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

Luis Manuel Sarmiento-Machado

Efeitos da ingestão da cianobactéria *Limnospira (Spirulina platensis) spp.* na promoção/progressão tumoral na hepatocarcinogênese química em camundongos fêmeas C3H/He

Tese de Doutorado apresentado à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor (a) em Ciências: área de concentração em Patologia.

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Orientador: Luís Fernando Barbisan

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1. Câncer de Fígado. 2. Carcinoma Hepatocelular. 3. Hepatocarcinogênese in vivo e in vitro. 4. Quimioprevenção. 5. Neoplasias Benignas e Malignas. I. Título.

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Efeitos da ingestão da cianobactéria *Limnospira (Spirulina platensis) spp.* na promoção/progressão tumoral na hepatocarcinogênese química em camundongos fêmeas C3H/He

Impacto Científico Esperado: Os resultados apresentados nesta tese são inovadores, já que na atualidade não foram avaliados os efeitos da cianobactéria *Limnospira (Spirulina platensis) spp.* no desenvolvimento tumoral hepático em camundongos fêmeas, sendo apenas dois estudos os que avaliaram efeitos na hepatocarcinogênese em camundongos machos. A importância disto se dá no fato de que o sexo de uma espécie (seja humano ou roedor), tem influência na suscetibilidade ou resistência a fatores carcinogênicos, no qual geralmente as mulheres (ou neste caso os camundongos fêmeas), aparentam ser mais resistentes dado a fatores hormonais (*i.e* estrogênio). Além disso, este é o primeiro estudo em avaliar os efeitos morfológicos do consumo da cianobactéria em baço, rins e mucosa uterina. Assim, meu trabalho tenta esclarecer o "viés de sexo *in vivo*" presente na literatura pré-clínica mundial, sobretudo na área da carcinogênese experimental, apresentando novidades incrementais e empíricas.

Impacto Social: Dado que o nosso estudo tem como alvo a quimioprevenção, a *Limnospira spp.* não apresentou diferenças significativas contra o desenvolvimento tumoral hepático. Do ponto de vista de extrapolação para o consumo humano, isto é importante porque, possivelmente a suplementação desta cianobactéria não seja efetiva na prevenção da carcinogênese hepática. Muitos produtos de origem natural são comercialmente promovidos sob à premissa de serem preventivos ou curativos contra doenças, principalmente crônicas (câncer, diabetes, doenças cardiovasculares), os quais não apresentam evidências destes efeitos em ensaios pré- e/ou clínicos. No entanto, no geral, o consumo demonstrou-se seguro experimentalmente, e achados científicos que isto atestem, podem promover a cadeia produtiva da *Limnospira*, que tem impacto social comprovado.

Impacto Econômico: Atrelado ao impacto social, o impacto econômico pode estar associada à estudos científicos que comprovem sua segurança, como o nosso, promovendo sua cadeia produtiva.

Effects of dietary cyanobacteria *Limnospira (Spirulina platensis) spp.* on promotion/progression of hepatocarcinogenesis on chemically induced female mice C3H/He

Expected Scientific Contribution: At sharing the results we produced through a Thesis online and eventually on a well-regarded scientific paper, we are certain that these findings are a novelty not only in the expertise area of *in vivo* chemically induced carcinogenesis models, but on the phycology area as well. This is the first study that assessed the chemopreventive effects of cyanobacteria *Limnospira spp.* against liver carcinogenesis on a female mice model, since there is only two studies with the same approach using male rodents. It is noteworthy that sex hormones may play a role against carcinogens, in which estrogen has demonstrated anticarcinogenic properties on a study, adding to the fact that the tumor burden on female mice is inferior to males. Moreover, this is the first study that investigated the *Limnospira* effects on kidneys, spleen and uterine mucosa through microscopic analysis. Thus, my work seeks to overcome the clear "sex bias" present in the global preclinical literature, particularly in the field of experimental carcinogenesis, by presenting incremental and empirical advances.

Social Contribution: Regarding liver tumor development, we have found that *Limnospira spp.* on diethylnitrosamine (DEN) has no statistical significance when compared to DEN-only treatment group on female mice..However, overall, consumption proved to be experimentally safe, and scientific findings supporting this safety may promote the Limnospira production chain, which has a demonstrated social impact.

Economic Contribution: In addition to its social impact, the economic impact may be associated with scientific studies demonstrating its safety, such as ours, thereby promoting its production chain.

UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Botucatu

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE LUIS MANUEL SARMIENTO MACHADO, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 27 de fevereiro de 2026, às 14h30min, no(a) Sala da Pós-graduação IBB, realizou-se a defesa de TESE DE DOUTORADO de LUIS MANUEL SARMIENTO MACHADO, intitulada "Efeitos da ingestão da cianobactéria *Limnospira (Spirulina platensis) spp.* na promoção/progressão tumoral na hepatocarcinogênese química em camundongos fêmeas C3H/He". A Comissão Examinadora foi constituída pelos seguintes membros: Prof. Dr. LUIS FERNANDO BARBISAN (Orientador(a) - Participação Presencial) do(a) Departamento de Patologia / UNESP / Câmpus de Botucatu - IBB, Prof. Dr. ALEXANDRE TODOROVIC FABRO (Participação Presencial) do(a) Departamento de Patologia e Medicina Legal / Faculdade de Medicina de Ribeirão Preto-USP, Profa. Dra. CAMILA CONTIN DINIZ DE ALMEIDA FRANCIA (Participação Presencial) do(a) Departamento de Anatomia (IBB) / UNESP / Câmpus de Botucatu - IBB, Após a exposição pelo doutorando e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, o discente recebeu o conceito final: Aprovado. Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Prof. Dr. LUIS FERNANDO BARBISAN

Walk into this world with your head up high

Deftones & Max Cavalera - Headup

Agradecimentos

A minha mãe Isamery, pela abnegação e empatia aos seus seres queridos, pela resiliência diante as adversidades e por ser a minha calma nas situações mais difíceis.

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E finalmente, o presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Código de Financiamento 001 – nº de processo: 88887.666645/2022-00

Resumo

O câncer do fígado é a segunda principal causa de morte entre os cânceres a nível mundial, sendo o carcinoma hepatocelular (CHC) o subtipo mais comum (75-90%). A *Limnospira (Spirulina platensis) spp.* (LP) é uma cianobactéria conhecida pelas suas propriedades anti-inflamatórias e antioxidantes observadas em estudos pré-clínicos anteriores. Assim, avaliámos se a dieta de 5% de LP atenua o desenvolvimento de tumores hepáticos no modelo de hepatocarcinogênese induzida pela dietilnitrosamina (DEN). Durante quatro semanas, camundongos fêmeas C3H/He neonatos foram alimentados com ração basal e receberam quatro injeções intraperitoneais de DEN (25 mg/kg) 0,9% NaCl veículo (controle) uma vez por semana, sendo depois divididos em quatro grupos: (G1) DEN (n=28), (G2) DEN + 5%LP (n = 28), (G3) controle (n=10) e (G4) controle + 5%LP (n = 10). Após o regime de DEN, G2 e G4 receberam ração basal contendo 5% de LP (p/p) por 43 semanas. Em seguida, todos os animais foram submetidos à eutanásia, protocolo nº CEUA 3210170322. O fígado e os tumores hepáticos foram coletados para análise histopatológica e armazenados a -80°C para análise de transcriptoma por RNA-seq, considerando-se o valor de $p < 0,05$ e o *fold-change* (FC) = 2,0. Também foram coletados o baço e os rins apenas para histopatologia. Os dados estatísticos foram comparados entre os grupos utilizando One-way ANOVA e Kruskal-Wallis. Qui-quadrado e Mann-Whitney U para incidência e multiplicidade de tumores, respectivamente. O consumo das dietas ($p>0,05$) e o peso corporal final foram semelhantes entre os grupos DEN (G1) e DEN+5%LP (G2). A incidência e a multiplicidade de adenomas hepatocelulares e CHC não diferiram entre os grupos DEN (G1) e DEN+5%LP (G2), assim como a proliferação de células tumorais Ki-67 foram similares.

Palavras-chave: C3H/He; dietilnitrosamina; hepatocarcinogênese; *Limnospira (Spirulina platensis) spp.;* neoplasias hepáticas; promoção-progressão; quimioprevenção.

Abstract

Liver cancer is the second leading cause of death among cancers worldwide, and hepatocellular carcinoma (HCC) the most common subtype (75-90%). *Limnospira (Spirulina platensis) spp.* (LP) is a cyanobacteria known for its anti-inflammatory and antioxidant properties observed in previous preclinical studies. Thus, we assessed whether LP attenuates liver tumor development during experimental hepatocarcinogenesis. During four weeks, neonatal female C3H/He mice received four intraperitoneal injections of DEN (25 mg/kg) or vehicle once a week, then allocated into four groups: (G1) DEN (n=28), (G2) DEN+5% LP (n = 28), (G3) control (n=10) and (G4) control+5% LP (n = 10). After DEN regimen, G2 and G4 received standard chow containing 5% LP for 43 weeks (protocol nº CEUA 3210170322). The liver and their tumors were collected for histopathological analyses and were frozen at -80°C for RNA-seq analysis, considering $p < 0.05$ and *fold change* (FC) = 2.0. Food consumption and final body weight were similar between groups. Incidence and multiplicity of hepatocellular adenomas and HCC did not differ between DEN (G1) and DEN + 5%LP (G2), as well as tumor cell proliferation Ki-67 were similar between these two groups. The transcriptomic profile did not elicit a protective effect of 5% LP on DEN-induced tumors. Overall, LP treatment was well tolerated and did not induce morphological alterations in other organs in non-target organs. In summary, LP do not exert a protective effect against liver tumor development.

Keywords: C3H/He; Chemoprevention; Diethylnitrosamine Hepatocarcinogenesis; *Limnospira;* Hepatic Neoplasms; Promotion-Progression; *(Spirulina platensis) spp.*

Súmario

Capítulo I Revisão de Literatura

1. Carcinoma Hepatocelular (CHC)

1.1 Câncer de fígado: dados gerais

O câncer de fígado é a sexta neoplasia mais incidente (4,3% dos casos) do mundo, e a terceira em mortalidade (7,8%), sendo a maioria dos casos (80%) do subtipo CHC, e o colangiocarcinoma intra-hepático (ICC em inglês), originário dos ductos biliares. A maioria dos casos de CHC derivam de um contexto fibrótico-cirrótico em 75-90% (Bray *et al.,* 2024). Além disso, é o nono mais incidente (2,7%) e o quinto (5,5%) em mortalidade nas mulheres (Bray *et al*., 2024). Essa disparidade pode estar relacionado a fatores hormonais e/ou ambientais, visto que o estrogênio apresenta papel protetor contra a hepatocarcinogênese, assim como o estilo de vida pode ser diferente entre os homens e as mulheres (Naugler *et al.,* 2007). Dois terços dos casos de CHC ocorrem no continente asiático (Bray *et al.,* 2024). Quanto ao aspecto socioeconômico, há uma tendência de aumento de casos nos países de Índice de Desenvolvimento Humano (IDH) alto em comparação aos de IDH baixo, o que pode estar relacionado a uma transição da predominância da etiologia viral no mundo para as não-virais (Yang *et al.,* 2022; Toh *et al*., 2023). Os principais fatores de risco do CHC no Ocidente envolvem a dieta rica em gorduras saturadas e açúcares (*Metabolic Dysfunction-Associated Steatotic Liver Disease- MASLD*), etilismo e tabagismo e Hepatite C (HCV); enquanto no Oriente são as infecções crônicas por Hepatite B (HBV) e a aflatoxina B1 (AFB1) (Baecker *et al.,* 2018; Younossi *et al*., 2023) **(Figura 1)**. O CHC é uma doença de baixa sobrevida, de aproximadamente 11 meses (Greten *et al*., 2005), visto que os pacientes são diagnosticados majoritariamente em estágios mais avançados, onde estratégias de cura/tratamento são escassas (Yang *et al.,*2019, Toh *et al.,* 2023; Nevola *et al*., 2023). O sorafenibe foi aprovado pela *Food and Drug Administration* (FDA) para o tratamento de CHC em estágio avançado, aumentando a sobrevida por três meses (Llovet *et al.,* 2008). Diante deste cenário, a busca de opções preventivas e/ou terapêuticas é necessário. Nos estágios iniciais de CHC, opções como a resseção cirúrgica, transplante de fígado, ou a ablação podem remover o tumor maligno *in situ*, e, portanto, erradicar a doença no paciente (Orcutt e Anaya., 2018; Yang *et al.,*2019, Nevola *et al*., 2023).

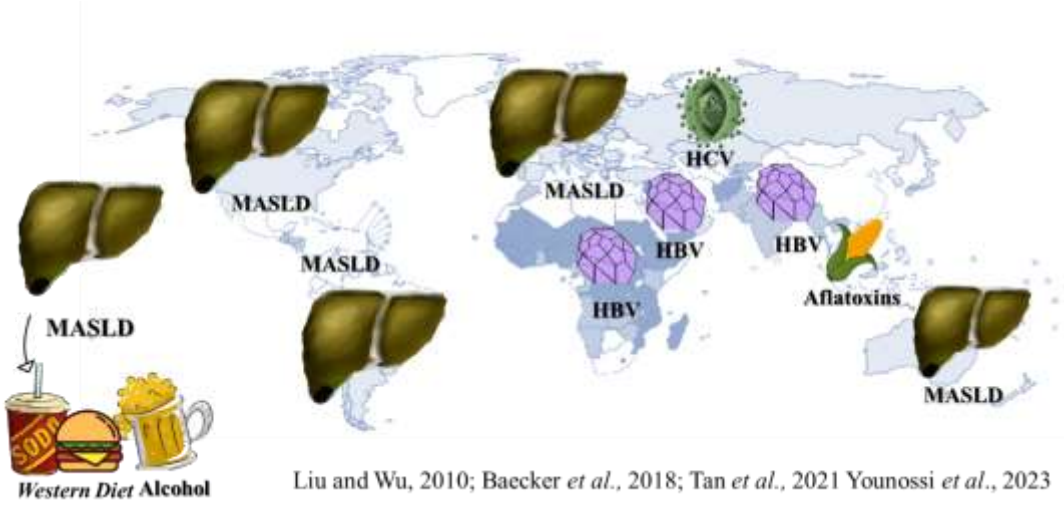

Figura 1. Os principais fatores de risco do câncer de fígado no mundo.

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