# RESSALVA

Atendendo solicitação do(a) autor(a), o texto completo desta dissertação será disponibilizado somente a partir de 27/02/2027.

**UNIVERSIDADE ESTADUAL PAULISTA "JÚLIO DE MESQUITA FILHO"**
**FACULDADE DE MEDICINA**

**Thiago Luiz Novaga Palacio**

# Identificação *in situ* de produtos do metabolismo muscular de ratos em resposta a modelo de dieta ocidental suplementada com Gama-orizanol

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Patologia.

Orientadora: Profa. Dra. Camila Renata Corrêa Camacho

**Botucatu**
**2025**

Thiago Luiz Novaga Palacio

# Identificação *in situ* de produtos do metabolismo muscular de ratos em resposta a modelo de dieta ocidental suplementada com Gama-orizanol

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Patologia.

Orientadora: Profa. Dra. Camila Renata Corrêa Camacho

Botucatu
2025

P153i

Palacio, Thiago Luiz Novaga
Identificação in situ de produtos do metabolismo muscular de ratos em resposta a modelo de dieta ocidental suplementada com Gama-orizanol / Thiago Luiz Novaga Palacio. -- Botucatu, 2025
65 p. : il., tabs.

Dissertação (mestrado) - Universidade Estadual Paulista (UNESP), Faculdade de Medicina, Botucatu
Orientadora: Camila Renata Correa Camacho

1. Obesidade. 2. Miosite. 3. Estresse oxidativo. 4. Compostos bioativos. 5. Metabolômica. I. Título.

Sistema de geração automática de fichas catalográficas da Unesp. Dados fornecidos pelo autor(a).

UNIVERSIDADE ESTADUAL PAULISTA

**Câmpus de Botucatu**

**ATA DA DEFESA PÚBLICA DA DISSERTAÇÃO DE MESTRADO DE THIAGO LUIZ NOVAGA PALACIO, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.**

Aos 27 dias do mês de fevereiro do ano de 2025, às 8h, no(a) Sala de Informática (Bloco V) - Unipex - FM/Botucatu - Unesp, realizou-se a defesa de DISSERTAÇÃO DE MESTRADO de THIAGO LUIZ NOVAGA PALACIO, intitulada **Identificação in situ de produtos do metabolismo muscular de ratos em resposta a modelo de dieta ocidental suplementada com Gama-orizanol**. A Comissão Examinadora foi constituída pelos seguintes membros: Profa. Dra. CAMILA RENATA CORREA CAMACHO (Orientador(a) - Participação Presencial) do(a) Unidade de Pesquisa Experimental (UNIPEX) / FM/Botucatu - Unesp, Profa. Dra. MARINA POLITI OKOSHI (Participação Presencial) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. FRANCIS LOPES PACAGNELLI (Participação Presencial) do(a) Universidade do Oeste Paulista - Presidente Prudente/SP. Após a exposição pelo mestrando e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, o discente recebeu o conceito final: APROVADO. Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Camila Renata Correa Camacho

Profa. Dra. CAMILA RENATA CORREA CAMACHO

# *Impacto potencial desta pesquisa*

**Título da Dissertação: Identificação *in situ* de produtos do metabolismo muscular de ratos em resposta a modelo de dieta ocidental suplementada com Gama-orizanol**

Impacto científico esperado: Aplicação de ferramentas de medicina de precisão para a identificação dos mecanismos incitados pelo tratamento com o Gama-orizanol, nas disfunções musculares induzidas pela obesidade relacionada ao consumo de dieta ocidental, impactando de forma importante o desenvolvimento de terapias alvo com esse composto bioativo.

Impacto social: Esta pesquisa irá auxiliar no desenvolvimento de terapias alvo com compostos bioativos em indivíduos com obesidade induzida por dieta ocidental. Essa contribuição se insere no objetivo de desenvolvimento sustentável relacionado a saúde e bem-estar da vida Humana.

Impacto econômico: Por ser uma medida terapêutica de baixo custo e inserção facilitada na rotina alimentar, o Gama-orizanol apresenta potencial de implantação nas terapias dietéticas relacionadas à obesidade e suas consequentes disfunções musculares.

# *Potential impact of this research*

**Dissertation Title: In *situ* identification of muscular metabolism products of rats in response to a Western diet model supplemented with Gamma-oryzanol**

Expected scientific impact: Application of precision medicine methods for the identification of the mechanisms incited by treatment with the Gamma-oryzanol in obesity-induced muscular dysfunctions related to the consumption of Western diet, significantly impacting the development of targeted therapies with this bioactive compound.

Social impact: This research will enable the development of targeted therapies with bioactive compounds in obese populations with Western diet-induced obesity. This contribution is part of the sustainable development goal related to the health and well-being of human life.

Economic impact: As it is a low-cost therapeutic measure with facilitated insertion into the eating routine, Gamma-oryzanol has potential for implementation in dietary therapies related to obesity and its consequent muscle dysfunctions.

# *Dedicatória*

Este trabalho é dedicado aos meus pais, Silvia Helena e Vagner Baqueta, que sempre foram o meu principal estímulo. Agradeço a vocês, que me ensinaram os princípios da determinação, honestidade e amor pelo que fazemos, sempre em busca da excelência, por terem transformado a minha vida.

Aos meus amados avós, Ignês Novaga e Pedro Novaga, que sempre me apoiaram com amor e generosidade. Embora nem sempre entendam completamente o meu campo de trabalho, sempre me ofereceram suporte, acolhimento e palavras de estímulo. Esta vitória também é de vocês, que representam o meu refúgio seguro, o meu lar.

À minha orientadora, Camila Renata Corrêa, cuja orientação foi fundamental para a concretização deste projeto. A sua vivência, paciência, entusiasmo e empenho não só clarearam o trajeto, como também me motivaram a investigar minhas ideias com autonomia e segurança no campo desafiador da ciência. Agradeço por sempre acreditar no potencial deste trabalho e por me proporcionar a oportunidade de alçar voos mais altos, demonstrando que a ciência é ao mesmo tempo desafiadora e fascinante.

# *Agradecimentos*

Desejo manifestar minha mais sincera gratidão à minha orientadora, Camila Renata Corrêa, pelo acolhimento e suporte desde o início da minha trajetória na iniciação científica. A sua constante orientação, paciência e estímulo foram essenciais para o meu desenvolvimento acadêmico e profissional.

Também sou grato a todos no Laboratório RedOx/Inflamação pela colaboração e suporte em todas as fases deste projeto. Especialmente, agradeço à minha noiva, Juliana Siqueira, que sempre esteve ao meu lado, não apenas como companheira de vida, mas como uma dupla dinâmica, incentivando-me em cada obstáculo e comemorando comigo cada vitória, e ao Pingo, nosso cãozinho que me acompanhou durante toda a elaboração deste trabalho.

Agradeço aos amigos que fiz ao longo deste tempo, Erika Nakandakare-Maia, Marina Salomé e Luis Eduardo, meus inseparáveis companheiros de Western Blot. Cada experimento, diálogo e instante compartilhado com vocês tornaram esta jornada muito mais agradável e prazerosa.

Agradeço à equipe do Departamento de Ciências Farmacêuticas da Universidade de Milão por me acolher durante a execução de uma parte crucial deste estudo. Um agradecimento particular aos docentes Giancarlo Aldini e Alfonsina D'Amato, cuja orientação e experiência foram cruciais para o êxito deste projeto.

As professoras Francis Lopes Pacagnelli, Thaís Regiani Cataldi, Marina Politi Okoshi, além dos professores Igor Otávio Minatel e Fernando Moreto, que participaram das bancas de qualificação e defesa, são minhas sinceras gratificações. Agradeço por disponibilizarem seu tempo e sabedoria para aprimorar este trabalho com observações e contribuições valiosas.

A Unidade de Pesquisa Experimental (UNIPEX) pela infraestrutura e assistência técnica que viabilizaram a realização deste estudo.

Também expresso minha gratidão à Dra. Márcia Guimarães da Silva, coordenadora do Programa de Pós-Graduação em Patologia, juntamente com a secretária Vânia do Amaral Soler, responsáveis pela organização e apoio que mantêm a excelência deste programa.

Por fim, sou grato à FAPESP pelos financiamentos que permitiram a realização deste estudo (processos 2023/06451-6 e 2024/04007-4) e pelo seu papel crucial no progresso da ciência brasileira.

**RESUMO**

A obesidade é caracterizada pelo acúmulo excessivo de gordura corporal e representa um fardo econômico global. Estima-se que até 2044, 75% da população adulta brasileira será obesa. A obesogênese está relacionada ao consumo frequente de dietas ultraprocessadas com pobre aporte nutricional que promove distúrbios estruturais, funcionais, metabólicos e do estado RedOX/inflamatório na musculatura esquelética comprometendo sua função. As substâncias bioativas naturais presentes em alimentos *in natura* ou minimamente processados contribuem para a regulação de processos biológicos importantes em diferentes órgãos e tecidos e têm se destacado como uma forma segura de tratamento para doenças crônicas não transmissíveis (DCNT) e distúrbios musculares relacionados a dieta. O gama-orizanol (γOz) é um éster do ácido ferúlico considerado um dos antioxidantes naturais mais potentes. As propriedades antiobesidade, anti-inflamatória, antidiabética e hipolipêmica atribuídas a este fitosterol podem fornecer uma abordagem de alto custo-benefício no tratamento de distúrbios musculares relacionados à dieta. O objetivo deste trabalho foi verificar a capacidade terapêutica do γOz nas alterações do estado RedOX/inflamatório, do perfil lipídico e metabólico nos músculos com capacidade oxidativa (Sóleo) e glicolítica (Extensor longo dos dedos (EDL)) de ratos submetidos ao consumo de dieta ocidental. Ratos Wistar machos (n=24) foram distribuídos aleatoriamente em dois grupos para receberem, *ad libitum*, dieta controle (C, n=12) e dieta rica em açúcar e gordura acrescida de 25% de sacarose na água de beber (HSF, n=12) durante 20 semanas para indução da obesidade. Após esse período, os animais foram redistribuídos em 4 grupos, recebendo, *ad libitum*, dieta controle (C, n=6), dieta controle + γOz (C + γOz, n=6), dieta HSF (HSF, n=6) e dieta HSF + γOz (HSF + γOz, n=6) por 10 semanas. O γOz foi acrescido a 0,5% na ração. O consumo foi aferido diariamente para avaliação da ingestão calórica e o peso aferido semanalmente. Foram avaliados no fim do estudo o índice de adiposidade e níveis plasmáticos de glicose, triglicérides e insulina. A resistência à insulina foi calculada pelo índice HOMA-IR. No tecido muscular, foram aferidos os marcadores inflamatórios (TNF-α e IL-6), do estresse oxidativo (Malondialdeído, carbonilação de proteínas e enzimas antioxidantes) e a expressão relativa do transportador de glicose 4 (GLUT-4). Os metabolitos e a abundância relativa de lipídeos musculares foram identificados e quantificados através da Cromatografia líquida de ultra alta eficiência acoplada à espectrometria de massas. Os animais que consumiram a dieta HSF apresentaram, em relação ao grupo controle, maior consumo calórico total, peso corporal, níveis de triglicérides, glicemia, insulina, resistência insulínica, desbalanço do estado RedOX/inflamatório e assinaturas lipidômicas e metabolômicas distintas através do modelo de ánalise discriminante de mínimos quadrados parciais (PLS-DA) em ambos os músculos. O γOz reduziu os níveis de triglicérides, insulina, resistência insulínica e melhorou o desbalanço do estado RedOX/inflamatório em ambos os músculos dos animais obesos. A fosfatidilcolina, fosfatidiletanolamina e os diacilgliceróis foram as principais classes de lipídios alteradas nos músculos Sóleo e EDL, enquanto os metabólitos 1-Metiladenosina, Citidina, Citosina, Guanina, Guanosina e inosina foram os principais influenciados nesses grupos musculares, apresentando respostas distintas ao γOz e fornecendo novas perspectivas quanto a futuros alvos terapêuticos desse composto nos tecidos musculares.

**Palavras-chave:** Adiposidade, doença muscular, biomarcadores, metabolômica, lipidômica.

**ABSTRACT**

Obesity is characterized by the excessive accumulation of body fat and represents a global economic burden. It is estimated that by 2044, 75% of the Brazilian adult population will be obese. Obesogenesis is related to the frequent consumption of ultra-processed diets with poor nutritional intake, which promotes structural, functional, metabolic and RedOX/inflammatory state disorders in the skeletal muscles, compromising their function. The natural bioactive substances present *in-natura* or minimally processed foods contribute to the regulation of important biological processes in different organs and tissues as a safe form of treatment for chronic non-communicable diseases (NCDs) and diet-related muscle disorders. Gamma-oryzanol (γOz) is an ester of ferulic acid that is considered one of the most potent natural antioxidants. The anti-obesity, anti-inflammatory, antidiabetic, and hypolipidemic properties attributed to this phytosterol may provide a cost-effective approach in the treatment of diet-related muscle disorders. The aim of this study was to verify the therapeutic capacity of γOz in the RedOX/inflammatory state, lipid and metabolic profile alterations in the muscles with oxidative (Soleus) and glycolytic (extensor digitorum longus (EDL)) capacity of rats submitted to the consumption of Western diet. Male Wistar rats (n=24) were randomly distributed into two groups to receive, *ad libitum*, a control diet (C, n=12) and a high sugar-fat diet plus 25% sucrose in drinking water (HSF, n=12) for 20 weeks to induce obesity. After this period, the animals were redistributed into 4 groups, receiving, *ad libitum*, control diet (C, n=6), control diet + γOz (C + γOz, n=6), HSF diet (HSF, n=6) and HSF + γOz diet (HSF + γOz, n=6) for 10 weeks. γOz was added to 0.5% in the diet. Food consumption was measured daily to assess caloric intake, and weight was measured weekly. At the end of the study, the adiposity index and plasma levels of glucose, triglycerides and insulin were evaluated. Insulin resistance was calculated using the HOMA-IR index. In muscle tissue, inflammatory markers (TNF-α and IL-6), oxidative stress (malondialdehyde, protein carbonylation and antioxidant enzymes) and relative expression of glucose transporter 4 (GLUT-4) were measured. The metabolites and the relative abundance of muscle lipids were identified and quantified by ultra-high performance liquid chromatography coupled to mass spectrometry. The animals that consumed the HSF diet presented, in relation to the control group, higher total caloric intake, body weight, triglyceride levels, glycemia, insulin, insulin resistance, imbalance of the RedOX/inflammatory state and distinct lipidomic and metabolomic signatures through the discriminant partial least squares analysis (PLS-DA) model in both muscles. γOz reduced triglyceride levels, insulin, insulin resistance and improved the imbalance of the RedOX/inflammatory state in both muscles of obese animals. Phosphatidylcholine, phosphatidylethanolamine and diacylglycerols were the main classes of lipids altered in the Soleus and EDL muscles, while the metabolites 1-Methyladenosine, Cytidine, Cytosine, Guanine, Guanosine and inosine have been altered in these muscle groups, presenting distinct responses to γOz and providing new perspectives regarding future therapeutic targets of this compound in muscle tissues.

**Keywords:** Adiposity, muscular disease, biomarkers, metabolomics, lipidomics.

# LISTA DE ILUSTRAÇÕES

## Capítulo 1. Revisão de Literatura



## Capítulo 2. Artigo Científico 1



## Capítulo 3. Artigo Científico 2



# LISTA DE TABELAS

## Capítulo 1. Revisão de Literatura



## Capítulo 2. Artigo Científico 1

## Capítulo 3. Artigo Científico 2



# LISTA DE ABREVIATURAS

| | |
|---|---|
| ACC | *Acetyl-CoA Carboxylase* |
| ACN | *Acetronitrile* |
| AKT | *Protein Kinase* |
| AMPK | *AMP-Activated Protein Kinase* |
| ASG | *Acyl Sterol Glycosides* |
| ATP | *Adenosine triphosphate* |
| BAT | *Brown adipose tissue* |
| Bcl-3 | *B cell lymphoma 3* |
| CAR | *Acylcarnitine* |
| CAT | *Catalase* |
| COX-2 | *Cyclooxygenase-2* |
| CTRL | *Control* |
| DG | *Diacylglycerol* |
| DGAT1 | *Diacylglycerol acyltransferase 1* |
| EDL | *Extensor Digitorum Longus* |
| EGCG | *Epigallocatechin 3-gallate* |
| ELISA | *Enzyme-linked immunosorbent assay* |
| ER | *Endoplasmic reticulum* |
| ES | *Sarcoplasmic reticulum* |
| Ffar4 | *Free Fat Acid Receptor-4* |
| FOXO1 | *Forkhead Box O1* |
| GLUT-4 | *Glucose Transporter-4* |
| $H_20$ | *water* |
| HMDB | *Human metabolome database* |
| HOMA-IR | *Homeostatic model assessment for insulin resistance* |
| HSF | *High sugar-fat* |
| IGF1 | *Insulin-like growth factor-1* |
| IkB-α | *kappa-B inhibitor alpha* |
| IL | *Interleukin* |
| IL-1B | *Interleukin-1β* |
| i-PrOH | *Isopropanol* |
| IRAP | *Insulin-responsive amino peptidase* |
| IRS-1 | *Insulin Receptor Substrate-1* |
| LKB-1 | *Serine–threonine liver kinase B1* |

| | |
|---|---|
| LPC | *Lysophosphatidylcholine* |
| MAFbx | *Muscle Atrophy F-box gene* |
| MAPK | *Mitogen-activated protein kinase* |
| MCP-1 | *Monocyte chemoattractant protein-1* |
| MDA | *Malondialdehyde* |
| miR-206 | *Micro RNA-206* |
| MTBE | *Methyl tert-butyl ether* |
| Munc-18 | *Mammalian uncoordinated-18* |
| MuRF1 | *Muscle RING-finger protein-1* |
| MyHC | *Myosin heavy chain isoforms* |
| NAE | *N-acylethanolamine* |
| NAFLD | *Nonalcoholic fatty liver disease* |
| NCCDs | *Non-communicable chronic diseases* |
| NFk-B | *Nuclear Factor-Kappa-β* |
| NRF-1 | *Nuclear Respiratory Factor-1* |
| NRF-2 | *Nuclear factor erythroid 2–related factor 2* |
| ORY | *Gamma-oryzanol* |
| PAI-1 | *Serine protease inhibitor* |
| PC | *Phosphatidylcholine* |
| PE | *Phosphatidylethanolamine* |
| PG | *Phosphatidyl-glycerol* |
| PGC-1α | *Peroxisome Proliferator-Activated Receptor Alpha* |
| PI | *Phosphatidylinositol* |
| PI3K | *Phosphatidylinositol-3 kinase* |
| PKA | *Protein kinase A* |
| PLS-DA | *Partial Least Squares Discriminant Analysis* |
| PPAR-γ | *Peroxisome proliferator-activated receptor gamma* |
| PS | *Phosphatidylserine* |
| PUFA | *Polyunsaturated fatty acids* |
| QC | *Quality control* |
| RAB | *Ras-associated binding* |
| RAGE/AGE | *Receptor for advanced glycation end products* |
| ROS | *Reactive Oxygen Species* |
| SCD | *Stearoyl-CoA Desaturase* |
| SIRT | *Sirtuin* |
| SM | *Sphingomyelin* |
| SOD | *Superoxide dismutase* |
| TFAM | *Mitochondrial Transcription Factor* |
| TLR | *Toll-Like Receptor* |
| TNf-α | *Tumoral Necrosis Factor Alpha* |
| VIP | *Variable Importance Projection* |
| WAT | *White Adipose Tissue* |
| WHO | *World Health Organization* |
| γOz | *Gamma-oryzanol* |

## SUMÁRIO

# Capítulo 1 – Revisão de Literatura



# Capítulo 2 – Artigo Científico 1



# Capítulo 3 – Artigo Científico 2



# Conclusão e contribuição científica

# *Capítulo 1 – Revisão de Literatura*

# 1. Background

## *1.1. Obesity and skeletal muscle dietary-related disorders*

According to the World Health Organization (WHO), in 2022, 2.5 billion adults were overweight, and more than 890 million adults were diagnosed with obesity, reflecting more than twofold increase in the global prevalence of these diseases between 1990 and 2022. Additionally, it was estimated that 37 million children under the age of 5 and over 390 million children and adolescents aged 5 to 19 years were estimated to be overweight(1,2).

The excess of macronutrients and energy intake from the chronic consumption of western diets, rich in simple sugars and saturated fats, contributes to the development of obesity. This condition is associated with processes of hypertrophy, hyperplasia, hypoxia, and necrosis of the adipose tissue, leading to macrophage infiltration, and a pro-inflammatory scenario marked by elevated levels of Tumoral Necrosis Factor Alpha (TNF-α) and interleukin 6 (IL-6). These changes are accompanied by an increase in Reactive Oxygen Species (ROS) and an impairment on RedOx state balance in response to the White Adipose Tissue (WAT) endothelial and microvascular dysfunction(3). This chronic pro-inflammatory and pro-oxidant condition established in the WAT can become systemic, affecting several organs and tissues, including skeletal muscle (Figure 1)(3).

Voluntary muscle is an important predictor of longevity and functional capacity, responsible for vital functions as locomotion, respiration and the conversion of chemical energy into mechanical energy(4,5). Constituting 40-50% of the total body mass in healthy eutrophic individuals, it performs both postural, fast and powerful contractions respectively observed in oxidative Soleus and glycolytic Extensor digitorium longus (EDL) muscles(4,6).

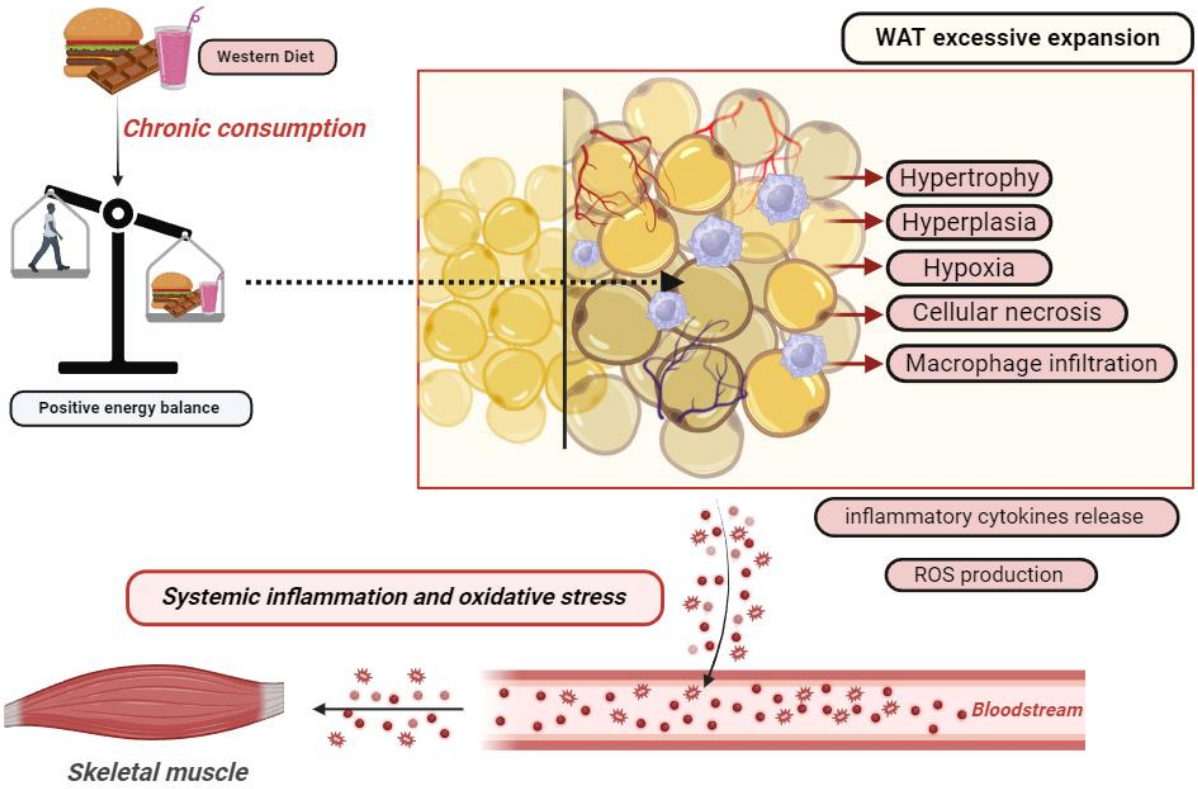


**Figure 1.** Obesity development. The chronic consumption of the western diet promotes the excessive expansion of the white adipose tissue characterized by the hypertrophy, hyperplasia, hypoxia, cell necrosis and macrophage infiltration process, leading to a systemic inflammatory and oxidative stress condition, affecting the skeletal muscle. Reactive Oxygen Species (ROS), White Adipose Tissue (WAT). Created with BioRender.com. Elaborated by the author.

Overweight and obesity conditions exert multiple effects on muscular tissue, including reduced insulin uptake, impaired phosphorylation of Insulin Receptor Substrate-1 (IRS-1) and reduced translocation of Glucose Transporter-4 (GLUT-4). These alterations contribute to hyperglycaemia, accompanied by ectopic fat deposition on the musculature, with intramuscular lipids stored as triacylglycerol within lipid droplets. This is associated with increased concentrations of lipotoxic intermediates, such as diacylglycerol and ceramides(7).

Insulin resistance and lipotoxicity reduce the primordial skeletal muscle functions including cellular respiration, adenosine triphosphate (ATP) production and β-oxidation of lipids. They also promote mitochondrial fragmentation, elevated ROS levels, and increased inflammatory cytokines IL-6, IL-8, IL-15, and TNF-α through the transcription of the pro-inflammatory factors Toll-Like Receptor 4 (TLR4) and Nuclear Factor-Kappa-B (NFk-B). Additionally, the reduction of AMP activated protein kinase alpha (AMPK-α), which regulates the myogenesis through microRNA-206 (miR-206) and its target cyclin D1, is associated with the depletion of the proliferation of muscle stem cells in the muscular regeneration processes (Figure 2)(7–16).

In addition, exposure to Western diets is also capable of altering several important markers that contribute to metabolic and energy disorder of skeletal muscles in obese individuals(17). Through the application of omics techniques, evidence suggests that the composition of lipids and amino acids in the skeletal muscles of healthy and obese individuals present clear differences regarding the anaplerosis capacity of the citric acid cycle and energy production, as well as disturbances in membrane phospholipids, capable of compromising the activity of endoplasmic and sarcoplasmic reticulum, Intensifying metabolic disorders(17,18).

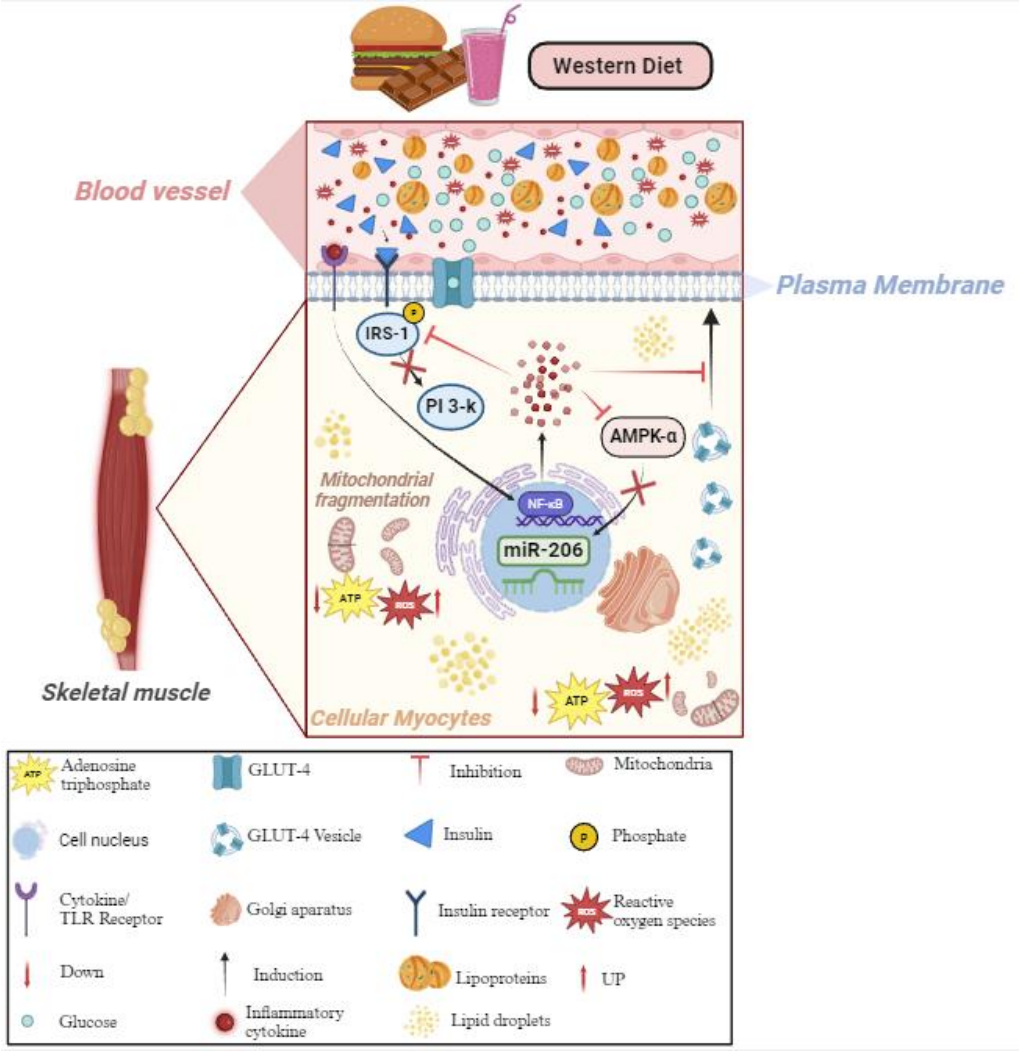


**Figure 2.** Skeletal muscle impairment. The RedOx/inflammatory state imbalance induces the insulin resistance and ectopic fat accumulation, affecting primordial functions such as mitochondrial energy production and β-oxidation, phosphorylation of the Insulin Receptor-1, translocation of the Glucose transporters type 4 and the myogenesis capacity. Insulin Receptor Substrate (IRS-1), phosphatidylinositol-3 kinase (PI3-K), AMP activated alpha (AMPK-α), Nuclear Factor-Kappa-β (NFk-B), Micro RNA-206 (miR-206). Created with BioRender.com. Elaborated by the author.

Western diets consumption, associated with excessive weight, leads to diminished muscle function, quality, and mass, increases the incidence risk of several metabolic comorbidities, and reduces the quality and life prospect of affected individuals(19). The investigation of therapeutic strategies involving natural foods has

## 4. Final Considerations and Conclusion

This review has highlighted the beneficial effects of natural compounds on dietary-related skeletal muscle dysfunction. The evidence reviewed demonstrates that various bioactive compounds derived from natural sources, such as polyphenols, flavonoids, and other plant-derived substances, can positively influence muscle health by mitigating inflammation, oxidative stress, and metabolic disturbances. The potential of γOz intervention as a preventive and therapeutic approach in obesity-induced dysfunctions in various organs and tissues enhancing overall metabolic balance is remarkable. On the other hand, science is just beginning to elucidate how γOz can revolutionize the treatment of dietary-related muscular disorders resulting from Western diets, thus pioneering investigations are needed in this mostly unexplored field.

## 5. References


1. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet [Internet]. 2020 Oct;396(10258):1223–49. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620307522
2. Okunogbe A, Nugent R, Spencer G, Ralston J, Wilding J. Economic impacts of overweight and obesity: current and future estimates for eight countries. BMJ Glob Heal [Internet]. 2021 Oct 4;6(10):e006351. Available from: https://gh.bmj.com/lookup/doi/10.1136/bmjgh-2021-006351
3. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci [Internet]. 2017;4:851–63. Available from: https://www.termedia.pl/doi/10.5114/aoms.2016.58928
4. Baskin KK, Winders BR, Olson EN. Muscle as a "Mediator" of Systemic Metabolism. Cell Metab [Internet]. 2015 Feb;21(2):237–48. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413114006093
5. Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, et al. PPARγ signaling and metabolism: the good, the bad and the future. Nat Med [Internet]. 2013 May 7;19(5):557–66. Available from: https://www.nature.com/articles/nm.3159
6. Mukund K, Subramaniam S. Skeletal muscle: A review of molecular structure and function, in health and disease. WIREs Syst Biol Med [Internet]. 2020 Jan 13;12(1). Available from: https://wires.onlinelibrary.wiley.com/doi/10.1002/wsbm.1462
7. Capozzi A, Saucier C, Bisbal C, Lambert K. Grape Polyphenols in the Treatment of Human Skeletal Muscle Damage Due to Inflammation and Oxidative Stress during Obesity and Aging: Early Outcomes and Promises. Molecules [Internet]. 2022 Oct 5;27(19):6594. Available from: https://www.mdpi.com/1420-3049/27/19/6594
8. Amouzou C, Breuker C, Fabre O, Bourret A, Lambert K, Birot O, et al. Skeletal Muscle Insulin Resistance and Absence of Inflammation Characterize Insulin-Resistant Grade I Obese Women. Moro C, editor. PLoS One [Internet]. 2016 Apr 25;11(4):e0154119. Available from: https://dx.plos.org/10.1371/journal.pone.0154119
9. Aguer C, Mercier J, Kitzmann M. Lipid content and response to insulin are not invariably linked in human muscle cells. Mol Cell Endocrinol [Internet]. 2010 Feb;315(1–2):225–32. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303720709005644
10. Aguer C, Foretz M, Lantier L, Hebrard S, Viollet B, Mercier J, et al. Increased FAT/CD36 Cycling and Lipid Accumulation in Myotubes Derived from Obese Type 2 Diabetic Patients. Lobaccaro JMA, editor. PLoS One [Internet]. 2011 Dec 16;6(12):e28981. Available from: https://dx.plos.org/10.1371/journal.pone.0028981
11. Mengeste AM, Rustan AC, Lund J. Skeletal muscle energy metabolism in obesity. Obesity [Internet]. 2021 Oct 31;29(10):1582–95. Available from: https://onlinelibrary.wiley.com/doi/10.1002/oby.23227
12. Borén J, Taskinen M -R., Olofsson S -O., Levin M. Ectopic lipid storage and insulin resistance: a harmful relationship. J Intern Med [Internet]. 2013 Jul 9;274(1):25–40. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.12071

13. Bell JA, Reed MA, Consitt LA, Martin OJ, Haynie KR, Hulver MW, et al. Lipid Partitioning, Incomplete Fatty Acid Oxidation, and Insulin Signal Transduction in Primary Human Muscle Cells: Effects of Severe Obesity, Fatty Acid Incubation, and Fatty Acid Translocase/CD36 Overexpression. J Clin Endocrinol Metab [Internet]. 2010 Jul 1;95(7):3400–10. Available from: https://academic.oup.com/jcem/article/95/7/3400/2596553
14. Løvsletten NG, Rustan AC, Laurens C, Thoresen GH, Moro C, Nikolić N. Primary defects in lipid handling and resistance to exercise in myotubes from obese donors with and without type 2 diabetes. Appl Physiol Nutr Metab [Internet]. 2020 Feb;45(2):169–79. Available from: http://www.nrcresearchpress.com/doi/10.1139/apnm-2019-0265
15. Chaurasia B, Summers SA. Ceramides in Metabolism: Key Lipotoxic Players. Annu Rev Physiol [Internet]. 2021 Feb 10;83(1):303–30. Available from: https://www.annualreviews.org/doi/10.1146/annurev-physiol-031620-093815
16. Holloway GP, Thrush AB, Heigenhauser GJF, Tandon NN, Dyck DJ, Bonen A, et al. Skeletal muscle mitochondrial FAT/CD36 content and palmitate oxidation are not decreased in obese women. Am J Physiol Metab [Internet]. 2007 Jun;292(6):E1782–9. Available from: https://www.physiology.org/doi/10.1152/ajpendo.00639.2006
17. Baker PR, Boyle KE, Koves TR, Ilkayeva OR, Muoio DM, Houmard JA, et al. Metabolomic analysis reveals altered skeletal muscle amino acid and fatty acid handling in obese humans. Obesity [Internet]. 2015 May;23(5):981–8. Available from: https://onlinelibrary.wiley.com/doi/10.1002/oby.21046
18. Grapentine S, Bakovic M. Significance of bilayer-forming phospholipids for skeletal muscle insulin sensitivity and mitochondrial function. J Biomed Res [Internet]. 2019 May 31;34(1):1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35081680
19. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Mamun A Al, Bonneux L. Obesity in Adulthood and Its Consequences for Life Expectancy: A Life-Table Analysis. Ann Intern Med [Internet]. 2003 Jan 7;138(1):24. Available from: http://annals.org/article.aspx?doi=10.7326/0003-4819-138-1-200301070-00008
20. Nor-Liyana J, Siroshini K, Nurul-Syahirah M, Chang W, Nurul-Husna S, Daryl J, et al. .Phytochemical analysis of Elateriospermum tapos and its inhibitory effects on alphaamylase, alpha-glucosidase and pancreatic lipase. J Trop For Sci [Internet]. 2019 May 17;31(2):240–8. Available from: https://info.frim.gov.my/infocenter_applications/jtfsonline/jtfs/v31n2/240-248.pdf
21. Martirosyan D, Miller E. Bioactive Compounds: The Key to Functional Foods. Bioact Compd Heal Dis [Internet]. 2018 Jul 31;1(3):36. Available from: https://ffhdj.com/index.php/BioactiveCompounds/article/view/539
22. Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. A natural solution for obesity: Bioactives for the prevention and treatment of weight gain. A review. Nutr Neurosci [Internet]. 2015 Feb 3;18(2):49–65. Available from: http://www.tandfonline.com/doi/full/10.1179/1476830513Y.0000000099
23. Möller NP, Scholz-Ahrens KE, Roos N, Schrezenmeir J. Bioactive peptides and proteins from foods: indication for health effects. Eur J Nutr [Internet]. 2008 Jun 27;47(4):171–82. Available from: http://link.springer.com/10.1007/s00394-008-0710-2
24. Gooda Sahib N, Saari N, Ismail A, Khatib A, Mahomoodally F, Abdul Hamid A. Plants' Metabolites as Potential Antiobesity Agents. Sci World J [Internet]. 2012;2012:1–8. Available from: http://www.hindawi.com/journals/tswj/2012/436039/
25. Korhonen H, Pihlanto A. Food-derived Bioactive Peptides - Opportunities for Designing Future Foods. Curr Pharm Des [Internet]. 2003 Jun 1;9(16):1297–308. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1381-6128&volume=9&issue=16&spage=1297
26. D'Orazio N, Gammone MA, Gemello E, De Girolamo M, Cusenza S, Riccioni G. Marine Bioactives: Pharmacological Properties and Potential Applications against Inflammatory Diseases. Mar Drugs [Internet]. 2012 Apr 5;10(12):812–33. Available from: http://www.mdpi.com/1660-3397/10/4/812
27. Phelan M, Kerins D. The potential role of milk-derived peptides in cardiovascular disease. Food Funct [Internet]. 2011;2(3–4):153. Available from: http://xlink.rsc.org/?DOI=c1fo10017c
28. Elias RJ, Kellerby SS, Decker EA. Antioxidant Activity of Proteins and Peptides. Crit Rev Food Sci Nutr [Internet]. 2008 May 8;48(5):430–41. Available from: http://www.tandfonline.com/doi/abs/10.1080/10408390701425615
29. Martirosyan DM, Singh J. A new definition of functional food by FFC: what makes a new definition unique? Funct Foods Heal Dis [Internet]. 2015 Jul 1;5(6):209. Available from:

https://ffhdj.com/index.php/ffhd/article/view/183
30. Bagherniya M, Mahdavi A, Shokri-Mashhadi N, Banach M, Von Haehling S, Johnston TP, et al. The beneficial therapeutic effects of plant-derived natural products for the treatment of sarcopenia. J Cachexia Sarcopenia Muscle [Internet]. 2022 Dec 12;13(6):2772–90. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcsm.13057
31. Rondanelli M, Miccono A, Peroni G, Guerriero F, Morazzoni P, Riva A, et al. A Systematic Review on the Effects of Botanicals on Skeletal Muscle Health in Order to Prevent Sarcopenia. Evidence-Based Complement Altern Med [Internet]. 2016;2016:1–23. Available from: http://www.hindawi.com/journals/ecam/2016/5970367/
32. Uto NS, Amitani H, Atobe Y, Sameshima Y, Sakaki M, Rokot N, et al. Herbal Medicine Ninjin'yoeito in the Treatment of Sarcopenia and Frailty. Front Nutr [Internet]. 2018 Dec 12;5. Available from: https://www.frontiersin.org/article/10.3389/fnut.2018.00126/full
33. Rodríguez-Pérez C, Segura-Carretero A, del Mar Contreras M. Phenolic compounds as natural and multifunctional anti-obesity agents: A review. Crit Rev Food Sci Nutr [Internet]. 2019 Apr 28;59(8):1212–29. Available from: https://www.tandfonline.com/doi/full/10.1080/10408398.2017.1399859
34. Nascimento R de P do, Moya AMTM, Machado AP da F, Geraldi MV, Diez-Echave P, Vezza T, et al. Review on the potential application of non-phenolic compounds from native Latin American food byproducts in inflammatory bowel diseases. Food Res Int [Internet]. 2021 Jan;139:109796. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0963996920308218
35. Brogi L, Marchese M, Cellerino A, Licitra R, Naef V, Mero S, et al. β-Glucans as Dietary Supplement to Improve Locomotion and Mitochondrial Respiration in a Model of Duchenne Muscular Dystrophy. Nutrients [Internet]. 2021 May 12;13(5):1619. Available from: https://www.mdpi.com/2072-6643/13/5/1619
36. Ibarra A, Cases J, Roller M, Chiralt-Boix A, Coussaert A, Ripoll C. Carnosic acid-rich rosemary ( Rosmarinus officinalis L.) leaf extract limits weight gain and improves cholesterol levels and glycaemia in mice on a high-fat diet. Br J Nutr [Internet]. 2011 Oct 28;106(8):1182–9. Available from: https://www.cambridge.org/core/product/identifier/S0007114511001620/type/journal_article
37. Wolfram S, Wang Y, Thielecke F. Anti-obesity effects of green tea: From bedside to bench. Mol Nutr Food Res [Internet]. 2006 Feb 8;50(2):176–87. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mnfr.200500102
38. Oishi K, Yamamoto S, Itoh N, Nakao R, Yasumoto Y, Tanaka K, et al. Wheat Alkylresorcinols Suppress High-Fat, High-Sucrose Diet-Induced Obesity and Glucose Intolerance by Increasing Insulin Sensitivity and Cholesterol Excretion in Male Mice. J Nutr [Internet]. 2015 Feb;145(2):199–206. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022316622086102
39. Palacio TLN, Siqueira JS, de Paula BH, Rego RMP, Vieira TA, Baron G, et al. Bergamot ( Citrus bergamia ) leaf extract improves metabolic, antioxidant and anti-inflammatory activity in skeletal muscles in a metabolic syndrome experimental model. Int J Food Sci Nutr [Internet]. 2023 Jan 2;74(1):64–71. Available from: https://www.tandfonline.com/doi/full/10.1080/09637486.2022.2154328
40. Gao P, Fang L, Pan Y, Jiang L. Effect of Grape Seed Proanthocyanidins on Fat Metabolism and Adipocytokines in Obese Rats. Metabolites [Internet]. 2023 Apr 17;13(4):568. Available from: https://www.mdpi.com/2218-1989/13/4/568
41. Szkudelska K, Szkudelski T. Resveratrol, obesity and diabetes. Eur J Pharmacol [Internet]. 2010 Jun;635(1–3):1–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299910002001
42. Rivera L, Morón R, Zarzuelo A, Galisteo M. Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. Biochem Pharmacol [Internet]. 2009 Mar;77(6):1053–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006295208008605
43. Bradford PG. Curcumin and obesity. BioFactors [Internet]. 2013 Jan 22;39(1):78–87. Available from: https://iubmb.onlinelibrary.wiley.com/doi/10.1002/biof.1074
44. Sharma R, Matsuzaka T, Kaushik MK, Sugasawa T, Ohno H, Wang Y, et al. Octacosanol and policosanol prevent high-fat diet-induced obesity and metabolic disorders by activating brown adipose tissue and improving liver metabolism. Sci Rep [Internet]. 2019 Mar 26;9(1):5169. Available from: https://www.nature.com/articles/s41598-019-41631-1
45. Mosikanon K, Arthan D, Kettawan A, Tungtrongchitr R, Prangthip P. Yeast β–Glucan Modulates Inflammation and Waist Circumference in Overweight and Obese Subjects. J Diet Suppl [Internet]. 2017 Mar 4;14(2):173–85. Available from: https://www.tandfonline.com/doi/full/10.1080/19390211.2016.1207005

46. Huang Y, Zhu X, Chen K, Lang H, Zhang Y, Hou P, et al. Resveratrol prevents sarcopenic obesity by reversing mitochondrial dysfunction and oxidative stress via the PKA/LKB1/AMPK pathway. Aging (Albany NY) [Internet]. 2019 Apr 15;11(8):2217–40. Available from: https://www.aging-us.com/lookup/doi/10.18632/aging.101910
47. Haramizu S, Asano S, Butler DC, Stanton DA, Hajira A, Mohamed JS, et al. Dietary resveratrol confers apoptotic resistance to oxidative stress in myoblasts. J Nutr Biochem [Internet]. 2017 Dec;50:103–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0955286316305861
48. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature [Internet]. 2006 Nov 1;444(7117):337–42. Available from: https://www.nature.com/articles/nature05354
49. Hiramoto S, Yahata N, Saitoh K, Yoshimura T, Wang Y, Taniyama S, et al. Dietary supplementation with alkylresorcinols prevents muscle atrophy through a shift of energy supply. J Nutr Biochem [Internet]. 2018 Nov;61:147–54. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0955286317311099
50. Liu J, Hao Y, Wang Z, Ni F, Wang Y, Gong L, et al. Identification, Quantification, and Anti-inflammatory Activity of 5- n -Alkylresorcinols from 21 Different Wheat Varieties. J Agric Food Chem [Internet]. 2018 Sep 5;66(35):9241–7. Available from: https://pubs.acs.org/doi/10.1021/acs.jafc.8b02911
51. Dianita R, Jantan I, Amran A, Jalil J. Protective Effects of Labisia pumila var. alata on Biochemical and Histopathological Alterations of Cardiac Muscle Cells in Isoproterenol-Induced Myocardial Infarction Rats. Molecules [Internet]. 2015 Mar 16;20(3):4746–63. Available from: http://www.mdpi.com/1420-3049/20/3/4746
52. Wang Z, Li Q, Hao Y, Wang Z, Yang H, Liu J, et al. Protective effect of 5-heptadecylresorcinol against obesity-associated skeletal muscle dysfunction by modulating mitochondrial biogenesis via the activation of SIRT3/PGC-1α signaling pathway. J Funct Foods [Internet]. 2022 Aug;95:105178. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1756464622002481
53. Li Q, Yang H, Song S, Liu J, Wang Z, Wang J. Bioactive Components in Whole Grains for the Regulation of Skeletal Muscle Function. Foods [Internet]. 2022 Sep 7;11(18):2752. Available from: https://www.mdpi.com/2304-8158/11/18/2752
54. Yu Y, Mendoza TM, Ribnicky DM, Poulev A, Noland RC, Mynatt RL, et al. An Extract of Russian Tarragon Prevents Obesity-Related Ectopic Lipid Accumulation. Mol Nutr Food Res [Internet]. 2018 Apr 3;62(8). Available from: https://onlinelibrary.wiley.com/doi/10.1002/mnfr.201700856
55. Vandanmagsar B, Haynie KR, Wicks SE, Bermudez EM, Mendoza TM, Ribnicky D, et al. Artemisia dracunculus L. extract ameliorates insulin sensitivity by attenuating inflammatory signalling in human skeletal muscle culture. Diabetes, Obes Metab [Internet]. 2014 Aug 10;16(8):728–38. Available from: https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.12274
56. Ono T, Takada S, Kinugawa S, Tsutsui H. Curcumin ameliorates skeletal muscle atrophy in type 1 diabetic mice by inhibiting protein ubiquitination. Exp Physiol [Internet]. 2015 Sep 14;100(9):1052–63. Available from: https://physoc.onlinelibrary.wiley.com/doi/10.1113/EP085049
57. Romo-Vaquero M, Larrosa M, Yáñez-Gascón MJ, Issaly N, Flanagan J, Roller M, et al. A rosemary extract enriched in carnosic acid improves circulating adipocytokines and modulates key metabolic sensors in lean Zucker rats: Critical and contrasting differences in the obese genotype. Mol Nutr Food Res [Internet]. 2014 May 23;58(5):942–53. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mnfr.201300524
58. Jayanthy G, Roshana Devi V, Ilango K, Subramanian SP. Rosmarinic Acid Mediates Mitochondrial Biogenesis in Insulin Resistant Skeletal Muscle Through Activation of AMPK. J Cell Biochem [Internet]. 2017 Jul 21;118(7):1839–48. Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcb.25869
59. Ismaeel A. Effects of Betaine Supplementation on Muscle Strength and Power: A Systematic Review. J Strength Cond Res [Internet]. 2017 Aug;31(8):2338–46. Available from: https://journals.lww.com/00124278-201708000-00035
60. Senesi P, Luzi L, Montesano A, Mazzocchi N, Terruzzi I. Betaine supplement enhances skeletal muscle differentiation in murine myoblasts via IGF-1 signaling activation. J Transl Med [Internet]. 2013 Dec 19;11(1):174. Available from: https://translational-medicine.biomedcentral.com/articles/10.1186/1479-5876-11-174
61. Apicella JM, Lee EC, Bailey BL, Saenz C, Anderson JM, Craig SAS, et al. Betaine supplementation enhances anabolic endocrine and Akt signaling in response to acute bouts of exercise. Eur J Appl Physiol [Internet]. 2013 Mar 14;113(3):793–802. Available from:

http://link.springer.com/10.1007/s00421-012-2492-8
62. Du J, Shen L, Zhang P, Tan Z, Cheng X, Luo J, et al. The regulation of skeletal muscle fiber-type composition by betaine is associated with NFATc1/MyoD. J Mol Med [Internet]. 2018 Jul 6;96(7):685–700. Available from: http://link.springer.com/10.1007/s00109-018-1657-2
63. Ma J, Meng X, Kang SY, Zhang J, Jung HW, Park YK. Regulatory effects of the fruit extract of Lycium chinense and its active compound, betaine, on muscle differentiation and mitochondrial biogenesis in C2C12 cells. Biomed Pharmacother [Internet]. 2019 Oct;118:109297. Available from: https://linkinghub.elsevier.com/retrieve/pii/S075333221932623X
64. Pei J, Prasad M, Mohamed Helal G, El-Sherbiny M, Abdelmonem Elsherbini DM, Rajagopal P, et al. Beta-Sitosterol Facilitates GLUT4 Vesicle Fusion on the Plasma Membrane via the Activation of Rab/IRAP/Munc 18 Signaling Pathways in Diabetic Gastrocnemius Muscle of Adult Male Rats. Rethinam S, editor. Bioinorg Chem Appl [Internet]. 2022 Aug 11;2022:1–18. Available from: https://www.hindawi.com/journals/bca/2022/7772305/
65. Sulaiman A, Sulaiman A, Sert M, Safwan Ali Khan M, A. Khan M. Functional and Therapeutic Potential of γ -Oryzanol. In: Functional Foods - Phytochemicals and Health Promoting Potential [Internet]. IntechOpen; 2021. Available from: https://www.intechopen.com/books/functional-foods-phytochemicals-and-health-promoting-potential/functional-and-therapeutic-potential-of-em-em-oryzanol
66. Francisqueti-Ferron FV, Garcia JL, Ferron AJT, Nakandakare- Maia ET, Gregolin CS, Silva JP das C, et al. Gamma-oryzanol as a potential modulator of oxidative stress and inflammation via PPAR-y in adipose tissue: a hypothetical therapeutic for cytokine storm in COVID-19? Mol Cell Endocrinol [Internet]. 2021 Jan;520:111095. Available from: https://linkinghub.elsevier.com/retrieve/pii/S030372072030397X
67. Tuncel NB, Yılmaz N. Gamma-oryzanol content, phenolic acid profiles and antioxidant activity of rice milling fractions. Eur Food Res Technol [Internet]. 2011 Oct 5;233(4):577–85. Available from: http://link.springer.com/10.1007/s00217-011-1551-4
68. P. Borade B, C. Badgujar K, Wagh K, More K, R. Pawar A. A Review on Nutritional Powerhouse, Exploring the Health Benefits of Rice Bran. Asian J Pharm Res [Internet]. 2024 May 28;169–74. Available from: https://asianjpr.com/AbstractView.aspx?PID=2024-14-2-13
69. de Souza CB, Lima GPP, Borges CV, Dias LCGD, Spoto MHF, Castro GR, et al. Development of a functional rice bran cookie rich in γ-oryzanol. J Food Meas Charact [Internet]. 2019 Jun 25;13(2):1070–7. Available from: http://link.springer.com/10.1007/s11694-018-00022-2
70. Wang L, Lin Q, Yang T, Liang Y, Nie Y, Luo Y, et al. Oryzanol Modifies High Fat Diet-Induced Obesity, Liver Gene Expression Profile, and Inflammation Response in Mice. J Agric Food Chem [Internet]. 2017 Sep 27;65(38):8374–85. Available from: https://pubs.acs.org/doi/10.1021/acs.jafc.7b03230
71. Sasiarini L, Sujuti H, Handayani D, Rudjianto A. Brown Rice: A Promising Therapeutic Strategy for Reducing Inflammatory Markers in the Adipose Tissue of Diet-Induced Obesity Rat Model. Curr Res Nutr Food Sci J [Internet]. 2024 Dec 15;12(3):1222–31. Available from: https://www.foodandnutritionjournal.org/volume12number3/brown-rice-a-promising-therapeutic-strategy-for-reducing-inflammatory-markers-in-the-adipose-tissue-of-diet-induced-obesity-rat-model/
72. Guo XX, Zeng Z, Qian YZ, Qiu J, Wang K, Wang Y, et al. Wheat Flour, Enriched with γ-Oryzanol, Phytosterol, and Ferulic Acid, Alleviates Lipid and Glucose Metabolism in High-Fat-Fructose-Fed Rats. Nutrients [Internet]. 2019 Jul 23;11(7):1697. Available from: https://www.mdpi.com/2072-6643/11/7/1697
73. Siqueira JS, Garcia JL, Ferron AJT, Moreto F, Sormani LE, Costa MR, et al. Proteomic study of gamma-oryzanol preventive effect on a diet-induced non-alcoholic fatty liver disease model. J Nutr Biochem [Internet]. 2024 May;127:109607. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0955286324000408
74. Francisqueti F, Minatel I, Ferron A, Bazan S, Silva V, Garcia J, et al. Effect of Gamma-Oryzanol as Therapeutic Agent to Prevent Cardiorenal Metabolic Syndrome in Animals Submitted to High Sugar-Fat Diet. Nutrients [Internet]. 2017 Nov 29;9(12):1299. Available from: http://www.mdpi.com/2072-6643/9/12/1299
75. Francisqueti-Ferron FV, Ferron AJT, Altomare A, Garcia JL, Moreto F, Ferreira ALA, et al. Gamma-oryzanol reduces renal inflammation and oxidative stress by modulating AGEs/RAGE axis in animals submitted to high sugar-fat diet. Brazilian J Nephrol [Internet]. 2021 Jun 18; Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-28002021005051301&tlng=en

*Potential* (IntechOpen, 2021). doi:10.5772/intechopen.97666.
16. Francisqueti, F. *et al.* Effect of Gamma-Oryzanol as Therapeutic Agent to Prevent Cardiorenal Metabolic Syndrome in Animals Submitted to High Sugar-Fat Diet. *Nutrients* **9**, 1299 (2017).
17. IBGE—Instituto Brasileiro de Geografia e Estatística Pesquisa de Orçamentos Familiares (POF) 2008–2009. Análise do Consumo Alimentar Pessoal No Brasil. https://www.ibge.gov.br/estatisticas/sociais/educacao/9050-pesquisa-de-orcamentos-familiares.html.
18. Son, M. J., Rico, C. W., Nam, S. H. & Kang, M. Y. Effect of Oryzanol and Ferulic Acid on the Glucose Metabolism of Mice Fed with a High-Fat Diet. *J. Food Sci.* **76**, (2011).
19. Luvizotto, R. D. A. M. *et al.* Lycopene supplementation modulates plasma concentrations and epididymal adipose tissue mRNA of leptin, resistin and IL-6 in diet-induced obese rats. *Br. J. Nutr.* **110**, 1803–9 (2013).
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, T. R. *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **28**, 412–419 (1985).
21. Uchiyama, M. & Mihara, M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. *Anal. Biochem.* **86**, 271–278 (1978).
22. Mesquita, C. S. *et al.* Simplified 2,4-dinitrophenylhydrazine spectrophotometric assay for quantification of carbonyls in oxidized proteins. *Anal. Biochem.* **458**, 69–71 (2014).
23. Marklund, S. L. Product of extracellular-superoxide dismutase catalysis. *FEBS Lett.* **184**, 237–239 (1985).
24. Aebi, H. [13] Catalase in Vitro. *Methods Enzymol.* **105**, 121–126 (1984).
25. Bradford, M. M. A Rapid and Sensitive Method for the Quantitation Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding. *Anal. Biochem.* **72**, 248–254 (1976).
26. Ellulu, M. S., Patimah, I., Khaza'ai, H., Rahmat, A. & Abed, Y. Obesity and inflammation: the linking mechanism and the complications. *Arch. Med. Sci.* **4**, 851–863 (2017).
27. Sheptulina, A. F., Antyukh, K. Y., Kiselev, A. R., Mitkovskaya, N. P. & Drapkina, O. M. Possible Mechanisms Linking Obesity, Steroidogenesis, and Skeletal Muscle Dysfunction. *Life* **13**, 1415 (2023).
28. Akhmedov, D. & Berdeaux, R. The effects of obesity on skeletal muscle regeneration. *Front. Physiol.* **4**, (2013).
29. Hildebrandt, X., Ibrahim, M. & Peltzer, N. Cell death and inflammation during obesity: "Know my methods, WAT(son)". *Cell Death Differ.* **30**, 279–292 (2023).
30. Sudhakaran, M. & Doseff, A. I. The Targeted Impact of Flavones on Obesity-Induced Inflammation and the Potential Synergistic Role in Cancer and the Gut Microbiota. *Molecules* **25**, 2477 (2020).
31. Wang, L. *et al.* Oryzanol Modifies High Fat Diet-Induced Obesity, Liver Gene Expression Profile, and Inflammation Response in Mice. *J. Agric. Food Chem.* **65**, 8374–8385 (2017).
32. Pinho, R. A. *et al.* High-fat diet induces skeletal muscle oxidative stress in a fiber type-dependent manner in rats. *Free Radic. Biol. Med.* **110**, 381–389 (2017).
33. Gugliandolo, A., Bramanti, P. & Mazzon, E. Activation of Nrf2 by Natural Bioactive Compounds: A Promising Approach for Stroke? *Int. J. Mol. Sci.* **21**, 4875 (2020).
34. Sinha, M. K. *et al.* Adipose Tissue Glucose Transporters in NIDDM: Decreased Levels of Muscle/Fat Isoform. *Diabetes* **40**, 472–477 (1991).
35. van Gerwen, J., Shun-Shion, A. S. & Fazakerley, D. J. Insulin signalling and GLUT4 trafficking in insulin resistance. *Biochem. Soc. Trans.* **51**, 1057–1069 (2023).
36. Wulandari, G. P. & Kristina, S. A. Direct and Indirect Cost of Obesity: A Systematic Review. *Glob. J. Health Sci.* **10**, 122 (2018).
37. Bagherniya, M. *et al.* The beneficial therapeutic effects of plant-derived natural products for the treatment of sarcopenia. *J. Cachexia. Sarcopenia Muscle* **13**, 2772–2790 (2022).

related to total energy homeostasis[58,59]. Kotzbeck et.al. (2018) explained that in obesity, the metabolic and secretory function of brown adipose tissue is declined and the tissue undergoes bleaching, contributing to the intensification of the disease, insulin resistance, hyperglycemia, leptin resistance, and the obesity typical inflammatory status[60]. These findings support the reduced levels of Inosine in the EDL muscle of the HSF group compared to the control group. The animals treated with ORY also demonstrated reduced levels of Inosine, which can be explained by the persistent obesity and constant adiposity index of the animals throughout the experiment.

## References


1. Løvsletten, N. G. *et al.* Treatment of human skeletal muscle cells with inhibitors of diacylglycerol acyltransferases 1 and 2 to explore isozyme-specific roles on lipid metabolism. *Sci. Rep.* **10**, 238 (2020).
2. Lee, S. *et al.* Skeletal muscle phosphatidylcholine and phosphatidylethanolamine respond to exercise and influence insulin sensitivity in men. *Sci. Rep.* **8**, 6531 (2018).
3. Mengeste, A. M., Rustan, A. C. & Lund, J. Skeletal muscle energy metabolism in obesity. *Obesity* **29**, 1582–1595 (2021).
4. Lee, J. H. & Jun, H.-S. Role of Myokines in Regulating Skeletal Muscle Mass and Function. *Front. Physiol.* **10**, (2019).
5. Sheptulina, A. F., Antyukh, K. Y., Kiselev, A. R., Mitkovskaya, N. P. & Drapkina, O. M. Possible Mechanisms Linking Obesity, Steroidogenesis, and Skeletal Muscle Dysfunction. *Life* **13**, 1415 (2023).
6. Akhmedov, D. & Berdeaux, R. The effects of obesity on skeletal muscle regeneration. *Front. Physiol.* **4**, (2013).
7. Prasad, M. *et al.* A Comprehensive Review on Therapeutic Perspectives of Phytosterols in Insulin Resistance: A Mechanistic Approach. *Molecules* **27**, 1595 (2022).
8. Trautwein, E. A. & Demonty, I. Phytosterols: natural compounds with established and emerging health benefits. *Oléagineux, Corps gras, Lipides* **14**, 259–266 (2007).
9. Vezza, T. *et al.* Phytosterols: Nutritional Health Players in the Management of Obesity and Its Related Disorders. *Antioxidants* **9**, 1266 (2020).
10. Rodríguez-Pérez, C., Segura-Carretero, A. & del Mar Contreras, M. Phenolic compounds as natural and multifunctional anti-obesity agents: A review. *Crit. Rev. Food Sci. Nutr.* **59**, 1212–1229 (2019).
11. Amouzou, C. *et al.* Skeletal Muscle Insulin Resistance and Absence of Inflammation Characterize Insulin-Resistant Grade I Obese Women. *PLoS One* **11**, e0154119 (2016).
12. Aguer, C., Mercier, J. & Kitzmann, M. Lipid content and response to insulin are not invariably linked in human muscle cells. *Mol. Cell. Endocrinol.* **315**, 225–232 (2010).
13. Lindholm, C. R. *et al.* A high-fat diet decreases AMPK activity in multiple tissues in the absence of hyperglycemia or systemic inflammation in rats. *J. Physiol. Biochem.* **69**, 165–175 (2013).
14. Xia, W. *et al.* Obesity causes mitochondrial fragmentation and dysfunction in white adipocytes due to RalA activation. *Nat. Metab.* **6**, 273–289 (2024).
15. Mattei, L. *et al.* Antioxidant and anti-inflammatory properties of gamma- oryzanol attenuates insulin resistance by increasing GLUT- 4 expression in skeletal muscle of obese animals. *Mol. Cell. Endocrinol.* **537**, 111423 (2021).
16. Manna, P. & Jain, S. K. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. *Metab. Syndr. Relat. Disord.* **13**, 423–444 (2015).
17. Borén, J., Taskinen, M. -R., Olofsson, S. -O. & Levin, M. Ectopic lipid storage and insulin resistance: a harmful relationship. *J. Intern. Med.* **274**, 25–40 (2013).
18. Bell, J. A. *et al.* Lipid Partitioning, Incomplete Fatty Acid Oxidation, and Insulin Signal

Transduction in Primary Human Muscle Cells: Effects of Severe Obesity, Fatty Acid Incubation, and Fatty Acid Translocase/CD36 Overexpression. *J. Clin. Endocrinol. Metab.* **95**, 3400–3410 (2010).
19. Cong, S. *et al.* Integrative proteomic and lipidomic analysis of Kaili Sour Soup-mediated attenuation of high-fat diet-induced nonalcoholic fatty liver disease in a rat model. *Nutr. Metab. (Lond).* **18**, 26 (2021).
20. Peeters, A. *et al.* Obesity in Adulthood and Its Consequences for Life Expectancy: A Life-Table Analysis. *Ann. Intern. Med.* **138**, 24 (2003).
21. Takagi, A. Lipid composition of sarcoplasmic reticulum of human skeletal muscle. *Biochim. Biophys. Acta* **248**, 12–20 (1971).
22. Vance, J. E. Phospholipid Synthesis and Transport in Mammalian Cells. *Traffic* **16**, 1–18 (2015).
23. Li, Y., Xu, S., Zhang, X., Yi, Z. & Cichello, S. Skeletal intramyocellular lipid metabolism and insulin resistance. *Biophys. Reports* **1**, 90–98 (2015).
24. Bergman, B. C. *et al.* Intramuscular Lipid Metabolism in the Insulin Resistance of Smoking. *Diabetes* **58**, 2220–2227 (2009).
25. Grapentine, S. & Bakovic, M. Significance of bilayer-forming phospholipids for skeletal muscle insulin sensitivity and mitochondrial function. *J. Biomed. Res.* **34**, 1–13 (2019).
26. Adamson, S. E. *et al.* Decreased sarcoplasmic reticulum phospholipids in human skeletal muscle are associated with metabolic syndrome. *J. Lipid Res.* **65**, 100519 (2024).
27. Palacio, T. L. N. *et al.* Bergamot ( Citrus bergamia ) leaf extract improves metabolic, antioxidant and anti-inflammatory activity in skeletal muscles in a metabolic syndrome experimental model. *Int. J. Food Sci. Nutr.* **74**, 64–71 (2023).
28. Siqueira, J. S. *et al.* Rice bran modulates renal disease risk factors in animals submitted to high sugar-fat diet. *Brazilian J. Nephrol.* **43**, 156–164 (2021).
29. dos Santos, M. P. *et al.* Higher insulin sensitivity in EDL muscle of rats fed a low-protein, high-carbohydrate diet inhibits the caspase-3 and ubiquitin-proteasome proteolytic systems but does not increase protein synthesis. *J. Nutr. Biochem.* **34**, 89–98 (2016).
30. Da Eira, D., Jani, S., Stefanovic, M. & Ceddia, R. B. Sucrose-Enriched and Carbohydrate-Free High-Fat Diets Distinctly Affect Substrate Metabolism in Oxidative and Glycolytic Muscles of Rats. *Nutrients* **16**, 286 (2024).
31. Topham, M. K. Diacylglycerol Kinases and Phosphatidic Acid Phosphatases. in *Encyclopedia of Biological Chemistry* 659–663 (Elsevier, 2013). doi:10.1016/B978-0-12-378630-2.00409-6.
32. Chen, G., Harwood, J. L., Lemieux, M. J., Stone, S. J. & Weselake, R. J. Acyl-CoA:diacylglycerol acyltransferase: Properties, physiological roles, metabolic engineering and intentional control. *Prog. Lipid Res.* **88**, 101181 (2022).
33. Bates, P. D. & Browse, J. The significance of different diacylgycerol synthesis pathways on plant oil composition and bioengineering. *Front. Plant Sci.* **3**, 147 (2012).
34. Tamilarasan, K. P. *et al.* Skeletal muscle damage and impaired regeneration due to LPL-mediated lipotoxicity. *Cell Death Dis.* **3**, e354–e354 (2012).
35. Ahmadian, M. *et al.* PPARγ signaling and metabolism: the good, the bad and the future. *Nat. Med.* **19**, 557–566 (2013).
36. Mukund, K. & Subramaniam, S. Skeletal muscle: A review of molecular structure and function, in health and disease. *WIREs Syst. Biol. Med.* **12**, (2020).
37. Oishi, K. *et al.* Wheat Alkylresorcinols Suppress High-Fat, High-Sucrose Diet-Induced Obesity and Glucose Intolerance by Increasing Insulin Sensitivity and Cholesterol Excretion in Male Mice. *J. Nutr.* **145**, 199–206 (2015).
38. Montell, E. *et al.* DAG accumulation from saturated fatty acids desensitizes insulin stimulation of glucose uptake in muscle cells. *Am. J. Physiol. Metab.* **280**, E229–E237 (2001).
39. Eichmann, T. O. & Lass, A. DAG tales: the multiple faces of diacylglycerol--stereochemistry, metabolism, and signaling. *Cell. Mol. Life Sci.* **72**, 3931–52 (2015).

40. Levenson, A. S. Nutrients and phytonutrients as promising epigenetic nutraceuticals. in *Medical Epigenetics* 741–816 (Elsevier, 2021). doi:10.1016/B978-0-12-823928-5.00022-0.
41. Lair, B., Laurens, C., Van Den Bosch, B. & Moro, C. Novel Insights and Mechanisms of Lipotoxicity-Driven Insulin Resistance. *Int. J. Mol. Sci.* **21**, (2020).
42. Sharma, A. K. *et al.* Basal re-esterification finetunes mitochondrial fatty acid utilization. *Mol. Metab.* **71**, 101701 (2023).
43. Patriarca, E. J. *et al.* The Multifaceted Roles of Proline in Cell Behavior. *Front. Cell Dev. Biol.* **9**, (2021).
44. Catalán, V., Frühbeck, G. & Gómez-Ambrosi, J. Inflammatory and Oxidative Stress Markers in Skeletal Muscle of Obese Subjects. in *Obesity* 163–189 (Elsevier, 2018). doi:10.1016/B978-0-12-812504-5.00008-8.
45. Blanco, A. & Blanco, G. Amino Acid Metabolism. in *Medical Biochemistry* 367–399 (Elsevier, 2017). doi:10.1016/B978-0-12-803550-4.00016-1.
46. Schrauwen, P. & Hesselink, M. K. C. Reduced tricarboxylic acid cycle flux in type 2 diabetes mellitus? *Diabetologia* **51**, 1694–1697 (2008).
47. Krawczyk, H. The stilbene derivatives, nucleosides, and nucleosides modified by stilbene derivatives. *Bioorg. Chem.* **90**, 103073 (2019).
48. Bohnsack, K. E., Kleiber, N., Lemus-Diaz, N. & Bohnsack, M. T. Roles and dynamics of 3-methylcytidine in cellular RNAs. *Trends Biochem. Sci.* **47**, 596–608 (2022).
49. Cadet, J. Oxidative damage to DNA: formation, measurement and biochemical features. *Mutat. Res. Mol. Mech. Mutagen.* **531**, 5–23 (2003).
50. Bettio, L. E. B., Gil-Mohapel, J. & Rodrigues, A. L. S. Guanosine and its role in neuropathologies. *Purinergic Signal.* **12**, 411–26 (2016).
51. Kim, I. S. & Jo, E.-K. Inosine: A bioactive metabolite with multimodal actions in human diseases. *Front. Pharmacol.* **13**, (2022).
52. LW, J. & ME, T. NUCLEOSIDES, NUCLEOTIDES, DNA, AND RNA. *Access Med.* (2018).
53. Sasaki, A. T. Dynamic Role of the GTP Energy Metabolism in Cancers. *Keio J. Med.* **65**, 21 (2016).
54. Niu, K., Bai, P., Zhang, J., Feng, X. & Qiu, F. Cytidine Alleviates Dyslipidemia and Modulates the Gut Microbiota Composition in ob/ob Mice. *Nutrients* **15**, (2023).
55. Xiong, W. *et al.* N1-methyladenosine formation, gene regulation, biological functions, and clinical relevance. *Mol. Ther.* **31**, 308–330 (2023).
56. Li, Y. *et al.* The Change of Skeletal Muscle Caused by Inflammation in Obesity as the Key Path to Fibrosis: Thoughts on Mechanisms and Intervention Strategies. *Biomolecules* **15**, 20 (2024).
57. Jeyaraj, F. T. & Voruganti, V. S. Multifaceted role of inosine in complex diseases and human health. *Nutr. Rev.* **83**, e506–e507 (2024).
58. Willemsen, N., Kotschi, S. & Bartelt, A. Fire up the pyre: inosine thermogenic signaling for obesity therapy. *Signal Transduct. Target. Ther.* **7**, 375 (2022).
59. Pfeifer, A., Mikhael, M. & Niemann, B. Inosine: novel activator of brown adipose tissue and energy homeostasis. *Trends Cell Biol.* **34**, 72–82 (2024).
60. Kotzbeck, P. *et al.* Brown adipose tissue whitening leads to brown adipocyte death and adipose tissue inflammation. *J. Lipid Res.* **59**, 784–794 (2018).