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Sobre os efeitos quimiopreventivos e antitumorais do guaraná,

Paullinia cupana Mart *var. sorbilis*, em modelos experimentais

in vivo e *in vitro*

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RESUMO

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O câncer é a segunda maior causa de morte no Brasil, atrás apenas de doenças cardíacas. Por isto, é evidente que grandes recursos sejam direcionados para a pesquisa no descobrimento de novas opções com a finalidade de erradicar esta doença. Dentre estas opções, a quimioprevenção do câncer tem chamado a atenção já que, mesmo com os imensos avanços no conhecimento sobre os mecanismos da carcinogênese e conseqüente desenvolvimento de novas drogas, os dados estatísticos de mortalidade não se tornaram menores. Somando-se a estes fatos, deve ser considerado que no Brasil o tratamento padrão do câncer não chega a todas as pessoas por ser extremamente caro. Desta forma, a quimioprevenção do câncer com fatores presentes na dieta ou oriundos de fontes consideradas baratas como fitoterápicos, deve ser apreciada. Assim, este trabalho teve como objetivo avaliar os efeitos quimiopreventivos e antineoplásicos de uma planta brasileira, o guaraná (*Paullinia cupana* Mart var. *sorbilis*). Foram utilizados alguns experimentos em camundongos como indução genotóxica em fígado pela Dietilnitrosamina (DEN); carcinogênese pulmonar induzida pela 4-(metilnitrosamino)-1-(3-piridil)-1-butanona (NNK), uma nitrosamina presente no tabaco; tumor ascítico de Ehrlich; disseminação hematógena de melanoma B16/f10; e cultivo de células tumorais e não tumorais. Além disso, caracterizou-se o papel da Conexin43 na carcinogênese pulmonar induzida pelo NNK e os efeitos do guaraná sobre o receptor CAR e sua ação quando da administração do ligante do CAR, 1,4-bis[2-(3,5-dichloropiridiloxi)]benzeno (TCPOBOP). Pudemos observar efeitos quimiopreventivos e antineoplásicos do guaraná dependendo do modelo utilizado, demonstrando que seu modo de ação principal é a redução da proliferação celular. Além disso, observamos que os tumores de pulmão dos animais tratados com a planta apresentavam menor tamanho, menor grau maligno, menor índice de proliferação celular e menor ativação do fator de transcrição CREB. Observamos também que a Conexina43 (Cx43) tem importante papel na carcinogênese pulmonar induzida pelo NNK, atuando como

supressor tumoral e em fases tardias possivelmente tendo papel inverso, ou seja, como um oncogene. Caracterizamos os efeitos do guaraná sobre a ativação do receptor CAR e demonstramos que, por si só, o guaraná induz a expressão do CAR, além de alterar a expressão de alguns de seus transcritos como a CYP2B10 e CYP3A11. Ao analisarmos os efeitos de extratos de guaraná sobre células de tumor de pulmão (E9) *in vitro*, verificamos o mesmo efeito antiproliferativo, diminuindo a expressão do PCNA e da Conexina43 de maneira dose-dependente, além de verificar um aumento da expressão do receptor CAR. Ao fim propomos uma hipótese de mecanismo de ação baseando-se nas alterações encontradas oriundas da administração do guaraná. Concluímos que o guaraná apresenta componentes com ação antitumoral em camundongos, tendo efeito quimiopreventivo ou antineoplásico dependendo do modelo utilizado.

Palavras chave: Guaraná. Câncer. Quimioprevenção do câncer. Receptor CAR. Conexina43. Biotransformação de xenobióticos.

ABSTRACT

FUKUMASU, H. **On the chemopreventive and antineoplastic effects of guarana, *Paullinia cupana* Mart var. *sorbilis*, in *in vivo* and *in vitro* experimental models.** [Sobre os efeitos quimiopreventivos e antineoplásicos do guaraná, *Paullinia cupana* Mart var. *sorbilis*, em modelos experimentais *in vivo* e *in vitro*]. 2008. 300 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2008.

Cancer is the second biggest cause of deaths in Brazil, only behind of cardiac diseases. As a result, it is evident that great resources for research will be directed towards the discovery of new options to eradicate this disease. Among these options, cancer chemoprevention has calling for attention since the huge advances in the knowledge of carcinogenesis and development of new drugs did not decrease statistical data on mortality due to cancer. In addition, it must be considered that in Brazil, cancer therapy is not available for all given that it is too expensive. Therefore, cancer chemoprevention with dietary factors or from medicinal plants has got to be treasured. Following these lines, the aim of this work was to evaluate the chemopreventive and antineoplastic effects of a Brazilian plant, *Paullinia cupana* Mart var. *sorbilis*, most known as guarana. It was used several experiments in mice and cell culture essays as: protection against DEN-induced DNA damage; NNK-induced lung carcinogenesis; Ehrlich Ascitic Tumor; metastasis of B16/f10 melanoma cells; and cell culture of a tumorigenic and a non-tumorigenic cell lines. Additionally, it was characterized the role of Connexin43 in the NNK-induced lung carcinogenesis and the effects of guarana on the CAR receptor before and after the administration of TCPOBOP. We note a chemopreventive or antineoplastic effect of guarana depending on the model employed and showed that the mode of action responsible for these effects was reduced cell proliferation. Also, the lung tumors of guarana-treated animals were smaller, less aggressive, with decreased cell proliferation and CREB activation. On the other hand, we observed that Connexin43 have an important role on NNK-induced lung carcinogenesis because it may act as a tumor suppressor and in advanced stages as an oncogene. The effects of guarana on the CAR activation were characterized and we showed that guarana induces CAR mRNA expression, altering the levels of its transcripts as CYP2B10 and CYP3A11. We also examined the effects of guarana extracts on a lung tumor cell culture (E9 cells) and demonstrated the same

antiproliferative effect observed previously, by decreased PCNA and Connexin43 proteins in a dose-dependent manner along with an increase in CAR protein. At last we hypothesized a mechanism of action for guarana effects basing in our findings. We concluded that guarana presents substances that have antitumoral effects in mice, enclosing a chemopreventive or antineoplastic effect depending on the model studied.

Keywords: guarana. Cancer. Cancer Chemoprevention. CAR receptor. Connexin43. Xenobiotic metabolism.

Capítulo 1

Introdução:

Câncer, carcinogênese e quimioprevenção

1 Câncer, Carcinogênese e Quimioprevenção

1.1 INTRODUÇÃO

A ciência biológico-biomédica avança a uma velocidade muito grande, e a tendência é que com os novos métodos e o conhecimento científico acumulado a cada novo dia, as descobertas sobre os mais diferentes problemas que afligem a humanidade solucionem os enigmas de outrora. Porém, ao acompanhar mais a fundo esta "corrida" científica, um destes problemas continua fazendo cada vez mais vítimas pelo mundo todo, independentemente do avanço na medicina ocorrido nos últimos 50 anos: o câncer. No ano de 2002 verificou-se que 11 milhões de pessoas foram diagnosticadas e 7 milhões morreram por causa desta doença no mundo todo (KAMANGAR; DORES; ANDERSON, 2006). Obviamente que a disparidade entre as diferentes regiões do mundo levam a diferenças nos dados de incidência, morbidade e mortalidade, sendo possível notar que em países desenvolvidos, as curvas de mortalidade e de novos casos tendem a se estabelecer. Já nos países pobres tem ocorrido um aumento na incidência e mortalidade de pessoas com câncer, por causas diversas, porém principalmente causas consideradas evitáveis como aumento no consumo de tabaco, exposição a alimentos contaminados com toxinas (aflatoxina, por exemplo), prevalência de infecção por *Helicobacter pylori* etc. Os dados brasileiros do ano de 2000 indicaram que as neoplasias são a segunda maior causa de morte, ficando atrás apenas de doenças do sistema circulatório (INCA, INSTITUTO NACIONAL DO CÂNCER, 2003), sendo que entre 1979 e 2000 foi observado um aumento lento e gradativo no número de mortes por câncer de pulmão, próstata e mama; por outro lado, ocorreu uma diminuição nos casos de morte por tumor de estômago (INCA, INSTITUTO NACIONAL DO CÂNCER, 2003).

Sendo assim é lógico e esperado que seja feita ciência sobre o câncer, desde a pesquisa básica tentando compreender os diversos mecanismos que levam ao desenvolvimento progressivo da doença, à ciência traducional (do inglês, *translational medicine*) e aplicada (ou clínica). Ambas devem compreender e absorver o conhecimento básico para formular novas opções com intuito de diminuir o número de mortes causadas

por neoplasias. As alternativas para se reduzir a mortalidade gerada pelos cânceres são consideradas três principais: detecção precoce, prevenção e tratamento. Dentre estas opções, a mais plausível seria a prevenção, porém também é a mais controversa, como veremos a seguir.

1.2 O QUE É CÂNCER?

Câncer é considerado como sendo tumor (ou neoplasma, ou neoplasia) maligno, ou seja, que já possui a capacidade de invadir os tecidos adjacentes e gerar metástases em órgãos distantes. Porém a definição mais utilizada para neoplasma é a do médico oncologista britânico Rupert A. Willis, que em 1952 definiu "Neoplasma é uma massa anormal de tecido, no qual o seu crescimento excede e é descoordenado em relação ao tecido normal, e persiste da mesma maneira excessiva mesmo após a interrupção dos estímulos que levaram a sua formação" (WILLIS, 1952). O processo pelo qual o câncer se desenvolve é denominado de carcinogênese, onde diversas evidências demonstraram que em humanos e possivelmente em outras espécies animais, seja um processo de múltiplos passos que refletem alterações genéticas (e epigenéticas) que direcionam a transformação progressiva de células normais em derivados altamente malignos (HANAHAN; WEINBERG, 2000). Em humanos acredita-se que sejam necessários de 6 a 7 eventos independentes, seqüenciais e estáveis antes que as células cancerosas se tornem malignas (ARMITAGE; DOLL, 1954). Interessantemente, este modelo foi proposto por Epidemiologistas, antes do advento da biologia molecular (WEISS, 2004). Estes eventos, genéticos ou não, recaem sobre 6 grandes tipos de alterações que as células cancerosas podem apresentar, já denominados como os pontos chaves do câncer (*Hallmarks of cancer*): auto-suficiência em fatores de crescimento; insensibilidade aos fatores inibitórios; evasão da apoptose; neoangiogênese; potencial ilimitado de replicação e; invasão tecidual e metastatização (HANAHAN; WEINBERG, 2000). Devem-se ainda serem consideradas alterações que levem à geração de instabilidade cromossômica, potencialmente facilitando a ocorrência do acúmulo das alterações descritas (YAMASAKI; MIRONOV, 2000).

A carcinogênese além de ser caracterizada como um processo de múltiplos passos pode ser dividida em três fases para melhor compreensão e estudo: iniciação, promoção e progressão (BERENBLUM; SHUBIK, 1949). A iniciação consiste na primeira alteração, sendo aceito que esta seja responsável por impedir que a célula se diferencie terminalmente (TROSKO, 2007). A fase promocional consiste no período em que as células iniciadas crescem clonalmente sob a ação de substâncias não genotóxicas, induzindo a proliferação celular. Estas substâncias podem ser endógenas como no caso de infecções crônicas, como exemplo pode-se citara influência de *Helycobacter pylori* sob a carcinogênese de estômago. Podem também ser exógenas, onde xenobióticos não-genotóxicos geram este efeito promotor, como o fenobarbital para tumor de fígado, hidroxitolueno-butilado (BHT) para tumor de pulmão etc. A partir do momento que a lesão pré-neoplásica continua a crescer mesmo na ausência do agente promotor caracteriza-se o início da fase de progressão da carcinogênese. Nesta fase se localizam as lesões benignas (adenomas, por exemplo), assim como as malignas (adenocarcinomas). O modelo de carcinogênese colo-retal proposto no século passado (FEARON; VOGELSTEIN, 1990) condiz com esta teoria, onde se observa determinada seqüência característica de alterações envolvendo oncogenes (RAS) e genes supressores de tumor (Figura 1.1).

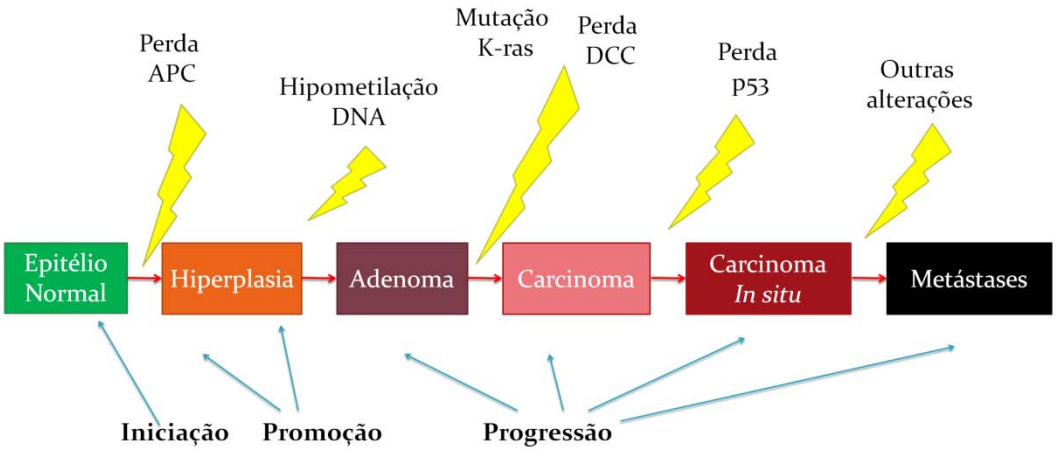

Figura 1.1 – Modelo de carcinogênese colo-retal genético. Baseado em descrições de Fearon e Vogelstein (FEARON; VOGELSTEIN, 1990)

1.3 QUIMIOPREVENÇÃO DO CÂNCER

O termo quimioprevenção do câncer foi cunhado a primeira vez por Michael Sporn (SPORN et al., 1976) e foi definido como sendo os meios pelos quais se pudesse interromper, reverter ou modular a carcinogênese. Desde então pesquisadores do mundo todo foram (e continuam) atraídos pela premissa de que "prevenir é melhor que remediar", o que no caso do câncer pode ser considerado uma regra. Isto se deve ao fato, conforme comentado acima, que o câncer ainda é uma doença que apresenta índices muito altos de mortalidade. Mesmo com os imensos avanços no conhecimento sobre os mecanismos da carcinogênese e conseqüente desenvolvimento de novas drogas, os dados estatísticos de mortalidade não serão mudados até que ocorra uma mudança fundamental na ênfase dada à pesquisa do câncer, direcionando maiores recursos para a prevenção do câncer do que para o tratamento de uma doença em estágio-final (SPORN; SUH, 2002b).

A quimioprevenção é dividida conceitualmente em três partes: prevenção primária, ou seja, prevenir o início do câncer em indivíduos saudáveis; prevenção secundária, ou seja, prevenir o câncer em pacientes com condições de pré-malignidade (que apresentem lesões pré-neoplásicas); e prevenção terciária, ou seja, prevenir que novos cânceres se desenvolvam em pacientes já curados com um câncer inicial. O exemplo de quimioprevenção de câncer de mama com tamoxifeno demonstrou resultados promissores, reduzindo 49 e 43% a incidência de tumores invasivos com prevenção primária e secundária, respectivamente (HONG; SPITZ; LIPPMAN, 2000). A utilização do tamoxifeno nestas condições ilustrou outro princípio geral da quimioprevenção: o número de pacientes e a duração do ensaio clínico são maiores em ensaios de prevenção primária do que de prevenção secundária ou terciária. Este fato leva-nos a considerar que quimioprevenção do câncer deve ser de alguma maneira direcionada para pessoas que tenham predisposição a determinado tipo de câncer, evitando assim medicar pessoas que provavelmente nunca terão câncer em determinado órgão. Além disso, as drogas quimiopreventivas devem por si só apresentarem baixo grau de toxicidade e custo, já que deverão ser consumidas por um longo período.

Estas drogas são classicamente divididas em agentes inibidores, bloqueadores e supressores da carcinogênese (WATTENBERG, 1985). Os agentes inibidores devem impedir a formação das substâncias carcinogênicas atuando sobre os agentes precursores; os agentes bloqueadores devem atuar sobre as substâncias carcinogênicas, sendo genotóxicas ou não, eliminando-as ou tornando-as menos tóxicas; e os agentes supressores devem agir sobre as manifestações malignas das células cancerosas, ou seja, impedindo a carcinogênese (WATTENBERG, 1985). A maneira mais racional para a quimioprevenção é estudar e testar novos agentes que atuem em alvos moleculares e celulares específicos (SPORN; SUH, 2002b). Referente a esta afirmação, já foi demonstrado que diversos fitoquímicos derivados de plantas, que fazem parte da dieta, interferem em estágios específicos da carcinogênese (SURH, 2003a). Estes fitoquímicos são componentes não nutritivos presentes na dieta que possuem efeito anticarcinogênico substancial. A quimioprevenção com os fitoquímicos presentes na dieta é considerada uma maneira para controlar o câncer de forma barata, rapidamente aplicável, aceitável e acessível (SURH, 2003a). Sendo assim, uma ótima alternativa para um país como o nosso que não possibilita a todos o acesso às melhores formas de tratamento de câncer sejam elas radio ou quimioterápica.

CONCLUSÕES

- O guaraná apresentou efeito quimiopreventivo e antineoplásico em modelos experimentais em camundongos e em cultivo de célula

- O modo de ação do guaraná é principalmente devido ao retardo da proliferação celular observada nas células tumorais

- O mecanismo de ação do guaraná em células tumorais não foi completamente elucidado, porém há indícios da participação do receptor CAR e da menor ativação do fator de transcrição CREB

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