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Instituto de Biologia Roberto Alcantara Gomes

Éric Heleno Freire Ferreira Frederico

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Orientador: Prof. Dr. Mario Bernardo Filho

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Banca examinadora:

Prof. Dr. Mario Bernardo Filho (Orientador)
Universidade do Estado do Rio de Janeiro - UERJ

Prof. Dr. Luís Cristóvão de Moraes Sobrino Pôrto
Universidade do Estado do Rio de Janeiro - UERJ

Prof.ª Dra. Anke Bergmann
Instituto Nacional de Câncer

Prof.ª Dra. Danúbia da Cunha de Sá Caputo
Faculdade Bezerra de Araújo

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DEDICATÓRIA

Dedico esta tese a minha família. Dodu na nhos sem manha.

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A recompensa de cumprir uma obrigação é a possibilidade de iniciar outra.

George Sand

RESUMO

FREDERICO, Éric Heleno Freire Ferreira. *Efeitos biológicos do exercício de vibração de corpo inteiro (EVCI) e de sua associação com um extrato aquoso de Coriandrum sativum (coentro) em ratos Wistar com e sem diabetes do tipo 1.* 2018. 63f. Tese (Doutorado em Biociências) - Instituto de Biologia Roberto Alcantara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

O exercício de vibração de corpo inteiro (EVCI) é gerado quando um corpo é exposto à vibração mecânica produzida numa plataforma oscilante/vibratória (POV). O uso clínico dos ECVI tem revelado achados, tais como, o aumento da força e potência muscular, melhora do equilíbrio, aumento da densidade mineral óssea e aspectos relacionados à qualidade de vida, importantes para a prevenção/tratamento de algumas doenças. Como o uso dos ECVI tem aumentado, o desenvolvimento de modelos experimentais para avaliar, de uma forma controlada, o efeito desses exercícios é desejável. A associação do EVCI e produtos naturais pode ser uma ferramenta importante no tratamento de doenças. Produtos naturais têm sido usados pelo Homem como fonte de alimento e medicamento. No entanto, o mecanismo de ação e a eficácia desses produtos na maioria dos casos carecem de validação cientifica. *Coriandrum sativum* (coentro) é uma planta herbácea que tem sido usado na medicina tradicional no tratamento de diabetes e distúrbios gastrintestinais. Assim, o objetivo desse estudo foi avaliar em ratos *Wistar* com e sem diabetes mellitus do tipo 1 (T1DM), o efeito da intervenção envolvendo EVCI com um extrato aquoso de coentro. Os animais foram separados em quatro grupos. Os ratos dos grupos controle e coentro receberam 1,0 mL de água deionizada e extrato de coentro (8mg/mL) respectivamente por gavagem. Os ratos que foram submetidos ao EVCI também receberam por gavagem 1,0 m/L de água deionizada. Os animais do grupo coentro + EVCI receberam 1,0 de extrato de coentro e foram submetidos ao EVCI. Todas as etapas descritas anteriormente foram realizadas também com animais com T1DM. A T1DM foi induzida pela injeção intraperitoneal de 150 mg/kg de aloxana. Foram avaliados a biodistribuição do radiofármaco pertecnetato de sódio ($Na^{99m}TcO_4$), a concentração de alguns biomarcadores plasmáticos, a massa corporal, consumo de ração e a consistência das fezes. Os resultados em ratos saudáveis mostraram uma diminuição da percentagem da radioatividade por grama (% ATI/g) no testículo nos ratos do grupo submetido ao EVCI comparado com o tratado com o extrato de coentro. Não foram encontradas alterações significativas nas concentrações de biomarcadores plasmáticos. O consumo de ração mostrou um aumento significativo nos ratos submetidos ao EVCI. Não foram encontradas diferenças na massa corporal. A análise da consistência das fezes mostrou uma diferença significativa na consistência entre o grupo tratado com extrato de coentro e os demais grupos. Em conclusão, foram verificadas modificações em alguns parâmetros bioquímicos/fisiológicos nos ratos saudáveis submetidos ao EVCI capaz de aumentar o consumo de ração sem alterar a massa corporal, e normatizar a consistência das fezes alterada pelo consumo de coentro, sendo que nos animais com T1DM não foram encontradas diferenças nos parâmetros estudadas com as referidas intervenções.

Palavras-chave: EVCI. Coentro. Biodistribuição. Biomarcadores. Massa corporal. Consumo de ração. Consistência das fezes.

ABSTRACT

FREDERICO, Éric Heleno Freire Ferreira. *Biological effects of whole body vibration (WBV) exercise and its association with an aqueous extract of Coriandrum sativum (coriander) in Wistar rats with and without type 1 diabetes*. 2018. 63f. Tese (Doutorado em Biociências) - Instituto de Biologia Roberto Alcantara Gomes. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

Whole body vibration (WBV) exercise is generated when a body is exposed to mechanical vibration produced in oscillating/vibratory platform. The clinical use of WBV exercise has revealed important findings, as the increase of muscle power and strength, improvement of balance, increase bone mineral density and aspects related to quality of life, and can be used in the prevention/treatment of diseases. As the use of WBV exercise has increased, the development of experimental models to evaluate, in controlled ways, the effect of this exercise is desirable. The association between WBV exercise and natural products would be an important tool in the management of diseases. Natural products have been used by human beings as food and medicine. However, the mechanism of action and the efficacy of these products in most cases lack scientific validation. *Coriandrum sativum* (coriander) is an herbaceous plant that been used in traditional medicine on the treatment of diabetes and gastrointestinal diseases. Following this idea, the aim of this study was to evaluate in *Wistar* rats with and without type 1 diabetes mellitus (T1DM), the biological effect of association between WBV exercise and an aqueous extract of coriander. The animals were separated equally in four groups. The control group received deionized water. The group treated with coriander received the extract of coriander. The rats that were exposed to WBV exercises also received deionized water. A group of animals received coriander and was exposed to WBV. All steps described above were also performed with animals with T1DM. The Diabetes was induced by intraperitoneal injection of 150 mg/kg alloxan. Were evaluated the biodistribution of sodium pertechnatate ($Na^{99m}TcO_4$), concentration of some plasma biomarkers, body mass, feed intake and stool consistency. The results in healthy rats showed a decrease in the percentage of radioactivity per gram (% ATI / g) in the testis in rats submitted to WBV exercise compared to that treated with coriander extract. There is no significant alteration on the concentrations of the plasma biomarkers. The feed intake showed a statistically significant increase in rats submitted to WBV exercise. No significant difference on the body mass was found. The stool analysis showed a statistical difference on the consistency between coriander group and all the other groups. In conclusion, it was verified modifications in some biochemical/physiological parameters of the rats submitted to WBV exercise which would be capable to increase the feed intake without changing the body mass, and normalizing the stool consistency altered by the coriander supplementation; and in animals with T1DM no difference was found in the studied parameters with these interventions.

Keywords: WBV exercise. Coriander. Biodistribution. Biomarkers. Body mass. Feed intake. Stool consistency.

LISTA DE ABREVIATURAS E SIGLAS

a.C	Antes de Cristo
ATI	Radioatividade incorporada
ATP	Adenosina Trifosfato
CEUA	Comitê de Ética para o Uso de Animais Experimentais
CK	Creatinina quinase
DHEA	Dehidroepiandrosterona
DM	Diabetes mellitus
DS	Deslocamento sincrônico
EGG	Eletrogastrografia
EVCI	Exercício de Vibração de Corpo Inteiro
HDL	*High Density Lipoprotein*/Lipoproteína de Alta Densidade
IDF	*International Diabetes Federation*
IMC	Índice de Massa Corporal
LDL	Low Density *Lipoprotein*/Lipoproteína de Baixa Densidade
OMS	Organização Mundial da Saúde
PET	*Positron Emission Tomography*
rpm	Rotação por minuto
T1DM	Diabetes mellitus do tipo 1
T2DM	Diabetes mellitus do tipo 2

LISTA DE SÍMBOLOS

%	Percentagem
@	Arroba
>	Maior que
$^{99}Mo/^{99m}Tc$	Gerador de molibdênio-99/tecnécio-99m
^{99m}Tc	Tecnécio-99m
^{99m}Tc-MDP	Metilenodifosfonato marcado com tecnécio-99m
HbA1	Hemoglobina glicada
Hz	Hertz
MBq	Megabecquerel
mg	Miligrama
mg/kg	Miligrama por kilograma
mg/mL	Miligrama por mililitro
mL	Mililitro
$Na^{99m}TcO_4$	Pertecnetato de sódio
NaCl	Cloreto de sódio
nm	Nanômetro
ºC	Grau Celsius

SUMÁRIO

INTRODUÇÃO

Exercício físico

Segundo a Organização Mundial da Saúde (OMS), a atividade física é definida como qualquer movimento corporal produzido pelos músculos esqueléticos que requer gasto de energia. O termo “atividade física” não pode ser confundida com “exercício”. Exercício, é uma modalidade de atividade física, que é planejada, estruturada e repetitiva, com o objetivo de melhorar ou manter a condição física (OMS, 2017).

A inatividade física é um dos fatores de riscos modificáveis mais prevalentes para aumentar a possibilidade de contrair doenças não-comunicáveis como as cardiovasculares, câncer e diabetes (Ding *et al*., 2016). É o quarto principal fator de risco para a mortalidade global causando um número estimado de 3,2 milhões de morte em todo o mundo. Apesar dos efeitos benéficos da atividade física serem bem conhecidos, 30% da população mundial não consegue os níveis recomendados para os benefícios na saúde. Os níveis atuais de inatividade física são em parte devido à participação insuficiente na atividade física durante o tempo de lazer e ao aumento do comportamento sedentário durante atividades ocupacionais e domésticas. Do mesmo modo, um aumento no uso dos modos "passivos" de transporte também tem sido associado ao aumento dos níveis de inatividade física (OMS, 2017).

Ainda de acordo com a OMS, o aumento da urbanização resultou em vários fatores ambientais que podem desencorajar a participação na atividade física, tais como: violência, tráfego de alta densidade, baixa qualidade do ar, poluição, falta de parques e instalações esportivas/recreativas (OMS, 2017).

Ao longo dos anos, alguns estudos têm mostrado o potencial do exercício aeróbico e de resistência na melhora de biomarcadores plasmáticos específicos relacionados a diferentes doenças (Ceci *et al*., 2014; Tomeleri *et al*., 2017). Além disso, o exercício físico pode melhorar a aptidão aeróbica, a força, o poder e a cognição, superar a fadiga e a depressão e melhorar a qualidade de vida (Seguin e Nelson, 2003; Beltran Valls *et al*., 2014).

Evidências indicam que a atividade física pode modular os mecanismos epigenéticos associados com uma variedade de doenças (Santos-Rebouças e Pimentel, 2006; Sanchis-Gomar *et al*., 2012; Pareja-Galeano *et al*., 2014;). Uma modalidade de exercício que vem ganhando relevância no tratamento de algumas doenças é o exercício de vibração de corpo inteiro (EVCI).

Exercício de vibração de corpo inteiro (EVCI)

O EVCI é um exercício de baixa resistência baseado na estimulação física através da vibração mecânica transmitida pelo corpo quando um indivíduo está em contato com a base da plataforma em funcionamento (Rittweger, 2010). Este tipo de exercício pode ser facilmente acessível a grandes populações devido a sua natureza minimamente invasiva, pouco efeitos adversos, baixo custo, simplicidade, e curta duração (Kessler e Hong, 2013).

Alguns parâmetros biomecânicos da vibração como a frequência, amplitude, e aceleração de pico precisam ser selecionados e adaptados às características de cada indivíduo. Em condições controladas, as vibrações mecânicas geram EVCI em condições boas e seguras (Rittweger, 2010). Ademais, deve ser definido um tempo de trabalho intercalado com um tempo de descanso e tempo total deve ser ajustado às características clinicas do indivíduo exposto (Rittweger, 2010; Rauch *et al*., 2010). Isso tem estimulado estudos sobre o efeito do EVCI, aplicado de forma segura, nos roedores (Pawlak *et al*., 2013; Keijser *et al*., 2017).

A aplicação terapêutica da vibração mecânica é antiga. É mencionada em registros da Grécia e Roma Antiga, onde era usado como terapia para melhorar a performance do corpo quando havia o comprometimento de áreas específicas. De alguma forma, foi observado que a vibração mecânica ajudava a melhorar a performance muscular (Calvert, 2002; Albasini e Rembitzki, 2010). No século XVI um livro japonês mencionava os potenciais benefícios da vibração para a saúde (Snow, 1904, Kaeding, 2016). Neste caso, foi descrita a aplicação da vibração para o alívio de distúrbios reumáticos e suporte da cura de ossos fraturados pela aplicação de vibrações (Snow, 1904; Kaeding, 2016). Aproximadamente em 1864, o médico sueco Gustav Zander (1835-1920) criou e testou máquinas que eram capazes de aplicar vibração predominantemente para fins terapêuticos. Tanto a frequência como a amplitude podiam ser ajustadas nesses dispositivos (Calvert, 2002; Kaeding, 2016). O neurologista francês Jean-Martin Charcot (1825-1893) começou a experimentar os EVCI no final de sua carreira. Ele simulou passeios de trem ou carruagem em uma cadeira vibratória especialmente desenvolvida. Com isso, conseguiu reduzir sintomas de Parkinson e melhorar o bem-estar por uma aplicação diária de 30 minutos (Goetz, 2009; Charcot, 2011). Charcot foi capaz de variar a frequência, a direção da vibração e sua intensidade. Muito mais importante, ele notou que uma intervenção terapêutica com EVCI deve ser adaptada ao indivíduo e suas necessidades (Kaeding, 2016).

John Harvey Kellogg (1852-1943) talvez seja o pioneiro mais popular do EVCI moderno. Ele inventou cadeiras vibratórias, barras e plataformas, como as que podem ser encontradas no mercado atualmente e usou-as em seu *Battle Creek Sanatorium* para medidas terapêuticas (Calvert, 2002; Stoppani, 2004).

No início do século XX, o interesse no uso terapêutico de EVCI diminuiu, talvez devido ao impacto das duas guerras mundiais (Kaeding, 2016). Na década de 1960, o Professor Biermann desenvolveu o *Rhythmischeneuromuskulare Stimulation*, que é o precursor direto dos aparelhos de hoje (Biermann, 1960; Stoppani, 2004). A partir de 1970, esse método foi desenvolvido por Vladimir Nazarov e usado pelos atletas da equipe olímpica soviética em diversas modalidades de esportes (Nazarov e Spivak, 1985; Stoppani, 2004). Os soviéticos perceberam que o EVCI não era apenas benéfico para a performance dos seus atletas, mas tinha também um enorme benefício nos astronautas que sofriam perda de massa muscular e densidade óssea por passarem longos períodos de gravidade zero no espaço (Hand *et al*., 2009). Nazarov e Spivak foram os primeiros a perceber que há uma conexão entre um aumento na capacidade muscular e a aplicação de EVCI (Albasini *et al*., 2010; Madou, 2011).

No final dos anos 1990, um dos primeiros a se envolver no uso do EVCI nos esportes populares foi Guus van der Meer (ex-treinador da equipe olímpica holandesa). Ele desenvolveu provavelmente o mais popular dispositivo para o EVCI, a *Power Plate* (Stoppani, 2004). Em 1996, o primeiro dispositivo com deslocamento alternado da base foi certificado na Alemanha (Albasini *et al*., 2010). Este tipo específico de dispositivo tem sido frequentemente usado em terapias ao longo do tempo (Kaeding, 2016).

Na atualidade, EVCI tem sido mais amplamente utilizado no tratamento e prevenção de doenças, e em esportes competitivos de equipe e individuais, como futebol, basquete ou golfe. Parece ser especialmente razoável durante o aquecimento e o resfriamento, e para o treinamento de flexibilidade (Cochrane, 2013; Kaeding, 2016; Morel *et al*., 2017).

Ações diretas e indiretas são associadas aos efeitos do EVCI e os efeitos indiretos podem ser associados com o sistema neuroendócrino em diferentes níveis (Prisby *et al*., 2008). O uso clínico dos EVCI tem revelado importantes achados (Rittweger, 2010; Cochrane, 2013), tais como, o aumento da força e potência muscular, melhora do equilíbrio, aumento da densidade mineral óssea (Russo *et al*., 2003; Verschueren *et al*, 2004; Weber-Rajek *et al*., 2015), aspectos relacionados à qualidade de vida e diminuição do risco de quedas (Alvarez-Barbosa *et al*., 2014; Yang *et al*., 2015). No entanto, os efeitos indesejáveis foram relatados em uma revisão (Sá-Caputo *et al*., 2015), como prurido nos membros inferiores, vertigem (Crewther *et al*., 2004), desconforto grave do quadril, dor na mandíbula, pescoço e membros inferiores (Cronin *et al*., 2004) e hematúria (Franchignoni *et al*., 2013). O efeito do EVCI nas concentrações plasmáticas de alguns biomarcadores tem sido investigado em humanos (Goto e Takamatsu, 2005; Di Giminiani *et al*., 2014) e em animais (Naghii *et al*., 2012; Pawlak *et al*., 2013; Frederico *et al*., 2014; Monteiro *et al*., 2017).

Como o uso dos EVCI tem aumentado (ver base de dados PubMed utilizando a palavra-chave "*whole body vibration*"), o desenvolvimento de modelos experimentais para avaliar, de uma forma controlada, o efeito desses exercícios em órgãos e tecidos é desejável. Uma das possíveis formas de avaliar a ação dessas vibrações nos tecidos/órgãos é através da biodistribuição de radiofármacos, como já descrito para outros tipos de exercícios físicos (Souza *et al*., 2011) e outros fatores (Yurekli *et al*., 2005). Pereira *et al*. (2013) utilizando EVCI com 20 Hz e Frederico *et al*. (2014), com 12 Hz, reportaram o efeito do EVCI na biodistribuição de radiofármacos em ratos usando a plataforma oscilante/vibratória.

A associação do EVCI com produtos medicamentosos, como com o alendronato tem sido sugerida (Chen *et al*., 2014). Da mesma forma com extratos de produtos naturais (Naghii *et al*., 2012; Wei *et al*., 2015). O intuito seria de potencializar seus efeitos biológicos do referido exercício.

Medicina Tradicional e Produtos Naturais

A Medicina Tradicional é a mais antiga forma de cuidados de saúde no mundo e é utilizada na prevenção e tratamento de doenças físicas e mentais. Diferentes sociedades historicamente desenvolveram vários métodos de cura para combater uma variedade de doenças que ameaçam a saúde e a vida. A medicina tradicional também é conhecida como medicina complementar e alternativa, ou étnica, e ao longo dos anos tem desempenhado um papel fundamental no sistema de saúde em muitos países (OMS, 2000; Abdullahi, 2011). Os medicamentos utilizados são principalmente derivados de produtos naturais (Montaser e Luesch, 2011).

Nos termos mais simples, um produto natural usado clinicamente apresenta moléculas, de origem vegetal, animal ou mineral. Através do uso de produtos naturais, a medicina tradicional oferece alternativa relevante, sob vários aspectos, em relação a outras formas de medicina, explorando características físico-químicas, bioquímicas, farmacocinéticas e toxicológicas. Se uma forma de medicina tradicional for aplicada com sucesso, pode ajudar no desenvolvimento de novos medicamentos, resultando assim em muitos benefícios, tais como reduções significativas de custos (Yuan *et al*., 2016).

Apesar da contínua sofisticação de outros métodos para elaboração de novas drogas, os produtos naturais ainda constituem importante fonte para a descoberta de medicamentos para uso clínico. Isso foi demonstrado por Newman, Cragg e Snader, que analisaram o número de drogas derivadas de produtos naturais presentes no total de lançamentos de medicamentos de 1981 a 2002 (Newtman *et al*., 2003). Aproximadamente 50% dos novos fármacos introduzidos de 1994 a 2011 eram produtos naturais ou seus derivados (Montaser e Luesch, 2011).

Desde os tempos pré-históricos, o Homem utiliza produtos naturais também para o alívio e tratamento de doenças. De acordo com os registros fósseis, o uso de plantas como medicamento remonta pelo menos 60 000 anos (Fabricant e Farnsworth, 2001; Shi *et al*., 2010). O uso de produtos naturais como medicamentos deve, evidentemente, ter apresentado um tremendo desafio para os primeiros humanos. É altamente provável que, ao procurar alimentos, os primeiros humanos geralmente consumiram plantas venenosas, o que levou a vômitos, diarreia, coma ou outras reações tóxicas - talvez até a morte. No entanto, desta forma, os primeiros humanos foram capazes de desenvolver conhecimentos sobre materiais comestíveis e medicamentos naturais (Gao *et al*., 2007). Posteriormente, os seres humanos inventaram o fogo, aprenderam a fazer álcool, desenvolveram as religiões e fizeram avanços tecnológicos, e aprenderam a desenvolver novas drogas (Yuan *et al*., 2016).

Os produtos naturais interagem com uma grande variedade de proteínas e outros alvos biológicos, atuando também como moduladores de processos celulares (Koehn e Carter, 2005; Barker *et al*., 2013).

Um produto natural importante e interessante, utilizado na medicina tradicional no tratamento de algumas doenças, é o coentro (*Coriandrum sativum* L.) (Bogavac *et al*., 2015; Dastgheib *et al*., 2017).

Coriandrum sativum L.

Coriandrum sativum L. (coentro) é membro da família Apiacea. É uma planta herbácea originária da região do Mediterrâneo, mas é usado em várias culturas principalmente como tempero e planta medicinal (Seidemann, 2005). A família das Apiaceae é uma das mais importantes do ponto de vista científico e econômico no mundo das plantas medicinais, encontrando-se largamente distribuída em zonas de clima temperado (Sriti *et al*., 2010). Uma das vantagens do coentro é que diferentes partes da planta podem ser utilizadas assim como, as sementes, a planta jovem ou adulta, ou mesmo os extratos das mesmas (Diederichsen, 1996).

Apesar do seu sabor e qualidades aromáticas, coentro tem provado o seu valor como uma erva medicinal importante, conforme relatado por vários cientistas. Na verdade, é empregado em preparações medicinais contra distúrbios digestivos na medicina popular. No norte do Paquistão, a planta inteira de coentro é usada para tratar flatulências, disenteria, diarreia, tosse, complicações estomacais, icterícia e vômitos (Khan e Khatoon, 2008). Além disso, na medicina tradicional indiana o coentro é utilizado nos distúrbios dos sistemas digestivo, respiratório e urinário, pois possui atividades diaforéticas, diuréticas, antiflatulento e estimulantes. Na Turquia, uma infusão de sementes é utilizada como agente digestivo e antiflatulento e para aumentar o apetite (Ugulu *et al*., 2009). Este atributo benéfico do coentro foi descrito inicialmente em estudos com animais. A ação digestiva pode ser considerada mediada através da ação no fígado para secretar mais bile enriquecida em ácidos biliares e estimular atividades enzimáticas que participam da digestão, tanto de origem pancreática quanto intestinal. Essa estimulação da secreção biliar e das atividades das enzimas digestivas leva a um processo digestivo geral acelerado, resultando em uma redução importante na duração da passagem de alimento através do trato gastrintestinal (Platel e Srinivasan, 2004).

O suco fresco de coentro é extremamente vantajoso para curar muitas deficiências relacionadas a vitaminas e ferro (Bhat *et al*., 2014). As sementes têm propriedades diuréticas, hipoglicêmicas, além de combater o reumatismo e as neuralgias articulares. Existem também citações à sua atividade antioxidante, devido à presença de derivados do ácido caféico, flavonoides, terpenos e outras moléculas com atividade similar (Wangensteen *et al*, 2004). Por possuir altas concentrações de moléculas antioxidantes pode ainda ser usado no combate à formação de radicais livres, prevenindo o estresse oxidativo, que contribui para algumas das doenças, como Alzheimer, Câncer, Parkinson, doença de Crohn e o processo de envelhecimento (Isabelle *et al*., 2010; Manda *et al*., 2010).

O coentro é também uma das plantas medicinais tradicionalmente utilizadas para o controle glicêmico e, em alguns países, sendo que na Arábia Saudita, na Jordânia e no Marrocos, uma infusão de sementes de coentro é usada como agente antidiabético (Al Rowais, 2002; Otoom *et al*., 2006; Tahraoui *et al*., 2007).

Diabetes mellitus

Diabetes mellitus (DM) é uma doença metabólica crônica que ocorre quando o pâncreas perde a capacidade de produzir insulina, ou o corpo não consegue fazer um bom uso da insulina que produz (IDF, 2017). De acordo com a OMS, a DM afeta cerca de 422 milhões (550 milhões até 2030) de pessoas no mundo e é a maior causa de cegueira, insuficiência renal, ataque cardíaco, acidentes vasculares cerebrais e amputação de membros inferiores (OMS, 2017). Existem dois tipos principais de DM: tipo 1 (T1DM) e tipo 2 (T2DM). A T1DM ocorre quando há uma destruição autoimune das células β pancreáticas, resultando assim numa redução ou perda da capacidade da produção de insulina e hiperglicemia crônica. Ela afeta aproximadamente 10% de todos os casos da DM. Enquanto que o T2DM é caracterizado pela resistência à insulina e deficiência relativa de insulina (IDF, 2017).

A DM tem uma longa história, voltando para a antiguidade. No entanto, durante esse período, devido ao limitado conhecimento da anatomia, fisiopatologia e falta de ferramentas de diagnóstico, a doença permaneceu indefinida para os médicos (Karamanou *et al*., 2016). Apesar disso, os médicos da antiguidade observaram as características distintas da DM e propuseram várias abordagens terapêuticas. Em papiros Ebers, datado de 1500 a.C, podem ser encontradas descrições de pacientes que sofriam de sede excessiva, micção abundante e eram tratados com extratos de plantas.

Na China antiga, Chang Chung-Ching (160 a 219), descreveu poliúria, polidipsia e perda de peso como sintomas de uma doença específica. No século VII, Chen Chuan descreveu urina doce no indivíduo e denominou a doença de *Hsiao kho ping*, mencionando seus sintomas característicos: sede intensa, ingestão hídrica abundante e grandes quantidades de urina cujo sabor é doce (Peumery**,** 1987; Karamanou *et al*., 2016).

Antigos egípcios, índios, chineses e árabes tentaram descrever os sinais e sintomas clínicos relacionados possivelmente com a DM. Poucos são os protagonistas da história dessa doença que contribuíram significantemente, não só para seu diagnóstico e tratamento, mas também para o desenvolvimento de noções atuais sobre a doença. Isso permitiu estudo mais intensos e estabelecimento de uma nova especialidade médica, a diabetologia (Karamanou *et al*., 2016).

Thomas Willis (1621-1675), médico e anatomista inglês, comentou sobre urina doce em pacientes com diabetes, cunhando também o termo *mellitus* (doce). Terapeuticamente, considerou benéfico para a doença uma "dieta moderadamente refrescante” e ele mencionou que legumes, arroz e amido branco poderiam melhorar o *status* do paciente (Furdell, 2009).

Um momento de relevância na história da DM ocorreu em 1889 após as experiências de Minkowski e von Mering. Em 1889, von Mering trabalhava no Instituto Hoppe Seyler na Universidade de Estrasburgo, e Minkowski visitou o Instituto para examinar alguns livros da biblioteca. Eles se conheceram acidentalmente e conversaram sobre lipanina, um óleo contendo ácidos graxos livres e que von Mering usava para administrar a pacientes que sofriam de distúrbios digestivos. Minkowski não era a favor da ingestão de lipanina. Em seguida foi discutido se o pâncreas teria papel na digestão e absorção de gorduras. Como resultado da discussão, decidiram realizar uma pancreatectomia em um cachorro. Logo após a operação, o animal desenvolveu poliúria. Minkowski examinou a urina e descobriu que continha 12% de açúcar. Inicialmente, Minkowski acreditava que o cachorro desenvolveu DM devido ao fato de que von Mering o havia tratado há muito tempo com a florizina. Então repetiu a pancreatectomia em mais três cachorros que não tinham açúcar na urina antes da operação e todos desenvolveram a glicosúria (von Mering e Minkowski, 1889; Karamanou *et al*., 2016). Posteriormente, Minkowski implantou uma pequena porção de pâncreas subcutaneamente, e observou que a hiperglicemia foi prevenida até o implante ser removido ou degenerado espontaneamente (von Mering e Minkowski, 1889).

Minkowski e von Mering demonstraram que o pâncreas era uma glândula de secreção interna importante para a manutenção da homeostase da glicose. Também permitiram que novos estudos fossem realizados por Banting e Best, com relevante impacto na compreensão da DM (Karamanou *et al*., 2016).

Em 1920, Moses Barron, médico em Minnesota, publicou um artigo “*The relation of the islets of Langerhans to diabetes*”, com referência especial aos casos de litíase pancreática **(**Barron, 1920; Karamanou *et al*., 2016), que mencionava que a continuação das experiências de Minkowski e von Mering poderia levar a descoberta de uma substância capaz de controlar a DM. Influenciado por este artigo, Banting intensificou seus estudos sobre diabetes.

Em 1923, o Prêmio Nobel de Medicina foi concedido a Frederick Banting e John MacLeod pela descoberta da insulina. Foi concluído assim um passo crucial na história da DM. Ao longo dos próximos anos, os métodos de purificação de insulina melhoraram e novas formulações de insulina foram desenvolvidas (Karamanou *et al*., 2016).

Devido à relevância e consequências indesejáveis da DM, estudos, também através de modelos experimentais, que possam favorecer melhor entendimento e controle dessa doença são desejáveis.

Efeitos biológicos

Diversos modelos experimentais têm sido usados para avaliação de efeitos biológicos de produtos naturais de forma isolada, ou em conjunto com a exposição às vibrações mecânicas (Wei *et al*., 2015), como a biodistribuição de radiofármacos (Cardoso *et al*., 2017), o consumo de alimentos (Frederico *et al*., 2017a), a massa corporal (Cardoso *et al*., 2017), a consistência das fezes (Frederico *et al*., 2017a), a concentração de biomarcadores plasmáticos (Monteiro *et al*., 2017), o processo de cicatrização (Weinheimer-Haus *et al*., 2014) e análise dos constituintes ósseos (Wei *et al*., 2015).

Um dos modelos envolveu o uso de radiofármaco (Ogawa *et al*., 2011; Amin *et al*., 2015). O radiofármaco pertecnetato de sódio ($Na^{99m}TcO_4$) é distribuído através dos líquidos vasculares e intersticiais e apresenta normalmente uma captação preferencial na tiroide, estômago, trato intestinal, e glândulas salivares (Saha, 2010). Vários fatores, como a terapia com drogas, com radiação, processos cirúrgicos, condições de dieta, além de doenças podem alterar a biodistribuição de diferentes radiofármacos (Bernardo-Filho *et al*., 2005, Vallabhajosula *et al*., 2010). Se desconhecido, este fato poderá acarretar a repetição do exame ou mesmo resultar em uma interpretação inadequada da imagem cintilográfica, gerando assim falsos positivos ou negativos com possíveis consequências indesejáveis para o paciente e seu diagnóstico/tratamento (Bustani *et al*., 2009). Desse modo, torna-se atraente usar esse modelo experimental na tentativa de melhor entendimento de fenômenos biológicos relacionados também com a DM, em animais saudáveis ou com T1DM.

A determinação da concentração de biomarcadores pode ajudar no entendimento de mecanismos de ação relacionados à algumas respostas biológicas. Rittweger (2010) sugeriu que as alterações na concentração de biomarcadores plasmáticos devido às respostas endócrinas relacionadas aos exercícios permitem acompanhar o efeito biológicos desses exercícios. O efeito do EVCI isolado nas concentrações plasmáticas de alguns biomarcadores tem sido investigado em humanos (Goto e Takamatsu, 2005; Di Giminiani *et al*., 2014), e em animais (Naghii *et al*., 2012; Pawlak *et al*., 2013; Frederico *et al*., 2014; Monteiro *et al*., 2015), assim como a sua associação com plantas medicinais (Frederico *et al*., 2017a; Cardoso *et al*., 2017).

Outro modelo experimental utilizado é a análise da massa corporal. O aumento da adiposidade em indivíduos pode comprometer o controle metabólico. Em doenças como a T1DM pode aumentar a resistência à insulina e pode ser associado com um perfil lipídico aterogênico (Maahs *et al*., 2011) e um maior risco de doenças cardiovasculares (Specht *et al*., 2013). Cardoso *et al*., 2017 analisaram a massa corporal de ratos *Wistar* saudáveis submetidos ao EVCI associado a um extrato aquoso de *Chenopodium ambrosioides*. A exposição ao exercício físico e o tratamento com plantas medicinais podem ser importantes no entendimento de sistemas que controlam o equilíbrio energético através da análise da massa corporal (Pan e Myers, 2018).

Os processos fisiológicos que sustentam a vida reduzem constantemente as reservas de energia corporais, que devem ser substituídas pela ingestão de alimentos; portanto, a alimentação é um comportamento obrigatório para a sobrevivência (Schroeder e Leinninger, 2017). Cardoso *et al.*, 2017 avaliaram o consumo de ração de ratos *Wistar* saudáveis submetidos ao EVCI associado a um extrato aquoso de *Chenopodium ambrosioides*. Definir a biologia da ingestão é necessário não só para entender a sobrevivência imediata, mas também para tratar e, em última instância, prevenir, a desregulação alimentar que põe em perigo a saúde e o bem-estar do indivíduo. Por exemplo, a ingestão de calorias em excesso, juntamente com a atividade física e a taxa metabólica insuficientes, resulta em aumento da adiposidade (Budd e Peterson, 2014). Assim sendo, torna-se importante avaliar o consumo de ração de ratos com ou sem T1DM.

A análise da consistência das fezes também ajuda na compreensão de processos biológicos. Por ser difícil de quantificar com testes simples, a sua análise é bastante subjetiva (Schiller, 2012). Dieta, medicamentos e doenças podem alterar a consistência das fezes (Schiller *et al*., 2017). Cada categoria (escala de Bristol) da consistência reflete diferenças no conteúdo de água, com a diminuição da atividade de água, associado com o trânsito intestinal prolongado, limitando o crescimento microbiano através da redução da mobilidade de nutrientes e atividade enzimática dificultada (Schiraldi *et al*., 2012). Consequentemente, a categorização da escala de Bristol resume o impacto de dois principais, e obviamente relacionados, fenômenos que moldam o ecossistema intestinal: taxa de trânsito intestinal e atividade da água (Vandeputte *et al*., 2015). Frederico *et al.* (2017a) sugeriram uma escala adaptada para avaliação da consistência de fezes de ratos.

1 **OBJETIVOS**

1.1 **Objetivo geral**

O objetivo deste estudo foi avaliar o efeito biológico do EVCI em associação com um extrato aquoso de *Coriandrum sativum* em ratos *Wistar* saudáveis e com diabetes do tipo 1.

1.2 **Objetivos específicos**

Avaliar em ratos *Wistar*, com ou sem diabetes do tipo 1, submetidos à vibração de 50 Hz gerada em plataforma com deslocamento sincrônico da base e tratados com extrato de *Coriandrum sativum:*

a) a biodistribuição do radiofármaco $Na^{99m}TcO_4$;
b) as concentrações de biomarcadores plasmáticos;
c) a consistência das fezes;
d) a massa corporal dos animais;
e) o consumo diário de alimentação.

2 **METODOLOGIA E RESULTADOS**

As metodologias desenvolvidas nessa tese, assim como os resultados são apresentados em um artigo já publicado e em um manuscrito que foi submetido à uma revista científica.

O projeto de pesquisa foi aprovado pelo Comitê de Ética para o Uso de Animais Experimentais (CEUA) do Instituto de Biologia Roberto Alcantara Gomes (IBRAG) sob o parecer: CEUA/041/2013.

Artigo publicado: Whole body vibration exercise associated with extract of *Coriandrum sativum* modifies some biochemical/physiological parameters in rats.

Frederico, EHFF; Cardoso, ALBD; Guimarães, CAS; Almeida, LP; Neves, RF; Sá-Caputo, DC; Moreira-Marconi, E; Dionello, CF; Morel, DS; Paineiras-Domingos, LL; Costa-Cavalcanti, RG; Gonçalves, CR; Arnóbio, A; Asad, NR; Bernardo-Filho, M.

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Manuscrito submetido: The effect of whole body vibration exercise and *Coriandrum sativum* L. in *Wistar* rats with type 1 diabetes mellitus

Frederico, EHFF; Cardoso, ALBD; Guimarães, CAS; Barros-Conceição, L; Moura-Fernandes, MC; Morel, DS; Dionello, CF; Moreira-Marconi, E; Sousa-Gonçalves, CR; Sá-Caputo DC; Judex S; Bernardo-Filho, M [2]

3 **DISCUSSÃO**

Modelos experimentais visando estudar o efeito de intervenção empregando um produto natural ou sintético em associação com EVCI são desejáveis. Neste estudo, o objetivo foi verificar se a combinação do EVCI com um extrato aquoso de coentro poderia potencializar os efeitos biológicos de tratamentos isolados dos referidos agentes em ratos *Wistar* saudáveis ou com diabetes.

Foi escolhido o EVCI porque pode ser de fácil acesso a grandes populações devido a sua natureza minimamente invasiva, poucos efeitos colaterais, baixo custo, simplicidade, e curta duração (Kessler e Hong, 2013; Jing *et al*., 2017). Da mesma forma, o coentro é uma das plantas medicinais mais comumente utilizadas na redução de glicose na medicina popular, o que o torna útil no tratamento da DM.

Foram avaliados nesse estudo, os efeitos do tratamento com EVCI e um extrato de coentro na biodistribuição do radiofármaco $Na^{99m}TcO_4$, na concentração de alguns biomarcadores plasmáticos, no consumo de ração, na massa corporal e na consistência de fezes em ratos *Wistar*.

Considerando os animais saudáveis (ver artigo publicado, página 25), em intervenção com EVCI (50 Hz durante quarenta dias) e um extrato de coentro, foi verificado aumento na captação do radiofármaco $Na^{99m}TcO_4$ no testículo apenas em animais do grupo tratado com coentro em comparação com ratos do grupo submetido ao EVCI. Frederico *et al*. (2014) demostraram que a associação entre coentro e EVCI (12 Hz, doze dias) aumentou captação do $Na^{99m}TcO_4$ no baço. Em 2010, Sharma *et al*. relataram a eficácia profilática do coentro em testículos de camundongos expostos a chumbo. Além disso, a suplementação de extrato aquoso de coentro também provocaria um aumento da densidade de esperma, em comparação com o grupo tratado com nitrato de chumbo. Os efeitos biológicos dos EVCI em um órgão parecem também depender da frequência utilizada (Pereira *et al*., 2013; Frederico *et al*., 2014). Miyazaki (2000) avaliou a eletrogastrografia (EGG) na exposição de voluntários masculinos saudáveis a vibrações de 4, 8 e 16 Hz. Foi observado que apenas as vibrações de 4 e 8 Hz diminuíram a amplitude da EGG.

A determinação do efeito do WBV de 40 dias (50 Hz) no nível de biomarcadores plasmáticos em ratos tratados com coentro não mostrou alterações significativas nas concentrações dos biomarcadores estudados. Embora os protocolos com EVCI usados por outros autores não foram exatamente similares ao utilizado neste estudo, o resultado corrobora com o de Pawlak *et al*. (2013) que mostraram que o EVCI (50 Hz) com duração de 3 ou 6 meses não afeta as concentrações de biomarcadores no soro sanguíneo de ratos. Naghii *et al*. (2012), usando um protocolo diferente, determinaram as concentrações de lipídios plasmáticos (colesterol total, LDL e HDL) em ratos submetidos às vibrações nas frequências de 10-50 Hz e não encontraram alteração nas concentrações desses biomarcadores, embora tenham encontrado diferenças significativas nos níveis plasmáticos de creatina quinase (CK). Os níveis de CK no plasma foram significativamente maiores no grupo submetido à vibração em comparação com o controle.

Em relação a massa corporal, a comparação dos animais entre os grupos mostrou que não houve alteração significativa nesse parâmetro em ratos tratados 40 dias simultaneamente com coentro e EVCI. É importante ressaltar que, esse resultado não está associado ao consumo de ração, que foi maior em ratos submetidos ao EVCI. Este achado pode ser associado aos achados relatados por Wang e Kerrick *et al*. (2002) que verificaram que aplicando vibração em fibras isoladas ou intactas ocorre aumento específico no *turnover* de ATP. Estes resultados estão de acordo com os do Huang *et al*. (2014) que relataram em camundongos com obesidade induzida por uma dieta rica em gordura (HFD), não houver diferença na massa corporal entre o grupo HFD e o controle sedentário, HFD e o grupo submetido ao EVCI com relativa baixa intensidade (5,6 Hz, 0,13 g) (HFD + VL) ou de alta intensidade (13 Hz, 0,68 g) (HFD + VH). Além disso, Di Loreto *et al*. (2004) descreveram que, uma vez que as respostas hormonais, com exceção da norepinefrina, não são afetadas pela exposição aguda ao EVCI, não se espera que esse tipo de exercício reduza a massa de gordura.

O efeito da associação de EVCI de 40 dias (50Hz) com coentro no consumo de ração em ratos mostrou alterações entre os grupos. Um aumento significativo na ingestão alimentar foi encontrado em animais do grupo submetido ao EVCI. Este resultado difere de Frederico *et al*. (2014) que não relataram diferença na quantidade de alimento consumido entre os grupos. Huang *et al*. (2014) também não mostraram diferença na ingestão de energia entre os grupos estudados usando um protocolo diferente.

A consistência das fezes de animais submetidos a diferentes tratamentos permitiu verificar que os ratos que consumiram apenas coentro tiveram a consistência das fezes classificada como tipo 1 (dura). Nos animais submetidos ao EVCI associado com coentro, a consistência das fezes foi normal (tipo 2). Esse achado indicou que o EVCI atuaria em algum processo fisiológico/metabólico no sistema gastrintestinal que seria relacionado à normalização da consistência das fezes. Considerando o sistema gastrintestinal, Ishitake *et al*. (1998) relataram que o EVCI suprime a mobilidade gástrica em homens saudáveis. Além disso, as fezes duras (tipo 1) em animais tratados com coentro pode ser justificada devido ao efeito deste produto natural que é usado na medicina tradicional para o tratamento de doenças gastrintestinais, como a diarreia (Usmanghani, *et al*., 2003).

Considerando os animais com T1DM, verifica-se que existe falta de informação sobre os efeitos hipoglicêmicos das plantas medicinais e exercício físico no tratamento da T1DM. A nossa hipótese foi que a associação do coentro com o EVCI melhoraria alguns aspectos clínicos da T1DM. Neste estudo, a combinação do coentro e EVCI em ratos *Wistar* com T1DM foi verificada em alguns órgãos (através da biodistribuição de $Na^{99m}TcO_4$), em alguns biomarcadores plasmáticos, na massa corporal, no consumo de ração e na consistência de fezes.

Em nossos resultados, não foi encontrada alteração na captação (% ATI/g) do $Na^{99m}TcO_4$ nos órgãos estudados. Este achado indica que a intervenção com EVCI e/ou coentro não foi capaz de promover modificações bioquímicas/fisiológicas importantes nesses órgãos de ratos com T1DM. Ogawa *et al*. (2011) mostraram que as imagens de tomografia por emissão de pósitrons (PET) não revelaram diferença significativa na taxa de captação entre os ratos *Wistar* adultos machos submetidos ao EVCI e o controle. Por outro lado, Amin *et al*. (2015) relataram uma influência fisiológica do EVCI sobre a qualidade da imagem cintilográfica aumentando a captação óssea do ^{99m}Tc metilenodifosfonato (^{99m}Tc-MDP), proporcionando uma maior qualidade de imagem. No entanto, não relataram o dispositivo de vibração usado, nem os parâmetros biomecânicos, que são importantes para determinar a intensidade do exercício.

Também foi avaliado o efeito do coentro e/ou do EVCI (50 Hz, plataforma vertical)) em alguns biomarcadores plasmáticos nos animais com T1DM. Os resultados não mostraram alterações significativas nas suas concentrações. Esse achado está de acordo com resultados em ratos saudáveis (Frederico *et al*., 2017a) onde foram usados os mesmos parâmetros biomecânicos (50 Hz). Em um outro estudo com vibração mecânica com 25 Hz (Frederico *et al*., 2017b), foi encontrada uma diminuição da amilase. Monteiro *et al*. (2017) também encontraram uma diminuição nos níveis de LDL após exposição de 10 Hz. Possivelmente, esses resultados são atribuídos a um diferente tipo de plataforma para obtenção de vibração (plataforma com descolamento alternado da base) e parâmetros biomecânicos diferentes utilizados (10 e 25 Hz). Erceg *et al*. (2015) não encontraram diferenças nas concentrações de biomarcadores ósseos em um programa de EVCI de 10 semanas em jovens latinos com sobrepeso.

O efeito do coentro e/ou EVCI na massa corporal mostrou que não há diferença entre os grupos. Este achado corrobora com Frederico *et al*. (2017a), usando um mesmo desenho de estudo, mas em ratos machos saudáveis. Chen *et al*. (2016) relataram que a massa corporal do grupo submetido ao EVCI não diferiu significativamente durante o período experimental de 6 semanas em comparação com os grupos de controle sedentário e EVCI+ dehidroepiandrosterona (DHEA), em camundongos. Além disso, Sun *et al*. (2015) não relataram diferenças significativas entre o grupo controle e o grupo EVCI em grupos de dieta com alto teor de gordura ou grupo de dieta normal em ratos Sprague-Dawley machos. Lin *et al*. (2015) também não mostraram diferenças na massa corporal em camundongos de meia idade com ou sem um regime de EVCI de 4 semanas. Por outro lado, de Vries *et al*. (2014) relataram após o diagnóstico de DM, que a massa e o índice de massa corporal (IMC) aumentaram rapidamente, com o ganho de massa mais rápido durante as primeiras 2 semanas em crianças e adolescentes com T1DM. Em relação ao extrato de coentro, Aissaoui *et al*. (2002) mostraram que a administração oral diária durante 30 dias em ratos *Meriones shawi* obesos-hiperglicêmicos-hiperlipidêmicos não teve nenhum efeito significativo na massa corporal.

Não houve diferença no consumo de ração em ratos com T1DM submetidos ao EVCI e/ou tratados com coentro. Este resultado difere de Frederico *et al*. (2017a) que mostrou um aumento no consumo de ração em animais saudáveis submetidos ao EVCI. Cardoso *et al*. (2017) também descreveram uma maior ingestão alimentar no grupo EVCI quando comparado aos outros grupos. Vale ressaltar que esses dois estudos foram realizados em animais saudáveis. Com um achado similar, Chen *et al*. (2016) demonstraram que o EVCI e/ou suplementação de DHEA não alterou a ingestão de ração em camundongos.

Apesar do coentro ser usado para o tratamento de algumas doenças gastrintestinais, como diarreia (Usmanghani *et al*., 2003), não foi encontrada alteração na consistência das fezes. Este fato pode ser explicado devido à má absorção ou danos no nervo pélvico causados por neuropatia periférica diabética. Isso levaria a um aumento na frequência de movimento intestinal (de la Luz Nieto *et al*., 2015), minimizando assim o efeito do coentro. Os achados no presente estudo corroboram com Cardoso *et al*. (2017), que estudando o efeito da associação do EVCI e um extrato aquoso de *Chenopodium ambrosioides*, em ratos *Wistar* machos, não encontraram alteração na consistência das fezes. Frederico *et al*. (2017a) mostraram uma alteração na consistência das fezes em ratos saudáveis que consumiram apenas coentro em comparação com os outros grupos.

O presente estudo tem algumas limitações, como o pequeno número de animais em cada grupo. No entanto, seguiu-se os critérios de estratégias de redução de animais em pesquisa, publicado por de Boo, e Hendriksen em 2005. Além do mais, um tipo especial de gaiola não foi usado para separar as fezes. Os ratos submetidos ao EVCI foram imobilizados na plataforma. Isso poderia induzir o estresse da imobilidade, que potencialmente poderia alterar alguns parâmetros fisiológicos dos ratos. Como os ratos do grupo controle não foram submetidos ao estresse de imobilidade, a concentração plasmática de biomarcadores específicos relacionados ao estresse poderia ser considerada. A sugestão de novos modelos experimentais envolvendo a exposição de animais ao (i) EVCI com parâmetros biomecânicos (frequência, deslocamento pico a pico e aceleração de pico) e tempo de exposição diferentes e (ii) outros. No entanto, serão necessários mais estudos para tentar entender melhor os efeitos biológicos do envolvimento da associação do EVCI e um extrato aquoso de coentro em ratos *Wistar* saudáveis. O estudo com ratos comT1DM também tem algumas limitações, já que alguns hormônios de interesse (exemplo: insulina) não foram medidos. Uma análise da hemoglobina glicada (HbA1) também seria interessante para o diagnóstico da DM.

CONCLUSÃO

Pode-se concluir que (i) nos animais saudáveis, foram verificadas modificações em alguns parâmetros bioquímicos/fisiológicos nos ratos submetidos ao EVCI capaz de aumentar o consumo de ração sem correspondente aumento da massa corporal, e normatizar a consistência das fezes alterada pelo consumo de coentro, (ii) sendo que nos animais com T1DM não foram encontradas diferenças nos parâmetros estudados com as referidas intervenções.

Estudos adicionais envolvendo EVCI e plantas medicinais em animais também tratados com insulina são necessários. Da mesma forma, seriam desejadas investigações expondo os animais ao EVCI, utilizando parâmetros biomecânicos diferentes.

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ANEXO A – Formato final do 1º artigo científico

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Research Article

Whole body vibration exercise combined with an extract of *Coriandrum sativum* modify some biochemical/physiological parameters in rats

Éric H.F.F. Frederico[1], André L.B.D. Cardoso[2], Carlos A.S. Guimarães[3], Lívia P. Almeida[3], Rosane F. Neves[3], Danúbia C. Sá-Caputo[2], Eloá Moreira-Marconi[4], Carla F. Dionello[2], Danielle S. Morel[2], Laisa L. Paineiras-Domingos[2], Rebeca G. Costa-Cavalcanti[3], Cintia R. Sousa-Gonçalves[2], Adriano Arnóbio[3], Nasser R. Asad[3] and Mario Bernardo-Filho[3]

[1]Programa de Pós-graduação em Biociências, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ 20551-030, Brasil; [2]Programa de Pós-Graduação em Ciências Médicas, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ 20551-030, Brasil; [3]Laboratório de Vibrações Mecânicas e Práticas Integrativas e Complementares, Departamento de Biofísica e Biometria, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ 20551-030, Brasil; [4]Programa de Pós-Graduação em Fisiopatologia Clínica e Experimental, Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ 20551-030, Brasil

Correspondence: Éric H.F.F. Frederico (ericfrederico@msn.com)

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The aim of the present study was to evaluate the effect of the association of whole body vibration (WBV) exercise with an aqueous extract of coriander on the biodistribution of the radiopharmaceutical sodium pertechnetate, on the concentration of some plasma biomarker, on the feed intake, on the body mass, and on the stool consistency in rats. Rats were divided in four groups and submitted to different treatments for 40 days. The control group (CON) received deionized water. The group treated with coriander (COR) received the extract of coriander. The rats that were exposed to WBV exercises (WBV-E) also received deionized water. A group of animals received coriander and was exposed to WBV (COR + WBV-E). We found in testis a decrease (0.13 ± 0.01 to 0.06 ± 0.03) of the percentages of injected radioactivity per gram (%ATI/g) in the WBV-E in comparison with the COR. There is no significant alteration on the concentrations of the plasma biomarkers. The feed intake showed a statistically significant increase in WBV-E. No significant difference on the body mass was found. The stool analysis showed a statistical difference on the consistency between COR (hard and dry, darker) and all the other groups (normal). In conclusion, it was verified that possible modifications in some biochemical/physiological parameters of the rats submitted to WBV exercise would be capable to increase the feed intake without changing the body mass, and normalizing the stool consistency altered by the coriander supplementation. Further studies are needed to try to understand better the biological effects involving the association of WBV exercise and coriander.

Introduction

Mechanical vibrations can be defined as a physical agent with harmonic oscillatory motion about an equilibrium point. They can be artificially produced in oscillating/vibratory platforms [1–3]. Furthermore, they can be transmitted to the body when there is a direct contact of the subject with the base of this platform in operation. The exposure to these vibrations generated in oscillating/vibratory platform produces whole body vibration (WBV) exercises [1,4].

The clinical use of the WBV exercises has been reviewed and important findings described [1,3] such as increased muscle strength and power, improved balance, increased bone mineral density [5–7], aspects related to quality of life and decrease the risk of falls [8,9]. In addition, a non-health promoting

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effects on blood profile was reported by Theodorou et al. [10]. However, undesirable effects have been reported in a revision (Sá-Caputo et al., 2015) as hot feet, itching of the lower limbs, vertigo [11], severe hip discomfort, pain of jaw, neck and lower limbs [12], and hematuria [13].

Rauch et al. [2] have discussed several parameters related to the use of WBV exercises and that must be considered. In consequence, the biomechanical parameters such as frequency, amplitude, and peak acceleration must be selected and adapted to the characteristics of each individual. In controlled conditions, the vibrations generate WBV exercise in good and safe conditions [3]. In addition, it should be set as a working time interspersed with a rest time [2–4].

The effect of the WBV exercises on the concentrations of some biomarkers has been investigated in human beings [14,15] and in animals [16–18].

As the use of the WBV exercises has been increased (see PubMed database, using the keyword 'whole body vibration'), the development of experimental models to evaluate, in a controlled manner, the effect of these exercises in organs and tissues is desirable. One of the possible ways to study these vibrations in tissues/organs, it is by evaluating the biodistribution of radiopharmaceuticals, as already described for physical activity [19], chemical [20], and physical (laser) agents [21]. Pereira et al. [22] (vibration with 20 Hz) and Frederico et al. [16] (vibration with 12 Hz) reported the effect of WBV exercise in the biodistribution of radiopharmaceuticals in rats using a side-alternating platform.

Authors have investigated the effect of the WBV exercise in association with some substances [23–26], including natural products [16,17].

Natural products have been used by human beings as food sources and as medications [27]. However, the mechanism of action and the efficacy of these natural products in most cases must be validated scientifically [28]. *Coriandrum sativum* (coriander) is an herbaceous plant that has been used in the management of patients with diabetes [29,30]. It is originally from the Eastern Mediterranean region, belonging to family *Apiaceae* [31]. Furthermore, it is grown in a wide range of environmental conditions [32]. It is cultivated for its aromatic leaves and seeds in North Africa, Central Europe, and Asia as a spice and a medicine [33]. Coriander is known to possess antifungal [34], antibacterial [35], and antioxidant [36] properties. In traditional medicine, it is used for gastrointestinal complications such as dyspepsia, flatulence, diarrhea, vomiting [37], and as an antiseptic and emmenagogue [38].

The aim of the present study was to evaluate the effect of the association of WBV exercise with an aqueous extract of coriander on the biodistribution of the radiopharmaceutical sodium pertechnetate ($Na^{99m}TcO_4$), on the concentration of some plasma biomarkers, on the body mass, on the feed intake, and on the stool consistency in *Wistar* rats.

Material and methods

Animals and ethical approach

Adult Wistar rats (n=20, 245–280 g) aging from 3 to 4 months. The animals were kept under care at average temperature of 25°C, relative humidity approximately 55% and light/dark cycle of 12 h and were fed with standard diet and water *ad libitum*. All experiments were conducted following the standards of the *Comitê de Ética Para o Uso de Animais Exprimentais* (CEUA), *Instituto de Biologia Roberto Alcantara Gomes* (IBRAG) that has approved the investigation (CEUA/041/2013).

Preparation of the extract of coriander

A commercial dry seed of coriander (*C. sativum*) was used (lot 075, validity up to May 2017, *Distribuidora de Cereais Crowne Ltda*, Rio de Janeiro). This natural product was chosen because it is also used as a medicinal plant. To prepare the extract, 80 mg of *C. sativum* was added to 10 ml of deionized water. Then, the preparation was vortexed for 1 min, centrifuged (clinical centrifuge, 15000 rpm, 15 min), and the supernatant was considered to be at a concentration of 8 mg/ml. The quality control of the preparation of the extract was controlled with spectrophotometer analysis (extract with optical density at 480 nm), as previously published [39].

Experimental procedures

The WBV exercise was performed everyday between 7.00 and 9.00 a.m. on a synchronous platform (Globus G-Vibe 800, Italy), which generated sinusoidal vertical vibrations at 50 Hz frequency, 0.78 mm amplitude, and peak acceleration of 7.84 g.

The Wistar rats (n=20) were divided equally in four groups. The control group (CON), that received by gavage [40] 1.0 ml of deionized water. The coriander group (COR), where animals received 1.0 ml of aqueous extract (8 mg/ml) also by gavage. The rats that were submitted to the vibration generated in the platform (WBV-E) also received 1.0 ml

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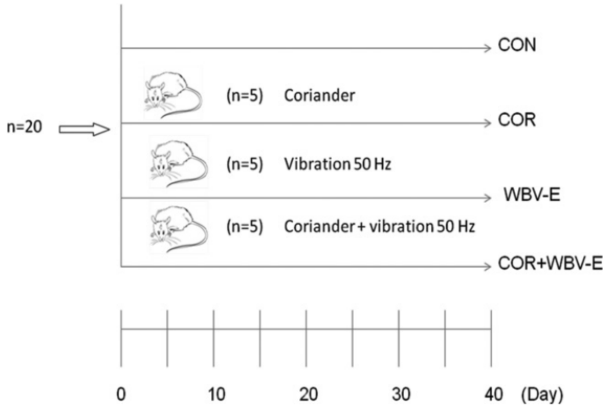

Figure 1. Experimental design.

20 Wistar rats were divided randomly in four groups, each one, in a cage. 1) CON - group received by gavage deionized water. 2) COR - received by gavage coriander. 3) WBV-E - received by gavage deionized water and were submitted to vibration generated in platform, 50Hz, 0.78 mm and 7.84 g peak acceleration or 4) COR+WBV-E - received bay gavage coriander and were submitted to vibration generated in platform, 50Hz, 0.78 mm and 7.84 g peak acceleration

of deionized water. Animals of the group (COR + WBV-E) received 1.0 ml of coriander (8g/ml) and were submitted to vibration generated in the platform. The animals received saline (group CON) or coriander extract (groups COR and COR + WBV-E) daily during 40 consecutive days. The animals of the groups WBV-E and COR + WBV-E were submitted every day during 40 consecutive days to vibrations generated in the platform.

The scheme of distribution of the groups is depicted in the experimental design that is shown in Figure 1.

The work time of the animals in the platform was 5 min, considering four bouts of 30 s separated by 1-min rest intervals. The animals were put in a man-made acrylic base fixed in the teeterboard of the platform with tape, as it is shown in Figure 2. Every day the animals of CON and COR groups were put close to the platform (approximately 30 cm) that was turn on, to avoid a possible bias of stress provoked by sound and other factors of the surrounding of the synchronous platform. However, the animals did not have a direct contact with the platform (Figure 2). This investigation used a similar frequency and total time per day reported by Pawlak et al. [18] in the treatment of the rats on the platform.

Administration of the radiopharmaceuticals and blood samples collection for biochemical analysis

One day after the different treatments (41th day), the animals were anesthetized with sodium thiopental. Just after the animals' anesthesia effect, the radiopharmaceutical $Na^{99m}TcO_4$ (1.85 MBq/ml) was administrated 0.3 ml (550 kBq) via ocular plexus. After 10 min, sample of blood was obtained from by cardiac puncture and used for biochemical analysis. Following, the animals were killed (CO_2 asphyxiation) (CONCEA, 2013), the organs (thyroid, stomach, bowel, kidney, liver, pancreas, brain, bone, lung, heart, spleen, muscle, penis, prostate, seminal vesicle, bladder, testis, and blood) were isolated, the radioactivity determined in a well counter, and the percentages of injected radioactivity per gram (%ATI/g) in the organs were calculated as reported elsewhere [22].

Sample of whole blood (without anticoagulant) was also withdrawn to determine the concentrations of selected plasma biomarkers (glucose, urea, creatinine, cholesterol, triglyceride, high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, creatine kinase (CK), calcium, magnesium, total protein, and albumin), were then measured in a clinical laboratory of the *Universidade do Estado do Rio de Janeiro*. The determinations were performed in automated equipment (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland).

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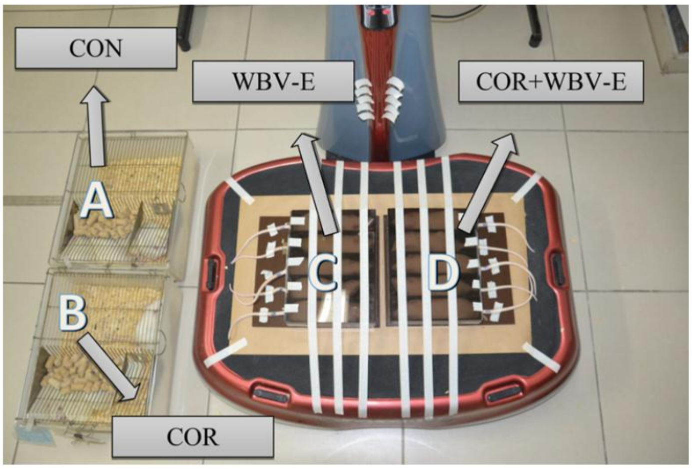

Figure 2. *Wistar* rats on (C and D) and close (A and B) of the platform
CON - control group; COR - group treated with coriander; WBV-E - whole body vibration exercise group; and COR+WBV-E - group treated with coriander and submitted to whole body vibration exercise.

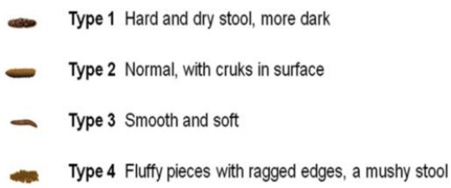

Figure 3. Bristol stool form scale adapted for *Wistar* rats

Body mass analysis

All the animals were weighed weekly on a digital balance (FILIZOLA BP6, São Paulo, Brazil). The mass of each animal was determined. The mass of the animals of each group was determined by percentage (%). The % was calculated as the ratio between the mass of animals in each week with the first day, and multiplied by 100.

Feed intake analysis

The feed intake was measured daily in each group. Five hundred grams of feed was offered daily. In the next day, the left feed was determined on a digital balance (FILIZOLA BP6, São Paulo, Brazil). The feed intake was calculated by the difference between 500 g and the left feed in each day. Following, the quantity of feed was completed daily to 500 g.

Stool consistency analysis

A stool consistency was made using a Bristol stool form scale [41] adapted as depicted in Figure 3. Three different, independent, and blinded evaluators have analyzed daily and qualitatively the consistency of the stool and according to the scale, they choose a value (Figure 3). The median of these three analyses was considered. The stool sample was collected before the gavage of the animals.

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Table 1 %ATI/g of the $Na^{99m}TcO_4$ in the various organs isolated from the animals submitted to different treatments

Organs	CON	COR	WBV-E	COR + WBV-E	*P*	^{2}
Thyroid	3.87 ± 1.98	3.14 ± 1.05	2.28 ± 1.30	3.34 ± 1.06	0.5758	0.1240
Stomach	1.36 ± 0.22	2.15 ± 1.26	1.46 ± 0.81	1.64 ± 0.91	0.4267	0.1545
Bowel	0.29 ± 0.10	0.35 ± 0.18	0.20 ± 0.10	0.31 ± 0.12	0.4885	0.1619
Kidney	0.34 ± 0.07	0.37 ± 0.12	0.29 ± 0.06	0.34 ± 0.06	0.5857	0.1210
Liver	0.38 ± 0.06	0.49 ± 0.14	0.42 ± 0.09	0.53 ± 0.17	0.2374	0.2352
Pancreas	0.12 ± 0.04	0.18 ± 0.03	0.14 ± 0.04	0.14 ± 0.05	0.3122	0.2548
Brain	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	0.02 ± 0.01	0.6474	0.1271
Bone	0.08 ± 0.03	0.11 ± 0.05	0.07 ± 0.02	0.09 ± 0.03	0.3221	0.1939
Lung	0.40 ± 0.12	0.47 ± 0.15	0.32 ± 0.05	0.42 ± 0.09	0.2658	0.2200
Heart	0.19 ± 0.07	0.19 ± 0.07	0.16 ± 0.05	0.17 ± 0.05	0.8711	0.0394
Spleen	0.22 ± 0.05	0.20 ± 0.09	0.16 ± 0.04	0.21 ± 0.06	0.4794	0.1376
Muscle	0.07 ± 0.01	0.08 ± 0.02	0.05 ± 0.01	0.06 ± 0.02	0.3943	0.2486
Penis	0.41 ± 0.04	0.40 ± 0.05	0.32 ± 0.06	0.41 ± 0.06	0.2491	0.2941
Prostate	0.17 ± 0.02	0.22 ± 0.07	0.15 ± 0.04	0.19 ± 0.02	0.0921	0.4952
Seminal vesicle	0.14 ± 0.04	0.11 ± 0.03	0.11 ± 0.05	0.11 ± 0.01	0.4840	0.1362
Bladder	0.31 ± 0.09	0.26 ± 0.10	0.27 ± 0.10	0.25 ± 0.08	0.9177	0.0421
Testis	0.09 ± 0.01	0.13 ± 0.01*	0.06 ± 0.03	0.10 ± 0.03	0.0302	0.5581
Blood	1.00 ± 0.27	1.13 ± 0.49	0.93 ± 0.23	1.24 ± 0.14	0.5133	0.1351

COR + WBV-E, group treated with coriander and submitted to vibration; WBV-E, group submitted to vibration generated in platform. Values are shown as the means ± SD. Adjusted *P* values (Student–Newman–Keuls correction) were considered statistically significant at $P<0.05$. $^*P<0.01$ compared with WBV-E; ^{2}, epsilon squared.

Statistical analysis

A normality test was done to determine if the data set is well-modeled by a normal distribution. As all the studied data do not follow a normal distribution, a Kruskal–Wallis test following the post-test Student–Newman–Keuls was done, for the statistical analysis of the results with BioEstat 5.3 (Instituto Mamiraua, Pará, Brasil). Data are presented as mean ± standard deviation (±SD), median ± interquartile range (IQR), or as percentage (%). Statistical significance was accepted at $P<0.05$. Epsilon-squared (^{2}) were analyzed to estimate the effect size. The ^{2} assumes the value from 0 (indicating no relationship) to 1 (indicating a perfect relationship). The values approximately 0.5 were considered in the present study as a moderate relationship. Effect sizes were analyzed to determine the magnitude of an effect independent of sample size as reported elsewhere (Tomczak and Tomczak, 2014). The ^{2} effect sizes were measured by the following formula:

$$\varepsilon^2 = \frac{H}{n^2 + 1/n + 1}$$

Where H is the value obtained in the Kruskal–Wallis test (the Kruskal–Wallis H-test statistic) and n is the total number of observations.

Results

Table 1 shows the %ATI/g of the $Na^{99m}TcO_4$ in the various organs isolated from the animals submitted to different treatments. It is possible to verify that in testis there was a significant (P=0.0032) alteration in the uptake of radiopharmaceutical in the animals submitted to the vibration (WBV-E group) in comparison with the COR group, with moderated relationship ($^2 = 0.5581$). In the other organs, there is no alteration statistically significant and the ^{2} is small.

After 40 days of treatment, there is no alteration ($P>0.05$) on concentrations of some plasma biomarkers (Table 2) in comparison with the CON, independently on the type of treatment (only Coriander or WBV, or with the association coriander and WBV). The ^{2}revealed values from 0.0204 to 0.3279, indicating a small relationship.

Considering the effect of 40-day WBV and its association with coriander on feed intake in rats treated with coriander, there is a significant difference on feed intake (Figure 4). The animals of the WBV-E group have more feed intake than that of the others groups. The CON and COR + WBV-E have the lowest feed intake. The ^{2} (not shown in the figure) was 0.2134, indicating small relationship.

The Table 3 shows the body mass (%) of the animals submitted to different treatments. The results showed no

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Table 2 Concentration of some plasma biomarkers that was determined in the animals submitted to different treatments

	CON	COR	WBV-E	COR+WBV-E	*P*	2
Glucose (mmol/l)	7.04 ± 0.90	6.78 ± 0.78	6.35 ± 0.56	6.33 ± 0.30	0.4211	0.1759
Urea (mmol/l)	7.93 ± 0.88	7.73 ± 0.51	7.97 ± 0.88	8.53 ± 1.14	0.6050	0.1026
Creatinine (µmol/l)	39.78 ± 4.42	35.36 ± 6.18	38.89 ± 4.42	35.36 ± 0.08	0.3391	0.1868
Cholesterol (mmol/l)	1.20 ± 0.23	1.26 ± 0.05	1.13 ± 0.19	1.13 ± 0.08	0.3186	0.2512
Triglyceride (mmol/l)	0.53 ± 0.08	0.51 ± 0.13	0.43 ± 0.08	0.41 ± 0.01	0.2371	0.3259
HDL (mmol/l)	1.06 ± 0.13	1.14 ± 0.03	1.23 ± 0.09	1.13 ± 0.15	0.1778	0.3279
AST (µKat/l)	2.14 ± 0.36	2.01 ± 0.45	2.06 ± 0.70	2.21 ± 0.80	0.9442	0.0224
ALT (µKat/l)	1.40 ± 0.24	1.19 ± 0.08	1.19 ± 0.12	1.15 ± 0.15	0.4565	0.1533
Alkaline phosphatase (µKat/l)	2.15 ± 0.45	1.90 ± 0.37	1.81 ± 0.42	1.73 ± 0.36	0.8199	0.0543
Total bilirubin (µmol/l)	1.37 ± 0.34	1.20 ± 0.34	1.37 ± 0.51	1.54 ± 0.34	0.8389	0.0469
Direct bilirubin (µmol/l)	0.68 ± 0.34	0.51 ± 0.17	0.86 ± 0.34	0.86 ± 0.17	0.3349	0.2424
Amylase (µKat/l)	44.08 ± 2.05	48.05 ± 8.06	44.91 ± 6.52	45.18 ± 5.58	0.9471	0.0204
Lipase (µKat/l)	0.11 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.5368	0.1209
CK (µKat/l)	25.19 ± 6.39	24.15 ± 5.91	25.46 ± 5.74	18.48 ± 3.59	0.3047	0.2790
Calcium (mmol/l)	2.40 ± 0.15	2.35 ± 0.07	2.38 ± 0.10	2.40 ± 0.10	0.8122	0.0530
Magnesium (mmol/l)	1.07 ± 0.16	0.95 ± 0.08	0.95 ± 0.08	0.95 ± 0.04	0.5569	0.1153
Total protein(g/l)	57.0 ± 2.0	57.0 ± 3.0	57.0 ± 3.0	60.0 ± 3.0	0.5147	0.1272
Albumin (g/l)	34.0 ± 2.0	33.0 ± 2.0	33.0 ± 1.0	36.0 ± 3.0	0.3822	0.1801

COR + WBV-E, group treated with coriander and submitted to vibration; WBV-E, group submitted to vibration generated in platform. Values are shown as the means ± SD; [2], epsilon squared.

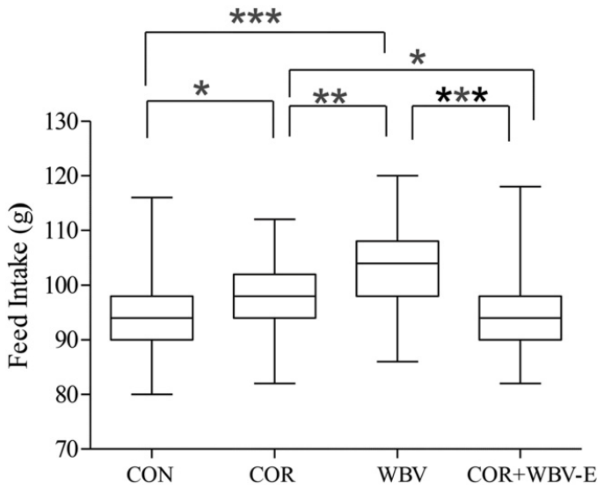

Figure 4. Feed intake (g) of animals submitted to different treatments.
Adjusted *p* values (Student-Newman-Keuls correction) were considred statistically significant at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

alterations among the groups in comparison with the CON, independently on the type of treatment (only coriander or WBV, or with the association coriander and WBV). The values of [2] varied from 0.3081 to 0.3893, indicating small relationship.

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Table 3 The body mass (%) of the groups of animals submitted to different treatments

Week(s)	CON	COR	WBV-E	COR + WBV-E	*P*	^{2}
0	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	100.00 ± 0.00	0.1003	0.3286
1	100.15 ± 9.44	103.78 ± 7.11	103.29 ± 5.19	102.58 ± 5.50	0.0661	0.3784
2	102.22 ± 9.25	105.82 ± 7.30	106.43 ± 6.74	104.52 ± 6.48	0.0603	0.3893
3	103.10 ± 8.49	106.99 ± 8.06	109.86 ± 7.70	107.58 ± 7.27	0.0899	0.3418
4	105.02 ± 10.1	109.32 ± 8.75	111.57 ± 7.33	109.35 ± 8.22	0.1190	0.3081
5	106.79 ± 9.79	110.19 ± 10.5	114.29 ± 7.47	110.48 ± 7.55	0.1180	0.3090

COR + WBV-E, group treated with coriander and submitted to vibration; WBV-E, group submitted to vibration generated in platform. Values are shown as %; ^{2}, epsilon squared.

Table 4 Stool consistency of animals submitted to different treatments

Day(s)	CON	COR	WBV-E	COR + WBV-E	*P*	^{2}
1–10	2.00 ± 0.00*	1.00 ± 1.00	2.00 ± 0.00†	2.00 ± 0.00*	0.0024	0.3697
11–20	2.00 ± 0.00‡	1.00 ± 0.00	2.00 ± 0.00‡	2.00 ± 0.00†	<0.0001	0.8154
21–30	2.00 ± 0.00‡	1.00 ± 0.00	2.00 ± 0.00‡	2.00 ± 0.00‡	<0.0001	0.8946
31–40	2.00 ± 0.00‡	1.00 ± 0.00	2.00 ± 0.75‡	2.00 ± 0.00‡	<0.0001	0.8222
Total (1–40)	2.00 ± 0.00‡	1.00 ± 0.00	2.00 ± 0.00‡	2.00 ± 0.00‡	<0.0001	0.6571

COR + WBV-E, group treated with coriander and submitted to vibration; WBV-E, group submitted to vibration generated in platform. Values are shown as the median ± IQR. Adjusted *P* values (Student–Newman–Keuls correction) were considered statistically significant at $^*P<0.05$, $^†P<0.01$, and $^‡P<0.001$. * compared with COR group; ^{2}, epsilon squared.

Considering the effect of 40-day WBV and its association with coriander on stool consistency, the results showed statistical difference ($P<0.05$) on the stool consistency between COR and all the other groups (CON, WBV-E, and COR + WBV-E) as shown in Table 4. The ^{2} was 0.6571 indicating a moderated relationship.

Discussion

Experimental models involving the evaluation of effects of WBV exercise in animals that consumed some substances [17,24,26] are very relevant and have stimulated our investigation. New models regarding the effect of other synthetic and natural products in association with WBV exercise using different biomechanical parameters and time of exposition are desirable. Naghii et al. [17] have evaluated the effect of consumption of some natural medicinal products (fatty acids, vitamin D, and boron) with WBV (10–50 Hz). In the present study, we hypothesized that the combination of WBV exercise and coriander supplementation could potentialize their biological effects in rats. In consequence, the effects of the treatments with WBV exercise and a medicinal product (coriander) extract on the biodistribution of the radiopharmaceutical $Na^{99m}TcO_4$, on the concentration of some plasma biomarkers, on the feed intake, on the body mass, and on the stool consistency in Wistar rats were assessed.

The pattern of the biodistribution of a radiopharmaceutical, in general, depends on physiological characteristics of an organ/tissue [42]. Previously, Pereira et al. [22] have shown that, in rats, the exposure to vibration with 20 Hz can alter the uptake of a radiopharmaceutical in some organs. Frederico et al. [16] reported that the association between coriander and WBV (12 Hz) increases the uptake of $Na^{99m}TcO_4$ in spleen. The determination of the uptake of the $Na^{99m}TcO_4$ in different organs (Table 1) permitted to verify the effect of the different treatments in some organs. The effect in the testis (Table 1) is only in animals of the COR group compared with rats of the WBV-E group, with an increase in the uptake of the radiopharmaceutical. In 2010, Sharma et al. [43] have reported the prophylactic efficacy of coriander on testis of lead-exposed mice. Moreover, the supplementation of aqueous coriander extract would also provoke an increase in sperm density, compared with lead nitrate-treated group.

The biological effects of the WBV exercises in an organ seem to be also dependent on the frequency [16,22]. Miyazaki, 2000 has evaluated the electrogastrography (EGG) in healthy male volunteers' exposure to vibrations of 4, 8, and 16 Hz. This author has observed that only the vibrations of 4 and 8 Hz have decreased the amplitude of the EGG.

The determination of the effect of 40-day WBV (50 Hz) on the level of plasma biomarkers in rats treated with coriander (Table 2) has shown no alterations on the concentrations of the studied biomarkers. Although the protocols with WBV used by other authors were not exactly the same that was used in the present study, it is shown an agreement

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with Pawlak et al. [18] that showed low-volume WBV (50 Hz) lasting 3 or 6 months does not affect biomarkers in blood serum of rats, using the same frequency. Moreover, the levels of the studied biomarkers were also consistent. Naghii et al. [17], using a different protocol, have determined the plasma lipid concentrations (total cholesterol, low-density lipoprotein (LDL), and HDL) in rats submitted to vibrations in the frequencies of 10–50 Hz and they did not found alteration in the concentrations of these biomarkers, although they have found significant differences in plasma levels of CK. The plasma CK levels were significantly higher in the vibration group compared with the controls.

The comparison of the animals among the groups has shown that there is no significant alteration on the body mass (Table 3) in rats treated 40 days simultaneously with coriander and WBV exercise. It is important to point out that, this finding is not associated with the feed intake, which was increased in rats exposed to the WBV exercise. It is very interesting and could associated with the results reported by Wang and Kerrick et al. [44] that verified that applying vibration to intact or skinned single fiber preparations occurs specific increase in ATP turnover. These results are in agreement with Huang et al. [45] that have reported in mice with obesity induced by a high-fat diet (HFD), no difference in body mass between HFD with sedentary control, HFD with WBV at relatively low-intensity (5.6 Hz, 0.13 g) (HFD + VL) or high-intensity (13 Hz, 0.68 g) (HFD + VH). In addition, Di Loreto et al. [46] reported that since hormonal responses, with the exception of norepinephrine, are not affected by acute WBV exposure, this type of exercise is not expected to reduce fat mass.

The effect of the association of 40-day WBV (50Hz) with coriander (Figure 4) on the feed intake in rats has shown alterations among the groups. An increase on the feed intake was found in animals of the WBV-E (Figure 4). This result differs from Frederico et al. [17] that reported no difference in the amount of feed between the groups. Huang et al. [45] also shown no difference on energy intake among the groups studied using a different protocol.

The stool consistency of animals submitted to different treatment (Table 4) permits to verify that rats that consumed coriander alone (COR) has the stool consistency classified as type 1. In the animals that are submitted to WBV associated with coriander (COR + WBV-E), the stool consistency is normalized (type 2). This finding indicated that the WBV would act in some physiological/metabolic step in the gastrointestinal system that would be related to the normalizing of the stool consistency. Considering the gastrointestinal system, Ishitake et al. [47] have reported that WBV suppresses gastric motility in healthy men. In addition, the hard stool (type 1) in animals treated with coriander can be justified due to the effect of this natural product that is used in traditional medicine for the treatment of gastrointestinal diseases, such as diarrhea [37].

The present study has some limitations, as the small number of animals in each group. However, it was followed the criteria of reduction strategies in animal research, published by [48]. Moreover, a special type of cage was not used to separate the stools and it was difficult to monitor the weight of the stools. The WBV-treated rats were immobilized at the platform. This could induce immobility stress, which potentially may alter some physiological parameters of the rats. As the control rats were not submitted to immobility stress, the plasma concentration of specific biomarkers related to stress could be considered in the present study. In addition, the suggestion of new experimental models involving the exposition of animals to the (i) WBV exercise generated by mechanical vibrations with different biomechanical parameters (frequency, peak-to-peak displacement, and peak acceleration) and several times of exposition and (ii) various synthetic and natural products are desirable to verify possible metabolic responses.

Despite the limitations and putting together all the findings, it is concluded that possible modifications in some biochemical/physiological parameters of the rats submitted to WBV exercise would be capable to increase the feed intake without changing the body mass, and normalizing the stool consistency altered by the coriander supplementation. Further studies are needed to try to understand better the biological effects of involving the association of WBV exercise and an aqueous coriander extract.

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Author Contribution

Frederico E.H.F.F. submitted the animals to the mechanical vibration, did the animals' gavage, the stool consistency analyses, the feed intake and the body mass mensuration, and drafted the manuscript. Cardoso A.L.B.D., Guimarães C.A.S., Almeida L.P., Neves R.F., Sá-Caputo D.C., Moreira-Marconi E., Dionello C.F., Morel D.S., Paineiras-Domingos L.L., Costa-Cavalcanti R.G., and Gonçalves C.R. helped on the animals' gavage and removal of organs. Arnóbio A. helped on the animals' removal of organs and did the statistical analysis. Asad N.R. helped on the draft of manuscript. Bernardo-Filho M. coordinated the study and helped on the draft of manuscript.

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

%ATI/g, percentages of injected radioactivity per gram; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CNPq, *Conselho Nacional de Pesquisa e Desenvolvimento*; CON, control group; CONCEA, *Conselho Nacional de Controle de Experimentação Animal*; COR, group treated with coriander; COR + WBV-E, group treated with coriander and submitted to the vibration generated in the platform; EGG, electrogastrography; ^{2}, epsilon-squared; FAPERJ, *Fundação de Amparo à pesquisa do Estado do Rio de Janeiro*; HDL, high-density lipoprotein; HFD, high-fat diet; HFD + VH, high-fat diet with whole body vibration at high-intensity; HFD + VL, high-fat diet with whole body vibration at relatively low-intensity; IQR, interquartile range; LDL, low-density lipoprotein; *P*, *P*-value; SD, standard deviation; UERJ, *Universidade do Estado do Rio de Janeiro*; WBV, whole body vibration; WBV-E, group of rats submitted to the vibration generated in the platform.

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ANEXO B - Formato final do 2º artigo científico submetido

The effect of whole body vibration exercise and *Coriandrum sativum* L. in *Wistar* rats with type 1 diabetes mellitus

Frederico, EHFF [1]; Cardoso, ALBD [2]; Guimarães, CAS [2]; Barros-Conceição, L [2]; Moura-Fernandes, MC [2]; Morel, DS [2]; Dionello, CF [3]; Moreira-Marconi, E [4]; Sousa-Gonçalves, CR [2]; Sá-Caputo DC [3]; Judex S,[5] Bernardo-Filho, M [2]

1- Programa de Pós-graduação em Biociências, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 20551-030, RJ, Brasil.
2- Laboratório de Vibrações Mecânicas e Práticas Integrativas, Departamento de Biofísica e Biometria, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 20551-030, RJ, Brasil.
3- Programa de Pós-graduação em Ciências Medicas, Faculdade de Ciências Medicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 20551-030, RJ, Brasil.
4- Programa de Pós-graduação em Fisiopatologia Clínica e Experimental, Faculdade de Ciências Medicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 20551-030, RJ, Brasil.
5- Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY 11794-5281, USA

Corresponding author
Éric H.F.F. Frederico – Laboratório de Vibrações Mecânicas e Práticas Integrativas, Departamento de Biofísica e Biometria, Instituto de Biologia Roberto Alcantara Gomes, Universidade do Estado do Rio de Janeiro, Avenida 28 de Setembro, 87, fundos, 4º andar, 20551031, Phone/Fax number: 55-21-28688332, Rio de Janeiro, RJ, Brazil. E-mail: ericfrederico@msn.com

ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by deficient insulin production and chronic hyperglycemia. Both *Coriandrum sativum* L. (coriander) and whole body vibration (WBV), a type of physical activity, may reduce plasma glucose concentration.

WBV exercise is generated when a body is exposed to mechanical vibration produced by an oscillating/vibratory platform. The association of medicinal plants and WBV exercise could be an important alternative tool for the management of some clinical conditions including T1DM. In *Wistar* rats with T1DM, here, we tested the combined biological effect of WBV with an aqueous extract of coriander. T1DM was induced with alloxan in *Wistar* rats (n=20) that were divided equally in four groups and submitted to different treatments for 4 weeks. Animals of control (CON) and coriander (COR) groups received 1.0 mL of deionized water or coriander (8 mg/mL), respectively. A subset of rats was submitted to whole body vibrations generated by a vertically oscillating plate (WBV-E). These rats also received 1.0 mL of deionized water. Rats of the COR + WBV-E group received 1.0 mL coriander and whole body vibrations. Results showed that none of the experimental treatments – coriander, WBV, or the combination of coriander and WBV - altered any of the metabolic outcome variables. These results demonstrate that, for the tested conditions, WBV exercise and coriander, alone or in combination did not promote biochemical/physiological modification capable to interfere in the evaluated parameters in rats with T1DM.
Keywords: Whole body vibration, *Coriandrum sativum* L, oscillating/vibratory platform, experimental model

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that occurs when the pancreas loses the capacity to make insulin, or when the body cannot properly use the insulin it produces (IDF, 2017). According to the World Health Organization (WHO), DM affects about 422 million (550 million by 2030) people around the world and is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation (WHO, 2017). Type 1 diabetes mellitus (T1DM) is an autoimmune destruction of insulin-producing pancreatic β cells characterized by remarkable reduction of insulin production and chronic hyperglycemia, accounting for approximately 10% of all cases of DM (IDF, 2017).

Drugs used for the management of DM may maintain blood glucose homeostasis with some unfavorable side-effects (Meier et al., 2015). Hence, medicinal plants that have hypoglycemic activities and low adverse effects are gaining importance. Ethno-medical studies revealed that extracts and isolated molecules derived from medicinal plants can be used to treat T1DM (Kumar et al., 2017). An example of a medicinal plant used as a hypoglycemic is *Coriandrum sativum* L., an annual herb and member of the Apiaceae Family

(Laribi et al., 2015) and popularly known as coriander. It originated from the Mediterranean region but is used in various cultures as a spice and medicinal plant (Seidemann, 2005).

Combining the potential benefits of medicinal plants with those of physical exercise may present a promising tool to prevent major health risks and diseases (Ali et al., 2017)(Alkhatib and Atcheson, 2017). Although the positive health effects of physical exercise are widely known, there is only a limited understanding of its influence on the immune system as well as autoimmune diseases including T1DM (Sharif et al., 2017).

Over time, individuals with T1DM tend to develop health problems that may preclude the use of physical exercise. For example, individuals with proliferative retinopathy are advised against strenuous physical exercise due to the possibility of a vitreous hemorrhage (Colberg et al., 2016). Thus, a treatment modality that confers the benefits of exercise without the associated physical constraints is desirable.

Whole body vibration (WBV) may be considered light-resistance exercise with mechanical vibrations transmitted into the body from a vibrating platform that an individual is standing on (Keijser et al., 2017). This kind of 'exercise' is effective in reducing neuropathic pain symptoms while provoking few contraindications (Kessler and Hong, 2013). WBV is broadly accessible to large populations due to its noninvasive nature, has few side effects, is relatively low-cost, simple to apply, and only requires short durations to become effective (Kessler and Hong, 2013; Jing et al., 2017). These considerations indicate that WBV exercise may have clinical potential in the management of T1DM (Kessler and Hong, 2013). This potential has stimulated investigations into WBV exercise using pre-clinical models including rodents (Pawlak et al., 2013; Weinheimer-Haus et al., 2014; Keijser et al., 2017).

The current study aimed at evaluating the effect of combining WBV exercise with an aqueous extract of coriander on (1) the biodistribution of the radiopharmaceutical sodium pertechnetate, (2) the concentration of specific plasma biomarkers, (3) body mass, (4) feed intake, and (5) stool consistency in *Wistar* rats with T1DM. We hypothesized that the concomitant treatment with coriander and WBV exercise will improve the metabolic state of rats with T1DM.

MATERIAL AND METHODS

Animals and Ethical approach:

Wistar rats (n=20, 243.1 ± 34.0 g), 3-4 months old, were maintained at an average temperature of 25 ± 2 °C, a relative humidity of 55%, and a light/dark cycle of 12h. All rates were provided with a standard diet and water *ad libitum*. Experiments were performed following the guidelines of the *Comitê de Ética Para o Uso de Animais Exprimentais* (CEUA), *Instituto de Biologia Roberto Alcantara Gomes* (IBRAG) that approved the investigation (CEUA/041/2013).

Induction of diabetes:

Diabetes was induced by intraperitoneal injection with 150 mg/kg alloxan monohydrate (Sigma-Aldrich, St Louis, MO, USA) freshly prepared in 0.9% NaCl (Olurishe et al., 2016). A single dose was administered to rats via a 0.5 mL syringe/needle. The diabetic status of rats was confirmed after 1week. Rats with fasting glucose levels of ≥ 11.1 mmol/L (200mg/dL) were considered diabetic (Emordi et al., 2016).

Preparation of the aqueous extract of Coriander:

A commercial dry seed of coriander (*Coriandrum sativum* L.) was used (lot 015, expiration date on June 2018, *Distribuidora de Cereais Crowne Ltda*, Rio de Janeiro, Brazil). To prepare the extract, 80 mg of coriander were added to 10 mL of deionized water. Then, the preparation was vortexed for 1 minute, centrifuged (clinical centrifuge, 1500 rpm, 15 minutes) and the supernatant was considered to be 8 mg/mL of coriander. The preparation of the extract was controlled by spectrophotometric analysis (extract with optical density at 480 nm) (Frederico et al., 2012).

Experimental procedures:

WBV exercise was applied every day between 11.00-12.00 a.m. through a vertically oscillating vibratory plate with the base oscillating up and down at the same time in a synchronous way (synchronous platform) (Globus G-Vibe 800, Italy). Sinusoidal vertical vibrations were generated with the following biomechanical variables: 50 Hz frequency, 0.78 mm amplitude and peak acceleration of 7.85 g.

Wistar rats with T1DM (n=20) were randomly divided in four groups. Control (CON) and coriander (COR) groups received 1.0 mL of deionized water and coriander (8 mg/mL) by gavage, respectively. Rats exposed to whole body vibration (WBV-E) also received 1.0 mL of deionized water. COR + WBV-E rats received 1.0 mL coriander and were exposed to WBV. Experimental procedures were applied for 5 days/week for 4 weeks. The experimental variables used in this current study were similar to our previous study (Frederico et al., 2017a).

Biodistribution of radiopharmaceutical $Na^{99m}TcO_4$ *and concentrations of plasma biomarkers*

To explore a treatment effect on organs, the biodistribution of radiopharmaceutical $Na^{99m}TcO_4$ and concentrations of specific plasma biomarkers were assessed.

One day after the experimental procedures were initiated, the rats were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg) (Wellington et al., 2013). The anesthetized animals were given 0.3 mL (550 kBq) of the radiopharmaceutical $Na^{99m}TcO_4$ (1.85 MBq/mL) via ocular plexus. The $Na^{99m}TcO_4$ was eluted (60 min prior) from a $^{99}Mo/^{99m}Tc$ generator (Frederico et al., 2017a).

After 10 min, blood samples from each rat were obtained by cardiac puncture. Concentrations of selected plasma biomarkers including glucose, urea, creatinine, cholesterol, triglyceride, high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, direct bilirubin, amylase, lipase, creatine kinase (CK), calcium, magnesium, total protein and albumin were determined. The assays were performed in the clinical laboratory of the *Universidade do Estado do Rio de Janeiro* in an automated manner (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland). Rats were killed by CO_2 asphyxiation following the *Conselho Nacional de Controle de Experimentação Animal* guideline (CONCEA, 2015).

Organs including thyroid, stomach, bowel, kidney, liver, pancreas, bone, lung, heart, spleen, muscle and bladder were harvested and radioactivity was determined in a well counter. Percentages of the injected radioactivity per gram (%ATI/g) in the organs were calculated as reported elsewhere (Frederico et al., 2017a).

Body mass analysis

Body mass of each animal was determined weekly with a digital balance (FILIZOLA BP6, São Paulo, Brazil). The relative (percent) change in body mass was calculated as the body mass ratio between each week and the first day (and multiplied by 100).

Feed intake analysis

500 g of feed was supplied daily to each group. The following day, leftover feed was counted on a digital balance (FILIZOLA BP6, São Paulo, Brazil). The feed intake was

calculated as the difference between the supplied 500 g and the leftover feed on each day. This number was divided by 5 (number of rats per group).

Stool consistency analysis

Stool consistency was analyzed using a form scale. Three different and independent evaluators daily analyzed the consistency of the stool and chose a value according to the scale. Values ranged from 1 to 4 as described (Frederico et al., 2017a) with Type 1 being hard, dry, and dark stool, Type 2 being normal with crucks in the surface, Type 3 being smooth and soft, and Type 4 being fluffy pieces with ragged edges (mushy stool). The median of these three analyses was considered. The stool sample was collected before the animals' gavage.

Statistical analysis

The statistical analysis of the data was performed with the aid of BioEstat 5.3 software (*Instituto Mamiraua*, Pará, Brazil). A normality test was done to determine if the data set is well-modeled by a normal distribution. As all data did not follow a normal distribution, a Kruskal-Wallis test was performed. Data were presented as mean ± standard deviation (±SD), median ± interquartile range (IQR) or as percentage (%). Statistical significance was accepted at $p < 0.05$. Epsilon-squared (ε^2) were used to estimate the effect size. The ε^2 assumes a value from 0 (indicating no relationship) to 1 (indicating a perfect relationship). Effect sizes were analyzed to determine the magnitude of an effect independent of sample size, as reported elsewhere (Tomczak and Tomczak, 2014). The ε^2 effect sizes were measured by the formula: $\varepsilon^2 = \frac{H}{n^2 + 1/n+1}$; where H is the value obtained from the Kruskal-Wallis test (the Kruskal-Wallis H-test statistic) and n is the total number of observations.

RESULTS

Biodistribution of radiopharmaceutical $Na^{99m}TcO_4$

The uptake of $Na^{99m}TcO_4$ in the various organs isolated from the rats with T1DM, after the application of WBV exercise and/or coriander supplementation, showed no statistically significant differences (p>0.05) in the organ %ATI/g between the different groups (Table 1). The values of ε^2 ranged from 0.05 to 0.36.

Table 1. %ATI/g of the $Na^{99m}TcO_4$ in the various organs isolated from rats with T1DM and exposed to the different treatments

ORGANS	CON	COR	WBV-E	COR+WBV-E	p	ε^2
Thyroid	5.17±2.19	5.13±3.35	6.97±0.95	6.85±1.70	0.26	0.26
Stomach	5.05±1.35	6.86±1.28	5.95±1.26	5.29±2.71	0.23	0.29
Bowel	1.24±0.32	3.06±1.75	1.40±0.00	1.42±0.68	0.24	0.28
Kidney	1.22±0.41	1.13±0.57	1.47±0.15	1.17±0.22	0.75	0.08
Liver	1.40±0.24	1.32±0.41	1.38±0.02	1.26±0.16	0.55	0.14
Pancreas	1.09±0.32	0.90±0.50	1.02±0.04	0.87±0.49	0.85	0.05
Bone	0.30±0.12	0.34±0.15	0.54±0.14	0.36±0.12	0.14	0.36
Lung	1.60±0.78	1.25±0.66	2.08±0.01	1.29±0.34	0.37	0.21
Heart	0.67±0.26	0.60±0.47	0.91±0.26	0.55±0.14	0.38	0.21
Spleen	0.72±0.24	0.58±0.30	0.85±0.16	0.59±0.16	0.33	0.23
Muscle	0.17±0.06	0.22±0.12	0.30±0.04	0.21±0.05	0.28	0.25
Bladder	0.65±0.17	0.78±0.25	1.00±0.37	1.15±0.71	0.44	0.18

CON- control group; COR- group treated with coriander, WBV-E - group submitted to vibration generated in platform, COR+ WBV-E - group treated with coriander and submitted to vibration. Values are shown as the means ± SD. ε^2- epsilon squared.

Plasma biomarkers concentration

The analysis of the concentration of plasma biomarkers of rats with T1DM demonstrated that all evaluated biomarkers were not significantly altered by the specific treatment (Table 2). The values of ε^2 range from 0.01 to 0.38.

Table 2-Concentration of selected plasma biomarkers determined in rats with T1DM subjected to different treatments

	CON	COR	WBV-E	COR+WBV-E	p	ε^2
Glucose (mmol/L)	36.1±2.32	37.30±3.88	39.69±0.19	38.40±2.29	0.32	0.24
Urea (mmol/L)	14.71±3.82	15.40±3.57	20.81±7.05	16.45±5.39	0.56	0.14
Creatinine (µmol/L)	31.82±7.96	38.01±8.84	35.36±12.38	33.59±7.07	0.74	0.08
Cholesterol (mmol/L)	1.66±0.39	1.88±0.88	1.98±0.53	1.60±0.32	0.70	0.10
Triglycerides (mmol/L)	1.74±0.75	1.75±0.85	1.75±0.60	1.83±1.03	0.99	0.01
HDL (mmol/L)	1.49±0.23	1.39±0.18	1.53±0.02	1.35±0.21	0.52	0.15
AST (µKat/L)	1.88±0.57	2.44±0.49	2.84±0.36	1.96±0.62	0.13	0.38

ALT (µKat/L)	1.74±0.47	1.76±0.21	2.08±0.23	1.82±0.61	0.52	0.15
Alkaline Phosphatase (µKat/L)	7.65±3.47	6.70±2.95	8.91±3.05	6.31±3.23	0.86	0.05
Total Bilirubin (µmol/L)	2.05±0.51	1.71±0.34	2.22±0.17	2.05±0.34	0.40	0.20
Direct Bilirubin (µmol/L)	0.86±0.17	0.86±0.31	1.20±0.51	0.68±0.34	0.70	0.09
Amylase (µKat/L)	23.90±5.08	24.49±4.68	30.05±3.95	29.60±7.69	0.36	0.21
Lipase (µKat/L)	0.10±0.01	0.09±0.00	0.10±0.0	0.09±0.00	0.21	0.30
CK (µKat/L)	7.94±1.54	14.14±7.61	10.34±1.93	9.61±0.82	0.13	0.38
Calcium (mmol/L)	2.50±0.07	2.65±0.23	2.52±0.15	2.60±0.13	0.50	0.16
Magnesium (mmol/L)	1.03±0.04	1.11±0.12	1.07±0.12	1.11±0.08	0.42	0.19
Total Protein (g/L)	0.57±0.03	0.53±0.07	0.57±0.03	0.56±0.05	0.68	0.10
Albumin (g/L)	0.32±0.02	0.31±0.01	0.30±0.07	0.32±0.01	0.35	0.22

CON- control group; COR- group treated with coriander, WBV-E - group submitted to vibration generated in platform, COR+ WBV-E - group treated with coriar and submitted to vibration. HDL - high-density lipoprotein, AST - aspartate aminotransferase, ALT - alanine aminotransferase, CK - creatine kinase Values are sho as the means ± SD. ε^2- epsilon squared.

Body mass

There were no significant differences in % body mass of rats with T1DM between the different groups during the four-week protocol. There was also no change when the comparison was evaluated for each week. The values of ε^2 ranged from 0.01 to 0.05. During the first week, an about 16% (no significant) increase in % body mass was observed in rats of all groups. Further, the % body mass of rats exposed to WBV exercise showed a reduction (non-significant) at the end of the experimental study, a difference that was not observed in the other groups.

Table 3 - % body mass of rats with T1DM exposed to different treatments

Week	CON	COR	WBV-E	COR+WBV-E	*p*	ε^2
0	100.0±00.0	100.0±00.0	100.0±00.0	100.0±00.0	0.98	0.01
1	116.1±17.4	112.0±13.0	117.6±12.7	116.4±12.6	0.85	0.05
2	116.4±14.4	105.9±16.8	102.0±16.2	116.6±09.9	0.37	0.02
3	117.2±16.4	110.5±17.8	108.9±11.0	116.6±11.2	0.72	0.04
4	116.7±16.1	109.0±19.6	103.9±18.9	115.1±07.4	0.74	0.05

Total (0-4)	113.3±16.1	107.5±15.0	104.9±15.3	112.9±11.6	0.18	0.05

CON- control group; COR- group treated with coriander, WBV-E - group submitted to vibration generated in platform, COR+ WBV-E - group treated with coriander and submitted to vibration. Values are shown as % . ε^2- epsilon squared.

Feed intake

The feed intake of rats with T1DM subjected to the different interventions indicated no significant difference between groups (Figure 2). The value of ε^2 was 0.07.

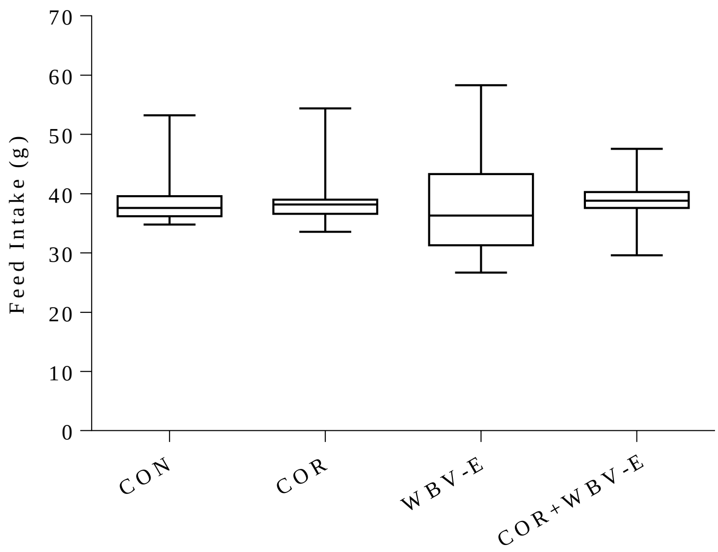

Figure 2- Feed intake of rats with T1DM exposed to different treatments

Stool consistency

Stool consistency of rats with T1DM indicated no significant differences between groups. The values of ε^2 ranged between 0.11 and 0.33.

Table 4 – Stool consistency of the rats with T1DM subjected to different treatments

Day	CON	COR	WBV-E	COR+ WBV-E	*p*	ε^2
01-05	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	0.55	0.11
06-10	2.00±0.00	2.00±0.00	2.00±1.00	2.00±0.00	0.13	0.30
11-15	2.00±0.00	2.00±1.00	2.00±0.00	2.00±0.00	0.25	0.22

16-20	2.00±0.00	2.00±1.00	2.00±0.00	2.00±0.00	0.10	0.33
21-26	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	0.39	0.16
Total (01-26)	2.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00	0.36	0.13

CON- control group; COR- group treated with coriander, WBV-E - group submitted to vibration generated in platform, COR+ WBV-E - group treated with coriander and submitted to vibration. Values are shown as the median ± IQR. ε^2- epsilon squared.

DISCUSSION

The lack of information on the effects of a hypoglycemic medicinal plant and low-intensity physical exercise on the management of T1DM (Ali et al., 2017; Sharif et al., 2017) stimulated the current study. It was hypothesized that the combination of coriander and WBV exercise may improve some metabolic conditions associated with T1DM. WBV exercise was selected because it is easily accessible to large populations, is non-invasive, has few side effects, is low cost and simple, and doesn't need to be applied for long durations to become effective (Kessler and Hong, 2013; Jing et al., 2017). Likewise, coriander is one of the most common herbs claimed to lower blood glucose levels, making it potentially useful for the treatment of DM. In this study, the effect of the combination of coriander and WBV exercise on *Wistar* rats with T1DM was tested via analysis of organs (through biodistribution of $Na^{99m}TcO_4$), plasma biomarkers, body mass, feed intake and stool consistency.

We did not find altered uptake (%ATI/g) of $Na^{99m}TcO_4$ in the studied organs, indicating that WBV and/or coriander were not capable of promoting changes in biochemical/physiological variables in organs of rats with T1DM. In a previous study using healthy rats (Frederico et al., 2017a), the results were similar as those observed here. Our data are also similar to those of Ogawa et al., 2011 who did not observe significant differences in the radiopharmaceutical ^{18}F-sodium fluoride uptake ratio in bone surrounding implants between rats subjected to WBV exercise and controls. On the other hand, Amin et al., 2015 reported a physiological influence of WBV exercise on the image quality related to skeletal scintigraphy with the radiopharmaceutical ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) by increasing the ^{99m}Tc-MDP osseous uptake. However, they did neither report the used vibration device nor the specific vibration variables.

We also investigated the effect of coriander and/or WBV exercise on specific plasma biomarkers. The results showed that none of the interventions caused differences in their concentrations. This finding is in agreement with our previous work, done in healthy rats

(Frederico et al., 2017a) using the same vibration variables. In another study (Frederico et al., 2017b), a decrease in amylase was found with WBV exercise. Monteiro et al., 2017 also found a decrease in LDL levels after exposure to 10 Hz whole body vibration. It is likely that differences in results can be attributed to different vibration devices (side-alternating system versus linear motions) and specific vibration variables used (e.g., frequency and acceleration). Erceg et al., 2015 also demonstrated no significant differences for bone biomarkers in a 10-week WBV exercise (30-40 Hz) program in overweight Latino boys.

Coriander and/or WBV exercise had no effect on body mass, consistent with Frederico et al., 2017a, who used an identical experimental design but in healthy young adult male rats. Chen et al., 2016 reported that body mass in WBV exercise mice did not change significantly during a 6-week experiment period compared to sedentary controls and WBV + dehydroepiandrosterone (DHEA) treated mice. In addition, Sun et al., 2015 reported no significant differences in body mass between controls and WBV rats subjected to either a high-fat diet or normal diet. Lin et al., 2015 also showed no differences in body mass of middle-aged mice with or without a 4-week WBV exercise regimen. On the other hand, de Vries et al., 2014 reported that after diabetes mellitus diagnosis, mass and body mass index increased rapidly, with the most rapid weight gain during the first 2 weeks in children and adolescents with T1DM. In relation to coriander, Aissaoui et al., 2012 found that the oral administration daily for 30 days to the obese–hyperglycemic–hyperlipidemic *Meriones shawi* rats did not have any significant effect on body mass.

There were no differences in feed intake in rats subjected to WBV exercise and/or treated with coriander. These results differ from Frederico et al., 2017a, that showed an increase in feed intake in rats of the WBV exercise group. In another report, Cardoso et al., 2017 also described a higher feed intake in WBV exercise group when compared with the other groups. It is worth mentioning that these two studies were performed in animals without T1DM. In agreement with our results, Chen et al., 2016 demonstrated that WBV exercise and/or DHEA supplementation did not alter feed intake in mice.

Despite coriander being used for the treatment of some gastrointestinal disorders, including diarrhea (Usmanghani et al., 2003), we did not observe altered stool consistency. This could be due to malabsorption or pelvic nerve damage caused by diabetic peripheral neuropathy which may increase bowel movement frequency (de la Luz Nieto et al., 2015), therefore minimizing the effect of coriander. Frederico et al., 2017a, demonstrated an alteration in stool consistency in healthy rats that consumed only coriander (and compared to other groups). The different health conditions of the animals reported Usmanghani et al., 2003 and Frederico et al., 2017a may explain the differential findings regarding stool consistency. Moreover, the findings in the current study corroborates with Cardoso et al., 2017 who investigated the effect of WBV exercise and an aqueous extract of *Chenopodium ambrosioides* in male *Wistar* rats. They also showed no alteration in stool consistency.

Some limitation of the current study should be considered. For instance, only a limited number of hormones were measured while others such as insulin were not investigated. An analysis of glycated hemoglobin (HbA1) would be interesting for the diagnosis of DM. Further, we only studied one specific vibration regime and it is entirely possible that an intervention with a different vibration frequency, vibration magnitude, or vibration duration would have produced significant effects.

Despite the limitations, we conclude that neither WBV exercise nor coriander improved the T1DM conditions in *Wistar* rats. If results from this rodent study can be directly translated to humans, they would indicate that the administration of insulin will continue to be necessary for individuals with T1DM. Further studies involving WBV and medicinal plants in individuals that take insulin are needed. It is possible that for these conditions, the combination of physical exercise and medicinal plant will provoke some beneficial biological effects.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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