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**SÃO PAULO STATE UNIVERSITY (UNESP)**

**"JÚLIO DE MESQUITA FILHO"**

**SCHOOL OF DENTISTRY, ARAÇATUBA**

**MASTER'S THESIS**

**RAFAEL RIBEIRO CORREIA**

# ANALYSIS OF CANCER CACHEXIA ASSOCIATED WITH TREATMENT WITH NANOPARTICLES CARRYING CHEMOTHERAPEUTIC DRUGS DOCETAXEL AND METHOTREXATE IN SPRAGUE-DAWLEY RATS SUBMITTED TO AEROBIC PHYSICAL TRAINING

**ARAÇATUBA – SP**

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# CURRICULAR DATA

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# DEDICATION

To all those for whom this work, a mere piece of a gigantic scientific puzzle, may be useful.

To all those who came before us, whether in recent times or in remote times, facing difficulties and persecutions, and who nevertheless dedicated their lives to science.

To all those who will succeed us, whether shortly or even in the distant future, perhaps even in a better world than mine, where creativity does not encounter bureaucratic, temporal, and ideological barriers, and who are not judged by the number of articles published, but by their quality.

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# EPIGRAPH

“Peace for our time”

Neville Chamberlain

***RESUMO***

A caquexia associada ao câncer é uma síndrome multifatorial caracterizada pela perda progressiva de massa muscular esquelética, resistente à reversão por suporte nutricional convencional. Este estudo investigou os efeitos dos quimioterápicos docetaxel e metotrexato, emulsificados em nanopartículas LDE, em associação ao exercício aeróbico, em um modelo de ratos com caquexia do câncer. No Capítulo 1, a análise dos efeitos de um protocolo de exercício moderado revelou que a atividade aeróbica agravou a caquexia, aumentando a massa tumoral, promovendo significativa atrofia muscular e alterando vias metabólicas como o ciclo do TCA, fosforilação oxidativa e gliconeogênese. Observou-se também ativação de vias de neurodegeneração no músculo esquelético e modificação na expressão gênica tumoral relacionada à organização da matriz extracelular, sugerindo que o exercício após a instalação do tumor pode resultar em sobrecarga e piora nos desfechos. O Capítulo 2 avaliou a combinação de LDE-docetaxel com exercício, que não foi eficaz na preservação do músculo tibial anterior. A redução da tolerância ao exercício e a regulação negativa de genes críticos para a regeneração muscular, como Cdk2, Nr4a1 e Atf3, indicaram comprometimento na recuperação muscular, evidenciando a complexa interação entre massa tumoral, o tratamento e a integridade muscular. No Capítulo 3, a investigação dos efeitos de LDE-metotrexato com exercício demonstrou que, embora houvesse redução no peso corporal total, a atrofia muscular foi acentuada, com desregulação de genes envolvidos na organização do citoesqueleto e na função mitótica, comprometendo a capacidade de regeneração muscular. Esses resultados indicam que, apesar da redução tumoral, as intervenções terapêuticas combinadas ao exercício impactaram negativamente a saúde muscular, ressaltando os desafios na gestão da caquexia em contextos oncológicos.

**Palavras-chave:** caquexia; exercício aeróbio; LDE; docetaxel; metotrexato; transcriptômica.

# ABSTRACT

Cancer cachexia is a multifactorial syndrome characterized by progressive skeletal muscle loss that remains unresponsive to conventional nutritional support. This study investigated the effects of the chemotherapeutic agents docetaxel and methotrexate, emulsified in LDE nanoparticles, in combination with aerobic exercise in a rat model of cancer cachexia. In Chapter 1, the analysis of a moderate exercise protocol revealed that aerobic activity exacerbated cachexia, increasing tumor mass, inducing significant muscle atrophy, and disrupting metabolic pathways such as the TCA cycle, oxidative phosphorylation, and gluconeogenesis. Neurodegenerative pathways were also activated in skeletal muscle, and tumor gene expression related to extracellular matrix organization was altered, suggesting that exercise following tumor onset may lead to overtraining and worsening outcomes. Chapter 2 evaluated the combination of LDE-docetaxel with exercise, which failed to preserve the tibialis anterior muscle. The observed reduction in exercise tolerance and downregulation of key genes involved in muscle regeneration, such as Cdk2, Nr4a1, and Atf3, indicated impaired muscle recovery, highlighting the complex interplay between tumor mass, treatment, and muscle integrity. Chapter 3 explored the effects of LDE-methotrexate combined with exercise, showing that while overall body weight decreased, muscle atrophy was pronounced, with significant gene dysregulation affecting cytoskeleton organization and mitotic function, thereby compromising muscle regenerative capacity. These findings suggest that although tumor reduction was achieved, the combined therapeutic and exercise interventions negatively impacted muscle health, underscoring the challenges in managing cachexia in oncological contexts.

**Keywords:** cachexia; aerobic exercise; LDE; docetaxel; methotrexate; transcriptomics.

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# ABBREVIATIONS

**ADP** - Adenosine Diphosphate
**AICAR** - Aminoimidazole-4-Carboxamide Ribonucleotide
**AMPK** - AMP-Activated Protein Kinase
**AP-1** - Activator Protein 1
**ATP** - Adenosine Triphosphate
**AT** - Adipose Tissue
**BAX** - BCL2 Associated X Apoptosis Regulator
**BAX** - Bcl-2-associated X protein
**BCE** - Before the Common Era
**BCL-2** - B-Cell Lymphoma 2
**BCL-xL** - B-cell lymphoma-extra large
**$Ca^+$** - Calcium Ion
**CAT** - Catalase
**CC** - Cancer Cachexia
**CD8+ T cells** - Cluster of Differentiation 8 Positive T Cells
**CEMIB/UNICAMP** - Animal Center of the University of Campinas
**CIFs** - Cancer-Inducing Factors
**CK** - Creatine Kinase
**Ckm** - Creatine Kinase, M-type
**COX-2** - Cyclooxygenase-2
**Des** - Desmin
**DNA** - Deoxyribonucleic Acid
**DMBA** - 7,2-Dimethylbenz(a)anthracene
**DTX** - Docetaxel
**E1** - Ubiquitin-Activating Enzyme
**E2** - Ubiquitin-Carrier Enzyme
**E3** - Ubiquitin-Protein Ligase
**EACH** - Exercise Anti-Cachectic Hypothetical
**EDL** - Extensor Digitorum Longus
**ERK** - Extracellular Signal-Regulated Kinase
**FADD** - Fas-Associated Death Domain
**Fas receptor** - Fas Cell Surface Death Receptor
**FBW** - Final Body Weight
**FBXO32** - F-Box Protein 32 (also known as Atrogin-1)
**FOXO3a** - Forkhead Box O3a
**GAS** - Gastrocnemius
**GLUT4** - Glucose Transporter Type 4
**GPx** - Glutathione Peroxidase
**HDL-c** - High-Density Lipoprotein Cholesterol
**HR** - Heart Rate
**Hras** - Harvey Rat Sarcoma Viral Oncogene
**IBW** - Initial Body Weight
**IFN-γ** - Interferon-Gamma
**IGF-1** - Insulin-Like Growth Factor-1
**IL-1β** - Interleukin-1 Beta
**IL-1ra** - Interleukin-1 Receptor Antagonist
**IL-4** - Interleukin-4
**IL-6** - Interleukin-6
**IL-10** - Interleukin-10
**LDE** - Lipid Nanoemulsion like Low-Density Lipoprotein (LDL)
**LDL** - Low-Density Lipoprotein
**LDL-c** - Low-Density Lipoprotein Cholesterol
**LDLR** - LDL Receptor
**LLC** - Lewis Lung Carcinoma
**Mb** - Myoglobin
**MCT4** - Monocarboxylate Transporter 4
**NF-κB** - Nuclear Factor Kappa B
**NK cells** - Natural Killer Cells
**NP** - Nanoparticle
**NR4A1** - Nuclear Receptor Subfamily 4 Group A
**NRF-1** - Nuclear Respiratory Factor 1
**NRF-2** - Nuclear Respiratory Factor 2
**$O_2$** - Oxygen
**PAHs** - Polycyclic Aromatic Hydrocarbons
**PDH** - Pyruvate Dehydrogenase
**PGC-1α** - Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha
**Pi** - Inorganic Phosphate
**RNA-seq** - RNA Sequencing
**ROS** - Reactive Oxygen Species
**SC** - Satellite Cell
**SD** - Sprague-Dawley
**SOD** - Superoxide Dismutase
**SOL** - Soleus
**STAT3** - Signal Transducer and

Activator of Transcription 3
**TA** - Tibialis Anterior
**TCA cycle** - Tricarboxylic Acid Cycle
**Tfam** - Mitochondrial Transcription Factor A
**TGF-β** - Transforming Growth Factor-Beta
**TNF-α** - Tumor Necrosis Factor-Alpha
**TRIM63** - Tripartite Motif Containing 63
**TWEAK** - TNF-Related Weak Inducer of Apoptosis
**Ub** - Ubiquitin
**UCP-3** - Uncoupling Protein 3
**VEGF** - Vascular Endothelial Growth Factor
**$VO_2$ Max** - Maximum Oxygen Consumption
**ZMP** - 5-Aminoimidazole-4-Carboxamide-1-β-D-Ribofuranosyl-5'-Monophosphate

# SUMMARY

**CONTENTS**

# INTRODUCTION

Cancer is one of the leading causes of death today [1]. It is estimated that in the period 2026-2030, 690,394 new cases will be diagnosed among women, while men will account for 757,806 new cases [2]. Worldwide, lung cancer is the most diagnosed type of cancer, accounting for around 12.4% of all cases globally (2.5 million new cases in 2022 alone), followed by breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%) and stomach cancer (4.9%) [3]. Risk factors for the development of cancer can be divided into 3 categories, namely 1) behavioral risks (smoking and alcoholism), 2) environmental and occupational risks (environmental pollution and occupational exposure to asbestos), and 3) metabolic risks (obesity and high glycemic index) [4].

Approximately 80% of patients with advanced cancer have cancer cachexia (CC) [5,6]. CC can manifest itself through weight loss, muscle weakness, anorexia, fatigue, and other multifactorial symptoms [7,8]. CC is defined as a multifactorial syndrome characterized by continuous loss of skeletal muscle mass (with or without loss of adipose tissue) that is not fully reversed by conventional nutritional support [9]. CC promotes a decrease in functional capacity, reduced quality of life and survival, constituting one of the main prognostic factors in the advanced stage of cancer [10]. It is estimated that 22-30% of causes of death from cancer are related to cancer cachexia [10]. However, due to the severity of each type of cancer, different incidences of cancer cachexia can be found, with 45% of lung cancer patients developing cachexia [11] and 25% with breast cancer [12], 28-80% of people with kidney disorders [13] and 85% for pancreatic cancer [14].

Nowadays, cachexia is an underestimated and under-researched muscle disease when compared to its causes. In general, it is estimated that 50% of cancer patients develop cachexia [6]. The etiology of cancer-induced cachexia is linked to metabolic disorders originating from the tumor, causing increased muscle catabolism and decreased protein synthesis [15]. The syndrome presents with 3 stages of severity, namely: 1) pre-cachexia, where there is a loss of body mass of up to 5% resulting from factors such as anorexia and insulin resistance; 2) cachexia characterized by a loss of body mass greater than 5% in the last 6 months; 3) refractory cachexia, a result of very advanced cancer (preterminal) associated with active catabolism, low-performance status and a life expectancy of fewer than 3 months [9]. However, there is still no consensus on the exact distinction between non-cachectic and pre-cachectic individuals [16,17].

The use of nanoemulsions has become an alternative in the biomedical field for the transport of drugs [18]. The encapsulation of drugs in their lipid interior protects them from degradation and reduces toxicity, as well as favoring their internalization into target

cells [19]. In this sense, Maranhão et al [20,21] developed a lipid nanoemulsion like LDL called LDE with impregnation in solid tumors after its administration into the bloodstream [20,21]. It was also successfully demonstrated by the group of Professor Maranhão, RC., that the use of the chemotherapy drug docetaxel (DTX) associated with LDE promoted significant reductions in aortic atheroma in rabbits [22], without demonstrating cytotoxic effects [22]. In this regard, the LDE nanoemulsion associated with DTX has also been shown to be effective in reducing prostate cancer [23]. Due to the versatility of LDE in drug delivery, the use of methotrexate associated with LDE has already been shown to be effective [24,25]. Methotrexate is indicated for the treatment of autoimmune diseases and chemotherapy for the treatment of cancer [26]. However, when used alone, it presents high cytotoxicity [27]. On the other hand, Maranhão et al. showed that the administration of LDE-MTX presents lower hematologic cytotoxicity [28]. It was found that the use of LDE associated with MTX reduces approximately 67% of macrophage infiltration in atherosclerotic plaques in rabbits [25]. However, we still do not know the effects of the use of LDE associated with chemotherapeutics (DTX and MTX) in cancer cachexia.

Physiological responses induced by physical exercise can mitigate the effects caused by senility and comorbidities, as well as minimize the impact of progressive loss of muscle mass associated with loss of strength and reduced physical performance, characterized as a syndrome called sarcopenia [29]. Furthermore, it is known in the current literature that physical exercise is useful for patients who develop cancer cachexia [30,31]. Skeletal muscle, an organ affected by cancer cachexia, improves with physical exercise, as it increases protein synthesis and mitochondrial biogenesis [32]. Moderate physical exercise (50 to 70% max HR) promotes physiological and muscular adaptations that are well described in the literature [33,34], inducing the release of anti-inflammatory cytokines derived from muscle contraction [35,36]. These cytokines are involved in inhibiting inflammation and regulating muscle energy metabolism [37,38]. These are the foundations that support the Exercise Anti-Cachectic Hypothetical – EACH [39], since, due to the endocrine characteristic of skeletal muscle during exercise [40,41] and the release of anti-inflammatory myokines, such as IL-1ra, IL-4, and IL-10, exercise becomes a tool against the progression of cachexia [42].

Given the advanced development of cancer and traditional treatments (chemotherapies, surgeries, and radiotherapy), attenuating cachexia in cancer patients has become an essential challenge. In this sense, studies that focus on the discovery of new

therapies are of utmost importance. In addition, studies on the efficacy and safety of physical exercise as a strategy associated with pharmacological action in the prevention of cancer cachexia are still inconclusive. To identify new paths for the treatment of cachexia, the present study characterized the genetic, molecular, and biochemical effects of LDE nanoemulsion carrying the chemotherapeutic agent docetaxel and methotrexate, associated with aerobic physical training. These results shed light on cancer cachexia and establish possible mechanisms of tumor action.

# FINAL CONSIDERATIONS

This thesis investigated the complex interactions between cancer cachexia, aerobic exercise, and chemotherapy drugs (docetaxel and methotrexate) emulsified in lipid-based nanoparticles (LDE) on skeletal muscle health in a rat model of cancer. The findings across the three chapters provide valuable insights into how these factors interplay at the molecular, transcriptomic, and morphological levels.

In **Chapter 1**, we demonstrated that while moderate aerobic exercise is often considered beneficial for skeletal muscle adaptations, in the context of cancer cachexia, it can have detrimental effects. The exercise protocol implemented in this study resulted in overtraining, evidenced by reduced exercise tolerance and exacerbated cachexia, as seen by decreased tibialis anterior muscle weight and increased tumor weight. Additionally, there was notable chemokine-mediated crosstalk between the tumor and muscle, particularly involving Cxcl6/Cxcr2 genes, which suggests that exercise under these conditions can potentially worsen outcomes by promoting a cachexia-like transcriptome and disrupting muscle energy metabolism.

**Chapter 2** expanded on this by investigating the effects of docetaxel (DTX) delivered via LDE nanoparticles in combination with exercise. The results showed that the LDE-DTX combination was not sufficient to prevent muscle wasting. This was accompanied by downregulation of genes critical for muscle regeneration, such as *Cdk2*, *Nr4a1*, and *Atf3*, further highlighting compromised muscle recovery. The use of electrical bioimpedance as a non-invasive monitoring tool showed promise in tracking the progression of cachexia and muscle loss over time, offering a potential clinical application for managing cachexia in cancer patients.

**Chapter 3** focused on the effects of methotrexate (MTX) carried by LDE nanoparticles in conjunction with exercise. The findings indicated that aerobic exercise exacerbated body weight loss, while all treatment groups involving LDE-MTX experienced muscle wasting compared to controls. The downregulation of key pathways involved in spindle microtubule attachment and organization in the CA+LDE-MTX+Ex group further suggests a mechanistic basis for the observed muscle atrophy. These results point to the complex and often counterintuitive effects of combining chemotherapy and exercise, particularly in the presence of cachexia.

**Overall Conclusion**: Collectively, these findings underscore the complexity of managing cancer cachexia, particularly about physical exercise and chemotherapeutic interventions. Both docetaxel and methotrexate, when delivered via LDE nanoparticles, and their combination with moderate exercise appears to compromise muscle health,

especially in the context of advanced cachexia. This thesis provides critical insights into the biological processes affected by these interventions, revealing potential biomarkers and therapeutic targets for better managing cachexia in cancer patients. Future research should focus on optimizing exercise protocols and exploring adjunctive treatments that can mitigate muscle loss while enhancing chemotherapy efficacy.

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