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Irisin: A small myocin with a wide potential

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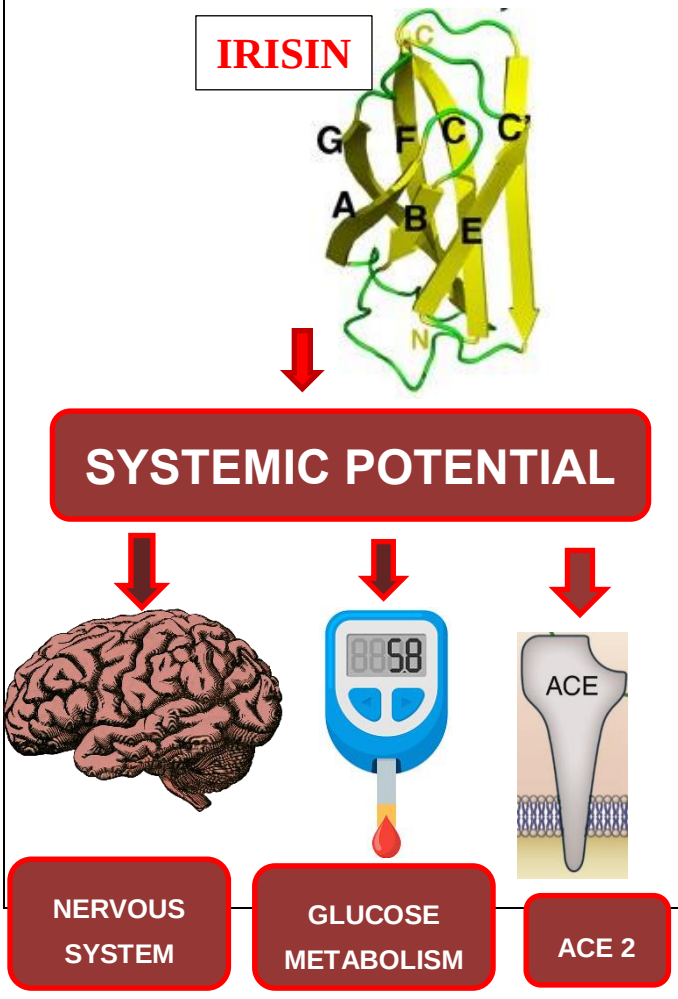
Graphical Abstract



Abstract.

During the spasmodic process, molecules are synthesized exercising various metabolic functions, and are called myocins. As an example of myocin, Irisina has become increasingly prominent in the scientific community. This peptide has a leading role in the metabolic activity of adipose tissue, being responsible for the process of browning the white adipose tissue to brown. However, several questions began to be raised about its activity in other organic systems, prompting several researchers. Considering this, this study aimed to identify in the literature the new possibilities for systemic action of Irisina. The bibliographic review of the scientific literature was used as a method for a critical analysis and appreciation of studies related to the theme. The steps related to the methodological process were: elaboration of the research question, adoption of the inclusion and exclusion

	criteria, reading and eligibility and construction of the results. The synthesis of Irisina has a direct relationship with the levels of PGC-1α. This enzyme is involved in the regulation of cellular homeostasis, mainly related to energy. Its overexpression occurs in skeletal muscle with increased physical activity. In addition to the effect already known under the darkening of adipose tissue, the literature exposes with greater quantity the studies that explore the effect of Irisina on the nervous system and in models of neurological diseases. The research extols the potential to increase concentrations of the brain-derived neurotrophic factor. Other studies indicate that the levels of this peptide increased, while blood glucose levels, as well as total cholesterol, decreased. Another study that reveals another promising potential is the ability of Irisin to modify the expression of regulatory genes for the ACE2 receptor. Therefore, it is concluded that the study of the effects of irisin contributes to the advancement in the knowledge of pathophysiology. In addition, it makes possible the discovery of modulating agents, suggesting that these peptides are possible therapeutic targets for the treatment of metabolic disorders and Alzheimer's disease.

Introduction *(optional)*

During the process of muscle contraction, peptides and glycopeptides are synthesized by myocytes, exercising several metabolic functions. These molecules called myocins act in the muscular tissue itself, in an autocrine way, but also, when entering the bloodstream, they exert endocrine regulatory effects in other metabolic pathways. These effects can occur through the activation of different receptors according to the autocrine or endocrine action [1].

Due to this potential to reach different systems and act in different receptors, the biological functions of myocins are not yet fully understood. In addition, there is no characterization of all more than 600 substances in this class [2]. Desire, which already has some clarification, Irisin has been standing out in research involving this theme. This peptide hormone is produced in greater quantity during physical exercise and property regarding the metabolism of adipose tissue, since it is responsible for the process of browning the white adipose tissue to brown [3-4].

This process occurs due to the promotion of oxygen consumption and thermogenesis by adipocytes, as well as an increase in the amount of cytochrome oxidase (Complex IV) due to the large

amount of mitochondria and vascularization offering the cell a dark color. This tissue has the key function of thermogenic action [5]. However, with the entry of this peptide into the bloodstream, new physiological functions have been identified, promoting a new glimpse into new therapeutic possibilities.

Thus, research seeking to unveil metabolic issues and even identify new therapeutic applications for physical activity are gaining greater scientific prominence. Therefore, this work aimed to identify in the literature as new possibilities for Irisin's systemic action. With this, it makes possible an appreciation of what is already known about the potential of this myocin and raises possibilities for new applications and investigations on physical activity and the use of this molecule for different therapies.

Materials and Methods *(optional)*

For the preparation of this study, a theoretical, qualitative and exploratory approach was adopted, using the method of narrative review of the literature for a broad glimpse of the academic scientific products for a general understanding of the adopted theme. In order to solidify the whole research, the PICo strategy was used as a question elaboration method. Thus, the population, interest and context were considered, resulting in: “what are the systemic effects of Irisin already exposed in the literature?”

The research took place in January 2021 in electronic databases with indexing of journals and scientific articles, such as the Virtual Health Library and Pubmed. The chosen search terms were “irisin”; "potential"; “Systemic activity” with the Boolean AND. As an inclusion criterion, there were studies in Portuguese, English and Spanish, and works published as scientific articles. Duplicate works were excluded and those that did not present the results in full. The most current and recent publications were preferred, however, there is no stipulation for a specific period of time.

The researchers then moved to the stage of choosing the research sample. The titles and abstracts were read in a preliminary way, then the studies were analyzed in full. Then, the main findings were selected and the state of the art of the topic in question was written, always referring to the research question so as not to deviate from the central objective of the investigation.

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Results and Discussion *(optional)*

To compose this study, nine works were published in full, published in scientific journals from 2013 to 2020. The main effects already identified for Irisin were on the Nervous System, however, the regulatory activities in the metabolism of lipids, carbohydrates and enzymatic expression can be highlighted, which will be detailed below.

The synthesis of Irisin has a direct relationship with the levels of the Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α). This enzyme is involved in the regulation of cellular homeostasis, mainly related to energy, since it is coupled to transcription factors or mitochondrial nuclear receptors, peroxisome activator, among others. This also highlights this enzyme as a protagonist in the activation of mitochondrial biogenesis. Its role in oxidative metabolism is specific to suit fasting and hepatic gluconeogenesis [6].

PGC-1α is overexpressed in skeletal muscle with increased physical activity. This is because many stimuli activate this molecule, one of which is the Adenosine Monophosphate-activated Protein

Kinase (AMPK) which increases in exercise due to the elevation of the AMP / ATP ratio and the high consumption of nutrients. PGC-1α binds to the peroxisome proliferating transcription γ (PPAR-γ) and to the nuclear estrogen-related α receptor (ERRα) [7].

This need for interaction with transcription factors occurs because PGC-1α cannot be linked directly to DNA. Thus, it stimulates the production of FNDC5, a type I membrane protein that undergoes proteolytic cleavage. The product of this reaction is Irisin, which is secreted from the muscle into the bloodstream, reaching the various systems [8].

In addition to the effect already known under the darkening of adipose tissue, the literature exposes with greater quantity the studies that explore the effect of Irisin on the nervous system and in models of neurological diseases. Alzheimer's disease was the highlight in the investigations, as it is a chronic, degenerative problem that, with the increasing aging of the world population, characterizes it as an ascending public health problem [9]. To date, there is no known and effective cure or form of prevention.

The research extols the potential to increase concentrations of the brain-derived neurotrophic factor (BDNF), which plays a role in the development of the nervous system, as well as related to neuronal plasticity [10]. The promotion of dentritogenesis has been identified, and therefore, a greater perspective of synapses, especially in dopaminergic neurons [11]. Another investigation revealed an inhibition of the amyloid beta protein, a protein identified as the central genesis of Alzheimer's, and attenuation of the effects of this disease [9].

An assessment of the levels of this myocin and other metabolic and physical factors after combined training in men with grade 1 obesity, revealed not only a considerable increase in the physical variables verified, such as muscle strength, lean mass, but also an inverse relationship between the levels of Irisin and glycemia. That is, with physical exercise, the levels of this peptide increased, while blood glucose levels, as well as total cholesterol, decreased. These findings may influence new possibilities in the therapy of patients with insulin resistance [12].

Another study that reveals another promising potential is the ability of Irisin to modify the expression of ACE2 receptor regulatory genes [13]. Considering the pandemic of COVID-19 and the role of ACE-2, being responsible for the recognition of the protein into which the virus enters cells, this discovery represents a better understanding of the good impact of physical exercises in non-sedentary patients affected by this infection. In addition to this discovery, a decrease in cell damage and the amount of intracellular lipids by this myocin has been demonstrated [14].

Conclusions *(optional)*

The practice of physical activity is a behavior that is of great importance to human health. The secretion of myocins by skeletal muscle during contraction that occurs during exercise promotes a series of changes in muscle and systemic metabolism, with Irisin being one of those peptides that is gaining prominence in scientific research due to its promising and active applications. Many studies indicate a great potential of this molecule in the nervous system, especially in the interference in chronic and degenerative pathological processes.

The promotion of dentritogenesis and neuroplasticity act as good possibilities in models of Alzheimer's disease. However, other effects, such as the decrease in blood glucose, cholesterol values, cell protection and modulation of regulatory genes, are also pointed out by researchers as good

therapeutic proposals, in in vivo and in vitro studies. Thus, in addition to the importance of this molecule for the darkening process of adipose tissue, an irisin represents a new therapeutic target for several health problems, including for some that still have no known cure or prevention to date.

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