonsini, Larysa Saboya Cavalotti
Expressão endógena de irisina na progressão e reparo da periodontite e em outras condições crônicas não transmissíveis [recurso eletrônico] / Larysa Saboya Cavalotti Perdonsini. – Curitiba, 2025.
1 recurso online : PDF

Dissertação (mestrado) – Programa de Pós-Graduação em Odontologia. Setor de Ciências da Saúde, Universidade Federal do Paraná, 2025.

Orientador: Prof. Dr. João Paulo Steffens

1. Periodontite. 2. Inflamação. 3. Doenças não transmissíveis. 4. Citocinas. 5. Miocinas. 6. Ratos. I. Steffens, João Paulo. II. Universidade Federal do Paraná. III. Título.

CDD 617.632

Maria da Conceição Kury da Silva CRB 9/1275

TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação ODONTOLOGIA da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **LARYSA SABOYA CAVALOTTI PERDONSINI**, intitulada: **Expressão endógena de irisina na progressão e reparo da periodontite e em outras condições crônicas não transmissíveis**, sob orientação do Prof. Dr. JOÃO PAULO STEFFENS, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de mestra está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 20 de Agosto de 2025.

Assinatura Eletrônica
21/08/2025 08:58:23.0
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Avaliador Externo (PONTIFICIA UNIVERSIDADE CATOLICA DO PARANÁ- PUCPR)

AGRADECIMENTOS

Primeiramente, agradeço a Deus por todas as bênçãos e por me fortalecer diariamente. À minha família, Mauricio e Enrico, que sempre estiveram ao meu lado, me apoiando em minhas decisões e sendo meu alicerce.

Aos meus pais e minha irmã, que, com esforço e dedicação, sempre me proporcionaram oportunidades de educação, muitas vezes abrindo mão de si mesmos para me oferecer o melhor.

Ao meu orientador Prof. Dr. João Paulo Steffens, pela confiança, orientação e compromisso exemplar com a pesquisa e com a formação acadêmica, sempre conduzidos com sabedoria e sinceridade.

À Universidade Federal do Paraná, pela estrutura e pelas oportunidades de capacitação oferecidas.

Aos colegas de pesquisa João Victor Schoemberger Roth, Priscila Alves Teixeira Ribas, Henrique Kenji Takarada e Mariana Ortelan Borges, que foram fundamentais para a concretização do artigo com o modelo animal; sem a colaboração e o empenho de cada um, esse trabalho não teria sido possível.

Aos colegas do programa, pela cumplicidade ao longo de todas as etapas, que tornaram essa jornada mais leve e enriquecedora.

RESUMO

A irisina é uma miocina derivada da clivagem da proteína FNDC5, reconhecida por seus efeitos anti-inflamatórios e reguladores do metabolismo. Embora seu papel nas condições crônicas não transmissíveis (CCNTs) ainda esteja sendo elucidado, a irisina tem se destacado como um potencial biomarcador ou modulador fisiológico em contextos inflamatórios sistêmicos e locais. Este trabalho integrou uma revisão de escopo e um estudo experimental com o objetivo de investigar o comportamento da irisina em CCNTs e durante a periodontite induzida em modelo animal. A revisão foi conduzida na base PubMed utilizando descritores MeSH combinando irisina com doenças cardiovasculares, respiratórias crônicas, diabetes mellitus tipo 2 e periodontite, com aplicação da estratégia PECOS; com sessenta e quatro estudos clínicos incluídos. Paralelamente, foi conduzido um estudo experimental longitudinal em ratos machos Wistar (n=48) divididos em grupos: Controle, Ligadura 7, 35 e 63 dias, Reparo 28 e 56 dias. com periodontite induzida por ligadura, avaliando-se a expressão de irisina no soro e no tecido gengival durante a progressão e o reparo da doença, além da dosagem de marcadores inflamatórios. Os níveis de irisina foram determinados por ELISA e os marcadores inflamatórios, por análise multiplex. Dos 64 estudos incluídos na revisão, a maioria relatou níveis significativamente reduzidos de irisina circulante em indivíduos com doenças cardiovasculares, diabetes tipo 2 e doenças respiratórias crônicas. Em contraste, níveis aumentados de irisina salivar foram observados em pacientes com periodontite. No modelo animal, a irisina sérica não apresentou variações significativas, enquanto a irisina no tecido gengival esteve significativamente aumentada no grupo Ligadura 7 dias, em comparação aos grupos Controle e Ligadura 63 dias. Durante o reparo, não foram observadas diferenças significativas. Além disso, foram observadas correlações negativas significativas entre irisina e TNF-α durante a progressão da doença**,** e correlações positivas com EGF e VEGF nas fases de reparo. Os achados reforçam o potencial da irisina como biomarcador de alterações inflamatórias e metabólicas, com comportamento distinto em doenças sistêmicas e locais.

Palavras-chave: citocinas; doenças não transmissíveis; inflamação; miocinas; periodontite; ratos.

ABSTRACT

Irisin is a myokine derived from the cleavage of the FNDC5 protein, recognized for its anti-inflammatory and metabolism-regulating effects. Although its role in chronic noncommunicable conditions (CNCCs) is still being elucidated, irisin has emerged as a potential biomarker or physiological modulator in systemic and local inflammatory contexts. This study integrated a scoping review and an experimental study with the aim of investigating the behavior of irisin in CNCCs and during periodontitis induced in an animal model. The review was conducted in PubMed using MeSH descriptors combining irisin with cardiovascular diseases, chronic respiratory diseases, type 2 diabetes mellitus, and periodontitis, applying the PECOS strategy; sixty-four clinical studies were included. At the same time, a longitudinal experimental study was conducted in male Wistar rats (n=48) divided into groups: Control, Ligation 7, 35, and 63 days, Repair 28 and 56 days. with ligature-induced periodontitis, evaluating irisin expression in serum and gingival tissue during disease progression and repair, in addition to the dosage of inflammatory markers. Irisin levels were determined by ELISA and inflammatory markers by multiplex analysis. Of the 64 studies included in the review, most reported significantly reduced levels of circulating irisin in individuals with cardiovascular disease, type 2 diabetes, and chronic respiratory diseases. In contrast, increased levels of salivary irisin were observed in patients with periodontitis. In the animal model, serum irisin did not show significant variations, while irisin in gingival tissue was significantly increased in the 7-day ligation group compared to the control and 63-day ligation groups. During repair, no significant differences were observed. In addition, significant negative correlations were observed between irisin and TNF-α during disease progression, and positive correlations with EGF and VEGF in the repair phases. The findings reinforce the potential of irisin as a biomarker of inflammatory and metabolic changes, with distinct behavior in systemic and local diseases.

Keywords: cytokines; noncommunicable diseases; inflammation; myokines; periodontitis; rats.

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LISTA DE ABREVIATURAS OU SIGLAS

ARRIVE – Animal Research: Reporting of In Vivo Experiments

EGF – Fator de Crescimento Epidérmico

IL-1β – Interleucina-1 Beta

IL-4 – Interleucina-4

IL-10 – Interleucina-10

TNF-α – Fator de Necrose Tumoral Alfa

VEGF – Fator de Crescimento Endotelial Vascular

FNDC5 – Fibronectin Type III Domain-Containing Protein 5

CNCC – Condição Crônica não Transmissível

CVD – Doença Cardiovascular

CRD – Doença Respiratória Crônica

T2DM – Diabetes Mellitus Tipo 2

WHO – Organização Mundial da Saúde

MeSH – Medical Subject Headings

PECOS – População, Exposição, Comparador, Desfecho, Desenho do Estudo

SUMÁRIO

1 INTRODUÇÃO

A irisina, uma miocina descoberta na última década, tem emergido como um mediador chave na interação entre a atividade física e a saúde metabólica, com implicações no controle de doenças inflamatórias e metabólicas (Chen et al., 2024; Boström et al., 2012). Seu nome foi inspirado na deusa grega Íris, mensageira dos deuses do Olimpo, conhecida por transmitir mensagens entre os deuses e os humanos (Grimal, 1987), numa analogia ao papel da irisina como molécula sinalizadora entre tecidos. A irisina é secretada pelos músculos esqueléticos e pelo tecido adiposo, sendo também expressa em órgãos como o cérebro, a polpa dental e o tecido periodontal (Roca-Rivada et al., 2013; Yang et al., 2021).

Ela é produzida a partir da clivagem da proteína Fibronectin Type III Domain Containing Protein 5 (FNDC5). Durante a atividade física, ocorre a ativação de um coativador transcricional denominado Peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC1-α), que estimula a expressão da FNDC5. A porção extracelular dessa proteína é clivada por mecanismos enzimáticos e liberada na circulação sanguínea, originando a irisina (Boström et al., 2012). Uma vez na corrente sanguínea, a irisina exerce efeitos hormônio like, atuando como mensageira entre o músculo e outros tecidos, promovendo efeitos sistêmicos como o aumento da termogênese, a regulação glicêmica e a redução de marcadores inflamatórios (Kurdiova et al., 2014; Mazur-Bialy et al., 2017).

Esses efeitos posicionam a irisina como uma possível aliada no tratamento de condições como doenças cardiovasculares, respiratórias, neurodegenerativas, diabetes tipo 2 e obesidade, que compartilham mecanismos fisiopatológicos relacionados à inflamação sistêmica e ao desequilíbrio metabólico (Mensah, Roth & Fuster, 2019; GBD 2019 Chronic Respiratory Diseases Collaborators, 2023; AlKhairi et al., 2019; Rabiee et al., 2020). Em paralelo, a periodontite é uma doença inflamatória crônica, multifatorial e progressiva, associada à destruição dos tecidos de suporte dentário, incluindo o ligamento periodontal e o osso alveolar, podendo resultar em perda dentária (Papapanou et al., 2018). Nesses contextos, a irisina tem sido

amplamente estudada por sua capacidade de modular citocinas inflamatórias e atuar como um possível biomarcador ou agente terapêutico (Kinane et al., 2017).

Embora os dados ainda sejam inconclusivos e por vezes contraditórios quanto aos níveis circulantes ou salivares dessa miocina em diferentes condições clínicas (Ijiri et al., 2015; Ahmed et al., 2023), seus efeitos promissores sobre a inflamação e regeneração tecidual justificam investigações mais aprofundadas.

2 CAPÍTULO 1

Irisin levels as a Biomarker of Inflammation and Metabolic Dysregulation in Chronic Noncommunicable Diseases: Insights from a Scoping Review

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Abstract

Aim: Irisin is a myokine generated by the proteolytic cleavage of fibronectin type III domain-containing protein 5 (FNDC5), expressed in multiple tissues, particularly skeletal muscle. Growing evidence suggests that irisin participates in the pathophysiology of chronic noncommunicable diseases (NCDs) as a potential biomarker and physiological modulator of inflammatory processes. Understanding its behavior across different NCDs may provide insights into disease monitoring and therapeutic strategies.

Methods: A scoping review was conducted following the PRISMA-ScR framework to map and synthesize current evidence on the association between circulating or local irisin levels and chronic NCDs. A systematic PubMed, combined the keyword “irisin” with MeSH terms for “type 2 diabetes mellitus,” “cardiovascular diseases,” “respiratory tract diseases,” and “periodontitis.” Only human studies in English were included. Study selection followed the PECOS strategy, addressing whether irisin levels differ between patients with NCDs and healthy controls. Data on study population, methodology, sample type, and main findings were narratively synthesized.

Results: Sixty-three clinical studies met the inclusion criteria. Most investigations on systemic conditions, cardiovascular disease, chronic respiratory disease, and type 2 diabetes mellitus, reported lower circulating irisin levels in affected patients, correlating with systemic inflammation, metabolic dysregulation, and disease severity. Conversely, limited evidence on oral disease revealed a distinct pattern: the two studies on periodontitis found increased salivary irisin levels, suggesting that local

tissue inflammation and remodeling may elicit a site-specific response independent of systemic concentrations.

Conclusions: Irisin displays a complex, context-dependent behavior across NCDs. Reduced systemic levels in metabolic and cardiovascular disorders contrast with localized increases in periodontitis, emphasizing the need to consider tissue-specific dynamics when interpreting irisin measurements. These findings support its potential as an integrative biomarker linking metabolism and inflammation, while highlighting the need for mechanistic and longitudinal studies.

Keywords: Myokines; Cytokines; Periodontitis; Diabetes Mellitus, Type 2; Pulmonary Disease, Chronic Respiratory Diseases; Cardiovascular Diseases; Noncommunicable Diseases

1. Introduction

Irisin is a myokine generated by the proteolytic cleavage of the fibronectin type III domain-containing protein 5 (FNDC5) and is secreted predominantly by skeletal muscle and adipose tissue, with additional expression in other tissues such as the brain, periodontal tissue, and dental pulp [1–4]. Since its identification, irisin has attracted increasing attention as a mediator of metabolic homeostasis and anti-inflammatory responses. Functionally, it promotes the browning of white adipose tissue, enhances thermogenesis, and contributes to systemic energy expenditure [5, 6]. By modulating glucose and lipid metabolism, irisin improves insulin sensitivity and may exert protective effects against metabolic dysfunction [7]. In addition, it displays immunomodulatory properties by suppressing pro-inflammatory cytokines such as TNF-α and IL-6, while favoring anti-inflammatory mediators, suggesting a role in counteracting chronic low-grade inflammation.

Beyond systemic metabolism, irisin also exerts significant effects on skeletal tissue and bone homeostasis. Preclinical studies have demonstrated that irisin promotes osteoblast proliferation and differentiation, stimulating bone matrix deposition through the activation of signaling pathways such as p38 MAPK, ERK1/2, and Wnt/β-catenin [5, 6]. It upregulates osteogenic markers including Runx2, alkaline phosphatase, and osteocalcin, enhancing bone formation and mineralization [8–10]. Concurrently, irisin inhibits osteoclastogenesis by modulating the OPG/RANKL axis and suppressing RANKL-induced NF-κB signaling, thereby reducing bone resorption. From an

osteoimmunological perspective, irisin helps maintain skeletal integrity by attenuating the effects of inflammatory cytokines that drive osteoclast activation and bone loss [10]. Its ability to promote an anti-inflammatory microenvironment, including the potential polarization of macrophages toward an M2 phenotype and the upregulation of IL-10, situates irisin at the intersection of the muscle–bone–immune axis [11–13]. These pleiotropic effects highlight its potential relevance in conditions involving systemic or localized bone loss, such as osteoporosis, diabetes-associated bone fragility, and periodontitis-related alveolar bone resorption.

Chronic noncommunicable diseases (NCDs), including cardiovascular diseases (CVDs), chronic respiratory diseases (CRDs), and type 2 diabetes mellitus (T2DM), represent a major global health burden and share a pathophysiology rooted in metabolic dysregulation and chronic inflammation [14]. CVDs encompass a spectrum of disorders affecting the heart and vasculature, such as coronary artery disease, heart failure, hypertension, and stroke [15]. They are characterized by endothelial dysfunction, oxidative stress, and persistent inflammatory responses, processes that may be influenced by myokines like irisin. Experimental data suggest that irisin may improve vascular health by enhancing nitric oxide bioavailability, reducing oxidative stress, and mitigating endothelial inflammation [5]. CRDs, including asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis, also involve chronic inflammatory responses and tissue remodeling [16]. Preliminary studies indicate that irisin could modulate pulmonary oxidative stress and inflammatory cascades, although its clinical role in respiratory diseases remains to be clarified [17, 18]. T2DM, the most common form of diabetes, is characterized by impaired glucose metabolism, insulin resistance, and hyperglycemia [19]. Irisin appears to contribute to glycemic control by promoting glucose uptake in skeletal muscle and improving insulin sensitivity, further linking physical activity and muscle-secreted myokines to metabolic health [20–22]. Collectively, these observations support the hypothesis that irisin acts as a metabolic and anti-inflammatory mediator, potentially contributing to the prevention or attenuation of NCD progression.

Periodontitis is another highly prevalent NCD of multifactorial origin, triggered by oral microbial dysbiosis and perpetuated by dysregulated host inflammatory responses, leading to progressive destruction of the periodontal ligament, alveolar bone, and other

supporting dental structures [23]. Recent epidemiological studies estimate that periodontitis affects approximately one billion people worldwide and has been ranked as the seventh most prevalent disease globally, contributing significantly to the burden of chronic conditions [24–26]. Its clinical consequences extend beyond tooth loss, as periodontitis promotes systemic inflammation and has been linked to the aggravation of CVD, T2DM, and CRDs [27]. Given its dual metabolic and anti-inflammatory functions, irisin has emerged as a molecule of interest in periodontal research [28, 29]. By promoting osteoblast activity, inhibiting osteoclast-mediated bone resorption, and attenuating local inflammation, irisin could represent a protective factor against alveolar bone destruction and a mediator of the bidirectional relationship between periodontitis and systemic diseases [29].

Despite growing interest, studies assessing circulating and salivary irisin levels have yielded inconsistent and sometimes contradictory results, reflecting differences in study design, disease stage, population characteristics, and detection methodologies [30–32]. These discrepancies hinder the establishment of irisin as a reliable biomarker or therapeutic target in chronic disease management. Given its multifaceted roles in metabolism, bone remodeling, and immunomodulation, a comprehensive assessment of irisin in multiple NCDs is warranted. Therefore, the objective of this scoping review is to summarize and critically evaluate current evidence on the alterations in irisin levels in CVD, CRDs, T2DM, and periodontitis, with an emphasis on its potential as a biomarker and physiological modulator in chronic disease contexts.

2. Materials and Methods

2.1. Protocol and registration

The methodological framework was based on the original Arksey and O'Malley approach with enhancements suggested by subsequent guidance, including the Joanna Briggs Institute recommendations and the PRISMA extension for scoping reviews (PRISMA-ScR) [33]. This scoping review also followed the procedures described in the EQUATOR network website and was registered in the Open Science Framework (OSF) database, doi: 10.17605/OSF.IO/2XZJP.

2.2 Objectives and focused question

This scoping review was designed to map and synthesize the existing human clinical evidence on the alteration of irisin levels in selected NCDs. The review process encompassed a systematic search, transparent study selection, structured data charting, and narrative synthesis to address the guiding question: Are irisin levels increased or decreased in individuals with CVDs, CRDs, T2DM, and periodontitis when compared to healthy controls?

2.3. Information sources

Information sources and search strategy were developed to capture all relevant human studies without temporal restriction. The PubMed database was queried using combinations of the keyword “irisin” with Medical Subject Headings (MeSH) terms representing the conditions of interest: “Type 2 Diabetes Mellitus,” “Cardiovascular Diseases,” “Respiratory Tract Diseases,” and “Periodontitis.” The Boolean operator AND was applied between “irisin” and each disease term to construct disease-specific search strings. Free-text variations and synonyms were considered where appropriate to maximize sensitivity. Search filters limited retrieval to studies involving human participants and publications in the English language. The full detailed search strategy, including exact strings and any applied modifications during iterative refinement, is provided in Supplementary Material 1. Searches were conducted up to the date of the final search execution. All retrieved records were exported to EndNote reference management software, where duplicate entries were identified and removed prior to screening.

2.4. Study Selection Criteria and Exclusion Criteria

Eligibility criteria included original primary research studies involving human subjects that reported measurements of circulating or local irisin levels in populations diagnosed with CVDs, CRDs, T2DM, or periodontitis. Observational study designs (cross-sectional, case-control, cohort) and interventional studies with appropriate baseline or comparator data were considered. Studies were required to include either a healthy control group or a clearly defined reference for comparison to allow assessment of directional changes in irisin. Exclusion criteria encompassed animal or in vitro studies, narrative reviews, editorials, commentaries, conference abstracts without full data, studies not reporting actual irisin measurements, and investigations focusing on

conditions outside the pre-specified disease categories (e.g., cancer) due to heterogeneity concerns.

2.5. Search strategy and selection process

Study selection proceeded in two phases. Titles and abstracts of deduplicated records were independently screened by two reviewers to identify potentially relevant articles (LSCP and JPS). Full texts of studies passing the initial screen were retrieved and assessed in detail against the eligibility criteria by the same pair of reviewers. Discrepancies in both screening and full-text eligibility decisions were resolved through consensus discussion, and if necessary, by consultation with a third reviewer (RSdM). Reasons for exclusion at the full-text stage were documented. A flow diagram summarizing the identification, screening, eligibility assessment, and inclusion of studies was constructed in accordance with PRISMA-ScR guidelines (Figure 1).

2.6. Data extraction and collection process

Data extraction was carried out using a standardized and piloted charting form implemented in Microsoft Excel and structured according to the Population, Exposure, Comparison, Outcome, and Study design (PECOS) strategy. The form was tested on a subset of included studies to ensure clarity and consistency between reviewers. Extracted information comprised bibliographic details (authors, year, geographic location), study design, characteristics of the study population (sample size, age distribution, sex, diagnostic criteria and definitions for the disease of interest, inclusion and exclusion criteria), description of the comparator or control group, type of biological sample analyzed (e.g., serum, plasma, saliva, gingival crevicular fluid), methods used for irisin quantification (assay type, manufacturer, sensitivity, sample handling and processing protocols), timing of sample collection relative to disease status or treatment, statistical adjustments for potential confounders, and primary findings. Specific outcomes recorded included the direction and magnitude of irisin level alterations, statistical significance, correlations with disease severity indices, inflammatory markers, and other relevant clinical parameters.

Data management procedures ensured traceability and reproducibility. All extracted data were double-checked for accuracy. The spreadsheet was used to facilitate sorting and grouping of studies by disease category and measurement characteristics.

Although formal critical appraisal of individual study quality was not performed, consistent with common scoping review methodology, methodological features with potential to influence interpretation (such as small sample sizes, cross-sectional design, heterogeneity in assay methodologies, lack of adjustment for confounders, and other sources of bias) were cataloged and considered during synthesis to contextualize findings.

2.7. Synthesis methods

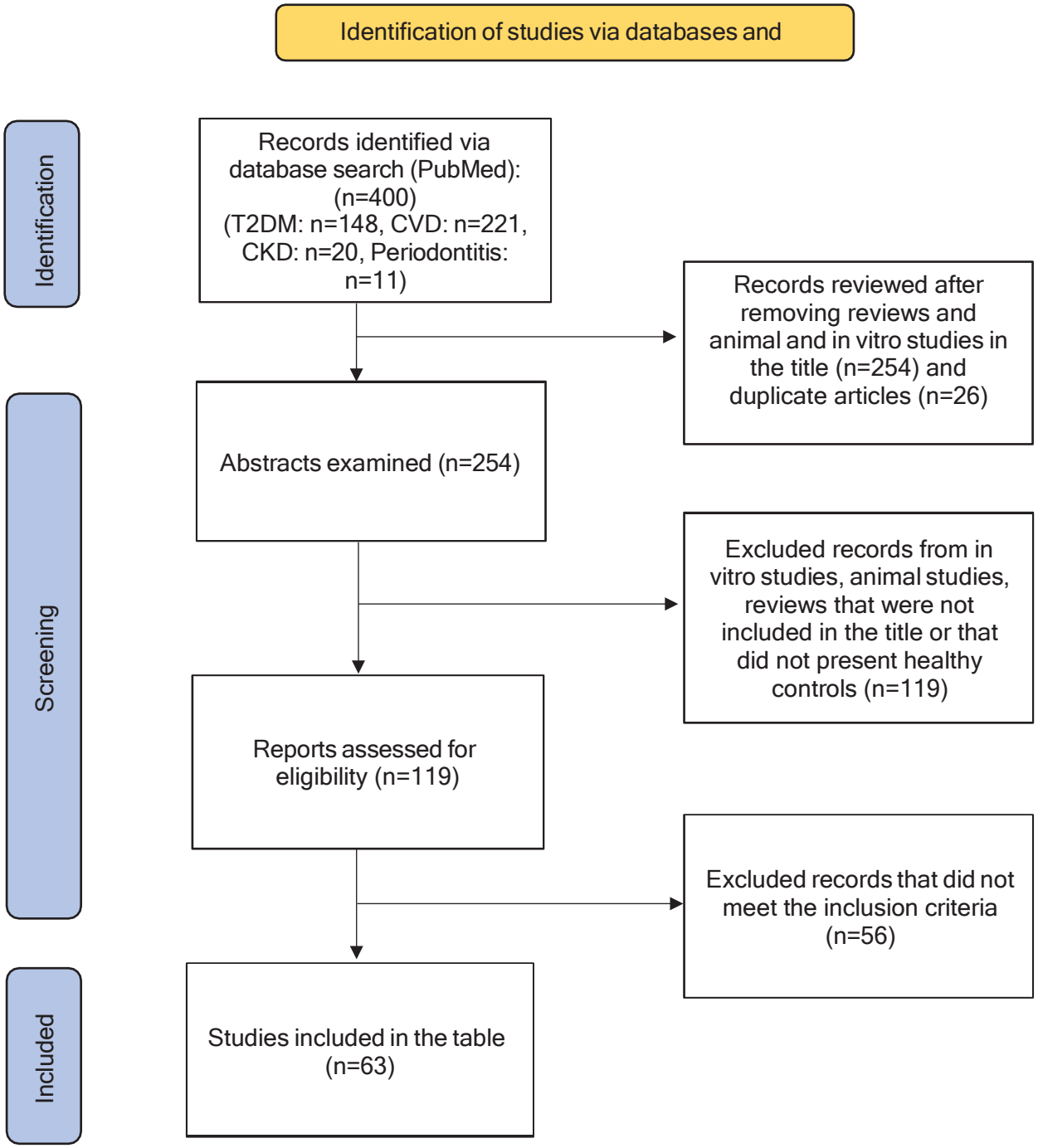
Synthesis of results was descriptive and narrative. Studies were organized by chronic disease category, and within each category, summaries highlighted patterns in irisin level alterations, distinctions between systemic versus local measurements, and methodological heterogeneity. Where available, secondary analyses such as associations of irisin with inflammatory biomarkers, metabolic parameters, and measures of disease severity were integrated. The complexity and context-dependence of irisin behavior across tissue compartments and disease states were explored, and conflicting or inconsistent findings were identified to outline knowledge gaps. Quantitative synthesis or meta-analysis was not undertaken due to substantial variability in study designs, populations, reference standards, irisin assay techniques, and outcome reporting, which precluded meaningful aggregation of effect estimates.

3. Results

3.1 Study selection

The systematic search of the databases yielded 400 records after applying the initial search strategy across the four predefined NCD categories. Following the removal of duplicates, in vitro and animal studies, reviews, and studies without healthy control groups, 254 abstracts were screened. After full-text review of 119 articles, 63 studies published between 2013 and 2025 met the eligibility criteria for inclusion in this scoping review (Figure 1). These studies assessed irisin levels in diverse biological samples, primarily serum and plasma, with a small subset evaluating salivary irisin in the context of oral disease.

Figure 1. Flowchart of the identification, screening, eligibility, and inclusion process of studies in the scoping review, based on the search strategy in the PubMed database.



3.2 Irisin in Periodontitis – Study characteristics

Only two clinical studies evaluated irisin levels in patients with periodontitis, both employing case-control or cross-sectional designs and including 40 participants each (Table 1) [34, 35]. Salivary irisin levels were significantly higher in patients with periodontitis compared with periodontally healthy controls, suggesting a localized increase in irisin associated with periodontal inflammation. One study additionally demonstrated a positive correlation between salivary irisin and interleukin-6, linking this myokine to local inflammatory activity [34]. Interestingly, serum irisin levels showed no significant differences between patients and controls [34], supporting the hypothesis that irisin may act as a site-specific mediator in the periodontal microenvironment rather than reflecting systemic alterations.

3.3. Irisin in Chronic Respiratory Diseases – Study characteristics

Four studies investigated irisin levels in patients with chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), sarcoidosis, and chronic lung graft dysfunction (Table 2) [36–38]. Most were cross-sectional or retrospective cohorts, conducted in Turkey, Italy, and Japan, with sample sizes ranging from 51 to 176 participants. Serum or plasma measurements predominated, and three of the four studies reported significantly lower irisin levels in affected patients compared with healthy controls. Reduced irisin was particularly notable in sarcoidosis and COPD, and plasma irisin was lower in lung transplant recipients who developed chronic graft dysfunction. One study in COPD patients did not identify a statistically significant difference in serum irisin levels between cases and controls [38], but it reported an inverse correlation between irisin and haptoglobin, supporting a possible immunomodulatory role for irisin even in the absence of absolute reductions. Overall, these findings suggest that reduced irisin may reflect systemic inflammation, impaired physical conditioning, and metabolic dysregulation commonly observed in chronic respiratory disease.

3.4. Irisin in Type 2 Diabetes Mellitus – Study characteristics

Type 2 diabetes mellitus (T2DM) was the most extensively studied condition, with 35 clinical studies evaluating circulating irisin levels across diverse populations (Table 3) [31, 32, 39–71]. Most investigations reported significantly lower irisin concentrations in serum or plasma of T2DM patients compared with healthy controls, often correlating

inversely with markers of metabolic dysregulation such as fasting glucose, insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), and lipid abnormalities [42, 43, 46, 53, 54]. Some studies further linked lower irisin to diabetic complications, including nephropathy, macrovascular disease, and retinopathy.

However, a subset of eight studies observed elevated irisin levels in specific contexts, particularly in patients with obesity, active inflammation, or in response to pharmacologic interventions such as exenatide or insulin infusion [32, 40, 45, 52, 55, 60, 61, 65, 66]. This paradoxical increase may represent a compensatory response to metabolic stress or early-stage disease. Two studies reported no significant difference in irisin levels between T2DM patients and controls [31, 39], and one longitudinal study showed that higher baseline irisin in prediabetic patients predicted progression to T2DM over time [41]. Collectively, these findings reveal a complex, context-dependent pattern for irisin in diabetes, influenced by disease stage, body composition, inflammatory status, and treatment.

3.5. Irisin in Cardiovascular Diseases – Study characteristics

Twenty-two studies examined irisin levels in patients with various cardiovascular diseases (CVDs), including acute myocardial infarction (AMI), chronic heart failure, coronary artery disease (CAD), systemic arterial hypertension, peripheral artery disease, and subclinical atherosclerosis (Table 4) [44, 72–92]. Most studies reported significantly reduced circulating irisin levels in patients with CVD compared with healthy controls. Reductions were most consistently observed in acute coronary events (e.g., AMI), heart failure, and CAD, supporting the hypothesis that irisin deficiency reflects endothelial dysfunction, impaired metabolic homeostasis, and heightened cardiovascular risk [72, 73, 77, 82, 83, 85].

A few studies documented increased irisin in specific circumstances, such as after antihypertensive therapy, percutaneous coronary intervention, or in healthy centenarians, suggesting that therapeutic interventions or exceptional physiological states may transiently elevate irisin levels [89, 92, 93]. Additionally, several studies highlighted correlations between irisin and markers of vascular health, including carotid intima-media thickness, lipid profiles, and inflammatory cytokines, underscoring its potential as a biomarker of cardiovascular risk.

3.6. Overall Patterns

Across all NCDs, a predominant trend of reduced systemic irisin levels emerged in CVD, T2DM, and CRD, aligning with the concept of irisin as a protective myokine whose deficiency may reflect chronic inflammation and metabolic imbalance. In contrast, periodontitis exhibited a localized increase in salivary irisin, possibly reflecting tissue-specific responses to local inflammation and bone remodeling. These findings support the hypothesis that irisin operates in a context- and tissue-dependent manner, with its interpretation as a biomarker requiring careful consideration of disease type, biological compartment analyzed, and systemic versus local influences.

4. Discussion

This scoping review comprehensively synthesized the evidence on irisin levels across four major chronic noncommunicable diseases: CVDs, CRDs, T2DM, and periodontitis. Sixty- three clinical studies were included, revealing heterogeneous but clinically meaningful patterns in circulating and local irisin behavior. Overall, the analysis demonstrates a predominant reduction of systemic irisin levels in patients with metabolic and cardiovascular disorders, contrasted by a localized increase in salivary irisin in periodontitis, suggesting a tissue- and disease-specific response.

Irisin as a Link Between Muscle, Metabolism, and Inflammation

Irisin, generated by the cleavage of FNDC5 and secreted primarily by skeletal muscle and adipose tissue, is recognized as a pleiotropic myokine with metabolic, anti-inflammatory, and osteo-anabolic properties [1–6]. Mechanistically, irisin stimulates the browning of white adipose tissue, enhances thermogenesis, and promotes energy expenditure, contributing to improved insulin sensitivity and glucose metabolism. It also exerts immunomodulatory effects, reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6) and enhancing anti-inflammatory mediators such as IL-10 [5]. In bone tissue, irisin supports osteoblast differentiation and matrix deposition through p38 MAPK, ERK1/2, and Wnt/β-catenin signaling, while inhibiting osteoclastogenesis via OPG/RANKL modulation [5, 6]. These molecular pathways position irisin as a biological link between physical activity, energy homeostasis, bone remodeling, and systemic inflammation, which are central pathophysiological features of the NCDs evaluated in this review.

Irisin in Cardiovascular Diseases

Among the 23 studies investigating cardiovascular conditions, reduced circulating irisin was the most consistent finding across patients with acute myocardial infarction, chronic heart failure, coronary artery disease, systemic hypertension, and subclinical atherosclerosis [72–83, 85, 94]. These findings are mechanistically aligned with the role of irisin as a vascular-protective myokine, capable of improving endothelial function, promoting nitric oxide production, and attenuating oxidative stress [5]. Experimental models have demonstrated that irisin can suppress vascular inflammation and improve lipid metabolism, processes that are often dysregulated in CVDs.

Clinically, low irisin levels may serve as a biomarker of endothelial dysfunction and adverse cardiovascular outcomes, as suggested by studies linking irisin reduction to increased carotid intima-media thickness, acute coronary syndromes, and heart failure severity [77, 79, 82]. Some studies also noted irisin increases following interventions such as antihypertensive therapy or percutaneous coronary intervention [89, 93], raising the hypothesis that irisin could be modulated by therapeutic or lifestyle interventions. However, heterogeneity in assay methods and patient characteristics limits its current utility as a routine biomarker, underscoring the need for standardized measurement and longitudinal studies.

Irisin in Type 2 Diabetes Mellitus

Type 2 diabetes mellitus accounted for the largest subset of studies (n=35), with the majority reporting reduced serum or plasma irisin levels in diabetic patients compared with healthy controls [42–44, 46–51, 53, 54, 56–59, 61, 62, 64, 68–71]. Lower irisin concentrations were commonly associated with worsening glycemic control, insulin resistance, dyslipidemia, and the presence of microvascular or macrovascular complications, suggesting that irisin may reflect the metabolic and inflammatory burden of diabetes [43, 54]. Mechanistically, irisin is believed to enhance glucose uptake in skeletal muscle via AMPK activation and to modulate adipokine secretion, which may mitigate systemic inflammation and insulin resistance [95, 96].

Notably, some studies reported elevated irisin levels, particularly in patients with obesity, early disease stages, or after pharmacological interventions such as insulin infusion and exenatide therapy [32, 40, 45, 52, 55, 60, 61, 65, 66]. This paradoxical

increase may reflect a compensatory response to metabolic stress, aimed at counteracting insulin resistance and promoting energy expenditure. Longitudinal data indicate that high baseline irisin levels in prediabetic individuals may predict progression to T2DM [41], suggesting dynamic regulation across disease stages. Clinically, these observations reinforce the context-dependent nature of irisin and highlight its potential role as a biomarker for metabolic risk stratification and possibly a target for therapeutic modulation.

Irisin in Chronic Respiratory Diseases

Four studies examined irisin levels in CRDs, including COPD, sarcoidosis, and chronic lung graft dysfunction [36–38, 97]. Most studies identified reduced systemic irisin, consistent with the known consequences of CRDs: chronic systemic inflammation, oxidative stress, and skeletal muscle deconditioning. Irisin levels correlated positively with physical activity in COPD patients [38], suggesting that muscle-derived irisin reflects functional capacity and that its deficiency could contribute to the catabolic state typical of advanced respiratory disease. Mechanistically, irisin's anti-inflammatory actions could theoretically mitigate pulmonary inflammation and remodeling, although this requires confirmation in interventional studies.

Irisin in Periodontitis and Localized Responses

In contrast to systemic NCDs, periodontitis demonstrated a localized increase in salivary irisin levels [34, 35]. This finding likely reflects a site-specific response to local inflammation and bone remodeling within the periodontium. Irisin is expressed in periodontal ligament cells, dental pulp, and osteoblasts, and its local upregulation may represent a paracrine or autocrine protective mechanism aimed at controlling osteoclastic bone resorption and modulating the inflammatory microenvironment [3]. The positive correlation between salivary irisin and interleukin-6 [34] further supports its involvement in local immune regulation. Interestingly, serum irisin levels in these patients did not differ significantly from controls [34], reinforcing the concept that local and systemic irisin dynamics may diverge, depending on tissue-specific regulation and disease compartmentalization.

Integrative Perspective and Clinical Implications

Taken together, the evidence indicates that irisin exhibits disease- and tissue-specific patterns across NCDs. A predominant systemic reduction is observed in metabolic and cardiovascular disorders, potentially reflecting muscle inactivity, insulin resistance, endothelial dysfunction, and chronic inflammation, all hallmarks of these conditions. In contrast, local increases in inflamed oral tissues suggest that irisin may also function as a tissue-specific modulator, possibly participating in osteoimmunological responses and localized tissue repair.

From a clinical perspective, these findings support the potential of irisin as an integrative biomarker linking metabolism, inflammation, and skeletal homeostasis. In CVDs and T2DM, low circulating irisin could serve as an indicator of metabolic and cardiovascular risk, while in periodontitis, salivary irisin may provide a non-invasive marker of local inflammatory activity and bone remodeling. Moreover, the evidence that irisin levels may rise in response to pharmacologic or lifestyle interventions raises the possibility of therapeutic modulation to improve outcomes in NCDs.

However, the translational application of irisin remains limited by methodological heterogeneity. Variations in assay methods, sample type (serum, plasma, saliva), disease stage, and comorbidities contribute to conflicting findings. Most studies were cross-sectional, precluding causal inference, and only a few evaluated longitudinal dynamics or intervention effects. Standardization of irisin measurement, combined with mechanistic and longitudinal studies, will be essential to clarify its role as a predictive biomarker or therapeutic target.

Concluding remarks

This scoping review highlights the complex and context-dependent behavior of irisin across major NCDs. A consistent pattern of reduced systemic irisin levels was observed in: CVDs, CRDs, and T2DM, supporting the concept that irisin deficiency reflects chronic inflammation, metabolic dysregulation, and muscle deconditioning, hallmarks of these systemic conditions. In contrast, periodontitis exhibited a localized increase in salivary irisin, suggesting that irisin may also act as a tissue-specific mediator of inflammation and bone remodeling within the oral microenvironment.

Mechanistically, these patterns align with the known functions of irisin as a pleiotropic

myokine that links skeletal muscle activity to systemic homeostasis. By promoting adipose tissue browning, enhancing glucose uptake, suppressing pro-inflammatory cytokines, and stimulating osteoblast differentiation while inhibiting osteoclast activity, irisin integrates metabolic regulation, immune modulation, and skeletal preservation. Its dual systemic and local behavior underscores the need to consider both biological compartment and disease context when interpreting irisin measurements.

Clinically, these findings position irisin as a promising integrative biomarker in chronic disease, with potential applications in risk stratification, disease monitoring, and therapeutic response evaluation. In systemic NCDs, low circulating irisin could reflect adverse metabolic and inflammatory profiles, whereas in periodontitis, salivary irisin may provide a non-invasive indicator of local tissue activity and bone turnover. Moreover, evidence that irisin levels can be modulated by pharmacologic and lifestyle interventions opens avenues for therapeutic exploration, although causality and clinical applicability remain to be fully established.

Future research should focus on longitudinal and mechanistic studies using standardized irisin assays to confirm its predictive value, clarify disease-stage dynamics, and evaluate its role as a therapeutic target. By bridging metabolism, immunity, and skeletal biology, irisin emerges as a key molecular link in the pathophysiology of NCDs, warranting continued investigation into its translational potential.

Table 1. Characteristics of the included studies regarding irisin and periodontitis.

Author/Year	Population/Study location	Intervention/ Exposure	Control	Outcome	Conclusions	Study design
Irisin X Periodontitis						
Turkmen et al., 2023	40 patients from Istanbul Medipol University	20 patients with grade B stage III	20 periodontally healthy patients.	↑ Salivary irisin in periodontitis; → no significant difference in serum irisin between groups.	Significant positive correlation between salivary irisin, IL-6, and clinical parameters. Positive correlation between BMI and IL-6 levels	Case-control
Khan et al., 2022	40 patients attended at FMH College of Medicine and Dentistry, Lahore, Pakistan	20 patients with chronic periodontitis (16 men and 4 women)	20 periodontally healthy patients (10 men and 10 women)	↑ Salivary irisin in periodontitis patients compared to healthy controls.	Positive but non-significant correlation between salivary irisin levels and clinical parameters in both groups, except for plaque percentage in healthy controls.	Cross-sectional

Table 2. Characteristics of the included studies regarding irisin and chronic respiratory diseases.

Author/Year	Population/Study location	Intervention/ Exposure	Control	Outcome	Conclusions	Study design
Irisin X Chronic Respiratory Diseases						
Kaya et al., 2024	176 individuals from Kocaeli University, Turkey	90 patients with sarcoidosis	86 healthy individuals	↓ Serum irisin in sarcoidosis patients compared to healthy controls.	Irisin was significantly lower in sarcoidosis. May serve as a potential biomarker. No significant difference in adiponectin levels.	Case-control
Cuttitta et al., 2023	51 patients treated at the outpatient pulmonary service of the National Research Council (CNR), Palermo, Italy	25 patients with Chronic Obstructive Pulmonary Disease (COPD)	26 healthy controls	→ Serum irisin levels in COPD patients similar to healthy controls.	In COPD patients, there was a significant inverse correlation between irisin, as well as a negative correlation between haptoglobin and irisin.	Cross-sectional
Shiotani et al., 2021	59 patients who underwent lung transplantation at Okayama University Hospital, Japan	With chronic graft dysfunction after living donor lung lobe transplantation (LDLLT-CLAD; n=11) With chronic graft dysfunction after deceased donor lung	Without chronic lung graft dysfunction (non-CLAD; n=41)	↓ Plasma irisin levels in LDLLT-CLAD patients compared to non-CLAD.	Significant association between emphysematous changes and CLAD severity in both LDLLT and CLT recipients	Retrospective cohort

		transplantation (CLT-CLAD; n=7)				
Ijiri et al., 2015	99 subjects from Osaka City University Hospital, Japan	72 patients with COPD	27 control subjects	↓ Serum irisin in COPD patients compared to healthy controls.	Significant correlation between irisin levels and physical activity in all subjects, irisin levels increased after 8-week exercise training	Cross-sectional

Table 3. Characteristics of the included studies regarding irisin and type 2 diabetes mellitus.

Author/Year	Population/Study location	Intervention/ Exposure	Control	Outcome	Conclusions	Study design
Irisin X Type 2 Diabetes						
Ahmed et al., 2023	90 participants from Beni-Suef University Hospital, Egypt	65 patients with T2DM	25 healthy controls	→ No significant difference in serum irisin levels between T2DM patients and healthy controls	Significant inverse correlation between irisin levels and hs-CRP and LDL	Case-control
Mathia et al., 2023	30 participants from Centro Universitário FMABC, Brazi	16 T2DM patients	14 healthy controls	→ No significant difference in plasma irisin levels in T2DM patients similar to healthy controls.	Positive correlation between irisin gene expression and BMI in T2DM patients; negative correlation between plasma irisin and BMI	Cross-sectional case-control
Yildiz Kopuz et al., 2022	76 individuals from Ankara Kecioren Training and Research Hospital, Turkey	38 newly diagnosed T2DM patients	38 healthy controls	↑ Serum irisin in newly diagnosed T2DM patients compared to healthy controls.	Positive association between irisin levels and fruit intake in T2DM patients, no association with overall diet quality	Case-control

Cherian et al., 2021	228 individuals from Dasman Diabetes Institute, Kuwait City, Kuwait	104 T2DM patients (66 obese, 38 non-obese)	124 non-diabetic controls (51 obese, 73 non-obese)	↑ Plasma irisin in T2DM and obese individuals compared to non-diabetic controls.	Irisin positively correlated with osteoactivin and osteoprotegerin.	Cross-sectional
He et al., 2021	322 adults with newly diagnosed prediabetes from the Yunyan community, Guiyang, China	161 participants who developed diabetes	161 individuals with prediabetes	↑ Serum irisin levels at baseline in prediabetic individuals who progressed to T2DM compared to those who did not.	A greater decrease in irisin levels during follow-up was correlated with an increased risk of diabetes	Nested case-control
Mostafa et al., 2021	120 individuals from Tanta University Hospital, Egypt	60 patients with newly diagnosed T2DM	60 healthy controls	↓ Serum irisin levels in T2DM patients compared to healthy controls	Negative correlation between irisin levels and fasting blood glucose, fasting plasma insulin, insulin resistance (HOMA-IR), and glycated hemoglobin	Observational parallel-group
Ali et al., 2020	138 subjects from Erfan Hospital, Jeddah, Saudi Arabia	46 T2DM patients with macrovascular complications	46 T2DM patients without macrovascular complications, 46 healthy controls	↓ Serum irisin in T2DM patients with macrovascular complications compared to those	Negative correlations between irisin and fasting blood glucose, insulin, HOMA-IR, HbA1c, and LDL	Case-control

				without and healthy controls.		
Huerta-Delgado et al., 2020	56 children and adolescents from Tecnológico de Monterrey, Hospital Zambrano Hellion, Mexico	21 T2DM patients and 19 Metabolic Syndrome	16 healthy controls	↓ Serum irisin levels in both T2DM and Metabolic Syndrome patients compared to healthy controls	Negative correlation between irisin levels and BMI, waist circumference, and triglycerides; positive correlation with total cholesterol, HDL, and LDL	Cross-sectional
AlKhairi et al., 2019	228 individuals from Dasman Diabetes Institute, Kuwait	104 T2DM patients	124 non-diabetic individuals	↑ Plasma irisin in T2DM and obese individuals compared to non-diabetic controls.	Positive correlation between irisin and Meteorin-like hormone; higher irisin levels in obese individuals compared to non-obese	Cross-sectional
Elizondo-Montemayor et al., 2019	40 children and adolescents from Tecnológico de Monterrey, Mexico	20 patients with T2DM	20 healthy controls	↓ Plasma irisin in pediatric T2DM patients compared to healthy controls.	Positive correlation between irisin and HDL-c	Cross-sectional
Tarboush et al., 2018	233 patients from Jordan University Hospital, Amman, Jordan	105 T2DM patients with diabetic retinopathy	94 T2DM patients without diabetic etinopathy and 34 healthy controls	↓ Plasma irisin in T2DM patients with diabetic retinopathy compared to those without retinopathy.	Negative correlation between irisin levels and HbA1c, triglycerides, and LDL;	Case-control

					positive correlation with HDL	
Li et al., 2018	514 participants from Baoding Central Hospital, China	424 T2DM patients subdivided into 4 groups based on hypertension grades	90 healthy controls	↓ Serum irisin in T2DM patients, with further reduction in those with hypertension, compared to healthy controls.	Irisin levels were negatively correlated with blood pressure, fasting blood glucose, and leptin levels	Observational cross-sectional
El-Lebedy et al., 2018	205 subjects from National Research Center, Cairo, Egypt	135 T2DM patients	70 healthy controls	↓ Serum irisin in T2DM patients with cardiovascular disease compared to those without and healthy controls.	Negative correlation between irisin levels and HbA1c, HOMA-IR, and triglycerides in CVD patients; lower irisin levels associated with 1.6 times increased risk of CVD in T2DM patients	Case-control
Saadeldin et al., 2018	69 female subjects from Cairo, Egypt	39 T2DM patients with atherosclerosis, 22 T2DM patients without atherosclerosis	8 healthy controls	↓ Serum irisin in T2DM patients with atherosclerosis compared to those without and healthy controls.	Positive correlation between irisin and fasting blood glucose in T2DM patients with atherosclerosis	Case-control

Shelbaya et al., 2018	90 subjects from Ain Shams University, Cairo, Egypt	30 patients with diabetic nephropathy, 30 patients with T2DM without complications	30 healthy controls	↓ Serum irisin in T2DM patients, with further reduction in those with diabetic nephropathy, compared to healthy controls.	Negative correlation between irisin levels and serum creatinine. Duration of diabetes was the strongest independent predictor of irisin levels	Case-control
Kamenov et al., 2017	128 men with metabolic syndrome from the Clinic of Endocrinology, University Hospital Alexandrovska, Medical University, Sofia, Bulgaria	90 men with T2DM	38 men without T2DM	↑ Serum irisin levels in men with hypogonadism and metabolic syndrome, especially in those with T2DM.	Significant negative correlation between irisin levels and serum testosterone; irisin was a predictor of hypogonadism	Nested case-control
Khidr et al., 2017	150 Egyptian male adults from Al-Zahraa Hospital, Al-Azhar University, Cairo, Egypt	60 T2DM patients with diabetic nephropathy, 40 T2DM patients with normoalbuminuria	50 healthy controls	↓ Serum irisin in T2DM patients, with a more pronounced decrease in those with diabetic nephropathy.	Significant correlations between irisin and metabolic parameters	Cross-sectional
Li et al., 2017	462 Chinese adults from Tianjin Metabolic Diseases Hospital, China	362 patients with T2DM	100 healthy controls	↓ Serum irisin levels in T2DM patients compared to healthy controls.	Lower irisin levels were associated with increased skin autofluorescence values, indicating a	Observational cross-sectional

					higher accumulation of Advanced Glycation End-products (AGEs) in T2DM patients	
Rana et al., 2017	79 T2DM patients from Heart of England NHS Foundation Trust, Birmingham, UK	79 T2DM patients with fasting plasma measurements	Reference values from healthy volunteers	↑ Plasma irisin levels in T2DM patients compared to healthy controls.	Positive correlation between elevated plasma irisin levels and E-selectin, indicating potential endothelial dysfunction in T2DM patients	Observational cross-sectional
Shanaki et al., 2017	162 subjects from outpatient clinics at Shariati Hospital, Tehran, Iran	41 with nonalcoholic fatty liver disease, 41 with type 2 diabetes, and 40 with both nonalcoholic fatty liver disease and type 2 diabetes	40 healthy controls	↓ Serum irisin levels in all patient groups (NAFLD, T2DM, and both) compared to healthy controls.	Negative correlation of irisin with IMC, positive correlation with adiponectin levels	Observational cross-sectional
Assyov et al., 2016	160 individuals from University Hospital "Alexandrovska", Medical University, Sofia, Bulgaria	60 with prediabetes, 50 with T2DM	50 with normal glucose tolerance	↓ Serum irisin levels progressively decreased from normal glucose tolerance to prediabetes, with the	Negative correlations between irisin and fasting plasma glucose, positive correlation with IMC	Cross-sectional

				lowest levels in T2DM patients.		
Hu et al., 2016	178 T2DM patients from the Department of Endocrinology, Qilu Hospital, Shandong University, China	35 patients with proliferative diabetic retinopathy, 22 with T2DM without retinopathy	62 healthy controls	↓ Serum irisin lower in T2DM with nephropathy, lowest in macroalbuminuria. Serum and vitreous irisin lower in proliferative retinopathy	Negative correlation between serum irisin levels and indicators of renal function (creatinine, urea) and insulin resistance.	Cross-sectional
Hwang et al., 2016	424 participants from the Seoul Metro City Diabetes Prevention Program, South Korea	137 with type 2 diabetes, 152 with prediabetes	135 with normal glucose tolerance	↓ Serum irisin levels were lower in T2DM and prediabetes groups compared to those with normal glucose tolerance.	Positive correlation between irisin levels and healthy metabolic parameters, such as reduced obesity, lower blood pressure, and improved glucose tolerance; inverse association with prediabetes/type 2 diabetes risk	Observational cross-sectional
Li et al., 2016	33 participants from Shanghai Tenth People's Hospital, China	20 patients with T2DM treated with continuous subcutaneous insulin infusion for 1 week	13 healthy controls	↑ Serum irisin concentrations were increased in T2DM patients after insulin	The increase in irisin levels was associated with improvements in	Interventional study

				infusion compared to pre-treatment.	lipid profiles and glycemic control	
Liu et al., 2016	108 participants from Beijing Chao-yang Hospital, China	54 patients treated with exenatide for 12 weeks	54 healthy controls with normal glucose tolerance	↓ Serum irisin lower in T2DM at baseline, ↑ increased after exenatide.	The increase in irisin levels was significantly correlated with decreases in fasting blood glucose and HbA1c after exenatide treatment	Interventional study
Shoukry et al., 2016	300 participants from outpatient clinics at Zagazig University, Egypt	150 T2DM patients and non-diabetic controls stratified into lean, overweight, and obese groups	150 healthy controls, subdivided into lean, overweight and obese individuals.	↓ Serum irisin lower in T2DM than in non-diabetic controls. ↑ Higher in obese non-diabetics than in lean controls.	Positive correlation between irisin and IMC. Negative correlation with insulin sensitivity	Cross-sectional
Wang et al., 2016	120 individuals from Qilu Hospital of Shandong University, China	40 patients with nonproliferative diabetic retinopathy (NPDR), 60 T2DM patients without non-DR	20 normal glucose tolerance controls	↓ Serum irisin lower in T2DM than in normal glucose tolerance. → No difference between NPDR and non-DR groups.	Negative correlation between irisin and IL-17A levels; potential protective role of irisin against DR through anti-inflammatory effects	Cross-sectional

Wang et al., 2016	140 individuals from Qilu Hospital of Shandong University, China	120 T2DM patients	20 healthy controls with normal glucose tolerance	↓ Serum irisin in T2DM patients than in healthy controls.	Positive correlation between irisin levels and insulin sensitivity; no significant association between irisin and pancreatic β-cell	Cross-sectional
García-Fontana et al., 2015	128 individuals from outpatient clinics at San Cecilio University Hospital, Granada, Spain	73 patients with T2DM	55 healthy controls	↑ Serum irisin higher in T2DM than in controls.	Inverse relationship between irisin and myostatin levels; positive association between irisin and fasting plasma glucose and triglycerides in T2DM patients	Case-control
Al-Daghri et al., 2015	164 Saudi adults from the Riyadh Cohort Study, King Saud University, Saudi Arabia	83 patients with T2DM	81 healthy controls	↑ Serum irisin in T2DM than in controls.	Positive association between habitual physical activity and circulating irisin in healthy controls only; lack of association in T2DM patients suggests possible irisin dysregulation in metabolic dysfunction	Cross-sectional

Duran et al., 2015	263 sedentary women from Ankara Numune Education and Research Hospital, Turkey	50 T2DM patients, 65 with both impaired fasting glucose and impaired glucose tolerance (IFG + IGT), 60 with isolated impaired fasting glucose (IFG), and 36 with isolated impaired glucose tolerance	52 normal glucose tolerance (NGT) controls	↓ Serum irisin in IFG + IGT and T2DM than in NGT.	Negative correlations between irisin and BMI, LDL-C, triglycerides, and postprandial glucose; positive correlation with HDL-C. Irisin levels decreased progressively with worsening glucose tolerance	Cross-sectional
Wang et al., 2015	200 participants from Dongguan People's Hospital, China	100 T2DM patients	100 healthy controls	↓ Serum irisin levels lower in T2DM than in controls; progressively lower with increasing albuminuria severity.	Positive correlation between irisin levels and flow-mediated dilation (FMD); negative correlation with urinary albumin excretion (UAE), indicating potential endothelial protective effects	Observational cross-sectional
Alis et al., 2014	144 participants from University Hospital Dr. Peset, Valencia, Spain	69 T2DM patients	75 euglycemic controls	↓ Serum irisin levels in T2DM patients than in euglycemic controls.	Inverse correlation between irisin and homocysteine levels; as homocysteine levels	Cross-sectional

					increased, irisin levels decreased	
Xiang et al., 2014	228 participants from Wuhan General Hospital, China	188 T2DM patients	40 healthy controls	↓ Serum irisin levels in T2DM patients compared to controls.	Positive correlation between irisin levels and flow-mediated dilation (FMD), suggesting a protective role of irisin in endothelial function	Cross-sectional
Choi et al., 2013	208 participants from Daegu, South Korea	104 T2DM patients	104 healthy controls with normal glucose tolerance	↓ Serum irisin levels in T2DM patients compared to controls.	An inverse association was observed between irisin levels and newly diagnosed T2DM. Higher irisin levels were linked to reduced odds of newly diagnosed diabetes	Cross-sectional

Table 4. Characteristics of the included studies regarding irisin and cardiovascular diseases.

Author/Year	Population/Study location	Intervention/ Exposure	Control	Outcome	Conclusions	Study design
Irisin X Cardiovascular Diseases						
Cao et al., 2025	202 individuals from Shanxi Provincial People's Hospital, China	112 patients with peripheral arterial disease	90 healthy individuals	↓ Serum irisin levels in PAD patients compared to healthy controls.	Irisin levels were reduced in PAD. The study suggests irisin as a potential biomarker and predictor for PAD development. Associated with higher Rutherford classification and smoking. associated with HDL levels.	Case-control
Fu & Xing, 2024	236 individuals from Ningbo Zhenhai People's Hospital, China	156 patients with CAS, divided by BMI	80 healthy adults with normal BMI	↓ Serum irisin levels in CAS patients compared to healthy controls.	Irisin levels were reduced in patients with CAS, especially those with overweight and obesity. Irisin was associated with lipid	Cross-sectional

					metabolism and severity of atherosclerosis, suggesting potential as a biomarker.	
Chai et al., 2023	207 patients from The First Hospital of Handan, Handan, China	86 patients who developed major adverse cardiovascular events within 1 year after intervention	121 patients without major adverse cardiovascular events	↓ Serum irisin levels in MACE group compared to non-MACE.	Irisin levels at admission were negatively correlated with AMI severity and predicted MACE with an AUC of 0.75	Retrospective cohort study
Carmona-Maurici et al., 2023	61 participants from Arnau de Vilanova University Hospital, Lleida, Spain	30 participants with atheromatous plaques	31 participants without atheromatous plaques	↓ Serum irisin in participants with atheromatous plaques than in those without.	Irisin levels were negatively correlated with carotid intima-media thickness and other atherogenesis-related parameters.	Prospective observational
Ismail et al., 2023	50 patients from Sohag University Hospital, Egypt	50 patients with Behçet's disease	50 healthy controls	↓ Serum irisin in Behçet's disease patients,	Lower irisin levels in Behçet's disease patients, especially	Case-control

				particularly those with subclinical atherosclerosis.	those with subclinical atherosclerosis, suggest its potential role as a protective biomarker against vascular dysfunction.	
Wang et al., 2023	300 patients from Xuanwu Hospital, Capital Medical University, Beijing, China	194 hypertensive patients	106 normotensive patients	↓ Serum irisin in hypertensive dialysis patients compared to normotensive.	Serum irisin levels showed a negative correlation with systolic blood pressure and pulse pressure; irisin, lean tissue mass, and serum calcium were independent predictors of systolic blood pressure	Cross-sectional

Csiky et al., 2022	104 patients from FMC Dialysis Center, Pécs, Hungary	52 patients on hemodialysis and 15 on peritoneal dialysis	37 healthy controls	↓ Serum irisin in both HD and PD patients compared to controls.	Negative correlations of irisin with HbA1c, intact parathyroid hormone (iPTH), and alkaline phosphatase, suggesting improvements in insulin sensitivity and inhibition of bone resorption	Cross-sectional
Huerta-Delgado et al., 2022	64 Hispanic patients from northeastern Mexico, Tec de Monterrey	32 patients with chronic heart failure under standard treatment (CHF)	32 healthy controls	↓ Serum irisin in CHF patients compared to controls.	Negative correlations were observed between irisin and brain natriuretic peptide, insulin levels, and insulin resistance index; no significant correlations were found with inflammatory cytokines	Cross-sectional

Berezin et al., 2022	208 patients from Vita-Centre, Zaporozhye, Ukraine	153 patients with heart failure	30 patients with T2DM without heart failure and 25 healthy volunteers	↓ Serum irisin in HF patients compared to T2DM without HF.	Irisin levels improved the predictive ability for heart failure with preserved ejection fraction, but not for heart failure with mildly reduced ejection fraction or heart failure with reduced ejection fraction	Prospective cohort
Remuzgo-Martínez et al., 2022	725 patients from multiple hospitals in Spain	Patients with carotid plaques and/or atherogenic index ≥4	Patients without carotid plaques and atherogenic index <4	↓ Serum irisin in patients with carotid plaques and worse lipid profile.	Irisin levels were reduced in patients with worse cardiovascular risk and subclinical atherosclerosis, indicating a potential protective and biomarker role in axial spondyloarthritis.	Observational cohort study

Dong et al., 2021	152 patients from Xuanwu Hospital, Capital Medical University, Beijing, China	Group with cardiovascular/cerebrovascular diseases: 47 patients	Group without cardiovascular/cerebrovascular diseases: 105 patients	↓ Serum irisin associated with higher cardiovascular and cerebrovascular mortality.	Cox regression identified lower irisin levels as an independent predictor for cardiovascular and cerebrovascular mortality, but not for all-cause mortality	Retrospective cohort study
Önalan Etem et al., 2021	450 patients recruited from Fırat University Hospital, Elazığ, Turkey	225 patients with acute myocardial infarction (AMI)	225 healthy controls	↓ Serum irisin in AMI patients compared to controls, especially within 24h post-AMI.	Irisin levels decreased in AMI. FNDC5 gene variants were mostly non-significant for irisin levels in AMI context.	Prospective case-control
Abd El-Mottaleb et al., 2020	86 participants from Assiut University Hospital, Egypt	33 with MI, 33 with MI and heart failure	20 controls	↓ Serum irisin in MI and HF groups compared to controls.	Low irisin levels may serve as a biomarker for MI severity and correlate with inflammation and dyslipidemia,	Case-control

					supporting its potential role in early cardiovascular risk assessment.	
Calan & Demirpence, 2019	110 participants from Tepecik and Bozyaka Hospitals, Izmir, Turkey	40 with active acromegaly, 30 with controlled acromegaly	40 healthy controls	↑ Serum irisin elevated in active and controlled acromegaly.	Elevated irisin levels in patients with acromegaly are associated with cardiovascular risk parameters	Cross-sectional
Tu et al., 2018	1325 recruited from three stroke centers in China	1205 Chinese patients with first-ever acute ischemic stroke (AIS)	120 healthy controls without psychiatric or neurological disorders	↓ Serum irisin lower in AIS patients with post-stroke depression	Reduced irisin levels may serve as an independent predictor of PSD risk	Cohort study
Anastasilakis et al., 2017	114 patients recruited from 424 General Military Hospital, Thessaloniki, Greece.	31 with myocardial infarction (MI) and 40 with stable coronary artery disease (CAD)	43 healthy controls without stenosis on angiography.	↓ Serum irisin levels in MI and CAD patients compared to healthy controls.	Decreased irisin in MI and CAD suggests reduced production due to limited blood supply	Non-randomized, interventional study

Deng et al., 2016	564 participants recruited from Yantai Hill Hospital, Yantai, China	350 patients with coronary artery disease (CAD) confirmed by angiography	214 healthy subjects	↓ Serum irisin levels in CAD patients compared to healthy controls.	Decreased serum irisin may be associated with CAD presence and severity	Cross-sectional
Abdullah Icli et al., 2016	98 participants from Necmettin Erbakan University Meram Faculty of Medicine, Turkey	48 patients with Behçet's disease (BD)	50 healthy controls with no regular medications or known diseases.	↓ Serum irisin levels in Behçet's disease patients compared to healthy controls.	Low serum irisin levels may independently predict subclinical atherosclerosis in BD	Prospective observational
Çelik et al., 2015	115 patients from Turgut Ozal University Hospital, Turkey	85 newly diagnosed, untreated hypertensive patients	30 age- and BMI-matched healthy controls without hypertension	↓ Serum irisin in hypertensive patients vs. controls; ↑ after treatment with valsartan or amlodipine; → no difference between drugs.	Both antihypertensive treatments elevated irisin, suggesting a potential role in energy homeostasis regulation in hypertension management.	Randomized controlled trial
Lee et al., 2015	137 individuals recruited from Yonsei University Health System,	102 peritoneal dialysis (PD)	35 healthy controls	↓ Serum irisin in PD patients than in controls	Low irisin in PD patients may predict sarcopenia and carotid atherosclerosis	Cross-sectional

	Seoul, South Korea					
Aydin et al., 2014	25 subjects, recruited from Elazig Education and Research Hospital, Türkiye.	11 patients with acute myocardial infarction (AMI)	14 healthy controls	↓ Irisin in both saliva and serum in AMI patients, especially within the first 48h.	Irisin in saliva and serum may provide additional diagnostic information for AMI	Observational study
Emanuele et al., 2014	437 participants recruited University of Pavia, Italy, with collaboration from institutions in Spain	79 healthy centenarians, 178 young patients with early myocardial infarction	180 age- and sex-matched healthy young controls	↑ Serum irisin in centenarians; ↓ in young MI patients; → intermediate levels in young healthy controls	Elevated irisin in centenarians may indicate its role in vascular protection and lifespan extension, whereas lower levels in MI patients could relate to cardiovascular risk	Cross-sectional observational

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Supplemental Material 1. Search strategies in PubMed for each chronic disease category and irisin.

SS1: (("irisin"[All Fields] OR "irisin s"[All Fields]) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields])) AND ((humans[Filter]) AND (english[Filter]))

SS2: (("irisin"[All Fields] OR "irisin s"[All Fields]) AND ("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields])) AND ((humans[Filter]) AND (english[Filter]))

SS3: (("irisin"[All Fields] OR "irisin s"[All Fields]) AND (("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("respiratory tract diseases"[MeSH Terms] OR ("respiratory"[All Fields] AND "tract"[All Fields] AND "diseases"[All Fields]) OR "respiratory tract diseases"[All Fields] OR ("respiratory"[All Fields] AND "diseases"[All Fields]) OR "respiratory diseases"[All Fields]))) AND ((humans[Filter]) AND (english[Filter]))

SS4: (("irisin"[All Fields] OR "irisin s"[All Fields]) AND ("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields])) AND ((humans[Filter]) AND (english[Filter]))

2 CAPÍTULO 2

Expression of endogenous irisin and associated markers during periodontitis progression and repair in male rats[1]

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[1] Aceito pelo periódico Periodontal and Implant Research em 18/08/2025

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Acknowledgements

The authors would like to acknowledge the substantial assistance from the technicians from the Animal Facility at Positivo University; the technicians from the Stomatopathology Laboratory (UFPR) Bruna Cordeiro and Karla Cabral for their assistance with histological processing; and the technicians from the Multiuser Laboratory at PUC-PR for their support with multiplex analyses.

Funding

This study was supported by the Paraná State Research Foundation (Araucaria Foundation, Curitiba, PR, Brazil; Grant #70/2021).

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Abstract

This study aimed to evaluate the expression of endogenous irisin in serum and gingival tissue during the progression and repair of ligature-induced periodontitis in male rats, as well as its correlation with inflammatory markers. Forty-eight male Wistar rats were randomly assigned to experimental groups (n = 8/group): Control (no ligature); Ligature (7, 35, and 63 days); and Repair (28 and 56 days). Periodontitis was induced by placing a subgingival cotton ligature around the first molars. Repair was initiated by removing the ligature after 7 days. Serum and gingival tissue irisin levels were measured using enzyme-linked immunosorbent assay (ELISA), and a panel of inflammatory markers was assessed via multiplex analysis. No significant differences in serum irisin levels were found among the ligated groups or compared to the control group. However, gingival tissue irisin levels were significantly increased in the Ligature 7-day group compared to both the control and Ligature 63-day groups. In the Repair groups, no significant differences were observed compared to the Ligature 7-day group. A significant negative correlation was found between gingival irisin levels and tumor necrosis factor-alpha (TNF-α) during periodontitis progression, while significant positive correlations were observed with epidermal and vascular endothelial growth factors (EGF and VEGF, respectively) during periodontal repair. In conclusion, gingival irisin levels increase early during periodontitis progression, suggesting its role as a disease marker, and do not significantly decrease at the studied repair time points.

Keywords: Periodontitis; Periodontal Disease; Inflammation; Rats; Myokines; Cytokines.

Introduction

Irisin, a myokine with hormone-like properties identified in the last decade, has been investigated for its role in the diagnosis, treatment, and prevention of inflammatory and metabolic diseases [1]. Secreted by skeletal muscles during moderate to intense physical activity, irisin is derived from the cleavage of the extracellular portion of the FNDC5 protein and acts on various tissues and organs upon entering the bloodstream [2]. It plays a central role in regulating energy metabolism and thermogenesis, as well as contributing to glucose homeostasis, resulting in benefits against obesity and other metabolic disorders [3]. Irisin has also shown potential as a therapeutic ally in combating neurodegenerative diseases [4]. Another important feature is its anti-inflammatory effect, as it reduces the expression and secretion of inflammatory cytokines, reinforcing its contribution to overall health [5]. This mechanism may underlie some of the health benefits associated with physical activity, including protection against diseases linked to chronic inflammation [5–8].

Irisin has been investigated in various inflammatory diseases due to its potential to reduce inflammation, regulate cytokines and inflammatory pathways. In inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, studies indicate that irisin can improve inflammation and stimulate bone formation which is often compromised by chronic inflammation [5, 9]. In rheumatoid arthritis, irisin acts to reduce inflammatory markers such as tumor necrosis factor alpha (TNF-α), which plays a crucial role in the progression of the disease progression [10]. In cases of obesity and type 2 diabetes, irisin has shown positive effects in improving insulin sensitivity, regulating glucose metabolism and weight control, which contributes to a reduced risk of inflammatory cardiovascular diseases such as atherosclerosis [1, 2]. Furthermore, in neurodegenerative diseases such as Alzheimer's, irisin has been shown to promote

anti-inflammatory proteins, helping to attenuate disease progression, improve cognition, and stimulate neurogenesis [11].

Periodontitis is a chronic, inflammatory, multifactorial and non-communicable disease associated with a dysbiotic biofilm, which can lead to tooth loss [12]. The inflammatory response plays a key role in the destruction of the supporting tissues [13]. Irisin has shown potential in promoting the growth, migration and matrix formation of in periodontal ligament cells [14], as well as enhancing the osteogenic behavior of these cells and osteoblasts [15]. Studies involving irisin administration in animal models have demonstrated its anti-inflammatory and regenerative effects on periodontal tissues, including the promotion of bone regeneration, modulation of the inflammatory response, reduction of pro-inflammatory cytokines such as TNF-α, and inhibition of osteoclast activity, which is responsible for bone resorption [16].

Despite the benefits of irisin administration in preclinical models, cross-sectional observational research indicates, conversely, a positive correlation between the levels of this myokine in saliva and the severity of periodontitis, suggesting its potential as a biomarker of periodontal inflammation [17–19]. However, the direction of the association in cross-sectional studies remains unclear. In this context, the use of an animal model has the advantage of facilitating the establishing a temporal relationship between irisin and periodontitis. Therefore, this study aimed to evaluate endogenous serum and gingival irisin levels during the progression and repair of experimental periodontitis in rats, as well as their correlation with inflammatory markers.

Materials and methods

Animals

All experimental protocols were approved by the Positivo University Institutional Ethics Committee for Animal Experimentation (protocol #7.1/2021) and carried out in accordance with the Brazilian Society of Science in Laboratory Animals (SBCAL) and National Council for the Control of Animal Experimentation (CONCEA). This study was developed and reported following the ARRIVE (Animal Research: Reporting of In Vivo Experiments) standards. Forty-eight male Wistar rats, weighing between 200 and 250 g, aged approximately eight weeks, were housed in a temperature-controlled environment (23 ± 2 °C), with 12-hour light cycles and with free access to food and water.

Animals were randomly assigned to three main groups: Control (n=8), Ligature (n=24) and Repair (n=16). We used a list randomizer (www.random.org/lists) to generate a sequence containing 8xControl, 24xLigature and 16xRepair. Animals in the same group were then placed in the same cage until it reached a maximum of 3 animals/cage. This randomization process was repeated for the different timepoints within each group. Induction of experimental periodontitis began 7 days before baseline in the repair groups. For those groups, the ligatures were removed at baseline and the animals were euthanized at two different timepoints (n=8/group): after 28 and 56 days. In the ligation groups, animals were euthanized at 7, 35 and 63 days (n=8/group). These timepoints correspond to the same used for the repair groups (28 days and 56 days after 7 days of ligature). The animals in the control group were not ligated and were euthanized at the end of the experiment (day 63; n=8).

Induction of experimental periodontitis and periodontal repair

The induction of experimental periodontitis was carried out under intraperitoneal anesthesia, using ketamine (0.08mL/100g b.w.) and xylazine (0.04ml/100g b.w.). To induce periodontitis, a #30 cotton ligature was placed subgingivally around the lower first molars, bilaterally [20]. Briefly, an exploratory probe was used to create space between the first and second molars. Then, the cotton ligature was inserted and tied to the mesial of the first molar using a triple knot. In the repair groups, ligatures were removed after 7 days using an exploratory probe under inhalation anesthesia with 4% isoflurane.

Euthanasia and sample collection

At the end of the study, the animals were euthanized with an overdose of anesthetic (ketamine and xylazine) and via cardiac puncture. The mucogingival tissues around the lower right first molars were removed using a rectangle design on the buccal and lingual aspects of the teeth. Briefly, the scalpel blade was initially positioned in the edentulous region mesial to the first molar, over the ridge. Then, a new incision was made perpendicular to the long axis of the tooth, apically, to a point apical to the bone crest. Another perpendicular incision was made along the bone crest until the mesial aspect of the second molar (distal aspect of the first molar). Lastly, another incision was made to include the distal papilla of the first molar. This tissue was then dissected, placed in aluminum foil, transferred to a plastic tube and stored in dry ice. Gingival tissue proteins were extracted with T-PER containing protease inhibitor (Sigmafast, Sigma-Aldrich, St. Louis, MO, USA) and total protein was quantified using the Bradford method (Bio-Rad Laboratories, Inc., Hercules, CA, USA) to normalize the results. The blood obtained from the cardiac puncture was centrifuged for 10 min at 3,000 rpm. Then, the supernatant (serum) was collected, moved to another plastic

tube, and stored at -80 °C until the analysis of irisin and inflammatory markers.

ELISA and multiplex analyses

Irisin levels in serum and gingival tissue were analyzed using ELISA (Rat Irisin ELISA Kit, Elabscience, Wuhan, Hubei, China), according to the manufacturer's instructions. Additionally, all gingival and serum samples were submitted to a multiplex assay (MILLIPLEX® Rat Cytokine/Chemokine Magnetic Bead Panel, Merck KGaA, Darmstadt, Germany) for the quantification of inflammatory markers interleukin (IL)-1β, IL-4, IL-6, IL-10, TNFα, interferon (IFN)-γ, Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor (EGF, except in serum samples due to a technical problem with the manufacturer).

Sample Size Calculation and Statistical Analysis

This was a secondary analysis of a study involving ligature progression and repair [21]. For the primary study, radiographic bone loss was considered the primary outcome. For a relevant intergroup difference of ten points with a standard deviation of seven points, eight animals per group were needed, with alpha set at 5% and a power of 80%. Secondary outcomes included histological analysis and inflammatory markers. For the current study, an a priori sample size calculation was conducted, based on salivary irisin reported in previous research [22]. In that study, control patients had salivary irisin levels of 8.34□12.73 pg/ml, while periodontitis patients had a mean increase of 19.2 pg/mL. For those parameters, a similar sample size of 8 per group were needed for a power of 85%, considering alpha at 5%. All sample size calculations were performed using software (https://clincalc.com/stats/samplesize.aspx).

For the statistical analysis, the homogeneity of the variances and the normality of the data distribution were checked using the Levene and Shapiro-Wilk tests, respectively. One-way ANOVA or Kruskal-Wallis was used if these criteria were met or not, respectively. In case of statistical significance, Tukey's and Dwass-Steel-Critchlow-Fligner (DSCF) post-hoc tests were used after ANOVA or Kruskal-Wallis, respectively. The correlation between serum and gingival tissue irisin levels in periodontal progression and repair was analyzed using Spearman's correlation test. All analyses were carried out using Jamovi software, considering a significance level of $p<0.05$.

Results

No animals or ligatures were lost in this experiment. There were no statistically significant differences in irisin levels among control and Ligature groups in serum. On the other hand, median levels of irisin in gingival tissues in the Ligature 7d group were 4.3x times higher than in the control group (3.5 and 0.8 ng/mg, respectively; $p<0.05$). Levels of irisin in gingival tissues were also significantly higher in Ligature 7d compared to Ligature 63d, but not when compared to Ligature 35d (Figure 1).

Serum irisin levels were not significantly different from Ligature 7d at 28 or 56 days of repair. Similarly, gingival tissue irisin during repair was not statistically different among the groups. It was reduced by 7x and 4.4x at 28 and 56 days of repair, respectively, when compared to Ligature 7d, but this difference was not statistically significant ($p>0.05$) (Figure 2).

The correlation between irisin and inflammatory mediators during periodontitis progression revealed a significant negative association only with TNF-α in gingival tissues (Spearman’s rho=-0.5; $p=0.03$) (Table 1). During periodontal repair, and using

Ligature 7d group as baseline, there were significant positive associations between irisin in gingival tissue and growth factors, EGF and VEGF ($p<0.01$). There were no significant associations in serum (Table 2).

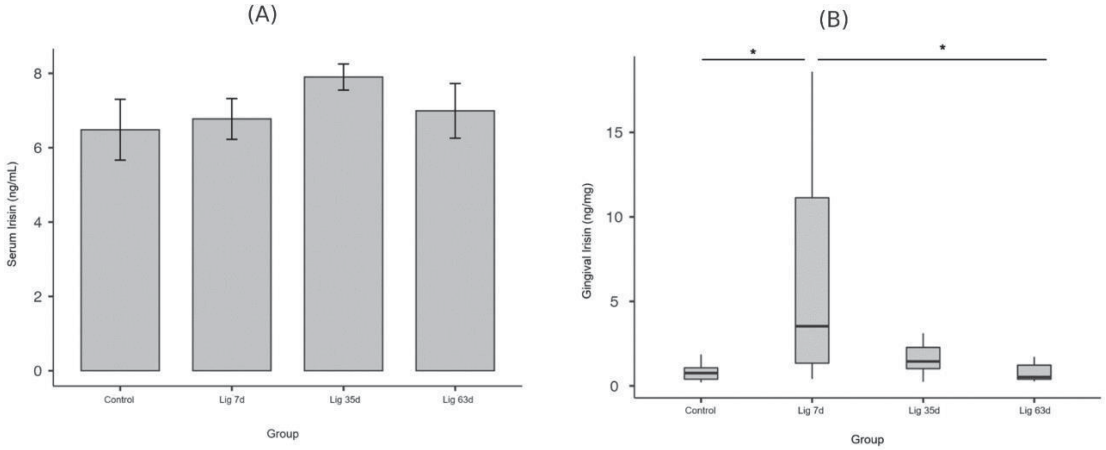

Figure 1. Irisin levels in (A) serum (ng/ml) and (B) gingival tissue (ng/mg), during periodontitis progression.

d, days. Column charts represent data analyzed by parametric test (one-way ANOVA). Boxplots represent data analyzed by non-parametric test (Kruskal-Wallis and DSCF post-hoc tests). *p<0.05 compared to Control and Ligature 63 days.

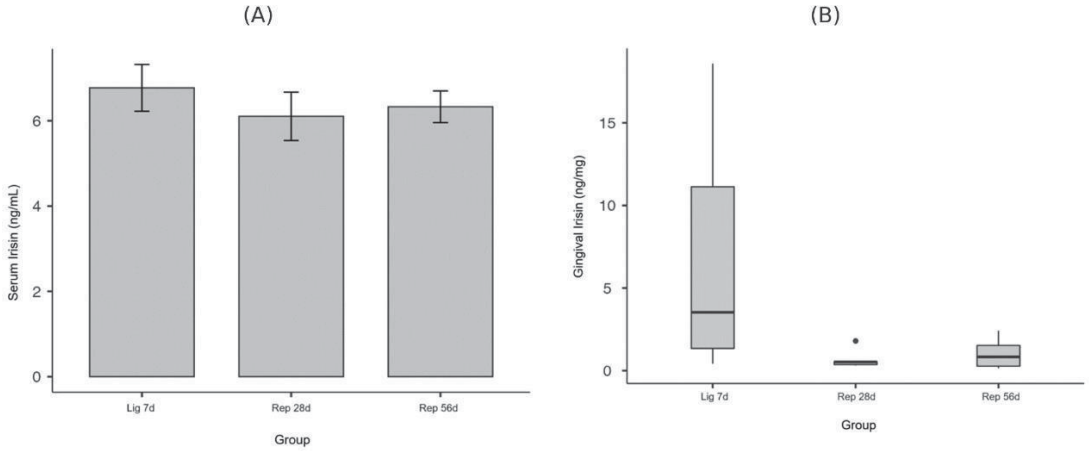

Figure 2. Irisin levels in (A) serum (ng/ml) and (B) gingival tissue (ng/mg), during periodontal repair.

d, days. Column charts represent data analyzed by parametric test (one-way ANOVA). Boxplots represent data analyzed by non-parametric test (Kruskal-Wallis). Dot – outlier. No statistically significant differences were observ

		Serum Irisin	Gingival Irisin
IL-1β	Spearman's rho	0.184	0.412
	p-value	0.450	0.058
TNF-α	Spearman's rho	-0.302	-0.495
	p-value	0.134	**0.027**
IL-4	Spearman's rho	-0.249	0.370
	p-value	0.263	0.090
IL-10	Spearman's rho	0.308	0.305
	p-value	0.214	0.147
EGF	Spearman's rho	-	-0.009
	p-value	-	0.965
VEGF	Spearman's rho	0.084	-0.022
	p-value	0.702	0.923

EGF not analyzed in serum samples. Spearman correlation test; p-values in bold indicate statistical significance.

Table 1. Correlation between the concentration of inflammation-related analytes and irisin in serum and gingival tissue during the progression of experimental periodontitis.

Analyte	Parameter	Serum irisin	Gingival irisin
IL-1β	Spearman's rho	0.441	0.274
	p-value	0.069	0.256
TNF-α	Spearman's rho	-0.236	0.042
	p-value	0.317	0.865
IL-4	Spearman's rho	-0.269	0.209
	p-value	0.281	0.376
IL-10	Spearman's rho	0.306	0.312
	p-value	0.216	0.180
EGF	Spearman's rho	-	0.690
	p-value	-	**0.001**
VEGF	Spearman's rho	0.022	0.612
	p-value	0.927	**0.008**

EGF not analyzed in serum samples. Spearman correlation test; p-values in bold indicate statistical significance.

Table 2. Correlation between the concentration of inflammation-related analytes and irisin in serum and gingival tissue during periodontal repair, including the 7-day ligature group.

Discussion

This study investigated irisin levels in serum and gingival tissue during experimental periodontitis in male rats, highlighting its dynamic response throughout the progression and repair phases, as well as its association with inflammatory cytokines and growth factors. Our results show that irisin levels in gingival tissue increase significantly during the early progression of ligature-induced periodontitis (7 days) and do not significantly decrease after ligature removal. Additionally, we found positive associations between irisin levels and EGF and VEGF during periodontal repair.

The use of periodontal ligature for 7 days was chosen to induce periodontitis, as this model significantly increased bone loss in the animals reported in this study when compared to control animals [21]. Moreover, this experimental model and time point is frequently reported in the literature, as it reproduces the formation of a local inflammatory environment, favoring the accumulation of bacterial biofilm around the teeth and inducing immune responses and bone loss compatible with periodontitis [23, 24].

Evaluation of serum irisin in the Control, Ligature 7d, Ligature 35d and Ligature 63d groups revealed no statistically significant differences, suggesting that, under the conditions of this study, serum irisin was not modulated by the metabolic changes associated with ligature-induced periodontitis. This finding is in accordance with a previous study that showed no significant alterations in the serum of periodontitis patients [22]. In fact, irisin appears to have predominantly localized effects on specific tissues, such as bone and gingiva, rather than producing measurable systemic changes [25].

The exact sources of irisin and its homeostatic role in periodontal tissue are still under investigation. The primary source of irisin is muscle and adipose tissue, but

several other tissues, including the tongue, have been shown to express it [26]. In rats, irisin was shown to be expressed in cells from the periodontal ligament, while only a weak immunofluorescent signal was observed in the alveolar bone [15]. In human cells, recent findings using 3D a culture of periodontal ligament cells demonstrated that recombinant irisin promotes extracellular matrix formation and enhances cellular differentiation and tissue remodeling capacity [27]. In our study, the high levels of irisin in gingival tissues observed 7 days after the induction of periodontitis indicate an initial response to inflammation. Additionally, during periodontitis progression, irisin levels in gingival tissue showed a significant negative correlation with TNF-α. Taken together, these findings suggest a potential compensatory response in irisin production to regulate pro-inflammatory cytokines, while promoting anti-inflammatory mechanisms to mitigate tissue damage and facilitate early repair [5]. These findings are in agreement with previous human studies which showed a significant increase in local (salivary) levels of irisin in periodontitis patients [18, 22].

The periodontal repair model has shown some conflicting data in the literature, with studies suggesting stable, increased, or decreased bone loss after ligature removal [20, 21, 28]. As stated above, this was a secondary analysis of a study evaluating the radiographic, histological and inflammatory characteristics of periodontitis progression and repair in different timepoints, which are reported elsewhere [21]. Briefly, the rats analyzed in the present study showed a time-dependent increase in bone loss while ligature was kept, accompanied by increased percentage of inflammatory cells at all timepoints, while reducing in fibroblasts and extracellular matrix. Ligature removal resulted in no significant changes in bone loss at either timepoints (28 or 56 days), but significantly decreased the percentage of inflammatory cells and blood vessels, while increasing fibroblasts and extracellular

matrix at 56 days [21], similarly to what happens in humans after treating periodontitis. Now, irisin levels in gingival tissue showed a clear reduction during periodontal repair, but without statistically significant differences with Ligature 7d. These results contrast with the findings from studies that administered exogenous irisin for bone formation analysis [16, 29]. It is important to note that those studies used irisin injections, while our study assessed its endogenous levels. This highlights what we refer to as the 'irisin paradox': while exogenous administration seems to result in positive anti-inflammatory effects, its endogenous levels in periodontitis are suggested to be biomarkers of the disease. As we speculated above, this is probably due to a compensatory mechanism in irisin production aimed at modulating inflammation.

In our study, there was a significant correlation between irisin levels in gingival tissues and the growth factors EGF and VEGF during periodontal repair. These growth factors play essential roles in periodontitis repair, influencing epithelial regeneration, angiogenesis and tissue remodeling after damage caused by the inflammatory process [30–32]. EGF is involved in cell proliferation, migration and differentiation, and is essential for the regeneration of epithelial and connective tissues. In periodontitis, its activity is related to the stimulation of cell proliferation, accelerating the repair of periodontal tissues and modulating the inflammatory response, favoring an environment conducive to tissue regeneration [32]. VEGF, in turn, plays a critical role in angiogenesis, promoting the formation of new blood vessels essential for the adequate supply of oxygen and nutrients to the gingival tissues affected by the disease. The vascularization facilitated by VEGF also enhances the immune response, allowing a more efficient transport of defense cells for the control of inflammation and elimination of residual pathogens [33]. Exogenous administration of irisin has been shown to significantly increase VEGF expression in a bone fracture model in rats,

promoting angiogenesis during the bone healing process [34]. Furthermore, irisin stimulated cell migration and capillary tube formation in human umbilical vein endothelial cells (HUVECs), with increased expression of angiogenic genes, including VEGF [35]. Although those associations still need to be mechanistically explored, the body of evidence suggests a role for irisin in the context of angiogenesis and tissue regeneration.

To the best of our knowledge, this is the first study to investigate the longitudinal relationship between periodontitis progression and endogenous irisin levels. From a translational perspective, our findings are important not only to confirm irisin as a biomarker of periodontitis (as we longitudinally show that periodontitis precedes higher irisin levels), but also to pave the way to identifying its potential as therapeutic target. For instance, if the increased irisin levels are indeed counteracting the pro-inflammatory environment during periodontitis progression, its administration could potentially favor inflammatory resolution. On the other hand, some limitations must be acknowledged, such as the exclusive use of male rats, which potentially restricts the generalizability of the results, as males may have significantly lower irisin levels than females [36]. The sample size calculation was based on salivary irisin levels in humans due to lack of information in the gingival tissues of rats during periodontitis. However, high variability in gingival irisin was observed. Future studies should further explore the basic mechanisms of action of irisin in different oral and periodontal cell types, as well as establish therapeutic interventions, in order to better elucidate its potential mechanisms and clinical applications.

Conclusion

Irisin in gingival tissue increases early during periodontitis progression, and it does

not significantly decrease at the studied repair timepoints. Additionally, correlation with TNF-α and growth factors during periodontitis progression and repair, respectively, suggests that irisin may help counteract inflammation and promote resolution.

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3 CONSIDERAÇÕES FINAIS

As investigações neste projeto contemplam duas abordagens, com o objetivo de compreender o papel da irisina no contexto de doenças inflamatórias crônicas: uma revisão de escopo em seres humanos e um estudo experimental em modelo animal de periodontite.

A partir da revisão da literatura, foi possível observar que, embora os dados sobre os níveis circulantes de irisina em diferentes CCNTs ainda sejam inconsistentes, há indícios de que sua expressão esteja alterada em condições como doenças cardiovasculares, respiratórias, diabetes tipo 2 e periodontite, refletindo o potencial dessa miocina como biomarcador metabólico e inflamatório. A análise dos estudos revelou uma tendência à redução dos níveis séricos de irisina em pacientes com CCNTs sistêmicas, ao passo que, na periodontite, observou-se aumento salivar.

Em paralelo, o estudo experimental conduzido em ratos permitiu avaliar a expressão endógena de irisina em tecido gengival e soro durante a progressão e reparo da periodontite induzida por ligadura. Os resultados demonstraram que a irisina aumenta significativamente no tecido gengival nos estágios iniciais da inflamação periodontal, mas não apresenta redução significativa nos períodos de reparo, sugerindo um papel ativo na inflamação, possivelmente associado à modulação de citocinas como TNF-α, EGF e VEGF. Por outro lado, os níveis séricos permaneceram estáveis ou diminuíram em fases tardias, reforçando a hipótese de que a resposta da irisina no contexto inflamatório periodontal pode ser local.

As duas abordagens se complementam ao integrar evidências de estudos clínicos transversais em humanos com dados experimentais obtidos de forma longitudinal em modelo animal. Enquanto os estudos em humanos permitem observar associações entre níveis de irisina e diferentes condições crônicas, eles são, em sua maioria, limitados a recortes pontuais e não capturam a dinâmica da irisina. O modelo animal, por outro lado, possibilitou acompanhar a variação da irisina ao longo da progressão e do reparo periodontal, fornecendo uma perspectiva temporal e controlada que contribui para a compreensão de seus possíveis mecanismos de ação.

Os achados reforçam o conceito de que a irisina pode ser biomarcador de inflamação ou até mesmo alvo terapêutico em doenças crônicas. Ainda assim, para validar esses resultados ainda dependemos da realização de estudos longitudinais em humanos, que permitam investigar com maior profundidade o comportamento da irisina ao longo do curso clínico das condições crônicas não transmissíveis.

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ANEXOS

Parecer: 7.1/2021

COMITÊ DE ÉTICA EM PESQUISA NO USO DE ANIMAIS DA UNIVERSIDADE POSITIVO – CEUA/UP

Curitiba – PR, 20 de maio de 2021

CERTIFICADO

Certificamos que o projeto **''Impacto do exercício físico sobre o reparo periodontal – Estudo *in vivo* sobre o momento da atividade no tratamento periodontal.'',** sob a responsabilidade de **JOÃO CÉSAR ZIELAK,** que envolve a utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto humanos), para fins de pesquisa científica (ou ensino) - encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle de Experimentação Animal (CONCEA), e foi **APROVADO** pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS DA UNIVERSIDADE POSITIVO – CEUA/UP.

- **Finalidade:( ) Ensino (X) Pesquisa Científica ( ) Pós-Graduação**
- **Espécie/linhagem/raça:** *Rattus norvegicus, albinus, Wistar*
- **Nº de animais:** 80
- **Origem**: Biotério da Universidade Positivo

Thais Andrade Costa Casagrande
Coordenadora - CEUA/UP

Comissão de Ética no Uso de Animais da Universidade Positivo - CEUA/UP

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