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UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Campus de Botucatu

PG-BGA

POSSÍVEL AÇÃO SINÉRGICA DE COMPONENTES DA PRÓPOLIS SOBRE CÉLULAS DE CARCINOMA DE LARINGE HUMANA (HEp-2): MECANISMOS DE RESISTÊNCIA E MORTE CELULAR

LÍVIA MATSUMOTO DA SILVA

Dissertação apresentada ao Instituto de Biociências, Campus de Botucatu, UNESP, para obtenção do título de Mestre no Programa de Pós-Graduação em Biologia Geral e Aplicada, Área de concentração *Biomoléculas: estrutura e função.*

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1. Própole. 2. Fenóis. 3. Citotoxicidade. 4. Células. 5. Glicoproteínas.

Palavras-chave: Células HEp-2; Citotoxicidade; Compostos fenólicos; Glicoproteina-P; Própolis.

"Cada pessoa tem seu próprio deserto a atravessar. E a cada vez será necessário desmascarar as miragens e também contemplar os milagres: o instante, a aliança, a douta ignorância e a fecunda vacuidade."

Jean-Yves Leloup

Revisão de Literatura

Resumo

Própolis e seus compostos fenólicos são conhecidos por apresentarem propriedades antioxidantes e anticâncer. Recentemente, os mecanismos de ação da propolis têm sido objeto de investigação. Este estudo teve como objetivo elucidar os efeitos da própolis e três compostos fenólicos (ácido cafeico - Caf, ácido dihidrocinâmico - Cin; ácido *p*-cumárico - Cou) na mesma proporção que são encontrados em nossa amostra de própolis, isoladamente ou em combinação, sobre células de carcinoma epidermóide de laringe humano (HEp-2). A viabilidade celular, tipo de morte e parada do ciclo celular, geração de espécies reativas de oxigênio (ROS) e a possível capacidade da própolis em induzir o efluxo de doxorrubicina (DOX) via inibidor de glicoproteína-P (P-gp) foram avaliadas. A própolis exerceu um efeito citotóxico em células HEp-2 e apresentaram um valor de IC_{50} igual a 80 µg/mL, enquanto que os compostos isolados (isoladamente ou em combinação) não mostraram efeito sobre a viabilidade celular após 72 h. Assim, concentrações mais elevadas destes compostos foram testadas e Caf ($IC_{50:}$ 1.332 µM) induziu necrose em células HEp-2, enquanto que a própolis induziu apoptose em células HEp-2, ambos, provavelmente devido à geração de ROS. A amostra de própolis induziu parada do ciclo celular na fase G2/M e Caf na fase S. Própolis ou seus componentes, com exceção de Caf, pode agir como um potencial inibidor de P-gp por modulação da atividade da P-gp, inibindo o efluxo de DOX. Sendo assim, os dados sugeriram que a própolis exerceu efeitos citotóxicos contra células HEp-2 e alguns mecanismos são discutidos. O seu potencial como um fármaco anti-tumoral deve ser investigado em ensaios futuros.

Palavras-chave: Própolis; Compostos fenólicos; Efeito citotóxico; células HEp-2.

Abstract

Propolis and its phenolic compounds are known for their antioxidant and anticancer properties. Propolis mechanisms of action have been the subject of research recently. This study aimed to elucidate the effects of propolis and three phenolic compounds (caffeic acid – Caf; dihydrocinnamic acid – Cin; *p*-coumaric acid – Cou) in the same proportion they are found in our propolis sample, alone or in combination, towards human larynx epidermoid carcinoma (HEp-2) cell. Cell viability, apoptosis/necrosis and cell cycle arrest, generation of reactive oxygen species (ROS) and the ability of propolis to induce doxorubicin (DOX) efflux using a P-glycoprotein (P-gp) inhibitor (verapamil) were assayed. Propolis exerted a cytotoxic effect in HEp-2 cells and exhibited an IC_{50} value of 80 µg/mL, whereas the isolated compounds (alone or in combination) had no effect on cell viability after 72 h. Hence, higher concentrations of these compounds were tested and Caf (IC_{50}: 1.332 µM) induced necrosis in HEp-2 cells, while propolis induced apoptosis, both, probably due to ROS generation. Propolis induced cell cycle arrest at G2/M phase and, Caf at S phase. Propolis or its components, except Caf, can act as a P-gp inhibitor by modulating P-gp activity and inhibiting the efflux of DOX. Altogether, data suggested that propolis exerted cytotoxic effects against HEp-2 cells and some mechanisms are discussed. Its potential as an antitumor drug should be investigated in further assays.

Key words: Propolis; Phenolic compounds; Cytotoxic effect; Hep-2 cells.

1. Câncer: características gerais

Câncer é o termo genérico dado a um conjunto de doenças que apresentam o crescimento desordenado de células que podem vir a invadir tecidos e órgãos, podendo espalhar-se para outras regiões do corpo (1). Um acúmulo de alterações genéticas permite que as células rompam uma série de barreiras proliferativas, conferindo algumas características comuns a todas as células tumorais como: autossuficiência em sinais de crescimento, ausência de resposta a sinais anti-crescimento, evasão da apoptose, potencial replicativo ilimitado, angiogênese, invasão tecidual e metástase (2). As condições para o desenvolvimento tumoral são multifatoriais e podem agir em conjunto ou sequencialmente para promover sua iniciação, quando o organismo está susceptível à instabilidade genética e metabólica (3, 4).

O câncer é uma das principais causas de morte em todo o mundo, apresentando uma grande complexidade etiológica e complexas interações entre o tumor e seu microambiente. Além disso, a incidência cresce conforme a longevidade e a adoção de hábitos considerados fatores de risco como consumo de álcool e tabaco, hábitos alimentares, exposição à radiações, etc. (5, 6). Apesar de tantos anos dedicados a estudos para a sua compreensão, o câncer ainda continua sendo uma doença que carece de maiores investigações e terapias eficazes (7).

Linhagens celulares imortalizadas são uma ferramenta valiosa na investigação molecular, bioquímica, genética e imunológica de células derivadas de tecidos neoplásicos, usadas como modelo experimental *in vitro*. O uso destas linhagens mostra-se crível, pois permite avaliar as contribuições funcionais das anormalidades genômicas, visto que a transcrição desregulada presente nos tumores primários humanos é conservada nas linhagens celulares (8).

Diversas células têm sido utilizadas nos estudos de câncer de cabeça e pescoço, como HEp-2, HEp-3 e KB. Em trabalhos realizados por nosso grupo de pesquisa, temos utilizado as células da linhagem HEp-2, frequentemente utilizada como modelo de estudos sobre carcinogênese e mutagênese (9-11). Essa linhagem tem uma alta taxa de proliferação e ciclo celular de 23 horas (12). Elas foram descritas inicialmente como sendo derivadas de carcinoma epidermóide da laringe, mas subsequentemente foi encontrado um perfil genético que a identifica como a linhagem celular HeLa, com base em análise de isoenzimas, provavelmente por contaminação com estas células (ATCC® CCL-23™).

Sendo assim, é interessante que haja estudos que promovam uma melhor compreensão das características moleculares que podem predizer ou indicar a via de ação de agentes terapêuticos de diferentes tipos de carcinomas, e que possam fornecer subsídios para tratamentos alternativos aos tradicionais quimioterápicos.

2. Produtos naturais e câncer

O uso de plantas medicinais e metabólitos microbianos tem ampliado a expectativa de vida, seja empiricamente ou a partir da síntese de medicamentos de origem natural (13). Nos últimos 25 anos, mais de 75% dos produtos antitumorais foram obtidos de fontes naturais ou sintetizados industrialmente a partir de princípios ativos purificados das mesmas. Dos 140 agentes antitumorais disponíveis desde a década de 40, mais de 60% são oriundos de compostos naturais (14). Esses agentes atuam através de mecanismos que incluem indução de apoptose, clivagem do DNA mediada pela inibição pela topoisomerase I ou II, permeabilização mitocondrial, inibição de enzimas envolvidas na transdução de sinal ou no metabolismo celular, e por inibição da angiogênese (13).

Estudos também têm investigado o efeito da administração de produtos naturais concomitantemente com fármacos (15, 16), a fim de obter uma interação entre ambos por efeito aditivo, sinérgico, antagônico ou potencializador, com o intuito de compreender os efeitos causados pelos agentes antitumorais *in vitro*, para que, futuramente, esta cominação possa ser útil em novos tratamentos, sem interferência na eficiência, diminuindo os efeitos colaterais dos quimioterápicos.

Além de plantas medicinais e metabólitos microbianos, existem também os opoterápicos obtidos a partir de glândulas, órgãos, tecidos ou secreções animais (17). Um exemplo de opoterápico é a própolis produzida por abelhas africanizadas (*Apis mellifera*). Vários autores têm relatado que a própolis e seus componentes representam candidatos promissores para a elaboração de novos fármacos, com efeitos imunomodulador, radioprotetor e principalmente como agentes citotóxicos, antitumoral e quimiopreventivo contra vários tipos de tumores, contribuindo com a expansão do arsenal existente de medicamentos contra o câncer (18-22).

Conclusão

Esta amostra de própolis inibiu o crescimento de células HEp-2 e induziu apoptose mediada pela produção de ROS. Os compostos fenólicos isolados (Caf, Cin e Cou) em concentrações encontradas na amostra de própolis não afetou a viabilidade celular, no entanto, maiores concentrações exerceram efeitos citotóxicos significativos. Particularmente, Caf exibiu uma atividade citotóxica maior do que Cin e Cou, induzindo necrose das células HEp-2. Além disso, a própolis foi capaz de modular a sensibilidade de células HEp-2 à DOX por inibição da atividade de P-gp. São necessárias maiores investigações para elucidar o envolvimento de própolis contra células tumorais.

ANEXO 1:

TABLE 1: Relative percentages of compounds, determined by GC-MS, from ethanolic extract of Brazilian propolis.

Component	Retention time (min)	% of total
Benzoic acid	9.3	0.193
Dihydrocinnamic acid	14	2.180
Dihydrocinnamic acid	22	0.860
Coumaric acid	26.5	0.382
Cafeic acid	28.6	0.297
Prenyl-*p*-coumaric acid	32.5	6.560
Flavonoids	35.8	1.142
Artepillin C	37.7	16.750
Trihydroxymethoxy flavonon	40.5	0.666
Tetrahydroxy flavonon	40.8	0.228
Triterpene	47.6	0.777
Triterpene	51	0.309

Retirado de: Conti BJ, Bufalo MC, Golim Mde A, Bankova V, Sforcin JM. Cinnamic Acid is partially involved in propolis immunomodulatory action on human monocytes. Evidence-based complementary and alternative medicine: eCAM. 2013;2013:109864. Epub 2013/06/14.

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