**UNIVERSIDADE ESTADUAL DE MONTES CLAROS**

**Daniel Silva Moraes**

# Sirtuínas e inflamação: efeitos metabólicos de um novo hidroxibutenolideo e papel do resveratrol no cérebro e cognição

**Montes Claros – MG**

**2022**

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# Sirtuínas e inflamação: efeitos metabólicos de um novo hidroxibutenolideo e papel do resveratrol no cérebro e cognição

Exame de Doutorado, Tese apresentada ao Programa de Pós-graduação em Ciências em Saúde (PPGCS) da Universidade Estadual de Montes Claros (Unimontes), como parte das exigências para a obtenção do título de Doutor em Ciências da Saúde.

Área de Concentração: Mecanismos e aspectos clínicos das doenças.
Orientador: Prof. Dr. Sérgio Henrique Sousa Santos
Discente: Daniel Silva Moraes

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M828s

Moraes, Daniel Silva.

Sirtuínas e inflamação [manuscrito]: efeitos metabólicos de um novo hidroxibutenolideo e papel do resveratrol no cérebro e cognição / Daniel Silva Moraes. – Montes Claros (MG), 2022.

56 f. : il.

Inclui bibliografia.

Tese (Doutorado) - Universidade Estadual de Montes Claros - Unimontes, Programa de Pós-Graduação em Ciências da Saúde /PPGCS, 2022.

Orientador: Prof. Dr. Sérgio Henrique Sousa Santos.

1. Obesidade. 2. Tecido adiposo. 3. Síndrome metabólica. 4. Sirtuínas. 5. Lactonas. 6. Butenolídeos. 7. Resveratrol. 8. Cognição. I. Santos, Sérgio Henrique Sousa. II. Universidade Estadual de Montes Claros. III. Título. IV. Título: efeitos metabólicos de um novo hidroxibutenolideo e papel do resveratrol no cérebro e cognição.

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**GOVERNO DO ESTADO DE MINAS GERAIS**

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**Mestrado e Doutorado em Ciências da Saúde**

**Anexo n° Folha Aprovação - Tese do Daniel Silva Mares/UNIMONTES/PRPG/PPGCS/2022**

**PROCESSO Nº 2310.01.0010201/2022-21**

**FOLHA DE APROVAÇÃO**

**Data da Defesa**: 01/09/2022 - webconferência, via plataforma "Meet"

**NOME DO(A) DISCENTE**: Daniel Silva Moares

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( x ) Doutorado Acadêmico em Ciências Da Saúde

**TÍTULO DO TRABALHO DE CONCLUSÃO DE CURSO (TCC):"SIRTUÍNAS E INFLAMAÇÃO: EFEITOS METABÓLICOS DE UM NOVO HIDROXIBUTENOLIDEO E**

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**LINHA DE PESQUISA**: Etiopatogenia e Fisiopatologia das Doenças

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Documento assinado eletronicamente por **André Luiz Sena Guimarães, Professor(a)**, em 19/12/2022, às 13:46, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 47.222, de 26 de julho de 2017.

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Para meus pais que apostaram que daria certo e para Amanda e Luiz Davi que deram sentido a esse trabalho.

## AGRADECIMENTOS

Agradeço aos colegas do grupo e do laboratório de pesquisa, sempre presentes na rotina diária de bancada, biotério e estudos. Para sempre me lembrarei com carinho das conquistas que alcançamos juntos, as tentativas, erros e acertos de técnicas e experimentos, o manejo cuidadoso dos animais no biotério, os problemas sofridos e resolvidos. Parabéns a todos que fazem o máximo com o mínimo. Em especial: Jaciara, Rogério, Vitor, Emisael, Marcela, Sabrina, Amanda, Luiz Paulo, Raquel, Joyce, Sara e Marileide.

Agradeço aos meus familiares. Meus pais Ernandes e Dilma por sempre me apoiarem, incentivarem e acreditarem no caminho que escolhi. Sem a ajuda deles seria impossível chegar até aqui. Agradeço aos meus irmão e amigos pelo companheirismo, por estarem ao meu lado nos mementos fáceis e difíceis; tristes e felizes; de vitória e derrota.

Agradeço a minha esposa Amanda e ao meu filho Luiz Davi pelo amor e sentido que representam em minha vida. Sem eles todas as conquistas seriam vazias.

Agradeço a todos os mestres e professores que contribuíram para meu aprendizado escolar, acadêmico, profissional e de vida, todos de alguma forma somaram para que chegasse até aqui. Em especial ao Dr. João Marcus por me dar oportunidade, pelos seus conselhos, cobranças e ensinamentos. Aos professores e amigos Dr. André Luiz Sena, Dra. Carla Silvana, Dra. Luciana Colares e Dr. Alfredo sempre solícitos a ajudar e colaborar, com quem também aprendi muito observando e conversando. Ao meu orientador Dr. Sérgio Henrique pela paciência, confiança e perseverança, durante todo esse processo nem consigo mensurar a evolução que tive como pesquisador e ser humano, obrigado por cada palavra, principalmente as cobranças, foi uma honra trabalhar ao lado de um profissional de relevância e referência.

“Amar e mudar as coisas me interessa mais”[1]

[1] Alucinação - Belchior

## RESUMO

A obesidade é um dos principais problemas de saúde em todo o mundo. Sua incidência epidemiológica é crescente, assim como a mortalidade decorrente de doenças metabólicas e comorbidades como síndrome metabólica e diabetes melitus tipo 2. Sirtuínas são enzimas reguladoras de histona desacetilases de material genético, profundamente envolvidas em inúmeras tarefas fisiológicas, incluindo metabolismo, função cerebral e envelhecimento. O objetivo deste trabalho é a avaliação dos efeitos metabólicos da Hidroxibutenolídeo (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona) em modelo animal de indução de obesidade e a avaliação do papel do resveratrol na cognição, cérebro e sirtuínas. A Tese se divide em uma pesquisa experimental realizada com um modelo animal (camundongos Swis) de indução de obesidade e síndrome metabólica e uma revisão sistemática sobre sirtuínas e cérebro. Os animais foram divididos em SD; SD+FS; HF e HF+FS e a indução de obesidade durou 13 semanas. A droga foi administrada por gavagem na dose de 70 mg/kg/dia durante 30 dias, foram coletados os dados de peso corporal, consumo alimentar e testes glicêmicos. Após a eutanásia dos animais as dosagens bioquímicas foram aferidas; coleta e armazenamento dos tecidos; histologia; mensuração da área de adipócitos do tecido adiposo branco e RT-PCR para os genes SIRT1, SIRT3, SIRT5 e NFKβ. Foi realizada uma análise por One Way ANOVA e Teste T de Student, os resultados foram apresentados em valores absolutos e relativos, utilização de média e desvio padrão e apresentados em graficos e figuras. Os valores de peso corporal reduziram após o tratamento com a droga (ST+LS: -7.81 ±4.39, p = 0.0247 e HF+FS: -11.77 ±9.59, p = 0.0334). Em ambos os testes glicêmicos e na glicemia de jejum os valores para os grupos tratados foi menor ($p<0,05$). A adiposidade (ST+FS: 0.017 ±0.011; HF+FS: 0.062 ±0.017) e o volume de tecido adipose branco epididimal diminuiu nos grupos que receberam a droga, assim como a área dos adipócitos para o grupo HF+FS. A expressão de SIRT1 foi maior nos grupos que receberam a Hidroxibutenolídeo. A sirtuína mais estudada é a SIRT1, que desempenha um papel essencial na prevenção e evolução dos neurotranstornos. O resveratrol é um polifenol, que pertence a uma família de compostos identificados como estilbenos, predominantemente concentrado em uvas e vinho tinto. O tratamento com 3-cloro-4-(p-clorofenilsulfonilamino)-5-hidroxifuran-2(5H)-ona

promoveu diminuição do peso corporal e do volume de tecido adiposo branco; menor área de adipócitos; melhora do metabolismo da glicose e diminuição da triglicerinemia e super expressão de SIRT1. Assim como a nova hidroxibutenolídeo testada, o resveratrol é uma substância natural com vários efeitos benéficos já comprovados, dentre eles a ativação de sirtuínas que contribuem para a prevenção de problemas de cognição e doenças neurodegenerativas.

**Palavras-chave:** Obesidade; tecido adiposo, síndrome metabólica. Sirtuínas. lactonas. Butenolídeos. Resveratrol. Cognição.

## ABSTRACT

Obesity is one of the main health problems worldwide. Its epidemiological incidence is increasing, as is the mortality due to metabolic diseases and comorbidities such as metabolic syndrome and type 2 diabetes mellitus. Sirtuins are histone deacetylases regulatory enzymes of genetic material, deeply involved in numerous physiological tasks, including metabolism, brain function and aging. . The objective of this work is to evaluate the metabolic effects of Hydroxybutenolide (3-chloro-4-(p-chlorophenylsulfonylamino-5-hydroxyfuran-2(5H)-one) in an animal model of obesity induction and to evaluate the role of resveratrol in cognition, brain and sirtuins.The thesis is divided into an experimental research carried out with an animal model (Swis mice) of obesity and metabolic syndrome induction and a systematic review on sirtuins and brain.The animals were divided into SD, SD+FS; HF and HF+FS and obesity induction lasted 13 weeks. The drug was administered by gavage at a dose of 70 mg/kg/day for 30 days, data on body weight, food consumption and glycemic tests were collected. After euthanasia of the animals, the biochemical dosages were measured, tissue collection and storage, histology, measurement of the white adipose tissue adipocyte area and RT-PCR for the SIRT1, SIRT3, SIRT5 and NFKβ genes. T of Stu dent, the results were presented in absolute and relative values, using mean and standard deviation and presented in graphs and figures. Body weight values decreased after drug treatment (ST+LS: -7.81 ±4.39, p = 0.0247 and HF+FS: -11.77 ±9.59, p = 0.0334). In both glycemic tests and fasting glucose, the values for the treated groups were lower ($p<0.05$). Adipose (ST+FS: 0.017 ±0.011; HF+FS: 0.062 ±0.017) and epididymal white adipose tissue volume decreased in the groups that received the drug, as well as the adipocyte area for the HF+FS group. The expression of SIRT1 was higher in the groups that received hydroxybutenolide. The most studied sirtuin is SIRT1, which plays an essential role in the prevention and evolution of neurodisorders. Resveratrol is a polyphenol, which belongs to a family of compounds identified as stilbenes, predominantly concentrated in grapes and red wine. Treatment with 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one promoted a decrease in body weight and white adipose tissue volume; smaller area of adipocytes; improved glucose metabolism and decreased triglycerinemia and overexpression of SIRT1. Like the new hydroxybutenolide tested, resveratrol is a natural substance with several proven beneficial effects, including the activation of sirtuins that contribute to

the prevention of cognition problems and neurodegenerative diseases.

**Keywords:** Obesity; adipose tissue, metabolic syndrome. Sirtuins. lactones. Butenolides. Resveratrol. Cognition.

**SUMÁRIO**

## 1 INTRODUÇÃO

O termo “epidemia” foi direcionado pela primeira vez para obesidade no relatório da Organização Mundial da Saúde (OMS) de 1998 que aborda o problema em nível global. Como qualquer doença crônica o conceito de epidemia se comporta diferente aqui do que na sua descrição mais tradicional empregada para doenças transmissíveis. Uma epidemia de gripe, por exemplo têm um surto, um pico, uma diminuição e, eventualmente, uma estabilização. No caso da obesidade o aumento não foi repentino como em um surto, mas progressivo e sempre crescente [1, 2].

Durante quase toda a história da humanidade a escassez de alimentos era um dos principais problemas da raça humana, na pré-história os caçadores coletores conviviam com a realidade de que se encontrassem alimento deveriam comer o máximo possível para adquirir reservas, e até o século 20 eram raras as pessoas que conheciam a ideia de excesso de comida ou comer até se “empanturrar”. Após a segunda guerra mundial mudanças no estilo de vida, na produção de alimentos e no mercado de consumo fizeram com que hoje mais pessoas morram de problemas decorrentes do excesso de peso corporal do que de fome [3].

A transformação desta relação do homem com o alimento foi fator contribuinte para mudanças na saúde das populações. O excesso de peso e doenças metabólicas, somados ao envelhecimento e urbanização, bem como a perda de protagonismo das doenças transmissíveis para as doenças crônicas, proporcionaram a transição demográfica e epidemiológica que reconfiguraram o cenário da saúde pública no Brasil e no mundo [4, 5]. As taxas de sobrepeso e obesidade continuam em crescimento global implacável, sendo que 30% da população (mais de 2 bilhões de pessoas) se encontra neste estado. O Global Burden of Disease Group relatou em 2017 que “desde 1980, a prevalência da obesidade dobrou em mais de 70 países e aumentou continuamente na maioria dos outros países” [6].

Algumas discussões têm atribuído o sobrepeso à uma questão de hábito e estilo de vida e renegado o seu status de doença crônica, porém mesmo que o índice de massa corporal (IMC) não seja considerado um indicador tão confiável para classificação da obesidade, diminuir o seu potencial causador de dano como doença crônica é um erro. A obesidade costuma ser o ponto de partida para muitas comorbidades,

principalmente as que atingem o coração, como insuficiência cardíaca, arritmias, hipertensão arterial, dislipidemias e por fim o infarto agudo do miocárdio (6). No Brasil, em 2006 11,8% da população era obesa, treze anos depois, em 2019, essa proporção quase dobrou (20,3%)[7]. Outro fator de risco cardiovascular importante é a Síndrome Metabólica (SM), cuja prevalência na população brasileira chega a 38,4%, sendo muito maior em idosos (66,1%) e a circunferência da cintura é superior ao indicado pela OMS em 65,5% da amostra [8]

A Síndrome Metabólica tem a obesidade abdominal como um dos seus sinais, inclui se ainda a hipertensão arterial, dislipidemias e alterações no metabolismo da glicose. Em conjunto os componentes responsáveis pela SM causam desordens metabólicas complexas que se retroalimentam em uma representação clássica de um indivíduo com doenças crônicas não transmissíveis [9, 10]. A SM é um fator de risco para doenças cardiovasculares mesmo sem diabetes melitus tipo 2 (DM2) concomitante e inclui resistência à insulina, hiperinsulinemia, disglicemia, dislipidemia e hipertensão. Os distúrbios são, respectivamente, avaliados por meio de seis índices para o diagnóstico: circunferência da cintura, glicemia de jejum, triglicérides, lipoproteína de alta densidade (HDL), colesterol e pressão arterial [11].

Esses problemas têm uma grande relevância em saúde pública, basta ver pela abrangência epidemiológica e geográfica. Segundo a OMS, em 2016, mais de 1,9 bilhão de adultos, com 18 anos ou mais, estavam acima do peso, destes, mais de 650 milhões eram obesos. Em 2020, 39 milhões de crianças menores de 5 anos estavam acima do peso ou obesas. A maioria da população mundial vive em países onde o sobrepeso e a obesidade matam mais pessoas do que o baixo peso. Diante disto, não se pode ignorar o fato de a obesidade ser pivô de várias outras doenças crônicas, sendo ela totalmente evitável, seja por medidas de prevenção ou tratamento, merece atenção acadêmica e sanitária para mitigar seus efeitos e diminuir sua prevalência [12].

As dimensões epidemiológicas de uma doença mostram o quanto ela é relevante em seu impacto na saúde das pessoas. Para se começar a pensar em possíveis tratamentos clínicos é preciso ir para mecanismos biomoleculares. O sistema renina-angiotensina (SRA) influi severamente no tecido adiposo [13]. Os níveis de Angiotensina II (Ang II) e de sua enzima catalisadora, a enzima conversora de angiotensina (ECA), estão relacionados à obesidade e diabetes [14]. A Angiotensina

II por si só, já é um potente agente pró-inflamatório, pró-oxidante e pró-trombótico que afeta a sinalização intracelular da insulina [15]. O eixo produtor da Ang II é contrabalanceado pela enzima conversora de angiotensina II (ECAII) que converte Angiotensina 1-7 (Ang 1-7), que por sua vez ativa o receptor MAS melhorando o metabolismo da glicose e da gordura, diminuindo assim a gordura corporal [16]. Outras vias metabólicas de interesse são as ligadas às sirtuínas (SIRT 1-7), apontadas como responsáveis pelo balanço energético, regulação metabólica e inflamação [17].

As sirtuínas são desacetilases proteicas dependentes de nicotinamida adenina dinucleotídeo (NAD)+ e enzimas monoadenosina difosfato (mono-ADP) ribosiltransferase que regulam diversos processos biológicos, incluindo metabolismo energético, respostas ao estresse, regulação do DNA e longevidade [18]. A família das sirtuínas compreende 7 membros (SIRT1–SIRT7) que possuem domínios catalíticos e de ligação a NAD+ conservados. Os terminais N e C flanqueadores das diferentes sirtuínas são distintos um do outro, o que contribui para as diferenças entre as sirtuínas na localização subcelular, atividade enzimática e especificidade do substrato [19].

As sirtuínas ativam enzimas que desempenham importante papel em diversos processos celulares, dentre eles silenciamento de genes, metabolismo, resistência ao estresse e aumento do tempo de vida em resposta a restrição calórica [20, 21] Pesquisas têm apontado resultados interessantes como a alta expressão de SIRT1 no tecido adiposo branco de humanos obesos associado com um menor peso de gordura corporal e no tecido adiposo marrom a maior expressão de SIRT1 associada com menor porcentagem de gordura e maior consumo de oxigênio [22]. Alta expressão de SIRT1 e PGC1-α, induzida por ácido gálico, em modelo animal de obesidade causando um aumento da termogênese e melhora de distúrbios relacionados à obesidade [23] Interação de sirtuínas com ECA e ECAII proporcionando a melhora de parâmetros metabólicos de glicose e lipídios no tecido adiposo branco em modelo animal, induzida por resveratrol [24].

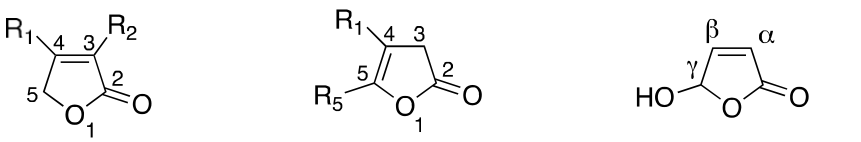
O resveratrol (3,5,4’-tri-hidroxiestilbeno) é um ativador natural das sirtuínas, composto polifenólico natural encontrado em diversos alimentos como uvas, amoras, amendoins e vinho tinto, além de outras plantas [25]. O tratamento oral com resveratrol parece modular o metabolismo em diferentes tecidos, no entanto, não há evidências sobre a

existência de receptores específicos, especialmente associados à sua absorção e farmacocinética [26]. A maioria dos estudos do resveratrol relata efeitos cardioprotetores, embora também existam evidências de outras terapias farmacológicas em várias doenças crônicas, como câncer, DM2 e doença de Alzheimer, além de suas propriedades antitrombóticas, antiosteoporóticas e antimicrobianas [25, 26]. Está bem estabelecido, como para outros polifenóis, que o resveratrol atua através de diferentes mecanismos. Este composto apresenta uma importante atividade antioxidante e interage com diferentes receptores, quinases e enzimas [27].

Assim como o resveratrol outras substâncias podem melhorar disfunções metabólicas e ajudar na redução de peso de pacientes obesos, essas soluções devem estar sempre em busca pela ciência. A Síntese Orgânica se preocupa com a eficiência da metodologia sintética e sua aplicação em uma síntese total, tanto se tratando de um produto natural ou uma nova substância com propriedades biológicas e físico-químicas desejadas [28]. Os produtos naturais bioativos são considerados fontes promissoras para o desenvolvimento de novos fármacos, pois as estruturas das moléculas de origem natural servem de modelo para a síntese de diversos compostos com o objetivo de avaliar suas atividades biológicas [29].

A utilização de lactonas butenólidas cíclicas de cinco membros com estruturas que podem ser representadas por anéis tipo I e II (Figura 1) e estão presentes em uma diversidade de produtos naturais isolados de plantas, algas e esponjas [30]. Quando se tem um hidroxigrupo na posição 5 do butenolida, tem-se - hidroxibutenolida ou 5-hidroxibutenolida [31].

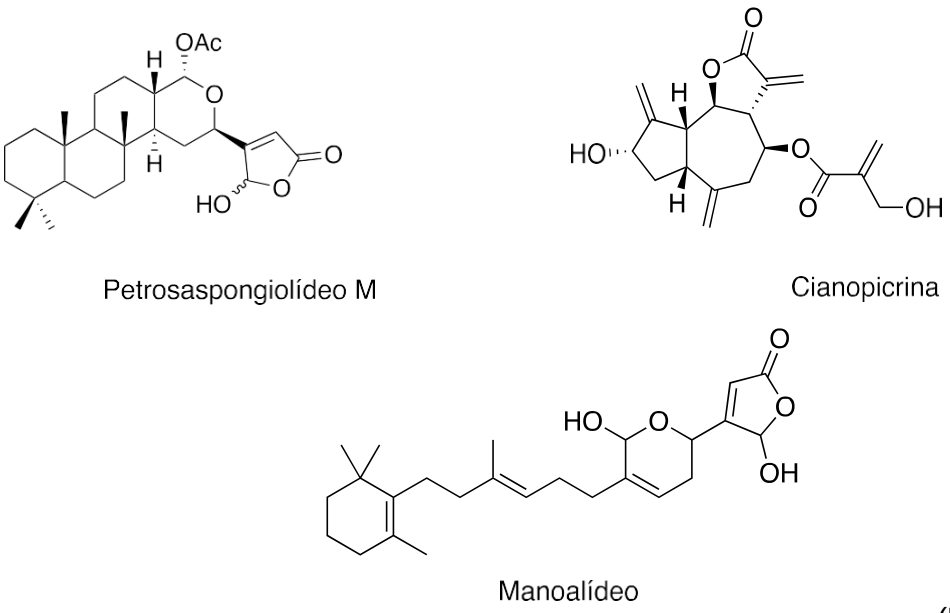
**Figura 1:** Estruturas gerais dos butenolídeos.




(Fonte: próprio autor)

Como exemplos desses butenolídeos de origem natural, pode-se destacar o petrosaspongiolida M que é um metabólito que pertence à família dos sesquiterpenos marinhos e tem em sua estrutura a unidade hidroxibutenolida, como pode ser visto na Figura 2. Este butenolida foi isolado da esponja marinha *Petrosaspongia nigra* e apresenta grande atividade anti-inflamatória [32] A manoalida é um composto isolado de uma esponja marinha e possui atividade anti-inflamatória [33]. A manoalida, cuja estrutura é mostrada na Figura 2, possui uma unidade 5-hidroxibutenolida com um substituto na posição 4 do anel furanona.

**Figura 2.** Estruturas de petrospongiolide M, cianopicrina e manoalide.




(Fonte: próprio autor)

A obesidade e seus problemas metabólicos decorrentes são responsáveis por altos custos e de serviços de saúde e vidas humanas [34]. Alternativas terapêuticas são de grande relevância, tanto para entender os processos biomoleculares envolvidos na patologia quanto para ampliar o arsenal de abordagens clínicas disponíveis. Seja o resveratrol,substâncias sintetizadas como a lactona butenolída ou ainda mudanças no estilo de vida, toda possível alternativa e campo de investigação é válida para apontar novos caminhos.

# 2 OBJETIVOS

## 2.1 Objetivo geral

O papel das sirtuínas na inflamação pela análise dos efeitos metabólicos de um Hidroxibutenolídeo (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona) em modelo animal de indução de obesidade e avaliação do efeito do resveratrol na cognição e cérebro.

## 2.2 Objetivos específicos

Descrever as alterações no perfil lipídico e glicêmico em modelo animal tratado com a substância (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona).

Analisar os genes associados com as mudanças metabólicas decorrentes do tratamento em modelo animal de indução de obesidade.

Avaliar o papel das vias de Sirtuínas nas amostras de tecido adiposo dos camundongos tratados com metabólicas (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona).

Descrever as relações entre Sirtuínas, cérebro e cognição encontradas na literatura.

## 3 PRODUTOS CIENTÍFICOS GERADOS

**3.1 Produto 1:** Oral treatment with a hydroxybutenolide (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona) improves metabolism reducing adiposity in obese mice

**Oral treatment with a hydroxybutenolide (3-cloro-4-(p-clorofenilsulfonilamino-5-hidroxifuran-2(5H)-ona) improves metabolism reducing adiposity in obese mice**

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**Abstract**

Obesity is one of the main health problems worldwide and its epidemiological incidence is increasing, as well as the mortality due to metabolic diseases and comorbidities associated with metabolic syndrome and type 2 diabetes mellitus. The aim of the present study was to evaluate the metabolic effects of a new hydroxybutonalide (3-chloro-4-(p-chlorophenylsulfonylamino-5-hydroxyfuran-2(5H)-one) in an obesity and metabolic syndrome animal model. The animals were divided into 4 groups: standard (SD); standard plus the new hydroxybutonalide (SD+FS); high-fat (HF) and high-fat plus the new hydroxybutonalide (HF+FS). The obesity was induced for 13 weeks. The drug was administered by gavage at a dose of 70 mg/kg/day for 30 days. The data on body weight, food consumption, and glycemic tests were obtained. Histology measured the white adipose tissue adipocyte area and we evaluated gene expression by RT-PCR for SIRT1, SIRT3, SIRT5, and NFKβ genes. The main results showed a decrease in body weight after the new drug treatment (ST+LS: -7.81 ±4.39, p = 0.0247 and HF+FS: -11.77 ±9.59, p = 0.0334). The glycemic tests and fasting glucose were

lower in the treated groups ($p<0.05$). Adipose tissue mass (ST+FS: 0.017 ±0.011; HF+FS: 0.062 ±0.017) and epididymal white adipose tissue volume, and triglycerides were reduced in the groups that received the hydroxybutonalide, as well as the adipocyte area for the HF+FS group. SIRT1 expression was higher in groups that received hydroxybutonalide. In conclusion, the main data showed that treatment with 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one improved metabolic profile and increased SIRT1 expression.

**Keywords:** Obesity; adipose tissue, metabolic syndrome. Sirtuins. lactones. Butenolides.

## Introduction

The increasing rates of obesity prevalence is a global health concern considering that excess weight gain can cause an augmented risk for several diseases, especially cardiovascular diseases, diabetes, and cancers [12]. The global food system seems to have a serious responsibility for the population's obesity since it rules a major part of the prices, quality, and marketing of food around the world. Epidemiologically, obesity affects mostly middle-aged adults from low-income countries, whereas in high-income countries it affects both sexes and all ages (2). On the other hand, increased obesity rates lead to a large health and financial burden in all sorts of countries [35]. Overweight and obesity are likely to reach levels of 89% and 85% in males and females respectively, by 2030. This will increase the obesity-related prevalence of coronary heart disease (CHD) by 97%, cancers by 61%, and type 2 diabetes by 21%. Consequently, increasing directly healthcare costs altogether [36].

The inflammation process is a biological response involved in the maintenance of body homeostasis and is currently receiving attention for its potential role in chronic diseases such as arthritis, diabetes, metabolic syndrome, and obesity [37]. Obesity is linked to a chronic low-grade inflammatory response characterized by the activation of pro-inflammatory signaling pathways and abnormal production of cytokines [38]. The inflammatory changes associated with obesity can be found in both immune and non-immune cells, including the abnormal production of adipokines, cytokines, and

chemokines that may further attract and activate immune cells [39]. Hence, a decreased inflammatory state may have beneficial effects on the pathophysiology of obesity and metabolic syndrome.

In this regard, sirtuins (SIRT) are a family of signaling proteins involved in metabolic regulation and may play an important role in reducing inflammation. The SIRT family contains seven enzymes in mammals (SIRT1–SIRT7) that share a stored core catalytic domain but differ in their cellular localization (mitochondrion, cytoplasm, or nucleus) and tissue distribution. Mitochondrial sirtuins (mainly SIRT3, 4, and 5) are well described in the literature to coordinate metabolic pathways involved in stress responses, aging, cardiometabolic diseases, hepatic metabolism, as well as other diseases [40]. This class of sirtuins seems to actively participate in the mechanisms by which mitochondrial functions are adapted to environmental requirements and metabolic demands. The sirtuins' role in signaling metabolic pathways is mainly due to their deacetylation capacity, which controls the activities of multiple proteins, consequently affecting enzymatic and protein cascades [41]. New drugs able to activate SIRT may be a promising therapeutic tool.

Butenolide lactones are chemical compounds present in a variety of natural products isolated from plants, algae, and sponges [30]. As examples of these butenolides of natural origin, we can highlight the petrosaspongiolide M, which is a metabolite belonging to the family of marine sesquiterpenes and has the hydroxybutenolide unit in its structure. This butenolide was isolated from the marine sponge Petrosaspongia nigra and has great anti-inflammatory activity [32]. Manoalide is a compound isolated from a marine sponge that also has anti-inflammatory activity [33].

Bioactive natural products are considered promising sources for the development of new drugs, as the structures of molecules of natural origin serve as a model for the synthesis of several compounds in order to evaluate their biological activities [29]. Thus, the objective of the present study was to evaluate the potential for improvement of obesity and metabolic alterations of a new butenolide 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one in an animal model of obesity and metabolic disturbances induction.

## Methodology

**Development of the substance 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one**

The synthetic route and dat characterization of the new compound have been described in the Supplementary Material, Figure 1.

**Animals**

For this experiment, 32 male Swiss mice at 8 weeks of age were used and allocated to the vivarium of the State University of Montes Claros. The mice were randomly assigned to four groups, two of which were fed a standard diet (SD) ad libitum while the other two with a 60% high-fat diet (HD) ad libitum for 13 weeks to induce obesity and metabolic syndrome. After this period, treatment started with the following groups, each with 8 animals: standard diet without Sulfonamide (DP); standard diet plus substance (DP+FS); high-fat diet without substance (DH) and high-fat diet plus substance (DH+FS). They were kept under controlled conditions of light (12-hour light and dark cycle) and temperature (21°C).

**Diet**

The standard diet (Purina – Labina®) is composed of 66% carbohydrates, 23% protein, and 11% fat, with a total of 3.95 Kcal per 1g. The high-fat diet is produced with 40.57% corn starch, 14% casein, 15.5% dextrinized starch, 10% sucrose, 10% soybean oil, 5% cellulose and fiber, 3.5 % AIN-93 M mineral mix, 1% AIN-93 vitamin mix, 0.18% L-cysteine, 0.25% choline bitartrate and 0.0008% tert-butylhydroquinone, a composition of 24 % of carbohydrates, 15% of proteins and 61% of fat, representing a total of 5.28 Kcal per 1g of diet. DH was prepared and packaged according to the determinations of the Official Association of Analytical Chemistry (17, 18) and all components were purchased by Rhoster® LTDA (São Paulo, SP, Brazil). Both diets were available ad libitum throughout the period of MS induction and treatment.

## Drug and administration

3-chloro-4-(p-chlorophenylsulfonylamino)-5- hydroxyfuran-2(5H)-one were diluted in filtered water and administered orally using the gavage technique, at a dose of 70 mg/kg/day, all days for 30 days. The animals in the non-medication control groups received water through a tube every day as well.

## Insulin sensitivity test (IST) and glucose tolerance test (TTG)

For TSI, exogenous insulin was administered at 0.75U/kg of animal weight in the intraperitoneal region and then checked for plasma glucose levels by blood samples from the tail of the mice at periods of 0, 15, 30, and 60 minutes after administration. In this test, the animals were evaluated after being fed. For TTG, the animals fasted overnight and D-glucose was administered intraperitoneally in the proportion of 2mg/g of animal weight while glucose levels were evaluated at 0, 15, 30, 60, and 120 minutes after administration. To measure blood glucose, a standard glucometer was used.

## Measurement of body weight, food intake, and tissue collection

The animals were weighed every three days throughout the period of MS induction and treatment and food intake was assessed daily. After the end of the treatment, the animals were euthanized by decapitation in a guillotine. Samples of blood, white adipose tissue (epididymal, subcutaneous, mesenteric, and retroperitoneal), brown adipose tissue, and liver were collected. Tissues were weighed and immediately frozen in liquid nitrogen and subsequently stored in a freezer at -80°C, a liver fragment was fixed in a 10% formaldehyde solution.

## Histological staining by hematoxylin and eosin

Liver tissue fixed in 10% formaldehyde was dehydrated through a graded alcohol and xylene series, then embedded in paraffin. 5µm sections were cut and prepared for hematoxylin and eosin staining. Images were obtained using optical microscopy, FSX100 Olympus® microscope (Life Science, USA), at 200X magnification. Five photos taken from random fields were obtained from each stained slide. The images

were analyzed using the public domain Java image processing program Image-J (Wayne Rasband, Research Services Branch, National Institute of Mental Health, Bethesda, Maryland, USA). The fat area of hepatocytes (steatosis) was determined by the area of fat droplets divided by the total area of the photo in $\mu m^2$.

**Reverse Transcription and Real Time PCR**

Total RNA from frozen liver samples was isolated using TRIzol reagent (Invitrogen Corp.®, San Diego, California, USA), treated with DNAse and M-MLV reverse transcriptase (Invitrogen Corp.®), and using random hexamer primers. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as endogenous and SIRT1, SIRT3, SIRT5, and NFKβ targets were amplified from cDNA from samples using specific primers and SYBR green reagent (Applied Biosystems®, USA) on a Plus One platform (Applied Biosystems®). The comparative CT method was applied to analyze the levels of gene expression between groups, using the 2-ΛΛCT equation.

**Statistical analysis**

All data were organized in Microsoft Excel (2010) software spreadsheets (Microsoft®, Redmond, Washington, USA) then transcribed into GraphPad Prism software (Version 5.0®, San Diego, California, USA) and analyzed with 95% accuracy. Confidence ($p<0.05$). The mean and standard deviation were applied to the values of the five animals in each group. One-Way ANOVA followed by Bonferroni post-test or T-Test for nonparametric samples followed by Mann-Whitney post-test evaluated the statistical significance of the means between the study groups. Two-Way ANOVA was applied for TSI and TTG followed by Bonferroni posttest and analysis of the area under the curve by One-Way ANOVA or T Test for non-parametric samples followed by Mann-Whitney post-test. To calculate adiposity, the weights of all WATs were added and the same was corrected by dividing by the weight of the animal.

## Ethical approval

All procedures and protocols used in the handling of animals followed the determinations of Resolution No. 879 of February 15, 2008, which provides the use of animals in research. This work was analyzed and approved as Process N° 126 by the ethics committee in animal research of the State University of Montes Claros.

## Results

The average body weight gain of the animals was gradual in all groups from the beginning of the experiment to the beginning of the treatment, in which a more accentuated weight loss was observed for mice from the FS groups. From week 14 to week 17, the ST+LS group presented considerable statistics (P = 0.0234). In the weight ratio, it is observed that the HF group was the only one with a gain after starting gavages, the association between ST and ST+LS was p = 0.0247 (ST: -1.1 ±4.16; ST+LS: -7.81 ±4.39) and HF with HF+FS was p = 0.0334 (HF: 3.52 ±12.15; HF+FS: -11.77 ±9.59). Before being euthanized, the animals in the ST group had an average of 44.83g (± 4.41) for body weight, those in the HF group 64.15g (±8.95) and HF+LS 50.02g (±9.36) coming closer to the standard group. The adiposity calculation showed an average of 0.033 (±0.007) for the ST group and 0.017 (±0.011) for the ST+LS group, among the animals that were fed a high-fat diet, the averages were 0.097 (±0.011), 0.106 (±0.024) and 0.062 (±0.017) respectively for HF and HF+FS. The weight of epididymal adipose tissue was lower in the ST+FS group, with a difference, p = 0.0054 for the ST group (ST: 0.556 ±0.199; ST+FS: 0.183 ±0.191).

Energy consumption was significantly lower in the HF+FS group (0.42 ±0.06) compared with the HF (0.51 ±0.13) (p = 0.0453). Regarding the glycemic profile, we can observe a significant difference between the HF and HF+FS groups (p = 0.0015) in the insulin sensitivity test and p = 0.0313 for the same groups in the glucose tolerance test. For fasting blood glucose, the FS groups were different from the ST and HF patterns (p = 0.0335 and p = 0.0096) (ST: 132.9 ±14.51; ST+FS: 110.6 ±8.18; HF: 128.8 ±15.59; HF+FS: 94.0 ±6.63).

The biochemical analyzes showed differences in the triglycerides and the total cholesterol dosages as shown in Figure 4. The measurement of the adipocyte area

was considerably lower in the LS-treated groups compared to the standard ST and HF groups (P = 0.0285 and P = 0.0125). In the RT-PCR analysis, the SIRT1 and SIRT3 genes showed relevant results for the treated groups (Figure 5).

## Discussion

The main findings of the present study showed that treatment with the new drug had improved several mice's metabolic aspects when compared to the control groups. The data showed a decrease in body weight and adiposity, as well as improved results in the IST and GTT (glycemic data), in addition to a decrease in the volume of adipocytes in the groups treated with butenolide. A higher Sirt1 gene expression was also observed in the FS groups.

The literature shows that some important isolated natural compounds, such as resveratrol and gallic acid, can decrease body weight as observed with the new drug tested in the present study. Recent data demonstrated that resveratrol administration with *Lactococcus lactis* subsp. promoted not only a decrease in body weight, but also lower levels of aminotransferase, total cholesterol, hepatic inflammatory markers, IL-6, and TNF-α expression [42]. Resveratrol replicates the effects of calorie restriction induced by activating SIRT1, a histone deacetylase [14,15]. SIRT1 was also considered the main target for the results found in the gallic acid treatment which increased the thermogenesis and decreased body weight and triglyceride levels (16). 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one reached similar results in the present study regarding body weight, serum triglyceride levels, and SIRT1.

Another important result was the improvement in the glycemic profile in the treated groups. This fact mirrors some already-known pharmacological use of a similar substance: a racemic dihydropyridine tetronamide known as BAY R3401 (219) with oral bioavailable hypoglycemic function [17]. This compound works as an allosteric inhibitor of the enzyme glycogen phosphorylase, which in turn is a catalyst in the glycogenolysis pathway, presenting therapeutic potential for type 2 diabetes treatment [46], sharing similarity with present research.

Obesity problems are, at least in part, due to the inflammatory state caused by the increase in the volume of fat in the adipocytes. [47–49]. The abnormal production of cytokines ends up activating more signaling pathways, which in turn, increase the inflammatory response and the growth of immune cells [50]. In a study that used zebrafish to induce a systemic inflammatory state with AlCl3 administration, the anti-inflammatory power of marine fungal metabolite butyrolactone I was observed. In this specific case, the neuroprotective effect of butyrolactone I was tested, which decreased peripheral levels of IL-1β and elevated TNF-α levels [51]. New butenolides isolated from the phytochemical investigation of the whole plant of *Tradescantia albiflora* were evaluated for their anti-inflammatory activity against LPS-stimulated nitric oxide production in RAW 264.7 cells, obtaining positive results [52].

A higher expression of SIRT1 has been also shown as an indicator of inflammatory response suppression, while the deletion of this gene causes the inverse effect on local inflammation [53, 54]. Sirtuins have been identified as important regulators of the immune system, with some studies showing that SIRT1 can repress inflammation in multiple tissues and macrophages (27). In the present research, the results point to a greater expression of SIRT1 in the groups that received 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one, which may modulate SIRT1 signaling pathway including the reduced obesity inflammatory effects.

## Conclusion

The main data o the present study showed that treatment with the new butenolide 3-chloro-4-(p-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5H)-one, was able to improve metabolic parameters, especially in the obese group, producing a decreased body weight and white adipose tissue volume and improvement in glucose metabolism. Finally, the new butenolide also increased the expression of the SIRT1 gene. Even with limitations regarding the elucidation of the specific new mechanism of action the literature supports the anti-inflammatory effect of similar compounds [13,15,16,23,24] opening the perspective of a promising new therapeutic drug.

## Figures

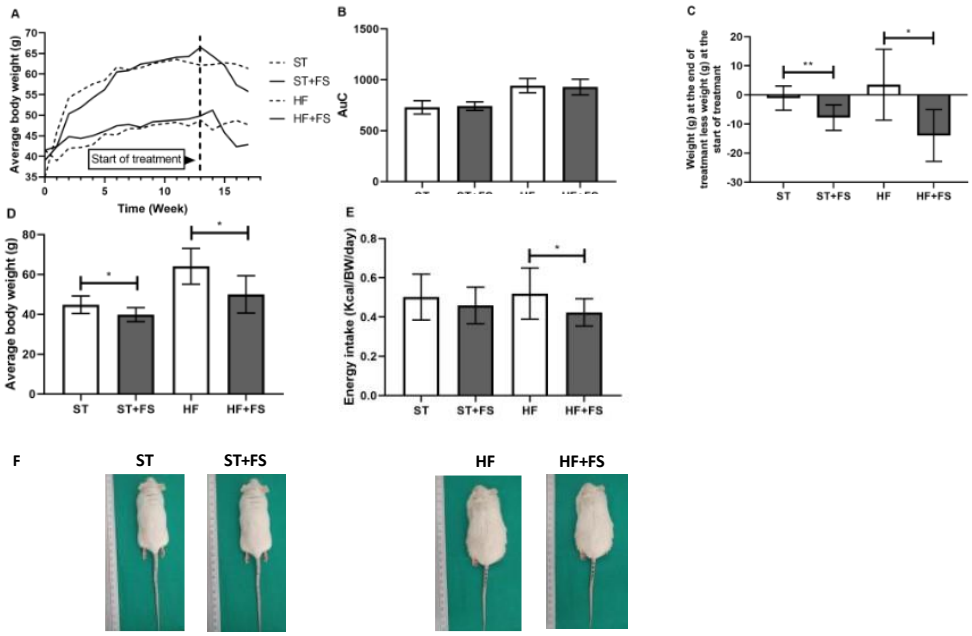


**Figure 1:** Body weight profile and energy consumption. A) Weight (g) during the experimental period; B) Analysis of area under the curve of graph A; C) Weight ratio, mean weight (g) at the end of treatment minus the mean weight before administration of the first dose of treatment drugs; D) Weight (g) before euthanasia; E) Total average of energy (Kcal/BW/day) consumption during the experiment; F) Photo of a representative animal from each group. *p<0,05; **p<0,01; ***p<0.001.

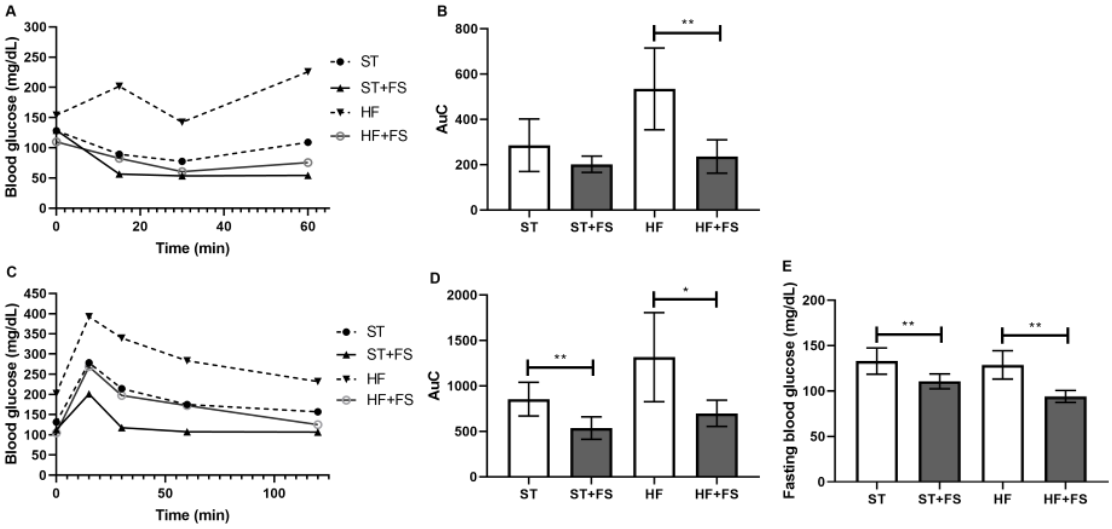


**Figure 2:** Glycemic profile. A) Glucose sensitivity test; B) Analysis of area under the curve of graph A; C) Glucose tolerance test; D) Analysis of area under the curve of graph C; D) Fasting blood glucose at the end of treatment. *p<0,05; **p<0,01; ***p<0.001.

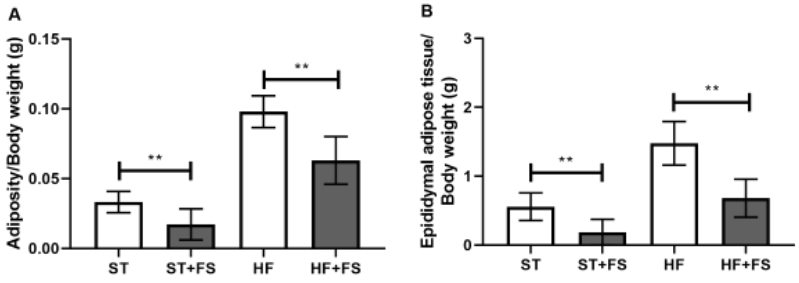


**Figure 3:** Biochemical profile A) Average adiposity by weight of collected adipose tissues (epididymal adipose tissue + subcutaneous adipose tissue + retroperitoneal adipose tissue + mesenteric adipose tissue + brown adipose tissue / BW); B) Mean epididymal adipose tissue weights / BW. *p<0,05; **p<0,01; ***p<0.001.

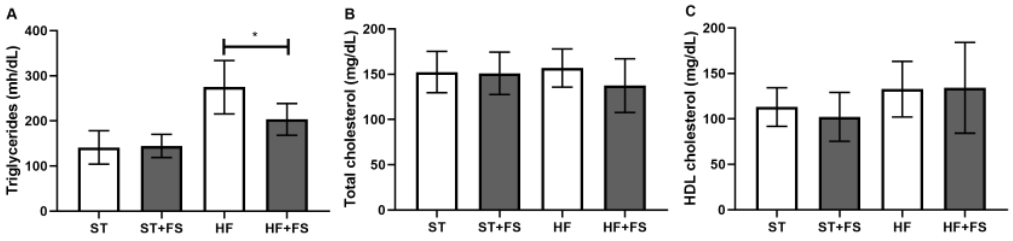


**Figure 4:** Biochemical tests. A) Triglycerides (mg/dL); B) total cholesterol (mg/dL); C) HDL cholesterol (mg/dL). *p<0,05; **p<0,01; ***p<0.001.

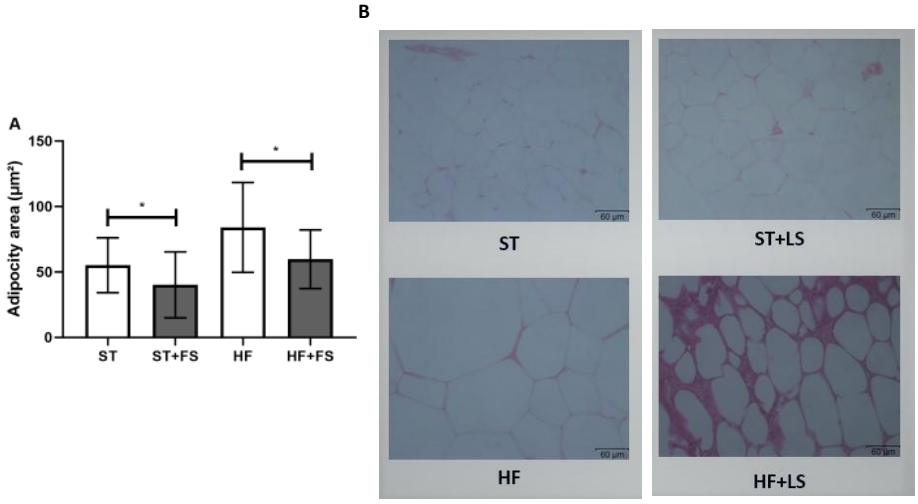


**Figure 5:** Histological analysis. A) Mean area of adipocytes (µm²) analyzed on histological slides; B) Representative photos of a histological slide of each group. *p<0,05; **p<0,01; ***p<0.001.

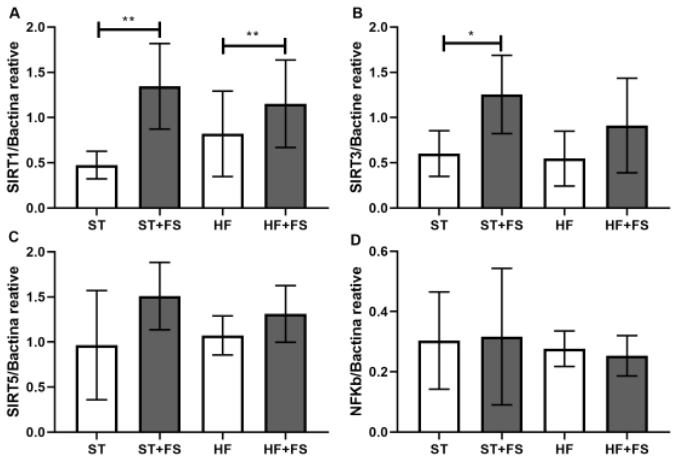


**Figure 6:** RT-PCR analysis. A) SIRT1 gene; B) SIRT3 gene; C) SIRT5 gene; D) NFKb gene. *p<0,05; **p<0,01; ***p<0.001.

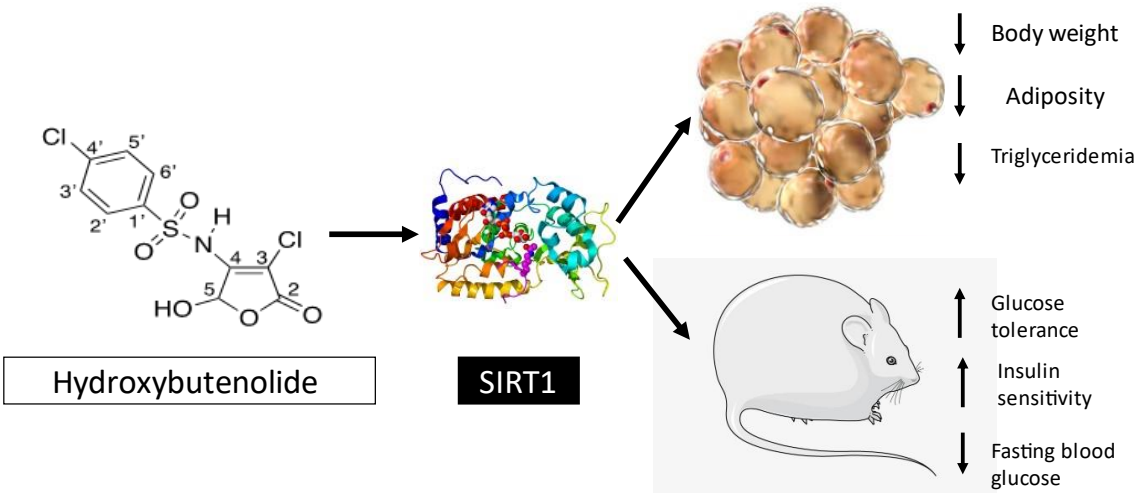


**Figure 7:** Graphic summary.

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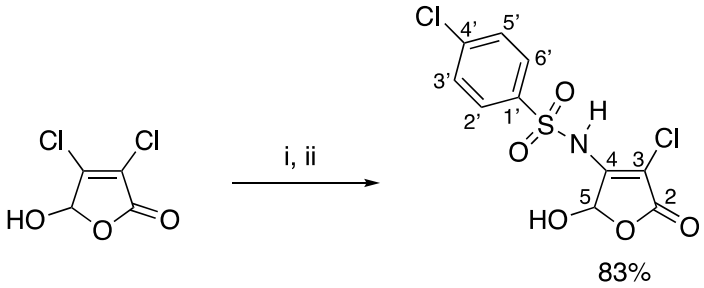
**SUPPLEMENTARY MATERIAL**




Reagents and conditions: (i) $H_2O$, KOH, 60 °C, 10 min.; (ii) 4-chlorobenzenesulfonamide, KOH, EtOH, 60 °C, 40 min.

**Figure 1.** Preparation of 3-chloro-4-(*p*-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5*H*)-one.

1. Synthesis

Infrared spectra were recorded on a PerkinElmer SPECTRUM 100, equipped with scanning from 4000 to 500 $cm^{-1}$. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Brucker DRX-400 Avance (400 MHz), using deuterated chloroform as a solvent and tetramethylsilane (TMS) as internal standard (□□= 0). High resolution mass spectra were recorded on a Shimatzu LCMS-IT-TOF. Analytical thin layer chromatography analysis was conducted on aluminum packed precoated silica gel plates.

Synthesis and characterization of 3-chloro-4-(*p*-chlorophenylsulfonylamino)-5-hydroxyfuran-2(5*H*)-one.

In a round-bottomed flask (100 mL), were added mucochloric acid (0.169 g, 1.0 mmol), distilled water (10.0 mL) and potassium hydroxide (2.8 mg, 0.05 mmol,). The system was kept under magnetic stirring at 60°C for 10 minutes. Then, 4-

chlorobenzenesulfonamide (1.0 mmol, 0.191 g) and KOH (0.05 mmol, 2.8 mg) were previously solubilized in ethanol, (10 mL) and dropped into this flask resulting yellowish solution that was kept under stirring and heating for 40 minutes. Concentrated HCl was then added and the pH was reduced to approximately 1.0. The resulting solution was extracted with chloroform (3 x 20 mL). The organic phases were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure, yielding a pale yellow solid that was recrystallized from a mixture of acetone:water (1:1). The product was obtained as yellow crystals in 83% yield (0.269 g). IR (ATR) □□□max/cm$^{-1}$) 3400-2200; 3329; 1726; 1325; 1148. $^{1}$H NMR (400 MHz, $CDCl_3$): $\delta$ 5,09 (bs, 2H, -NH, OH), 6,07 (s, 1H, H-5), 7,50 (d, 2H, $^{3}J$ = 8 Hz, H-3', H-5'), 7,85 (d, 2H, $^{3}J$ = 8 Hz, H-3', H-5'). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 96,6 (C-5), 127,9 (C-2', C-6', C-3), 129,5 (C-3', C-5'), 139,4 (C-4'), 140,1 (C-1'), 149,1 (C-4), 164,8 (C=O). HRMS calcd. for $C_{10}H_6Cl_2NO_5S^-$ $^{1}$: 321,9349, found 321,9289.

**3.2 Produto 2:** Sirtuins, brain and cognition: A review of resveratrol effects.

IBRO Rep 9 (2020) 45–51

Contents lists available at ScienceDirect

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

# Sirtuins, brain and cognition: A review of resveratrol effects

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ARTICLE INFO

*Keywords:*
Sirt
Polyphenol
Phytochemistry family
Wine
Central nervous system

ABSTRACT

Sirtuins (SIRTs) are a protein family with high preservation degree among evolutionary scale. SIRTs are histone deacetylases regulatory enzymes of genetic material deeply involved in numerous physiological tasks including metabolism, brain function and aging. Mammals sirtuins comprise seven enzymatic components (SIRT1–SIRT7). The highest studied sirtuin is SIRT1, which plays an essential position in the prevention and evolution of neuro- disorders. Resveratrol (3,5,4-trihydroxystylbene) (RSV) is a polyphenol, which belongs to a family compounds identified as stilbenes, predominantly concentrated in grapes and red wine. RSV is the must studied Sirtuin activator and is used as food supplementary compound. Resveratrol exhibits strong antioxidant activity, redu- cing free radicals, diminishing quinone-reductase-2 activity and exerting positive regulation of several en- dogenous enzymes. Resveratrol is also able to inhibit pro-inflammatory factors, reducing the stimulation of the nuclear factor kB (NF-kB) and the release of endogenous cytokines. Resveratrol treatment can modulate multiple signaling pathway effectors related to programmed cell death, cell survival, and synaptic plasticity. In this context, the present review looks over news and the role of Sirtuins activation and resveratrol effects on mod- ulating target genes, cognition and neurodegenerative disorders.

## Introduction

Sirtuins are enzymes catalogued as histone deacetylases (HDACs), which are proteins able to inhibit gene transcription for its skill to delete acetyl portions of the ϵ-acetamido unit in lysine inside histones (de Ruijter et al., 2003). The amino portion of preserved lysine contained in histone extremities is able to be reversible acetylated and deacetylated, which plays a relevant position on gene expression (Li et al., 2007). The histone modifications also play a role modulating DNA damage, genetic instability, pro-inflammatory genes and pre- mature aging (Krishnan et al., 2011; Ogiwara et al., 2011; Sarg et al.,2002; Vempati et al., 2010; Yuan et al., 2009). This progression can modify the chromatin arrangement between euchromatin and hetero- chromatin, in order to activate DNA restoration process to impaired locations (Yao and Rahman, 2012).

NF-κB-dependent pro-inflammatory genes transcript may also be regulated by HDACs through deacetylation of non-histone proteins (de Ruijter et al., 2003; Yao and Rahman, 2012). To date, several isoforms of HDAC have been recognized and grouped into classes (de Ruijter et al., 2003). Among these classes, the Sirtuins can be highlight as Class III members that use NAD + as a cofactor (Alcendor et al., 2007; Finkel et al., 2009; Lavu et al., 2008; Rajendrasozhan et al., 2009). The firstsirtuin family protein was identified in *Saccharomyces Cerevisiae* (Rine and Herskowitz, 1987), being appointed as regulator of silent in- formation 2 (Sir2) gene. Sir2, which is also expressed in *Caenorhabditis Elegans* and *Drosophila melanogaster*, was associated to aging and long- evity among other functions. Considering the mammals, Sirtuin 1 (SIRT1) was the first identified. Subsequently, other sirtuin family genes emerged constituting a total of seven (SIRT1 to SIRT7) (Donmez, 2012; Kelly, 2010a, b).

SIRTs are regulatory genes that modulate a high diversity of epi- genetic factors. These proteins play a primary function in the body's reactions to diverse stress forms and toxicity. Sirtuins adjust animal's lifetime interfering with biological factors related to metabolic alterations and also aging in mammals (Michan and Sinclair, 2007; Paraisoet al., 2013). The seven mammals' sirtuins (SIRT1 to SIRT7) have being extensively studied. Previous researches have demonstrated changes at the cellular level locations for each Sirtuin. The SIRT3, SIRT4 and SIRT5 are localized in mitochondria, while SIRT6 and SIRT7 are mainly nuclear, while SIRT2 and SIRT1 are both present in the nuclei and in

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https://doi.org/10.1016/j.ibror.2020.06.004
Received 17 March 2020; Accepted 20 June 2020
Available online 26 June 2020

the cytosol. (Paraiso et al., 2013; Lin et al., 2013). It is worth to repeat that a key function of nuclear sirtuins (SIRT 1, 2, 6 and 7) is the gene inflammation regulatory task.

Emerging as a promising tool on regulating SIRTs, resveratrol (RSV)is a polyphenol with several beneficial properties through their antioxidant and anti-inflammatory effects, modulating several cascades and effectors involved in the brain and cognitive regulation, specially SIRT1-mediated (Andrade et al., 2019; Sarubbo et al., 2018a, b).

## Sirtuins and brain

Several studies demonstrated that sirtuins plays a crucial role on aging, neural disorders and metabolic syndrome (Brachmann et al., 1995; Smith et al., 2000). Considering the 7 mammalian sirtuins, the overexpression of SIRT1 and/or its stimulation by certain natural chemical structures (resveratrol for instance), enhance health and life span (Chandrasekaran et al., 2019). SIRT1 modulates several gene components, however there are some priority transcription factors. We are able to highlight among these transcription factors the p53 (Vaziri et al., 2001), FoxO family members (Brunet et al., 2004), NF-κB (Yeung et al., 2004) and PGC-1α (Dominy et al., 2010; Rodgers et al., 2008). Changes in these components due to their deacetylation, alters the cell's life cycle and also the energy metabolism. SIRT1 cleaves NAD + into nicotinamide and 10-O-acetyl-ADP-ribose (Tanner et al., 2000) or 20- and 30-O-acetyl-ADP-ribose (Jackson et al., 2003) and therefore deacetylate lysine residues. SIRT1 activities require and increase NAD + cell content, which means a reduction in cell energy stock (Chalkiadaki and Guarente, 2012). SIRT1 activation by resveratrol is able to protect mice against high-fat induced obesity and insulin disturbance (Canto et al., 2012; Lagouge et al., 2006; Rajman et al., 2018). The described activation produces a decline in PGC-1α /acetylation and an increased activity of the same protein (Rodgers et al., 2008; Gerhart-Hines et al., 2007; Nemoto et al., 2005).

Recent findings showed the SIRT1 ability to improve mitochondrial breathing. The NAD + consumption pathways maintain cellular homeostasis protecting the dorsal root ganglia neurons from peripherals damage induced by high-fat diet (HFD), thus preventing neuropathy. It is important to note that the overexpression of SIRT1 was capable to avoid and treat the peripheral neuropathy stimulated by HFD. The authors suggested a mitophagia associated with NEDD4 that improves mitochondrial breathing capacity, increasing axonal development and reparation. SIRT1 is essential to this route by regulating mitochondrial role in the marginal nerve throughout PGC1-α modulation (Chandrasekaran et al., 2019). Cell culture researches showed that SIRT1 is detect in the nucleus of several cell lines (Michan and Sinclair, 2007) producing deacetylation activity of several transcription factors. SIRT1 protein, nevertheless, seems to have nuclear signs exportation and modulates the transport between the cytoplasm and the nucleus(Tanner et al., 2000; Sugino et al., 2010). Extranuclear location, particularly in mitochondria, has also been observed (Aquilano et al., 2013). Immunohistochemistry analyzes of samples with high SIRT1 expression demonstrated a clear location in the nuclei of CA1 neurons in the hippocampus.

The adverse effects of cadmium chloride in the maintenance and spatial-memory tasks in rats confirm the participation of reactive oxygen species, reduction of intracellular glutathione amount, and activation of inherent cell-death in this course. Cadmium chloride produces in the mice hippocampus a continued stimulation of Endoplasmic Reticulum (ER) with parallel decrease in the SIRT1 level and lower activity of the SIRT1/AMPK/Akt axis. Confirming this data, the rats treated with cadmium chloride and resveratrol presented improved memories and reduced reactive oxygen species generation with improved GSH and increased levels of Bcl-2 mediated by negative regulation of GAAD-153 (CHOP), in a mechanism dependent on SIRT1/AMPK/Akt. In complement, resveratrol inhibited cadmium chloride-induced hippocampal apoptosis, avoiding ER stress and subsequent initiation of proapoptotic genes downstream (Shati, 2019).

Nuclear factor of activated B-cells (NF-κB) is involved in physiolo- gical inflammatory processes and thus representing a promising target for inflammation-based neuronal therapy. Yang et al. demonstrated that resveratrol reduced inflammatory damage and promoted microglia polarization to the M2 phenotype in LPS-induced neuroinflammation. In addition, resveratrol ameliorated LPS-induced sickness behavior inmice. The promoting effects of resveratrol on M2 polarization were attenuated by knocking down PGC-1α. PGC-1α not only suppressed LPS-evoked M1 marker expression by inhibition of NF-κB activity but also increased M2 marker expression by coactivation of the STAT6 and STAT3 pathways (Yang et al., 2017). In other study, RSV inhibited the activation of NLRP3 and NF-κB in the hippocampal region caused by deficiency of estrogen, ameliorating ovariectomy-induced anxiety and depression-like behaviors (Liu et al., 2019). Fan et al. showed that SIRT1 mediates the anxiolytic effect of apelin-13 in chronic normobaric hypoxia-treated mice through the inhibition of NF-κB pathway. These results imply that dysfunction of the apelin-SIRT1-NF-κB axis in hippocampus represents a potential mechanism that results in the induction of neuroinflammation and reduction in neuroprotection, thus induces anxiety-like behavior in chronic normobaric hypoxia-treated mice (Fan et al., 2018). Altogether, these studies indicate the important role of the NF-κB inhibition in the resveratrol's neuroprotective effect.

## Resveratrol, brain and cognitive function

Resveratrol (3,4′,5-trihydroxystilbene; C14H12O3) (RSV) is a polyphenolic phytoalexin found in grapes, berries, peanuts, and wines, and belongs to a family of polyphenolic compounds known as stilbenes. RSV has been viewed as an antioxidant, anti-inflammatory, anti-apoptotic, anti-obesity and anticancer agent (Cvejic et al., 2010; Sahebkar et al., 2015; Shi et al., 2014). RSV is a low molecular weight compound with antimicrobial activity. There are two RSV forms, the -trans and -cis isomers. RSV plays a central role in the famous "French Paradox", that showed the inverse correlation between the occurrence of cardiovas-cular disease and the intake of red wine in French population. Today, RSV has been viewed as a neuroprotective agent.

Investigational data suggest that resveratrol (RSV) induces antinociception in the nervous system periphery through the opioid activation of receptors and by the release of endogenous and endocannabinoid opioids. RSV induces the antinociceptive effect against the inflammatory carrageenan agent. Two theories have been proposed to explain the effects of peripheral RSV antinociceptive involvement: (i) endocannabinoid anandamide (AEA) and 2-AG releasing subsequent stimulation subsequent to CB1R receptor activity and opioid receptor (OR) associated with an opioid endogen; (ii) opioids release the sti- mulation subsequently caused by OR activation and cause indirect ac- tivation of CB1R with the AEA used (Oliveira et al., 2019).

## Resveratrol and cognition

Postoperative cognitive diseases represent an important neurolo- gical problem in almost 25 % of the elderly people. In fact, this cog-nitive dysfunction induces hippocampus overproduction of proin- flammatory molecules [i.e. tumor necrosis fator alpha (TNF-α) and interleukin (IL) -1B]. Isoflurane anesthesia damages synaptic plasticity leading to neurological problems followed by cognitive dysfunction (Rachal Pugh et al., 2001; Terrando et al., 2010). In other study, elderly mice treated with intraperitoneal resveratrol 100 mg/kg in a total of 7 days, attenuating isoflurane hippocampal-dependent damage through anti-inflammatory effects (Toth et al., 2014). Considering the possible molecular routes mechanisms modulating these effects, SIRT1 involvement raised a great interest (Hasegawa and Yoshikawa, 2008). In particular, neuronal SIRT1 deacetylate p53 in the Lys residues pro- tecting multiple cells against apoptosis induced by DNA damage (Du et al., 2014) Fig. 1. Confirming these data, cell primary neurons studies

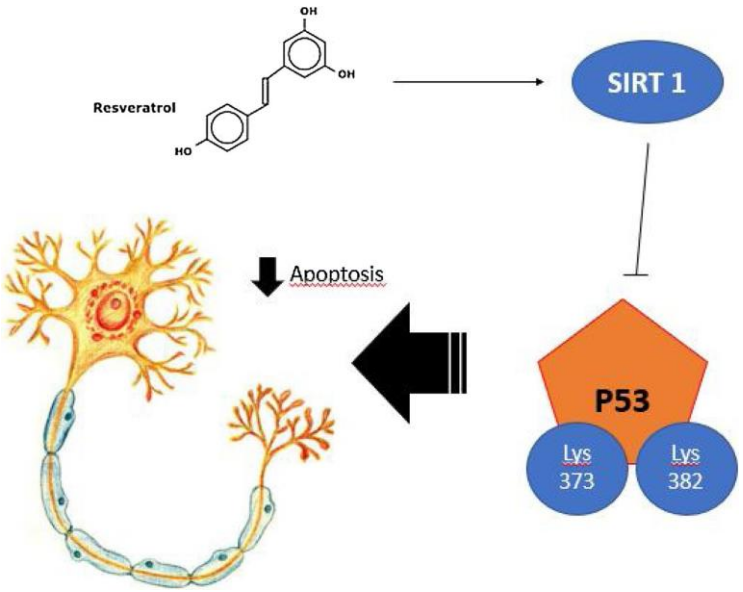


Fig. 1. Resveratrol improves cognition through an anti-oxidative mechanism by SIRT1-mediated deacetylation. Unpaired electrons escape the mitochondrial electron transport chain and react with molecular oxygen to produce superoxide, resulting in oxidative stress. Resveratrol acts on SIRT1, which induces ROS detoxifying enzymes that eliminate superoxide.

in mouse and rat models showed that SIRT1 intermediate neuronal protection working as a central actor in combating neurodegenerative disorders (Chen et al., 2015).

Resveratrol plays a central role as the key polyphenol capable to modulate SIRT1 expression and its main effects. SIRT1 activation by RSV can produce neural malleability in the hippocampus area (Hasegawa and Yoshikawa, 2008). This path relevance is also con- firmed in a mouse neuropathology induced model similar to Alzhei- mer's disease (AD). The authors showed that SIRT1 activation by RSV(30 mg/kg/day for 8 weeks) reduced Tau protein phosphorylation in- duced by the brain streptozotocin injection. These data confirms re- sveratrol role defending the hippocampal neuronal area of Tau and memories hyperphosphorylation commitment (Du et al., 2014). A re- cent study showed that RSV significantly increased SIRT1 expression inhibiting the memory impairment. The results were associated with increased acetylcholinesterase, malondialdehyde and reduced super- oxide dismutase (SOD) and glutathione levels in a diabetic rat model with concomitant Alzheimer's disease (Ma et al., 2019).

RSV also plays a role on improving the activation of AMPK-protein kinase (AMPK), which causes neurogenesis and mitochondrial biogen- esis, thus stimulating the biogenesis of neural differentiation in neu- rons. These properties are SIRT1 independent, considering the results obtained using SIRT1 inhibitors or studies performed in the SIRT1 knockout mice brain (Dasgupta and Milbrandt, 2007). It is now clearthe existence of a close interaction between SIRT1 and AMPK (Cantoet al., 2009). An Alzheimer disease mice model proved that exist a balance concerning SIRT1 and AMPK signaling linked to inflammatory changes which are required for the RSV protective effects against Abformation and cognitive plaque loss (Porquet et al., 2014). The con- firmation of a neural RSV effect was further validated in H19-7 rat neuronal hippocampus cells in vitro, where a 2 -h pre-treatment with RSV (75 mM) diminished the oxidative damage produced by Ab and reducing crucial synaptic proteins development and malleability (Regeet al., 2015). Other impaired source in AD, which can be redeemed byRSV, it is the neurovascular-coupling. An aging mice-model with cer- ebrovascular deficits was rescued by RSV treatment improving cortical neurovascular-coupling responses. The main effects were intermediated by downregulation of cortical NADPH production and ROS derived reduced effects (Toth et al., 2014) Fig. 2. Considering that SIRT1 constrains NADPH oxidase outcomes in rat aorta and defends against endothelial dysfunction, this path is fundamental to understand the bond between RSV and cerebromicrovascular vessel endothelial-func- tion (Zarzuelo et al., 2013).

The neurogenic effect of resveratrol is also an important protective factor for the central nervous system. RSV is able to cross the brain barrier through the circulatory system and causes improvement of antioxidant enzymes, in addition it extends the effects of the pathways linked to SIRT1 and induces glial activation, helping to increase neurogenesis in the hippocampus. Other results are the decrease in the expression of the amyloid precursor protein and the improvement of the special working memory (Gomes et al., 2018).

In a complementary way to SIRT1/AMPK involvement on the brain function, an analysis of gene expression across the genome showed as that resveratrol balance the hippocampal gene expression involved in neuronal origin and synaptic malleability (Hdac4, Hat1, Wnt7a, ApoE) and reduction of Jak-Stat pro-inflammatory signaling (IL-15, IL-22, Socs2 and Socs5) in streptozotocin-induced diabetic rats (Thomas et al., 2014). The use of resveratrol led to the expression of the hippocampal nerve growing component, decreasing pyramidal cell mortality in a hippocampus CA1 region, increasing spatial working memory in a vascular dementia rat-model (Anastacio et al., 2014). More indicationson the neural effect of RSV on the vascular associated dementia derived from a study showing how a permanent bilateral carotid (vessel) oc-clusion in a rat model, can be treated with daily RSV administration,improving memory/learning as assessed by the Morris water maze test. The exhaust dormancy and escape distances were expressively lower in RSV animals. In addition, after resveratrol, malonyldialdehyde amount, an oxidation indicator stress in neuronal disorders, diminished in the cortex and hippocampus; inversely, RSV treatment produced an in- crease in superoxide dismutase effects and glutathione levels (Ma et al., 2013).

In recent studies about resveratrol and brain, Zoe et al. showed that RSV may attenuate the inflammatory response and relieve traumatic brain injury by reducing reactive oxygen species production and in- hibiting NLR family pyrin domain containing 3 (NLRP3) activation. The effect of resveratrol on NLRP3 inflammasome and reactive oxygen species may also be SIRT1 dependent (Zou et al., 2018). In other study, RSV increased the expression of genes encoding known antioxidants

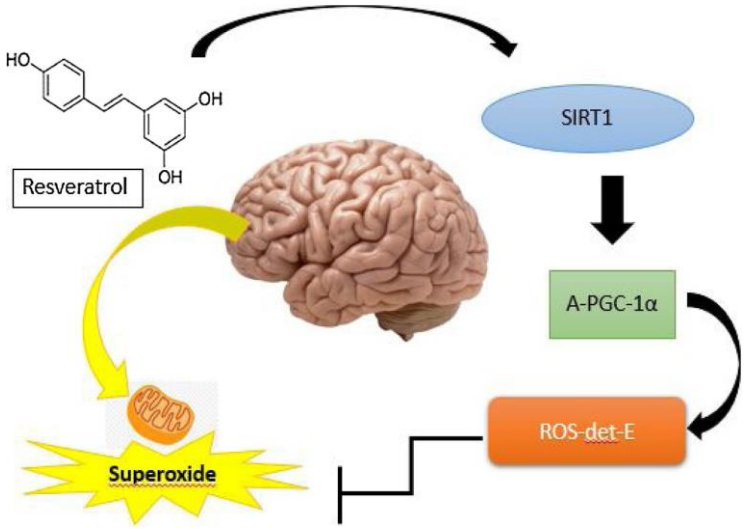


Fig. 2. SIRT1 is capable of deacetylate p53 in the Lys residues (Lys373 and / or Lys382) and protect multiple cells against Apoptosis induced by DNA damage.

and anti-aging factors (SIRT1 and SIRT3) in Alzheimer's disease patients (Cosin-Tomas et al., 2019). Le et al. demonstrated that resveratrol plays a neuroprotective role in neonatal hypoxic-ischemic brain injury by activating SIRT1 to inhibit HMGB1/TLR4/MyD88/NF-kB signalling and subsequent neuroinflammatory responses (Le et al., 2019). Additionally, Shen et al. showed that the neuroprotective effect of RSV on chronic unpredictable mild stress -induced cognitive impairment may rely on activating SIRT1/miR-134 pathway and then upregulating its downstream element-binding protein (CREB) and brain derived neurotrophic factor (BDNF) expression in hippocampus (Shen et al., 2018). Finally, RSV protected against learning and memory impairments in juvenile animals fed with a high-caloric diet, possibly via upregulation of p16 or downregulation of PPAR in the hippocampal CA1 region (Xu et al., 2018).

## Human treatment

Aging-related dementia is globally increasing substantially, parallel to the "grayish" world population (Hirtz et al., 2007). Importantly, re- cent global data indicate that mild cognitive problems disturbs 5.5–7.7% of individuals over 60 years old and 22 % of people over 70 (Apostolo et al., 2016), most often in those with neuropsychiatric symptoms (Bidzan et al., 2017). Considering this epidemiological data, it is essential to explore new tools that can downgrade dementia ad- vance. The decrease in cognitive capacity and dementia in adults has been investigated and several of its possible causes have been pointed out, among these genetic, nutritional and metabolic factors (Flirski and Sobow, 2005; Lahiri et al., 2007). Vascular injuries and inflammatoryfactors have been pointed as possible causes for these complications of the central nervous system (Jiang et al., 2017; Zhu et al., 2004). Theevidences suggests that RSV, with all its effects cited throughout thisreview, may be a good option with neuroprotective actions and could have positive effects against the deterioration of human cognition. Some vegetables also seem to inhibit the evolution of neuronal pro- blems (Cicero et al., 2018). Indeed, in addition to its helpful propertieson the central nervous system, RSV appears to be capable to actuate on numerous cellular mechanisms/signaling and consequently produce adiversity of biological results, theoretically valuable to elderly diseases, (evidently confirmed in randomized clinical-trials) (Erdogan and Vang, 2016). In particularly, despite RSV presented controversial data on the lipid profile (Cicero et al., 2017), this polyphenol also appears to be effective on treating several Metabolic Syndrome (MS) constituents, such as overweight, insulin-resistance (Patti et al., 2018) and blood- pressure issues (Fogacci et al., 2019). The key problems connected to the preventive therapy using RSV are due its low oral bioavailability associated to a short serum/plasma half-life (Rege et al., 2014). How- ever, medicinal new technologies seem to be capable to increase oral RSV bioaccessibility (Bonferoni et al., 2017; Ethemoglu et al., 2017). Although the majority of polyphenols seem to present an extremely low bioavailability after oral administration, several evidence demonstrate the beneficial effects obtained by this administration route. One of the hypothesis for the low bioavailability is the rapid metabolization of the polyphenol's compounds, including resveratrol. However, evidence support that the resveratrol's metabolites may also have the therapeutic properties, in addition to be found in higher concentrations in the tissues, including the central nervous system, than in the plasma (D'Archivio et al., 2010; Almeida et al., 2016). On the other hand, resveratrol's presents a high tolerability and safety profile without major pharmacological interface (cross-reaction) of this nutraceutical with orthodox known drugs. This is specific relevant, because the greatest efficient dementia medicines are generally not well tolerated, so not being prescript for the firsts disease phases (Banach et al., 2017; Fisheret al., 2017; Zanchetti et al., 2014).

## Conclusion and perspectives

The main literature data shows that Sirtuins should be considered some of the main targets on treating cognition problems and neurodegenerative diseases. Resveratrol exhibited the ability to ameliorate memory and cognition by controlling SIRT1 through AMPK and several other molecular pathways. RSV properties include antioxidative, anti-inflammatories, anti-apoptotic regulation and autophagyc properties, as well as its skills to improve cerebral blood flow and expand synaptic plasticity. In this context, Sirtuins activation and Resveratrol may be future solutions for brain diseases treatment and elderly comorbidities.

## Conflict of interest

The authors declare that they have no competing interest/disclosure (s).

## Acknowledgements

This work was partially supported by the Coordenadoria de Aperfeiçoamento do Pessoal de Nível Superior - Coordination of Superior Level Staff Improvement (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brazilian Council for Scientific and Technological Development (CNPq) and Fundação de Amparo à Pesquisa do Estado de Minas Gerais - Minas Gerais Research Foundation (FAPEMIG).

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## 4 CONSIDERAÇÕES FINAIS

O envolvimento da via das sirtuínas foi abordado aqui em dois processos diferentes e pelo uso de dois métodos científicos também diferentes, porém, ambos de forma positiva, apresentando resultados favoráveis no sistema metabólico e nervoso. O tratamento com 3-cloro-4-(p-clorofenilsulfonilamino)-5-hidroxifuran-2(5H)-ona mostrou alguns resultados interessantes, em modelo animal de indução de obesidade. Diminuição do peso corporal e do volume de tecido adiposo branco; melhora do metabolismo da glicose e diminuição da triglicerinemia. Neste caso, o envolvimento da super expressão de SIRT1, esteve envolvida. Assim como a nova hidroxibutenolida testada, o resveratrol é uma substância natural com vários efeitos benéficos já comprovados, dentre eles a ativação de sirtuínas que contribuem para a prevenção de problemas de cognição e doenças neurodegenerativas.

Mesmo com limitações quanto à elucidação do mecanismo de ação específico. O efeito anti-inflamatório já comprovado de substâncias semelhantes à estudada pode ser um indício de que a 3-cloro-4-(p-clorofenilsulfonilamino)-5-hidroxifuran-2(5H)-ona teria uma similaridade com o resveratrol, pelo menos em seu potencial de ativação de SIRT1. Por sua vez o efeito antioxidante, anti-inflamatórias, anti-apoptóticas e autofágicas, bem como suas habilidades para melhorar o fluxo sanguíneo cerebral e expandir a plasticidade sináptica, transformam o resveratrol em uma alternativa para o tratamento de doenças cerebrais e comorbidades em idosos.

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