Propolis, Chemoprevention and Use of Animals in Experimental Research: A Critical Review

Brizza Morena Ledo-Fernandes
Dentist, Federal University of Jequitinhonha and Mucuri Valeys (UFVJM), Diamantina, Minas Gerais, Brazil
Email:brizzaledo@yahoo.com.br
Ana Paula Cruz
Dentist, Federal University of Jequitinhonha and Mucuri Valeys (UFVJM), Diamantina, Minas Gerais, Brazil
Email:acruz_mg@yahoo.com.br
Sandra Aparecida Marinho
Department of Dentistry, State University of Paraiba, UEPB, Araruna, Paraíba, Brazil
Email:san_mar2000@yahoo.com.br
Flaviana Dornela Verli
Department of Basic Sciences, School of Basic and Health Sciences, Federal University of Jequitinhonha and Mucuri Valeys (UFVJM), Diamantina, Minas Gerais, Brazil
Email:flavianaverli@gmail.com
José Cristiano Ramos Glória
Department of Dentistry, School of Basic and Health Sciences, Federal University of Jequitinhonha and Mucuri Valeys (UFVJM), Diamantina, MG, 3910-000, Brazil
Email:jcristianosomar@hotmail.com
Ricardo Lopes-Rocha
Department of Dentistry, School of Basic and Health Sciences, Federal University of Jequitinhonha and Mucuri Valeys (UFVJM), Diamantina, MG, 3910-000, Brazil
Ricardo Lopes-Rocha, Departamento de Odontologia - UFVJM - Rua da Glória, 187; Campus I, Prédio 01, Postal Code: 39100-000, Diamantina, MG, Brazil, Tel: +55-38 3532-6063
Email:ricardolopes.ufvjm@gmail.com

1. INTRODUCTION

Carcinogenesis is a process involving several phases and characterized by changes in genetic, epigenetic and phenotypic factors [1]. This process has been the object of both *in vivo* and *in vitro* studies aimed at the determination of genetic mutations related to apoptosis, the control of cell division, metastatic potential and the activation of metabolic pathways of cancer cells [2]. Cancer cells from animals [3-5] or humans [3,6-9] are used under *in vitro* conditions to analyze the mechanisms of action of chemopreventive substances. To conduct such tests *in vivo*, carcinogenesis can be induced in animals through chemical [10-12,] or other means [13-15].

The main anti-carcinogenic effects of chemopreventive substances are the inhibition of absorption, changes in the activation and deactivation of the carcinogen, the blocking of its bond to DNA or the repair of mutated DNA [16-18]. Other chemotherapeutic effects include the inhibition of cancer cell proliferation by triggering apoptosis [19-21] and the inhibition of tumor progression through the promotion of anti-angiogenic activity [22-24].

Propolis is a resinous substance produced from vegetal resins and modified by salivary enzymes from the bee *Apis mellifera* [25-26]. More than 300 chemical compounds have been identified in propolis, such as flavonoids, polyphenols, phenolic acid, quinones, sesquiterpenes, coumarine, amino acids, steroids, glycerides and inorganic compounds [6,27]. In the last thirty years, propolis and its constituents have been extensively tested as chemopreventive agents due to their immunomodulating [28-30], antioxidant [31-32] and anti-carcinogenic [33-36] properties, which are often determined in studies involving animals, especially rats. The aim of the present review was to compile and analyze articles indexed in the MEDLINE/PubMed database that have tested propolis and/or its constituents in the chemoprevention of cancer, with an emphasis on the number of animals used and the duration of the experiments.

2. MATERIALS AND METHODS

A search of the MEDLINE/PubMed database was conducted on December 31st, 2014 using the key words *propolis, cancer, chemoprevention* and *carcinogenesis* in the following combinations: *propolis and chemoprevention*; *propolis and carcinogenesis*; and *propolis and cancer*. The inclusion criteria were articles published in MEDLINE/PubMed, written in English and published in the database up to December 31st, 2014. Duplicated articles and those that addressed other subjects or were published in other languages were excluded. Two hundred thirty papers were selected and classified as either research articles or reviews.

The variables analyzed in the research papers were: year of publication, type of study design, types of subject / specimens used, chemical analysis of propolis samples and conclusions over their efficacy in chemoprevention. Was done an analysis of the main objectives and results of clinical trials. Exploratory analysis was employed to determine the frequency and distribution of the data. The chi-square test was then used to compare year of publication to the number of animals used and the duration of animal experiments in the *in vivo* studies.

3. RESULTS

Seventeen articles were retrieved using the combination of the key words *propolis and chemoprevention;* 38 were retrieved with the combination of *propolis and carcinogenesis*; and 258 were retrieved with the combination of *propolis and cancer*. The initial total was 313 articles, 83 of which were excluded: 54 were duplicates; 24 did not address the subject of the present review; and five were not published in English. Among the 230 articles that met the inclusion criteria, 201 (87.4%) were *in vivo* or *in vitro* studies, five (2.2%) were clinical trials and 24 (10.4%) were review articles. The year of publication ranged from 1983 to 2014 and the number of articles published per year ranged from one to 1 to 34, with non-normal distribution (Figure 1).

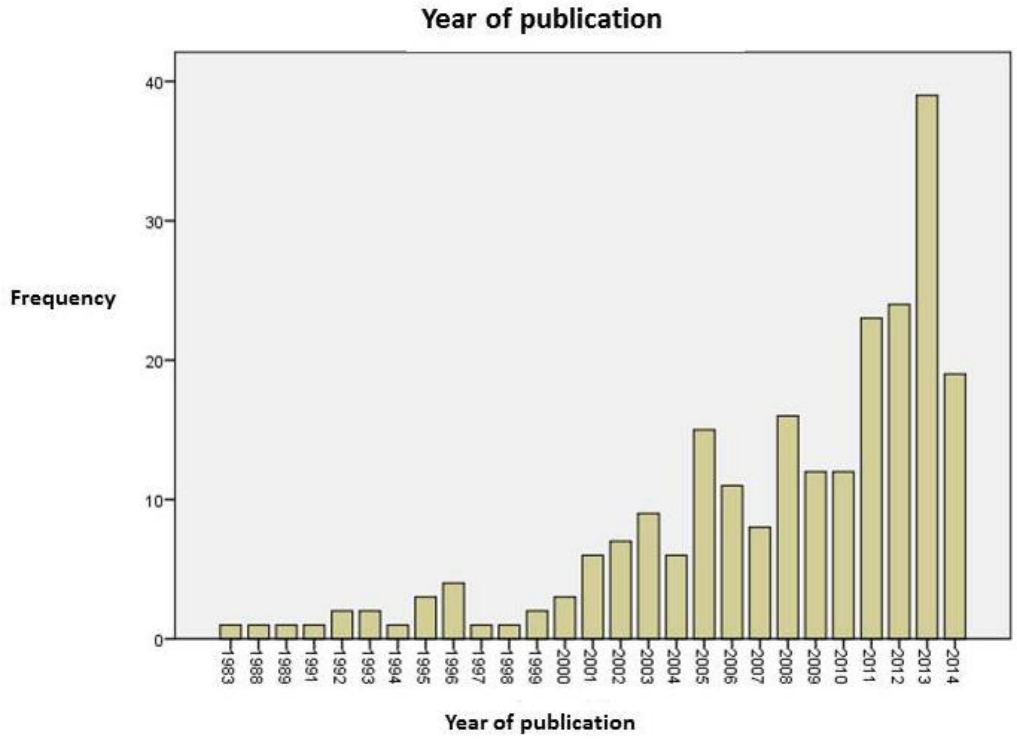

Figure 1: Annual distribution of number of articles published based on search performed on December 31st, 2014

The papers classified as in vivo studies (n = 74) with the respective sample sizes and running time of the study are listed in chart 1 (articles published between 1989 and 2001) and chart 2 (articles published between 2002 and 2014). The articles classified as clinical trials (n = 5), published between 2006 and 2014, are listed in chart 3, along with summaries of the main results. The review papers (n = 24), published between 1983 and 2014 are listed in chart 4.

Chart 1: Authors, year of publication, reference, sample size and experimental period of the studies published from 1989 to 2001.

Year	Authors / reference	Sample size	Experimental period (weeks)
1989	Scheller *et al.* (37)	40	7
1993	Frenkel *et al.* (38)	104	0
	Rao *et al*. (18)	88	1
1995	Rao *et al*. (39)	90	52
1996	Huang *et al*. (40)	28	3
	Matsushige *et al.*(41)	300	20
	Mitamura *et al.* (42)	45	20
1998	Kimoto *et al.* (43)	50	18
1999	Kimoto *et al.*(44)	82	36
2000	Kimoto *et al.* (33)	93	52
	Kawabe *et al.* (45)	265	39
2001	Kimoto *et al.* (36)	93	60

Chart 2: Authors, year of publication, reference, sample size and experimental period of the studies published from 2002 to 2014.

Year	Authors / reference	Sample size	Experimental period (weeks)	Year	Authors / reference	Sample size	Experimental period (weeks)
2002	Bazo *et al*. (17)	132	5	2002	Suzuki *et al*. (47)	20	5
	Borrelli *et al*. (46)	64	11				
	Orsolić *et al*. (15)	99	11		Liao *et al*. (48)	30	2
2003	El-khawaga *et al*. (19)	20	4	2003	Sugimoto *et al*. (49)	56	24
	Orsolić & Basić (30)	81	3				
	Orsolic *et al*. (14)	285	3		Orsolić & Basić (52)	144	3
2005	Chen *et al*. (35)	40	2	2005	Orsolić & Basić (a) (53)	105	2
	Lima *et al*. (50)	200	15		Orsolic *et al*.(a) (54)	105	2
	Mishima *et al*. (51)	121	4		Orsolic *et al*.(b) (55)	79	8
	Padmavathi *et al*. (12)	30	4		Kuo *et al*. (56)	32	4
2006	Padmavathi *et al*. (a) (32)	30	4	2006	Shimizu *et al*. (57)	25	4
2007	Ahn *et al*. (58)	45	1	2007	Benkovic *et al*. (59)	151	12
	Yasui *et al*. (11)	63	3		Díaz-Carballo *et al*. (61)	30	2
2008	Inoue *et al*. (16)	24	2	2008	Kim *et al*. (62)	8	3
	Ohta *et al*. (24)	15	2		Lee *et al*. (63)	30	1
	Beltrán-Ramírez et al. (60)	56	4				
2009	Albukhari *et al*. (64)	36	3	2009	Messerli *et al*. (66)	18	16
	Demestre *et al*. (65)	18	10				
	Said *et al*. (10)	63	30		Lin *et al*. (68)	24	4
2010	Cole *et al*. (13)	100	1	2010	Missima *et al*. (69)	64	4
	Jung *et al*. (67)	20	1		Oršolić *et al*. (70)	70	1
2011	Badr *et al*. 71	150	24	2011	Sobočanec *et al*. (74)	108	4
	Cavalcante *et al*.72	42	20		Wu *et al*. (75)	32	8
	Khan *et al*.73	40	11		Wu *et al*. (a) (76)		1
	Chuu *et al*.77	20	9		Ricardo *et al*. (81)	60	20
2012	Dornelas *et al*.78	92	40	2012	Sulaiman *et al*. (82)	30	8
	Dornelas *et al*.(a)79	88	40		Sun *et al*. (83)	21	9
	Huang *et al*. (80)	12	6				
	Chen *et al*. (84)	30	12		Rashid *et al*. (87)	30	24
2013	Lirdprapamongkol *et al*. (85)			2013	Sequetto *et al*. (88)	35	25
	Oršolić *et al*. (86)	144	12				
2014	Díaz-Carballo *et al*. (89)	5	1	2014	Motallebnejad *et al*. (92)	21	2
	Dornelas *et al*. (90)	125	40		Munari *et al*. (93)		
	Lisičić *et al*. (91)	69	12		Pinheiro *et al*. (94)	90	5

Chart 3: Authors, year of publication, reference number and main outcomes of clinical trials

Authors, year of publication and reference	Main objectives and results
Iljazović *et al.* (2006) (95)	The study aimed to treat HPV infection with phytotherapy combined with interferon in an attempt to define a treatment protocol for patients positive for HPV, since HPV infection is prone to neoplastic transformation. The results suggest that combination of interferon therapy with herbs and propolis in combination with B-complex is effective and can be a atraumatic treatment for HPV infection. Evidence of the effectiveness of this approach will depend on prospective tests in the future.
Abdulrhman *et al.* (2012) (96)	In this study, the authors evaluated the effectiveness of topical application of honey and a mixture of honey, beeswax, propolis and olive oil-extract in treatment of chemotherapy-induced mucositis oral. The results showed a faster wound healing in 2/3 of patients. Recommend conducting trials to test the use of honey, other bee products and olive oil in treatment of chemotherapy-induced oral mucositis.
Ishikawa (2012) (97)	The aim of this pilot study was to test the safety and efficacy of the use of propolis for the prevention of colon cancer in a high risk group. In folk medicine, propolis has been widely used for this purpose in various places around the world, but without being scientifically evaluated in humans. The results of this study did not show that the Brazilian propolis was effective in preventing changes that occur during the early stages of colon cancer. Moreover, their use can cause harmful side effects on muscle tissue, including myocardial cells
Tomaževič & Jazbec (2013) (98)	This study aimed to test the use of a complementary therapy with propolis as an alternative for the treatment of oral mucositis induced by chemotherapy, since the use of this substance has been reported, but without scientific evidence. According to the criteria adopted in this study for the diagnosis of severe oral mucositis, there was no statistical difference between the groups. According to these results, propolis can not be recommended for the treatment of severe oral mucositis.
Noronha *et al.* (2014) (99)	The objective of this phase II study was to evaluate the efficacy of a propolis mucoadhesive gel for the prevention of oral mucositis induced by radiation, used for the treatment of oral cancer. According to the results, the mucoadhesive gel propolis can be considered as a potential product for topical use for the prevention of oral mucositis induced by radiation. The authors recommend a phase III comparative study with more patients to confirm its effectiveness.

Chart 4: Authors, year of publication and reference number of review articles

Year of publication	Authors and references
1983	Havsteen (100)
2001	Heo (101)
2003	Ribeiro *et al*. (102)
2006	Khalil, Ribeiro *et al.* (27, 103)
2007	Sforcin (29)
2011	Calderón-Montaño *et al*.; Sorimachi & Nakamoto; Szliszka & Krol; Watanabe *et al.* (104-107)
2012	Akyol *et al*., Ozturk *et al*.; Sawicka *et al*.; Varoni *et al.* (108-111)
2013	Akyol *et al*.; Chang *et al*.; Kurek-Górecka; Lin *et al*.; Liu *et al*.(112-116)
2014	de Figueiredo *et al*.; Premratanachai & Chanchao; Rajendran *et al*.; Vagish Kumar; Tolba *et al*. (117-121)

The propolis samples tested in the articles analyzed in the present review had 22 different origins: Brazil [10, 11, 33, 36, 42, 43, 47, 51, 52, 53, 54, 57, 58, 66, 72, 81, 93, 94, 97, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138], Caribbean [139, 140], Chile [141], China [22, 83, 133, 142, 143, 144], Cuba [61, 145, 146, 147], Korea [148], Egypt [19, 71], Greece [149], the Netherlands [150] India [85, 151, 152, 153, 154], Indonesia [155], geopropolis (tropical countries) [156], Iraq [82], Mexico [3, 6, 157, 158], Myanmar [159, 160], Poland [114, 161], Portugal [162, 163], Sydney [13], Thailand [164, 165], Taiwan [80, 166, 167, 168, 169, 170,

171, 172, 173], Tunisia [34], Turkey [28, 174, 175, 176, 177, 178].

Chemical analyses of the propolis samples were conducted in a large portion of the research articles (percentage not available), which resulted in 144 isolated compounds. The caffeic acid phenethyl ester (CAPE) was the most frequently tested propolis's compound tested, 30.4% of studies (3, 5, 6, 7, 9, 14, 15, 18, 20, 22, 23, 31, 35, 38, 40, 46, 48, 55, 56, 60, 63, 64, 65, 68, 67, 75, 77, 84, 128, 157, 172, 173, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208), including eight reviews (108, 109, 110, 112, 113, 115, 116, 121). The following compounds were also frequently found: chysin, in 21 articles (3, 4, 6, 7, 53, 54, 76, 83, 85, 88, 144, 150, 157, 175, 190, 209, 210, 211, 212, 213, 214); artepelin-c, in 15 articles (8, 33, 36, 43, 57, 58, 65, 66, 122, 129, 130, 137, 173, 215), including one review [113] and galangin, in seven articles [3, 6, 7, 216, 217, 218] including one review [101].

Twenty-four (10.4%) of the 230 papers were review articles and the remaining 206 were research articles, five of which were clinical trials (2.1%). The remaining 201 research studies employed animals and cell cultures for the tests, 153 (76.1%) of which were *in vitro* studies and 74 (37.0%) were *in vivo* studies. In the *in vitro* studies, cancer cell cultures were the most common (49.3% of studies). All *in vivo* studies employed rats. In 26 (12.9%) studies, both rats and cell cultures were employed. Among the 74 *in vivo* studies, all of which were conducted in compliance with ethical norms regarding the use of animals in research, a total of 5015 rats of different species were used, with a mean of 70 animals per study. However, the sample size was not reported in three studies [76, 85, 93]. The duration of the animal experiments ranged from one to 60 weeks (mean: 12 weeks).

Considering a 27-year period spanning from 1988 to 2014, the findings show studies involving more animals and longer experimental times in the first half of this period (1988 to 2001), whereas studies conducted in the second half of the period (2002 to 2014) used fewer animals for a shorter length of time. These differences were statistically significant with regard to both the number of animals (p = 0.025) (Table 1) and duration of the animal experiments (p = 0.001) (Table 2).

In 218 research and review articles (94.7%), the authors reported positive results with regard to the chemopreventive or anti-cancer action of propolis and its constituents. In two studies (0.9%), the authors concluded that the propolis tested exhibited no chemoprevenitve action [10, 145]. In another two studies [0.9%), the results were inconclusive [81, 98]. This issue was not applicable in eight studies (3.6%].

Table 1: Number of *in vivo* studies that employed a smaller or larger number of animals stratified by period

	Smaller number of animals 5 to 70 (n %)	Larger number of animals 71 to 300 (n %)		
Number of articles / Period	n (%)	n (%)	Total	*p*-value*
1988 to 2001	4 (5.6%)	8 (11.3%)	12 (16.9%)	0.025
2002 to 2014	40 (56.3%)	19 (26.8%)	59 (83.1%)	
Total	44 (62%)	27 (38%)	71[#] (100%)	

*chi-square test
[#]Among total of 74 *in vivo* studies, it was not possible to obtain this data from three articles (143, 180, 203).

Table 2: Number of *in vivo* studies that employed animals for a shorter or longer length of time stratified by period

	Shorter length of time Up to 12 weeks	Longer length of time 13 to 60 weeks		
Number of articles / Period	n (%)	n (%)	Total	*p*-value*
1988 to 2001	4 (5.6%)	8 (11.1%)	12 (16.7%)	0.001
2002 to2014	48 (66.7%)	12 (16.7%)	60 (83.3%)	
Total	52 (72.2%)	20 (27.8%)	72[#] (100%)	

*chi-square test
[#]Among total of 74 *in vivo* studies, it was not possible to obtain this data from two articles (180, 203).

4. DISCUSSION

The focus of the present review was to perform a quantitative analysis of studies conducted to test propolis and/or its constituents for the prevention or treatment of cancer published in the Pubmed database in a 31-year period (1983 to 2014). During this period, between 1983 to 2014, there was no publication of a review with this approach. Considering the volume of studies addressing cancer and the use of propolis and the growing number of

publications in the Pubmed database, especially in the last three years, the present review could be useful with regard to the guidance and design of future studies.

In the analysis of the findings of the studies included in this review, more than 140 substances were isolated from propolis samples of different geographic origins, demonstrating that propolis has different chemical compositions due to divergences among the pastures used by bees in different locations [25, 219]. This variability underscores the need to submit each propolis sample to chemical analysis prior to testing it, which could result in the discovery of new substances that can be tested using an *in vitro* design. This is clearly seen in the study conducted by Li et al. (2010) [3], who isolated 36 new chemical components from a propolis sample of Mexican origin and demonstrated chemopreventive action in six types of cell cultures.

In the *in vivo* studies, one of the ways to determine the efficacy of the substance tested after the induction of carcinogenesis was to compare survival rates in different groups of animals. With this method, the survival rate is compared when all animals die as a result of induced cancer [19, 30, 35, 37, 48, 53, 54, 55, 59]. Even in experiments with a previously determined duration, euthanasia prior to the end of the experiments can occur due to signs of pain among the animals [33] or spontaneous death [15], which demonstrates the suffering to which animals used in this type of experiment are exposed. However, the chemopreventive efficacy of propolis can be evidenced using more carefully planned laboratory methods to avoid awaiting the death of animals due to cancerous tumors [220]. Indeed, the death of two animals in a previous study conducted by our research group involving the induction of cancer tumors [81] and the care that has been taken regarding aspects of the use of animals in research [221, 222] motivated us to perform the present review, in which the number of animals used and the duration of animal experiments were analyzed.

Significant reductions in sample size (p = 0.025) and duration of the experiment [p = 0.001]were found in more recently published studies. The calculation of sample size is a statistical resource that allows conducting a study that can provide scientific evidence using the smallest number of animals possible. However, this statistical resource is not always employed [223, 224]. According to recent 3Rs (reduction, refinement and replacement) concept regarding the use of animals in research [224], it is also recommended to make the proper choice of animal model adequate to the objectives of a given study [225]. and enhance the reproducibility of the results of clinical trials by improving the experimental design and conduction of laboratory tests [220].

The use of animals in research encompasses numerous aspects involving the wellbeing of the animals and norms with regard to euthanasia [223, 226], which are not always followed [223]. Due to the large time interval spanned in the present review (31 years) and the consequent methodological diversity encountered, the decision was made to restrict the analysis to the number of animals employed and duration of animals experiments, which may be considered a limitation of this study in comparison to the accurate analysis involving a larger number of aspects performed by Bara & Joffe (2014) [223]. This can be is explained by the uniformity of the sample analyzed by the authors cited, which involved studies published in only a six-month period.

Based on the present findings, the chemopreventive action of propolis has been researched and published for more than 30 years. The oldest publication was a review that explored a class of chemical compounds found in propolis [flavonoids]and reported on their biological properties [100]. Among the research articles, the oldest was published in 1988 [208], the authors of which addressed the cytotoxic action of CAPE, which is one of the chemical components isolated from propolis, showing that this substance has been investigated for more than 27 years and has demonstrated effective chemoprevention [3, 5, 6, 7, 9, 14, 15, 18, 20, 22, 23, 31, 35, 38, 40, 46, 48, 55, 56, 60, 63- 65, 67, 68, 75, 77, 84, 128, 157, 172, 173. Indeed, CAPE was the most frequent test substance in the present review and was also the focus of eight to the 24 reviews analyzed in this study [108-110, 112, 113, 115, 116, 121]. Despite the number of studies addressing CAPE, no clinical trial has yet tested this substance.

Among the clinical trials encountered, tests with new substances sought to diminish the harm caused by chemotherapy and radiotherapy in patients with cancer [96, 98, 99] and demonstrated the potential of propolis regarding the alleviation of side effects, such as mucositis [96, 99]. The lack of more clinical trials specifically designed to test the use of CAPE as a chemopreventive or anti-cancer agent may be linked to the ethical implications of this type of study [227] as well as the lack of preliminary tests prior to the conduction of the different phases of clinical trials, as suggested by Kummar et al. [2007] and defined by the

authors as “0” phase trials [228]. Moreover, factors beyond the will and ability of researchers, such as those linked to the personal choices of the participants [229], can hinder or even render unviable the use of a new substance in the test group, which may explain why propolis is only employed as a complement to traditional chemotherapy or for alleviating the side effects of such therapy [95-99].

Despite being exhaustively tested and having demonstrated positive chemopreventive effects in both *in vitro* and *in vivo* studies, few investigations have addressed the possible toxic effects of propolis [63]. In 2012, Ishikawa and colleagues [97] used propolis to prevent the future development of colon cancer in patients who had undergone surgery for the removal of intestinal polyps and found a side effect that may be harmful to cardiac muscle tissue. Further studies are recommended, in which efforts are made to use experimental animals in a more focused fashion to test the safety of the constituents of propolis that have proven to be effective in

chemoprevention, such as CAPE, as well as the possible toxic effects of such substances. Thus, greater knowledge and safety would allow the planning of well-designed clinical trials aimed at combating cancer in humans.

ACKNOWLEDGMENTS

The authors are grateful to the staff of the Central Library of the Federal University of Vales do Jequitinhonha e Mucuri [Brazil] for allowing access to the full texts of the articles analyzed in the present review.

REFERENCES

[1] Sugimura T, Terada M, Yokota J, Hirohashi S, Wakabayashi K. Multiple genetic alterations in human carcinogenesis. Environ Health Perspect. 1992 Nov;98:5-12.

[2] Sarasin A. An overview of the mechanisms of mutagenesis and carcinogenesis. Mutat Res. 2003 Nov;544(2-3):99-106.

[3] Li F, Awale S, Tezuka Y, Kadota S. Cytotoxicity of constituents from Mexican propolis against a panel of six different cancer cell lines. Nat Prod Commun. 2010a Oct;5(10):1601-6.

[4] Weng MS, Ho YS, Lin JK. Chrysin induces G1 phase cell cycle arrest in C6 glioma cells through inducing p21Waf1/Cip1 expression: involvement of p38 mitogen-activated protein kinase. Biochem Pharmacol. 2005 Jun 15;69(12):1815-27.

[5] Chiao C, Carothers AM, Grunberger D, Solomon G, Preston GA, Barrett JC. Apoptosis and altered redox state induced by caffeic acid phenethyl ester (CAPE) in transformed rat fibroblast cells. Cancer Res. 1995 Aug 15;55(16):3576-83.

[6] Li F, Awale S, Tezuka Y, Esumi H, Kadota S. Study on the constituents of Mexican propolis and their cytotoxic activity against PANC-1 human pancreatic cancer cells. J Nat Prod. 2010b Apr 23;73(4):623-7.

[7] Szliszka E, Czuba ZP, Bronikowska J, Mertas A, Paradysz A, Krol W. Ethanolic Extract of Propolis Augments TRAIL-Induced Apoptotic Death in Prostate Cancer Cells. Evid Based Complement Alternat Med. 2009a Nov 5.

[8] Shimizu K, Das SK, Hashimoto T, Sowa Y, Yoshida T, Sakai T, et al. Artepillin C in Brazilian propolis induces G(0)/G(1) arrest via stimulation of Cip1/p21 expression in human colon cancer cells. Mol Carcinog. 2005 Dec;44(4):293-9.

[9] Rao CV, Desai D, Kaul B, Amin S, Reddy BS. Effect of caffeic acid esters on carcinogen-induced mutagenicity and human colon adenocarcinoma cell growth. Chem Biol Interact. 1992 Nov 16;84(3):277-90.

[10] Said RA, Grassi TF, Scolastici C, Alves de Lima RO, Darros BR, Barbisan LF, et al. Absence of chemopreventive influence of propolis on the rat liver altered foci development. Exp Toxicol Pathol. 2010 Jul;62(4):405-12.

[11] Yasui Y, Miyamoto S, Kim M, Kohno H, Sugie S, Tanaka T. Aqueous and ethanolic extract fractions from the Brazilian propolis suppress azoxymethane-induced aberrant crypt foci in rats. Oncol Rep. 2008 Sep;20(3):493-9.

[12] Padmavathi R, Senthilnathan P, Sakthisekaran D. Therapeutic effect of propolis and paclitaxel on hepatic phase I and II enzymes and marker enzymes in dimethylbenz(a)anthracene-induced breast cancer in female rats. Comp Biochem Physiol C Toxicol Pharmacol. 2006 Jul;143(3):349-54.

[13] Cole N, Sou PW, Ngo A, Tsang KH, Severino JA, Arun SJ, et al. Topical 'Sydney' propolis protects against UV-radiation-induced inflammation, lipid peroxidation and immune suppression in mouse skin. Int Arch Allergy Immunol. 2010;152(2):87-97.

[14] Orsolic N, Sver L, Terzić S, Basić I. Peroral application of water-soluble derivative of propolis (WSDP) and its related polyphenolic compounds and their influence on immunological and antitumour activity. Vet Res Commun. 2005aOct;29(7):575-93.

[15] Orsolić N, Sver L, Terzić S, Tadić Z, Basić I. Inhibitory effect of water-soluble derivative of propolis and its polyphenolic compounds on tumor growth and metastasizing ability: a possible mode of antitumor action. Nutr Cancer. 2003a;47(2):156-63.

[16] Inoue K, Saito M, Kanai T, Kawata T, Shigematsu N, Uno T, et al. Anti-tumor effects of water-soluble propolis on a mouse sarcoma cell line in vivo and in vitro. Am J Chin Med. 2008;36(3):625-34.

[17] Bazo AP, Rodriguesa MA, Sforcin JM, de Camargo JL, Ribeiro LR, Salvadori DM. Protective action of propolis on the rat colon carcinogenesis. Teratog Carcinog Mutagen. 2002;22(3):183-94.

[18] Rao CV, Desai D, Simi B, Kulkarni N, Amin S, Reddy BS. Inhibitory effect of caffeic acid esters on azoxymethane-induced biochemical changes and aberrant crypt foci formation in rat colon. Cancer Res. 1993 Sep 15;53(18):4182-8.

[19] El-khawaga OA, Salem TA, Elshal MF. Protective role of Egyptian propolis against tumor in mice. Clin Chim Acta. 2003 Dec;338(1-2):11-6.

[20] Lee YJ, Kuo HC, Chu CY, Wang CJ, Lin WC, Tseng TH. Involvement of tumor suppressor protein p53 and p38 MAPK in caffeic acid phenethyl ester-induced apoptosis of C6 glioma

cells. Biochem Pharmacol. 2003 Dec 15;66(12):2281-9. (131)

[21] Akao Y, Maruyama H, Matsumoto K, Ohguchi K, Nishizawa K, Sakamoto T, et al. Cell growth inhibitory effect of cinnamic acid derivatives from propolis on human tumor cell lines. Biol Pharm Bull. 2003 Jul;26(7):1057-9.

[22] Izuta H, Shimazawa M, Tsuruma K, Araki Y, Mishima S, Hara H. Bee products prevent VEGF-induced angiogenesis in human umbilical vein endothelial cells. BMC Complement Altern Med. 2009 Nov 17;9:45.

[23] Lee KW, Kang NJ, Kim JH, Lee KM, Lee DE, Hur HJ, et al. Caffeic acid phenethyl ester inhibits invasion and expression of matrix metalloproteinase in SK-Hep1 human hepatocellular carcinoma cells by targeting nuclear factor kappa B. Genes Nutr. 2008 Feb;2(4):319-22.a

[24] Ohta T, Kunimasa K, Kobayashi T, Sakamoto M, Kaji K. Propolis suppresses tumor angiogenesis by inducing apoptosis in tube-forming endothelial cells. Biosci Biotechnol Biochem. 2008 Sep;72(9):2436-40.

[25] Bankova V. Chemical diversity of propolis and the problem of standardization. J Ethnopharmacol. 2005 Aug 22;100(1-2):114-7.

[26] Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem Toxicol. 1998 Apr;36(4):347-63.

[27] Khalil ML. Biological activity of bee propolis in health and disease. Asian Pac J Cancer Prev. 2006 Jan-Mar;7(1):22-31.

[28] Erhan Eroğlu H, Ozkul Y, Tatlisen A, Silici S. Anticarcinogenic and antimitotic effects of Turkish propolis and mitomycin-C on tissue cultures of bladder cancer. Nat Prod Res. 2008;22(12):1060-6.

[29] Sforcin JM. Propolis and the immune system: a review. J Ethnopharmacol. 2007 Aug 15;113(1):1-14.

[30] Orsolić N, Basić I. Immunomodulation by water-soluble derivative of propolis: a factor of antitumor reactivity. J Ethnopharmacol. 2003 Feb;84(2-3):265-73.

[31] Wang T, Chen L, Wu W, Long Y, Wang R. Potential cytoprotection: antioxidant defence by caffeic acid phenethyl ester against free radical-induced damage of lipids, DNA, and proteins. Can J Physiol Pharmacol. 2008 May;86(5):279-87.

[32] Padmavathi R, Senthilnathan P, Chodon D, Sakthisekaran D. Therapeutic effect of paclitaxel and propolis on lipid peroxidation and antioxidant system in 7,12 dimethyl benz(a)anthracene-induced breast cancer in female Sprague Dawley rats. Life Sci. 2006a May 8;78(24):2820-5.

[33] Kimoto T, Koya S, Hino K, Yamamoto Y, Nomura Y, Micallef MJ, et al. Renal carcinogenesis induced by ferric nitrilotriacetate in mice, and protection from it by Brazilian propolis and artepillin C. Pathol Int. 2000 Sep;50(9):679-89.

[34] Kouidhi B, Zmantar T, Bakhrouf A. Anti-cariogenic and anti-biofilms activity of Tunisian propolis extract and its potential protective effect against cancer cells proliferation. Anaerobe. 2010 Dec;16(6):566-71.

[35] Chen YJ, Liao HF, Tsai TH, Wang SY, Shiao MS. Caffeic acid phenethyl ester preferentially sensitizes CT26 colorectal adenocarcinoma to ionizing radiation without affecting bone marrow radioresponse. Int J Radiat Oncol Biol Phys. 2005 Nov 15;63(4):1252-61.

[36] Kimoto T, Koya-Miyata S, Hino K, Micallef MJ, Hanaya T, Arai S, et al. Pulmonary carcinogenesis induced by ferric nitrilotriacetate in mice and protection from it by Brazilian propolis and artepillin C. Virchows Arch. 2001 Mar;438(3):259-70.

[37] Scheller S, Krol W, Swiacik J, Owczarek S, Gabrys J, Shani J. Antitumoral property of ethanolic extract of propolis in mice-bearing Ehrlich carcinoma, as compared to bleomycin. Z Naturforsch C. 1989 Nov-Dec;44(11-12):1063-5.

[38] Frenkel K, Wei H, Bhimani R, Ye J, Zadunaisky JA, Huang MT, et al. Inhibition of tumor promoter-mediated processes in mouse skin and bovine lens by caffeic acid phenethyl ester. Cancer Res. 1993 Mar 15;53(6):1255-61.

[39] Rao CV, Desai D, Rivenson A, Simi B, Amin S, Reddy BS. Chemoprevention of colon carcinogenesis by phenylethyl-3-methylcaffeate. Cancer Res. 1995 Jun 1;55(11):2310-5.

[40] Huang MT, Ma W, Yen P, Xie JG, Han J, Frenkel K, et al. Inhibitory effects of caffeic acid phenethyl ester (CAPE) on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion in mouse skin and the synthesis of DNA, RNA and protein in HeLa cells. Carcinogenesis. 1996 Apr;17(4):761-5.

[41] Matsushige K, Basnet P, Hase K, Kadota S, Tanaka K, Namba T. Propolis protects pancreatic β-cells against the toxicity of streptozotocin (STZ). Phytomedicine. 1996 Sep;3(2):203-9. doi: 10.1016/S0944-7113(96)80037-7.

[42] Mitamura T, Matsuno T, Sakamoto S, Maemura M, Kudo H, Suzuki S, et al. Effects of a new clerodane diterpenoid isolated from propolis on

chemically induced skin tumors in mice. Anticancer Res. 1996 Sep-Oct;16(5A):2669-72.

[43] Kimoto T, Arai S, Kohguchi M, Aga M, Nomura Y, Micallef MJ, et al. Apoptosis and suppression of tumor growth by artepillin C extracted from Brazilian propolis. Cancer Detect Prev. 1998;22(6):506-15.

[44] Kimoto N, Hirose M, Kawabe M, Satoh T, Miyataka H, Shirai T. Post-initiation effects of a super critical extract of propolis in a rat two-stage carcinogenesis model in female F344 rats. Cancer Lett. 1999 Dec 1;147(1-2):221-7.

[45] Kawabe M, Lin C, Kimoto N, Sano M, Hirose M, Shirai T. Modifying effects of propolis on MeIQx promotion of rat hepatocarcinogenesis and in a female rat two-stage carcinogenesis model after multiple carcinogen initiation. Nutr Cancer. 2000;37(2):179-86.

[46] Borrelli F, Izzo AA, Di Carlo G, Maffia P, Russo A, Maiello FM, et al. Effect of a propolis extract and caffeic acid phenethyl ester on formation of aberrant crypt foci and tumors in the rat colon. Fitoterapia. 2002 Nov;73 Suppl 1:S38-43.

[47] Suzuki I, Hayashi I, Takaki T, Groveman DS, Fujimiya Y. Antitumor and anticytopenic effects of aqueous extracts of propolis in combination with chemotherapeutic agents. Cancer Biother Radiopharm. 2002 Oct;17(5):553-62.

[48] Liao HF, Chen YY, Liu JJ, Hsu ML, Shieh HJ, Liao HJ, Shieh CJ, Shiao MS, Chen YJ. Inhibitory effect of caffeic acid phenethyl ester on angiogenesis, tumor invasion, and metastasis. J Agric Food Chem. 2003 Dec 31;51(27):7907-12.

[49] Sugimoto Y, Iba Y, Kayasuga R, Kirino Y, Nishiga M, Alejandra Hossen M, et al. Inhibitory effects of propolis granular A P C on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. Cancer Lett. 2003 Apr 25;193(2):155-9.

[50] Lima RO, Bazo AP, Said RA, Sforcin JM, Bankova V, Darros BR, et al. Modifying effect of propolis on dimethylhydrazine-induced DNA damage but not colonic aberrant crypt foci in rats. Environ Mol Mutagen. 2005;45(1):8-16.

[51] Mishima S, Ono Y, Araki Y, Akao Y, Nozawa Y. Two related cinnamic Acid derivatives from Brazilian honey bee propolis, baccharin and drupanin, induce growth inhibition in allografted sarcoma S-180 in mice. Biol Pharm Bull. 2005 Jun;28(6):1025-30.

[52] Orsolić N, Basić I. Antitumor, hematostimulative and radioprotective action of water-soluble derivative of propolis (WSDP). Biomed Pharmacother. 2005 Dec;59(10):561-70.

[53] Orsolić N, Basić I. Water-soluble derivative of propolis and its polyphenolic compounds enhance tumoricidal activity of macrophages. J Ethnopharmacol. 2005 Oct 31;102(1):37-45.

[54] Orsolić N, Kosalec I, Basić I. Synergistic antitumor effect of polyphenolic components of water soluble derivative of propolis against Ehrlich ascites tumour. Biol Pharm Bull. 2005 Apr;28(4):694-700.

[55] Orsolić N, Terzić S, Mihaljević Z, Sver L, Basić I. Effects of local administration of propolis and its polyphenolic compounds on tumor formation and growth. Biol Pharm Bull. 2005 Oct;28(10):1928-33.

[56] Kuo HC, Kuo WH, Lee YJ, Lin WL, Chou FP, Tseng TH. Inhibitory effect of caffeic acid phenethyl ester on the growth of C6 glioma cells in vitro and in vivo. Cancer Lett. 2006 Mar 28;234(2):199-208.

[57] Shimizu K, Das SK, Baba M, Matsuura Y, Kanazawa K. Dietary artepillin C suppresses the formation of aberrant crypt foci induced by azoxymethane in mouse colon. Cancer Lett. 2006 Aug 18;240(1):135-42.

[58] Ahn MR, Kunimasa K, Ohta T, Kumazawa S, Kamihira M, Kaji K, et al. Suppression of tumor-induced angiogenesis by Brazilian propolis: major component artepillin C inhibits in vitro tube formation and endothelial cell proliferation. Cancer Lett. 2007 Jul 18;252(2):235-43.

[59] Benkovic V, Horvat Knezevic A, Brozovic G, Knezevic F, Dikic D, Bevanda M, et al. Enhanced antitumor activity of irinotecan combined with propolis and its polyphenolic compounds on Ehrlich ascites tumor in mice. Biomed Pharmacother. 2007 Jun;61(5):292-7.

[60] Beltrán-Ramírez O, Alemán-Lazarini L, Salcido-Neyoy M, Hernández-García S, Fattel-Fazenda S, Arce-Popoca E, et al. Evidence that the anticarcinogenic effect of caffeic acid phenethyl ester in the resistant hepatocyte model involves modifications of cytochrome P450. Toxicol Sci. 2008 Jul;104(1):100-6.

[61] Díaz-Carballo D, Malak S, Bardenheuer W, Freistuehler M, Peter Reusch H. The contribution of plukenetione A to the anti-tumoral activity of Cuban propolis. Bioorg Med Chem. 2008 Nov 15;16(22):9635-43.

[62] Kim DM, Lee GD, Aum SH, Kim HJ. Preparation of propolis nanofood and application to human cancer. Biol Pharm Bull. 2008 Sep;31(9):1704-10.

[63] Lee KJ, Choi JH, Hwang YP, Chung YC, Jeong HG. Protectiveeffect of caffeic acid phenethyl ester on tert-butylhydroperoxide-

inducedoxidativehepatotoxicity and DNA damage. Food Chem Toxicol. 2008 Jul;46(7):2445-50.

[64] Albukhari AA, Gashlan HM, El-Beshbishy HA, Nagy AA, Abdel-Naim AB. Caffeic acid phenethyl ester protects against tamoxifen-induced hepatotoxicity in rats. Food Chem Toxicol. 2009 Jul;47(7):1689-95.

[65] Demestre M, Messerli SM, Celli N, Shahhossini M, Kluwe L, Mautner V, et al. CAPE (caffeic acid phenethyl ester)-based propolis extract (Bio 30) suppresses the growth of human neurofibromatosis (NF) tumor xenografts in mice. Phytother Res. 2009 Feb;23(2):226-30.

[66] Messerli SM, Ahn MR, Kunimasa K, Yanagihara M, Tatefuji T, Hashimoto K, et al. Artepillin C (ARC) in Brazilian green propolis selectively blocks oncogenic PAK1 signaling and suppresses the growth of NF tumors in mice. Phytother Res. 2009 Mar;23(3):423-7.

[67] Jung BI, Kim MS, Kim HA, Kim D, Yang J, Her S, et al. Caffeic acid phenethyl ester, a component of beehive propolis, is a novel selective estrogen receptor modulator. Phytother Res. 2010 Feb;24(2):295-300.

[68] Lin WL, Liang WH, Lee YJ, Chuang SK, Tseng TH. Antitumor progression potential of caffeic acid phenethyl ester involving p75(NTR) in C6 glioma cells. Chem Biol Interact. 2010 Dec 5;188(3):607-15. doi: 10.1016/j.cbi.2010.09.002. Epub 2010 Sep 15.

[69] Missima F, Pagliarone AC, Orsatti CL, Araújo JP Jr, Sforcin JM. The Effect of propolis on Th1/Th2 cytokine expression and production by melanoma-bearing mice submitted to stress. Phytother Res. 2010 Oct;24(10):1501-7. doi: 10.1002/ptr.3142.

[70] Oršolić N, Benković V, Lisičić D, Dikić D, Erhardt J, Knežević AH. Protective effects of propolis and related polyphenolic/flavonoid compounds against toxicity induced byirinotecan. Med Oncol. 2010 Dec;27(4):1346-58. doi: 10.1007/s12032-009-9387-5. Epub 2009 Dec 16.

[71] Badr MO, Edrees NM, Abdallah AA, El-Deen NA, Neamat-Allah AN, Ismail HT. Anti-tumour effects of Egyptian propolis on Ehrlich ascites carcinoma. Vet Ital. 2011 Jul-Sep;47(3):341-50.

[72] Cavalcante DR, Oliveira PS, Góis SM, Soares AF, Cardoso JC, Padilha FF, Albuquerque Jr RL. Effect of green propolis on oral epithelial dysplasia in rats. Braz J Otorhinolaryngol. 2011 Jun;77(3):278-84.

[73] Khan MS, Devaraj H, Devaraj N. Chrysin abrogates early hepatocarcinogenesis and induces apoptosis in N-nitrosodiethylamine-inducedpreneoplastic nodules in rats. Toxicol Appl Pharmacol. 2011 Feb 15;251(1):85-94. doi: 10.1016/j.taap.2010.12.004. Epub 2010 Dec 15.

[74] Sobočanec S, Balog T, Šarić A, Mačak-Šafranko Ž, Štroser M, Žarković K, Žarković N, Stojković R, Ivanković S, Marotti T. Antitumor effect of Croatian propolis as a consequence of diverse sex-related dihydropyrimidine dehydrogenase(DPD) protein expression. Phytomedicine. 2011 Jul 15;18(10):852-8. doi: 10.1016/j.phymed.2011.01.015. Epub 2011 Feb 25.

[75] Wu J, Omene C, Karkoszka J, Bosland M, Eckard J, Klein CB, Frenkel K. Caffeic acid phenethyl ester (CAPE), derived from a honeybee product propolis, exhibits a diversity of anti-tumor effects in pre-clinical models of human breast cancer. Cancer Lett. 2011 Sep 1;308(1):43-53. doi: 10.1016/j.canlet.2011.04.012. Epub 2011 May 13.

[76] Wu NL, Fang JY, Chen M, Wu CJ, Huang CC, Hung CF. Chrysin protects epidermal keratinocytes from UVA- and UVB-induced damage. J Agric Food Chem. 2011 Aug 10;59(15):8391-400. doi: 10.1021/jf200931t.

[77] Chuu CP, Lin HP, Ciaccio MF, Kokontis JM, Hause RJ Jr, Hiipakka RA, Liao S, Jones RB. Caffeic acid phenethyl ester suppresses the proliferation of human prostate cancer cells through inhibition of p70S6K and Akt signaling networks. Cancer Prev Res (Phila). 2012 May;5(5):788-97. doi: 10.1158/1940-6207.CAPR-12-0004-T.

[78] Dornelas CA, Fechine-Jamacaru FV, Albuquerque IL, Magalhães HI, Dias TA, Faria MH, Alves MK, Rabenhorst SH, de Almeida PR, Lemos TL, Castro JD, Moraes ME, Moraes MO. Angiogenesis inhibition by green propolis and the angiogenic effect of L-lysine on bladder cancer in rats. Acta Cir Bras. 2012 Aug;27(8):529-36.

[79] Dornelas CA, Fechine-Jamacaru FV, Albuquerque IL, Magalhães HI, Souza AJ, Alves LA, Almeida PR, Lemos TL, Castro JD, Moraes ME, Moraes MO. Chemoprevention with green propolis green propolis extracted in L-lysine versus carcinogenesis promotion with L-lysine in N-Butyl-N-[4-hydroxybutyl] nitrosamine (BBN) induced rat bladder cancer. Acta Cir Bras. 2012 Feb;27(2):185-92.

[80] Huang WJ, Liang YC, Chuang SE, Chi LL, Lee CY, Lin CW, Chen AL, Huang JS, Chiu CJ, Lee CF, Huang CY, Chen CN. NBM-HD-1: A Novel Histone Deacetylase Inhibitor with Anticancer Activity. Evid Based Complement Alternat Med. 2012;2012:781417. doi: 10.1155/2012/781417. Epub 2011 Oct 20.

[81] Ricardo LR, Ribeiro BP, Soares SA, Lages LN, Oliveira FF, Dornela VF. Effects of propolis on lingual mucosa response of hamsters submitted to experimental carcinogenesis. Zhong Xi Yi Jie He Xue Bao. 2012 Dec;10(12):1443-50. doi: 10.3736/jcim20121217.

[82] Sulaiman GM, Ad'hiah AH, Al-Sammarrae KW, Bagnati R, Frapolli R, Bello E, Uboldi S, Romano M, Panini N, Scanziani E, Pezzolato M, Erba E, D'Incalci M. Assessing the anti-tumour properties of Iraqi propolis in vitro and in vivo. Food Chem Toxicol. 2012 May;50(5):1632-41. doi: 10.1016/j.fct.2012.01.022. Epub 2012 Jan 28

[83] Sun LP, Chen AL, Hung HC, Chien YH, Huang JS, Huang CY, Chen YW, Chen CN. Chrysin: a histone deacetylase 8 inhibitor with anticancer acti vity and a suitable candidate for the standardization of Chinese propolis. J Agric Food Chem. 2012 Nov 28;60(47):11748-58. doi: 10.1021/jf303261r. Epub 2012 Nov 15.

[84] Chen MJ, Shih SC, Wang HY, Lin CC, Liu CY, Wang TE, Chu CH, Chen YJ. Caffeic Acid phenethyl ester inhibits epithelial-mesenchymal transition of human pancreatic cance r cells. Evid Based Complement Alternat Med. 2013;2013:270906. doi: 10.1155/2013/270906. Epub 2013 Apr 4.

[85] Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Maruyama T, Athikomkulchai S, Viriyaroj A, Awale S, Yagita H, Ruchirawat S, Svasti J, Saiki I. A flavonoid chrysin suppresses hypoxic survival and metastatic growth of mouse b reast cancer cells. Oncol Rep. 2013 Nov;30(5):2357-64. doi: 10.3892/or.2013.2667. Epub 2013 Aug 20.

[86] Oršolić N, Car N, Lisičić D, Benković V, Knežević AH, Dikić D, Petrik J. Synergism between propolis and hyperthermal intraperitoneal chemotherapywit h cisplatin on ehrlich ascites tumor in mice. J Pharm Sci. 2013 Dec;102(12):4395-405. doi: 10.1002/jps.23755. Epub 2013 Oct 17.

[87] Rashid S, Ali N, Nafees S, Hasan SK, Sultana S. Amelioration of renal carcinogenesis by bee propolis: a chemo preventive approach. Toxicol Int. 2013 Sep;20(3):227-34. doi: 10.4103/0971-6580.121676.

[88] Sequetto PL, Oliveira TT, Soares IA, Maldonado IR, Mello VJ, Pizziolo VR, Almeida MR, Novaes RD.
The flavonoid chrysin attenuates colorectal pathol ogical remodeling reducing the number and severity of pre-neoplastic lesions in rats exposed to the carcinogen 1,2-dimethylhydrazine. Cell Tissue Res. 2013 May;352(2):327-39. doi: 10.1007/s00441-013-1562-5. Epub 2013 Mar 7.

[89] Díaz-Carballo D, Acikelli AH, Bardenheuer W, Gustmann S, Malak S, Stoll R, Kedziorski T, Nazif MA, Jastrow H, Wennemuth G, Dammann P, Feigel M, Strumberg D. Identification of compounds that selectively target highly chemotherapy refractory neuroblastomacancer stem cells. Int J Clin Pharmacol Ther. 2014 Sep;52(9):787-801. doi: 10.5414/CP202154.

[90] Dornelas CA, Cavalcanti BC, Magalhães HI, Jamacaru FV, Furtado FN, Juanes Cde C, Melo Nde O, de Moraes MO. Potential chemoprotective effects of green propolis, L-lysine and celecoxib on bone marrow cells and peripheral blood lymphocytes of Wistar rats subjected to bladder chemical carcinogenesis. Acta Cir Bras. 2014 Jul;29(7):423-8.

[91] Lisičić D, Benković V, Đikić D, Blažević AS, Mihaljević J, Oršolić N, Knežević AH. Addition of propolis to irinotecan therapy prolongs survival in ehrlich ascites tumor-bearing mice. Cancer Biother Radiopharm. 2014 Mar;29(2):62-9. doi: 10.1089/cbr.2013.1535. Epub 2014 Jan 2.

[92] Motallebnejad M, Abedi SM, Seyedmajidi M, Moghadamnia AA, Ashrafpour M, Salehi M, Moslemi D, Ghorbani A. Evaluation of protective effect of propolis on parotid salivary glands in gamma-irradiated rats. J Contemp Dent Pract. 2014 Jan 1;15(1):8-11.

[93] Munari CC, Furtado RA, Santiago ML, Manhas SS, Bastos JK, Tavares DC. Inhibitory effects of Baccharis dracunculifolia on 1,2-dimethylhidrazine-induced genotoxicity and preneoplastic lesions in rat colon. Eur J Cancer Prev. 2014 Jul;23(4):240-5. doi: 10.1097/CEJ.0000000000000039.

[94] Pinheiro KS, Ribeiro DR, Alves AV, Pereira-Filho RN, Oliveira CR, Lima SO, Reis FP, Cardoso JC, Albuquerque-Júnior RL. Modulatory activity of Brazilian red propolis on chemically induced dermal carcinogenesis. Acta Cir Bras. 2014 Feb;29(2):111-7. doi: 10.1590/S0102-86502014000200007.

[95] Iljazović E, Ljuca D, Sahimpasić A, Avdić S. Efficacy in treatment of cervicalHRHPVinfection by combination of beta interferon, and herbal therapy in woman with different cervical lesions.Bosn J Basic Med Sci. 2006 Nov;6(4):79-84.

[96] Abdulrhman M, Elbarbary NS, Ahmed Amin D, Saeid Ebrahim R. Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: a randomized controlled pilot study. Pediatr Hematol Oncol. 2012 Apr;29(3):285-92. doi: 10.3109/08880018.2012.669026.

[97] Ishikawa H, Goto M, Matsuura N, Murakami Y, Goto C, Sakai T, Kanazawa K. A pilot, randomized, placebo-controlled, double-blind phase 0/biomarker study on effect of artepillin C-rich extract of Brazilian propolis in frequent colorectal adenoma polyp patients. J Am Coll Nutr. 2012 Oct;31(5):327-37.

[98] Tomaževič T, Jazbec J. A double blind randomized placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. Complement Ther Med. 2013 Aug;21(4):306-12. doi: 10.1016/j.ctim.2013.04.002. Epub 2013 May 7.

[99] Noronha VR, Araujo GS, Gomes RT, Iwanaga SH, Barbosa MC, Abdo EN, Ferreira E Ferreira E, Viana Campos AC, Souza AA, Abreu SR, Santos VR. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. Curr Clin Pharmacol. 2014;9(4):359-64.

[100] Havsteen B. Flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol. 1983 Apr 1;32(7):1141-8.

[101] Heo MY, Sohn SJ, Au WW. Anti-genotoxicity of galangin as a cancer chemopreventive agent candidate. Mutat Res. 2001 May;488(2):135-50.

[102] Ribeiro LR, Salvadori DM. Dietary components may prevent mutation-related diseases in humans. Mutat Res. 2003 Nov;544(2-3):195-201.

[103] Ribeiro LR, Mantovani MS, Ribeiro DA, Salvadori DM. Brazilian natural dietary components (annatto, propolis and mushrooms) protecting against mutation and cancer. Hum Exp Toxicol. 2006 May;25(5):267-72.

[104] Calderón-Montaño JM, Burgos-Morón E, Pérez-Guerrero C, López-Lázaro M. A review on the dietary flavonoid kaempferol. Mini Rev Med Chem. 2011 Apr;11(4):298-344.

[105] Sorimachi K, Nakamoto T. Alternative medicine safety: Agaricus blazei and p ropolis. Comb Chem High Throughput Screen. 2011 Aug;14(7):616-21.

[106] Szliszka E, Krol W. The role of dietary polyphenols in tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-induced apoptosis for cancer chemoprevention. Eur J Cancer Prev. 2011 Jan;20(1):63-9.

[107] Watanabe MA, Amarante MK, Conti BJ, Sforcin JM. Cytotoxic constituents of propolis inducing anticancer effects: a review. J Pharm Pharmacol. 2011 Nov;63(11):1378-86. doi: 10.1111/j.2042-7158.2011.01331.x. Epub 2011 Sep 27.

[108] Akyol S, Ginis Z, Armutcu F, Ozturk G, Yigitoglu MR, Akyol O. The potential usage of caffeic acid phenethyl ester (CAPE) against chemotherapy-induced and radiotherapy-induced toxicity. Cell Biochem Funct. 2012 Jul;30(5):438-43. doi: 10.1002/cbf.2817. Epub 2012 Mar 20.

[109] Ozturk G, Ginis Z, Akyol S, Erden G, Gurel A, Akyol O. The anticancer mechanism of caffeic acid phenethyl ester (CAPE): review of melanomas, lung and prostate cancers. Eur Rev Med Pharmacol Sci. 2012 Dec;16(15):2064-8.

[110] Sawicka D, Car H, Borawska MH, Nikliński J.The anticancer activity of propolis. Folia Histochem Cytobiol. 2012 Apr 24;50(1):25-37. doi: 10.2478/18693.

[111] Varoni EM, Lodi G, Sardella A, Carrassi A, Iriti M. Plant polyphenols and oral health: old phytochemicals for new fields. Curr Med Chem. 2012;19(11):1706-20.

[112] Akyol S, Ozturk G, Ginis Z, Armutcu F, Yigitoglu MR, Akyol O. In vivo and in vitro antıneoplastic actions of caffeic acid phenethyl ester (CAPE): therapeutic perspectives. Nutr Cancer. 2013;65(4):515-26. doi: 10.1080/01635581.2013.776693.

[113] Chan GC, Cheung KW, Sze DM. The immunomodulatory and anticancer properties of propolis. Clin Rev Allergy Immunol. 2013 Jun;44(3):262-73. doi: 10.1007/s12016-012-8322-2.

[114] Kurek-Górecka A, Rzepecka-Stojko A, Górecki M, Stojko J, Sosada M, Swierczek-Zieba G. Structure and antioxidant activity of polyphenols derived from propolis. Molecules. 2013 Dec 20;19(1):78-101. doi: 10.3390/molecules19010078.

[115] Lin HP, Lin CY, Liu CC, Su LC, Huo C, Kuo YY, Tseng JC, Hsu JM, Chen CK, Chuu CP. Caffeic Acid phenethyl ester as a potential treatment for advanced prostate cancer targeting akt signaling. Int J Mol Sci. 2013 Mar 6;14(3):5264-83. doi: 10.3390/ijms14035264.

[116] Liu CC, Hsu JM, Kuo LK, Chuu CP. Caffeic acid phenethyl ester as an adjuvant therapy for advanced prostate cancer. Med Hypotheses. 2013 May;80(5):617-9. doi: 10.1016/j.mehy.2013.02.003. Epub 2013 Feb 23.

[117] de Figueiredo SM, Nogueira-Machado JA, Almeida Bde M, Abreu SR, de Abreu JA, Filho SA, Binda NS, Caligiorne RB. Immunomodulatory properties of green propolis. Recent Pat Endocr Metab Immune Drug Discov. 2014;8(2):85-94.

[118] Premratanachai P, Chanchao C. Review of the anticancer activities of bee products. Asian Pac J

Trop Biomed. 2014 May;4(5):337-44. doi: 0.12980/APJTB.4.2014C1262.

[119] Rajendran P, Rengarajan T, Nandakumar N, Palaniswami R, Nishigaki Y, Nishigaki I. Kaempferol, a potential cytostatic and cure for inflammatory disorders. Eur J Med Chem. 2014 Oct 30;86:103-12. doi: 10.1016/j.ejmech.2014.08.011.

[120] S VK. Propolis in dentistry and oral cancer management. N Am J Med Sci. 2014 Jun;6(6):250-9. doi: 10.4103/1947-2714.134369.

[121] Tolba MF, Omar HA, Azab SS, Khalifa AE, Abdel-Naim AB, Abdel-Rahman SZ. Caffeic acid phenethyl ester: A review of its antioxidant activity, protective effects against ischemia-reperfusion injury and drug adverse reactions. Crit Rev Food Sci Nutr. 2014 Nov 3:0.

[122] de Oliveira PF, Lima IM, Monteiro Neto Mde A, Bastos JK, da Silva Filho AA, Tavares DC. Evaluation of genotoxicity and antigenotoxicity of artepillin C in V79 cells by the comet and micronucleus assays. Nutr Cancer. 2013;65(7):1098-103. doi: 10.1080/01635581.2013.815233. Epub 2013 Aug 5.

[123] Frozza CO, Garcia CS, Gambato G, de Souza MD, Salvador M, Moura S, Padilha FF, Seixas FK, Collares T, Borsuk S, Dellagostin OA, Henriques JA, Roesch-Ely M. Chemical characterization, antioxidant and cytotoxic activities of Brazilian red propolis. Food Chem Toxicol. 2013 Feb;52:137-42. doi: 10.1016/j.fct.2012.11.013. Epub 2012 Nov 19.

[124] Hayakari R, Matsumiya T, Xing F, Tayone JC, Dempoya J, Tatsuta T, Aizawa-Yashiro T, Imaizumi T, Yoshida H, Satoh K. Effects of Brazilian green propolis on double-stranded RNA-mediated induction of interferon-inducible gene and inhibition of recruitment of polymorphonuclear cells. J Sci Food Agric. 2013 Feb;93(3):646-51. doi: 10.1002/jsfa.5892. Epub 2012 Sep 26.

[125] de Oliveira PF, Leandro LF, Montanheiro G, Bastos JK, da Silva Filho AA, Tavares DC. Baccharin prevents genotoxic effects induced by methyl methanesulfonate and hydrogen peroxide in V79 cells. J Food Sci. 2012 Aug;77(8):T138-42. doi: 10.1111/j.1750-3841.2012.02808.x.

[126] Endo S, Matsunaga T, Kanamori A, Otsuji Y, Nagai H, Sundaram K, El-Kabbani O, Toyooka N, Ohta S, Hara A. Selective inhibition of human type-5 17β-hydroxysteroid dehydrogenase (AKR1C3) by baccharin, a component of Brazilian propolis. J Nat Prod. 2012 Apr 27;75(4):716-21. doi: 10.1021/np201002x. Epub 2012 Apr 16.

[127] Franchi GC Jr, Moraes CS, Toreti VC, Daugsch A, Nowill AE, Park YK. Comparison of effects of the ethanolic extracts of brazilian propolis on human leukemic cells as assessed with the MTT assay. Evid Based Complement Alternat Med. 2012;2012:918956. doi: 10.1155/2012/918956. Epub 2011 Sep 28

[128] Kamiya T, Nishihara H, Hara H, Adachi T. Ethanol extract of Brazilian red propolis induces apoptosis in human breast cancer MCF-7 cells through endoplasmic reticulum stress. J Agric Food Chem. 2012 Nov 7;60(44):11065-70. doi: 10.1021/jf303004n. Epub 2012 Oct 24.

[129] Szliszka E, Zydowicz G, Mizgala E, Krol W. Artepillin C (3,5-diprenyl-4-hydroxycinnamic acid) sensitizes LNCaP prostate cancer cells to TRAIL-inducedapoptosis. Int J Oncol. 2012 Sep;41(3):818-28. doi: 10.3892/ijo.2012.1527. Epub 2012 Jun 25.

[130] Cheung KW, Sze DM, Chan WK, Deng RX, Tu W, Chan GC. Brazilian green propolis and its constituent, Artepillin C inhibits allogeneic activated human CD4 T cells expansion and activation. J Ethnopharmacol. 2011 Nov 18;138(2):463-71. doi: 10.1016/j.jep.2011.09.031. Epub 2011 Sep 22.

[131] Hattori H, Okuda K, Murase T, Shigetsura Y, Narise K, Semenza GL, Nagasawa H. Isolation, identification, and biological evaluation of HIF-1-modulating compounds from Brazilian green propolis. Bioorg Med Chem. 2011 Sep 15;19(18):5392-401. doi: 10.1016/j.bmc.2011.07.060. Epub 2011 Aug 4.

[132] Szliszka E, Zydowicz G, Janoszka B, Dobosz C, Kowalczyk-Ziomek G, Krol W. Ethanolic extract of Brazilian green propolis sensitizes prostate cancer cells to TRAIL-induced apoptosis. Int J Oncol. 2011 Apr;38(4):941-53. doi: 10.3892/ijo.2011.930. Epub 2011 Feb 1.

[133] Ishihara M, Naoi K, Hashita M, Itoh Y, Suzui M. Growth inhibitory activity of ethanol extracts of Chinese and Brazilian propolis in four human colon carcinoma cell lines. Oncol Rep. 2009 Aug;22(2):349-54.

[134] Awale S, Li F, Onozuka H, Esumi H, Tezuka Y, Kadota S. Constituents of Brazilian red propolis and their preferential cytotoxic activity against human pancreatic PANC-1 cancer cell line in nutrient-deprived condition. Bioorg Med Chem. 2008 Jan 1;16(1):181-9.

[135] Li F, Awale S, Tezuka Y, Kadota S. Cytotoxic constituents from Brazilian red propolis and their structure-activity relationship. Bioorg Med Chem. 2008 May 15;16(10):5434-40.

[136] Li H, Kapur A, Yang JX, Srivastava S, McLeod DG, Paredes-Guzman JF, et al. Antiproliferation of human prostate cancer cells by ethanolic extracts of Brazilian propolis and its botanical origin. Int J Oncol. 2007 Sep;31(3):601-6.

[137] Kimoto T, Aga M, Hino K, Koya-Miyata S, Yamamoto Y, Micallef MJ, et al. Apoptosis of human leukemia cells induced by Artepillin C, an active ingredient of Brazilian propolis. Anticancer Res. 2001 Jan-Feb;21(1A):221-8.

[138] Luo J, Soh JW, Xing WQ, Mao Y, Matsuno T, Weinstein IB. PM-3, a benzo-gamma-pyran derivative isolated from propolis, inhibits growth of MCF-7 human breast cancer cells. Anticancer Res. 2001 May-Jun;21(3B):1665-71.

[139] Acikelli AH, Gustmann S, Bardenheuer W, Klein J, Dembinski U, Kohl B, Yip KT, Nazif A, Stoll R, Strumberg D, Díaz-Carballo D. Flavonoids isolated from Caribbea propolis show cytotoxic activity in human cancer cell lines. Int J Clin Pharmacol Ther. 2013 Jan;51(1):51-3.

[140] Diaz-Carballo D, Freistã Hler M, Malak S, Bardenheuer W, Reusch HP. Mucronulatol from Caribbean propolis exerts cytotoxic effects on human tumor cell lines. Int J Clin Pharmacol Ther. 2008 May;46(5):226-35.

[141] Russo A, Cardile V, Sanchez F, Troncoso N, Vanella A, Garbarino JA. Chilean propolis: antioxidant activity and antiproliferative action in human tumor cell lines. Life Sci. 2004 Dec 17;76(5):545-58.

[142] Xuan H, Li Z, Yan H, Sang Q, Wang K, He Q, Wang Y, Hu F. Antitumor Activity of Chinese Propolis in Human Breast Cancer MCF-7 and MDA-MB-231 Cells. Evid Based Complement Alternat Med. 2014;2014:280120. doi: 10.1155/2014/280120.

[143] Sha N, Guan SH, Lu ZQ, Chen GT, Huang HL, Xie FB, et al. Cytotoxic constituents of chinese propolis. J Nat Prod. 2009 Apr;72(4):799-801.

[144] Usia T, Banskota AH, Tezuka Y, Midorikawa K, Matsushige K, Kadota S. Constituents of Chinese propolis and their antiproliferative activities. J Nat Prod. 2002 May;65(5):673-6.

[145] Camargo MS, Prieto AM, Resende FA, Boldrin PK, Cardoso CR, Fernández MF, Molina-Molina JM, Olea N, Vilegas W, Cuesta-Rubio O, Varanda EA. Evaluation of estrogenic, antiestrogenic and genotoxic activity of nemorosone, the major compound found in brown Cuban propolis. BMC Complement Altern Med. 2013 Jul 31;13:201. doi: 10.1186/1472-6882-13-201.

[146] Popolo A, Piccinelli LA, Morello S, Cuesta-Rubio O, Sorrentino R, Rastrelli L, et al. Antiproliferative activity of brown Cuban propolis extract on human breast cancer cells. Nat Prod Commun. 2009 Dec;4(12):1711-6.

[147] Cuesta-Rubio O, Frontana-Uribe BA, Ramírez-Apan T, Cárdenas J. Polyisoprenylated benzophenones in cuban propolis; biological activity of nemorosone. Z Naturforsch C. 2002 Mar-Apr;57(3-4):372-8.

[148] Park SI, Ohta T, Kumazawa S, Jun M, Ahn MR. Korean propolis suppresses angiogenesis through inhibition of tube formation and endotheli al cell proliferation. Nat Prod Commun. 2014 Apr;9(4):555-60.

[149] Pratsinis H, Kletsas D, Melliou E, Chinou I. Antiproliferative activity of Greek propolis. J Med Food. 2010 Apr;13(2):286-90.

[150] Banskota AH, Nagaoka T, Sumioka LY, Tezuka Y, Awale S, Midorikawa K, et al. Antiproliferative activity of the Netherlands propolis and its active principles in cancer cell lines. J Ethnopharmacol. 2002 Apr;80(1):67-73.

[151] Choudhari MK, Haghniaz R, Rajwade JM, Paknikar KM. Anticancer activity of Indian stingless bee propolis: an in vitro study. Evid Based Complement Alternat Med. 2013;2013:928280. doi: 10.1155/2013/928280. Epub 2013 May 16.

[152] Khacha-ananda S, Tragoolpua K, Chantawannakul P, Tragoolpua Y. Antioxidant and anti-cancer cell proliferation activity of propolis extracts from two extraction methods. Asian Pac J Cancer Prev. 2013;14(11):6991-5.

[153] Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Athikomkulchai S, Viriyaroj A, Awale S, Ruchirawat S, Svasti J, Saiki I. Chrysin overcomes TRAIL resistance of cancer cells through Mcl-1 downregulation by inhibiting STAT3 phosphorylation. I Int J Oncol. 2013 Jul;43(1):329-37. doi: 10.3892/ijo.2013.1926. Epub 2013 May 1.

[154] Thirugnanasampandan R, Raveendran SB, Jayakumar R. Analysis of chemical composition and bioactive property evaluation of Indian propolis. Asian Pac J Trop Biomed. 2012 Aug;2(8):651-4. doi: 10.1016/S2221-1691(12)60114-2.

[155] Kustiawan PM, Puthong S, Arung ET, Chanchao C. In vitro cytotoxicity of Indonesian stingless bee products against human cancer cell lines. Asian Pac J Trop Biomed. 2014 Jul;4(7):549-56. doi: 10.12980/APJTB.4.2014APJTB-2013-0039.

[156] da Cunha MG, Franchin M, de Carvalho Galvão LC, de Ruiz AL, de Carvalho JE, Ikegaki M, de Alencar SM, Koo H, Rosalen PL. Antimicrobial and antiproliferative activities of stingless bee Melipona scutellaris geopropolis. BMC

Complement Altern Med. 2013 Jan 28;13:23. doi: 10.1186/1472-6882-13-23.

[157] Hernandez J, Goycoolea FM, Quintero J, Acosta A, Castañeda M, Dominguez Z, et al. Sonoran propolis: chemical composition and antiproliferative activity on cancer cell lines. Planta Med. 2007 Nov;73(14):1469-74.

[158] Li F, He YM, Awale S, Kadota S, Tezuka Y. Two new cytotoxic phenylallylflavanones from Mexican propolis. Chem Pharm Bull (Tokyo). 2011;59(9):1194-6.

[159] Li F, Awale S, Tezuka Y, Kadota S. Cytotoxic constituents of propolis from Myanmar and their structure-activity relationship. Biol Pharm Bull. 2009 Dec;32(12):2075-8.

[160] Li F, Awale S, Zhang H, Tezuka Y, Esumi H, Kadota S. Chemical constituents of propolis from Myanmar and their preferential cytotoxicity against a human pancreatic cancer cell line. J Nat Prod. 2009a Jul;72(7):1283-7.

[161] Szliszka E, Sokół-Łętowska A, Kucharska AZ, Jaworska D, Czuba ZP, Król W. Ethanolic Extract of Polish Propolis: Chemical Composition and TRAI L-R2 Death Receptor Targeting Apoptotic Activity against Prostate Cancer Cells. Evid Based Complement Alternat Med. 2013;2013:757628. doi: 10.1155/2013/757628. Epub 2013 Nov 12.

[162] Valença I, Morais-Santos F, Miranda-Gonçalves V, Ferreira AM, Almeida-Aguiar C, Baltazar F. Portuguese propolis disturbs glycolytic metabolism of human colorectal cancer in vitro. BMC Complement Altern Med. 2013 Jul 19;13:184. doi: 10.1186/1472-6882-13-184.

[163] Valente MJ, Baltazar AF, Henrique R, Estevinho L, Carvalho M. Biological activities of Portuguese propolis: protection against free radical-induced erythrocyte damage and inhibition of human renal cancer cell growth in vitro. Food Chem Toxicol. 2011 Jan;49(1):86-92.

[164] Teerasripreecha D, Phuwapraisirisan P, Puthong S, Kimura K, Okuyama M, Mori H, Kimura A, Chanchao C. In vitro antiproliferative/cytotoxic activity on cancer cell lines of a cardanol and a cardol enriched from Thai Apis mellifera propolis. BMC Complement Altern Med. 2012 Mar 30;12:27. doi: 10.1186/1472-6882-12-27.

[165] Umthong S, Phuwapraisirisan P, Puthong S, Chanchao C. In vitro antiproliferative activity of partially purified Trigona laeviceps propolis from Thailand on human cancercell lines. BMC Complement Altern Med. 2011 May 6;11:37. doi: 10.1186/1472-6882-11-37.

[166] Suk FM, Lien GS, Huang WJ, Chen CN, Lu SY, Yang YC, Yan MD, Liang YC. A Taiwanese Propolis Derivative Induces Apoptosis through Inducing Endoplasmic Reticular Stress and Activating Transcription Factor-3 in Human Hepatoma Cells. Evid Based Complement Alternat Med. 2013;2013:658370. doi: 10.1155/2013/658370. Epub 2013 Oct 3.

[167] Chen CN, Hsiao CJ, Lee SS, Guh JH, Chiang PC, Huang CC, Huang WJ. Chemical modification and anticancer effect of prenylated flavanones from Taiwanese propolis. Nat Prod Res. 2012;26(2):116-24. doi: 10.1080/14786419.2010.535146. Epub 2011 Jul 27.

[168] Huang WJ, Lin CW, Lee CY, Chi LL, Chao YC, Wang HN, Chiou BL, Chen TJ, Huang CY, Chen CN. NBM-HD-3, a novel histone deacetylase inhibitor with anticancer activity through modulation of PTEN and AKT inbrain cancer cells. J Ethnopharmacol. 2011 Jun 14;136(1):156-67. doi: 10.1016/j.jep.2011.04.034. Epub 2011 Apr 20.

[169] Chen CN, Wu CL, Lin JK. Apoptosis of human melanoma cells induced by the novel compounds propolin A and propolin B from Taiwenese propolis. Cancer Lett. 2007 Jan 8;245(1-2):218-31.

[170] Huang WJ, Huang CH, Wu CL, Lin JK, Chen YW, Lin CL, et al. Propolin G, a prenylflavanone, isolated from Taiwanese propolis, induces caspase-dependent apoptosis in brain cancer cells. J Agric Food Chem. 2007 Sep 5;55(18):7366-76.

[171] Weng MS, Liao CH, Chen CN, Wu CL, Lin JK. Propolin H from Taiwanese propolis induces G1 arrest in human lung carcinoma cells. J Agric Food Chem. 2007 Jun 27;55(13):5289-98.

[172] Chen CN, Wu CL, Lin JK. Propolin C from propolis induces apoptosis through activating caspases, Bid and cytochrome c release in human melanoma cells. Biochem Pharmacol. 2004 Jan 1;67(1):53-66.

[173] Chen CN, Wu CL, Shy HS, Lin JK. Cytotoxic prenylflavanones from Taiwanese propolis. J Nat Prod. 2003 Apr;66(4):503-6.

[174] Barlak Y, Değer O, Colak M, Karataylı SC, Bozdayı AM, Yücesan F. Effect of Turkish propolis extracts on proteome of prostate cancer cell line. Proteome Sci. 2011 Dec 7;9:74. doi: 10.1186/1477-5956-9-74.

[175] Cogulu O, Biray C, Gunduz C, Karaca E, Aksoylar S, Sorkun K, et al. Effects of Manisa propolis on telomerase activity in leukemia cells obtained from the bone marrow of leukemia

patients. Int J Food Sci Nutr. 2009 Nov;60(7):601-5.

[176] Seda Vatansever H, Sorkun K, Ismet Deliloğlu Gurhan S, Ozdal-Kurt F, Turkoz E, Gencay O, Salih B. Propolis from Turkey induces apoptosis through activating caspases in human breast carcinoma cell lines. Acta Histochem. 2010 Nov;112(6):546-56. doi: 10.1016/j.acthis.2009.06.001. Epub 2009 Sep 4.

[177] Aliyazicioglu Y, Deger O, Ovali E, Barlak Y, Hosver I, Tekelioglu Y, et al. Effects of Turkish pollen and propolis extracts on respiratory burst for K-562cell lines. Int Immunopharmacol. 2005 Oct;5(11):1652-7.

[178] Gunduz C, Biray C, Kosova B, Yilmaz B, Eroglu Z, Sahin F, et al. Evaluation of Manisa propolis effect on leukemia cell line by telomerase activity. Leuk Res. 2005 Nov;29(11):1343-6.

[179] Tseng TH, Shen CH, Huang WS, Chen CN, Liang WH, Lin TH, Kuo HC. Activation of neutral-sphingomyelinase, MAPKs, and p75 NTR-mediating caffeic acid phenethyl ester-induced apoptosis in C6 glioma cells. J Biomed Sci. 2014 Jul 5;21:61. doi: 10.1186/1423-0127-21-61.

[180] Hsu TH, Chu CC, Hung MW, Lee HJ, Hsu HJ, Chang TC. Caffeic acid phenethyl ester induces E2F-1-mediated growth inhibition and cell-cycle arrest in human cervical cancer cells. FEBS J. 2013 Jun;280(11):2581-93. doi: 10.1111/febs.12242. Epub 2013 Apr 8.

[181] Kim EY, Ryu JH, Kim AK. CAPE promotes TRAIL-induced apoptosis through the upregulation of TRAIL receptors via activation of p38 and suppression of JNK in SK-Hep1 hepatocellular carcinoma cells. Int J Oncol. 2013 Oct;43(4):1291-300. doi: 10.3892/ijo.2013.2018. Epub 2013 Jul 15.

[182] Kuo YY, Lin HP, Huo C, Su LC, Yang J, Hsiao PH, Chiang HC, Chung CJ, Wang HD, Chang JY, Chen YW, Chuu CP. Caffeic Acid Phenethyl Ester Suppresses Proliferation and Survival of TW2.6 Human Oral Cancer Cells via Inhibition of Akt Signaling. Int J Mol Sci. 2013 Apr 24;14(5):8801-17. doi: 10.3390/ijms14058801.

[183] Omene C, Kalac M, Wu J, Marchi E, Frenkel K, O'Connor OA Propolis and its Active Component, Caffeic Acid Phenethyl Ester (CAPE), Modulate B reast Cancer Therapeutic Targets via an Epigenetically Mediated Mechanism of Action. J Cancer Sci Ther. 2013 Oct 21;5(10):334-342.

[184] Park MH, Kang DW, Jung Y, Choi KY, Min do S. Caffei acid phenethyl ester down regulates phospholipase D1 via direct binding and inhibition of NFκB transactivation. Biochem Biophys Res Commun. 2013 Dec 6;442(1-2):1-7. doi: 10.1016/j.bbrc.2013.09.105. Epub 2013 Oct 5.

[185] Tolba MF, Esmat A, Al-Abd AM, Azab SS, Khalifa AE, Mosli HA, Abdel-Rahman SZ, Abdel-Naim AB. Caffeic acid phenethyl ester synergistically enhances docetaxel and paclitaxel cytotoxicity in prostate cancer cells. IUBMB Life. 2013 Aug;65(8):716-29. doi: 10.1002/iub.1188. Epub 2013 Jul 11.

[186] Omene CO, Wu J, Frenkel K. Caffeic Acid Phenethyl Ester (CAPE) derived fro m propolis, a honey bee product, inhibits growth of breast cancerstem cells. Invest New Drugs. 2012 Aug;30(4):1279-88. doi: 10.1007/s10637-011-9667-8. Epub 2011 May 3

[187] Soda M, Hu D, Endo S, Takemura M, Li J, Wada R, Ifuku S, Zhao HT, El-Kabbani O, Ohta S, Yamamura K, Toyooka N, Hara A, Matsunaga T. Design, synthesis and evaluation of caffeic acid phenethyl ester-based inhibitors targeting a selectivity pocket in the active site of human aldo-keto reductase 1B10. Eur J Med Chem. 2012 Feb;48:321-9. doi: 10.1016/j.ejmech.2011.12.034. Epub 2011 Dec 29.

[188] Avcı CB, Gündüz C, Baran Y, Sahin F, Yılmaz S, Dogan ZO, Saydam G. Caffeic acid phenethyl ester triggers apoptosis through induction of loss of mit ochondrial membrane potential in CCRF-CEM cells. J Cancer Res Clin Oncol. 2011 Jan;137(1):41-7. doi: 10.1007/s00432-010-0857-0. Epub 2010 Mar 10.

[189] Basini G, Baioni L, Bussolati S, Grasselli F, Daquino C, Spatafora C et al. Antiangiogenic properties of an unusual benzo[k,l]xanthene lignan derived from CAPE (Caffeic Acid Phenethyl Ester). Invest New Drugs. 2010 Oct 6.

[190] Szliszka E, Czuba ZP, Domino M, Mazur B, Zydowicz G, Krol W. Ethanolic extract of propolis (EEP) enhances the apoptosis- inducing potential of TRAIL in cancer cells. Molecules. 2009 Feb 13;14(2):738-54.

[191] Chen MJ, Chang WH, Lin CC, Liu CY, Wang TE, Chu CH, et al. Caffeic acid phenethyl ester induces apoptosis of human pancreatic cancer cells involving caspase and mitochondrial dysfunction. Pancreatology. 2008;8(6):566-76.

[192] Jin UH, Song KH, Motomura M, Suzuki I, Gu YH, Kang YJ, et al. Caffeic acid phenethyl ester induces mitochondria-mediated apoptosis in human myeloid leukemia U937 cells. Mol Cell Biochem. 2008 Mar;310(1-2):43-8.

[193] Lee YY, Kao CL, Tsai PH, Tsai TH, Chiou SH, Wu WF, et al. Caffeic acid phenethyl ester preferentially enhanced radiosensitizing and increased oxidative stress in medulloblastoma cell line. Childs Nerv Syst. 2008 Sep;24(9):987-94.

[194] Hwang HJ, Park HJ, Chung HJ, Min HY, Park EJ, Hong JY, et al. Inhibitory effects of caffeic acid phenethyl ester on cancer cell metastasis mediated by the down-regulation of matrix metalloproteinase expression in human HT1080 fibrosarcoma cells. J Nutr Biochem. 2006 May;17(5):356-62.

[195] Xiang D, Wang D, He Y, Xie J, Zhong Z, Li Z, et al. Caffeic acid phenethyl ester induces growth arrest and apoptosis of colon cancer cells via the beta-catenin/T-cell factor signaling. Anticancer Drugs. 2006 Aug;17(7):753-62.

[196] Abdel-Latif MM, Windle HJ, Homasany BS, Sabra K, Kelleher D. Caffeic acid phenethyl estermodulatesHelicobacterpylori-inducednuclear factor-kappa B and activator protein-1expression in gastricepithelial cells. Br J Pharmacol. 2005 Dec;146(8):1139-47.

[197] Jin UH, Chung TW, Kang SK, Suh SJ, Kim JK, Chung KH, et al. Caffeic acid phenyl ester in propolis is a strong inhibitor of matrix metalloproteinase-9 and invasion inhibitor: isolation and identification. Clin Chim Acta. 2005 Dec;362(1-2):57-64.

[198] Gismondi A, Canuti L, Grispo M, Canini A. Biochemical composition and antioxidant properties of Lavandula angustifolia Miller essential oil are shielded by propolis against UV radiations. Photochem Photobiol. 2014 May-Jun;90(3):702-8. doi: 10.1111/php.12229.

[199] Huleihel M, Ishano V. Effect of propolis extract on malignant cell transformation by moloney murine sarcoma virus. Arch Virol. 2001 Aug;146(8):1517-26.

[200] Nomura M, Kaji A, Ma W, Miyamoto K, Dong Z. Suppression of cell transformation and induction of apoptosis by caffeic acid phenethyl ester. Mol Carcinog. 2001 Jun;31(2):83-9.

[201] Na HK, Wilson MR, Kang KS, Chang CC, Grunberger D, Trosko JE. Restoration of gap junctional intercellular communication by caffeic acid phenethyl ester (CAPE) in a ras-transformed rat liver epithelial cell line. Cancer Lett. 2000 Aug 31;157(1):31-8.

[202] Jaiswal AK, Venugopal R, Mucha J, Carothers AM, Grunberger D. Caffeic acid phenethyl ester stimulates human antioxidant response element-mediated expression of the NAD(P)H:quinone oxidoreductase (NQO1) gene. Cancer Res. 1997 Feb 1;57(3):440-6.

[203] Natarajan K, Singh S, Burke TR Jr, Grunberger D, Aggarwal BB. Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proc Natl Acad Sci U S A. 1996 Aug 20;93(17):9090-5.

[204] Su ZZ, Lin J, Prewett M, Goldstein NI, Fisher PB. Apoptosis mediates the selective toxicity of caffeic acid phenethyl ester (CAPE) toward oncogene-transformed rat embryo fibroblast cells. Anticancer Res. 1995 Sep-Oct;15(5B):1841-8.

[205] Su ZZ, Lin J, Grunberger D, Fisher PB. Growth suppression and toxicity induced by caffeic acid phenethyl ester (CAPE) in type 5 adenovirus-transformed rat embryo cells correlate directly with transformation progression.Cancer Res. 1994 Apr 1;54(7):1865-70.

[206] Guarini L, Su ZZ, Zucker S, Lin J, Grunberger D, Fisher PB. Growth inhibition and modulation of antigenic phenotype in human melanoma and glioblastoma multiforme cells by caffeic acid phenethyl ester (CAPE). Cell Mol Biol. 1992 Aug;38(5):513-27.

[207] Su ZZ, Grunberger D, Fisher PB. Suppression of adenovirus type 5 E1A-mediated transformation and expression of the transformed phenotype by caffeic acid phenethyl ester (CAPE). Mol Carcinog. 1991;4(3):231-42.

[208] Grunberger D, Banerjee R, Eisinger K, Oltz EM, Efros L, Caldwell M, et al. Preferential cytotoxicity on tumor cells by caffeic acid phenethyl ester isolated from propolis. Experientia. 1988 Mar 15;44(3):230-2.

[209] Lirdprapamongkol K, Sakurai H, Abdelhamed S, Yokoyama S, Athikomkulchai S, Viriyaroj A, Awale S, Ruchirawat S, Svasti J, Saiki I. Chrysin overcomes TRAIL resistance of cancer cells through Mcl-1 downregulation by inhibiting STAT3 phosphorylation. I Int J Oncol. 2013 Jul;43(1):329-37. doi: 10.3892/ijo.2013.1926. Epub 2013 May 1.

[210] Yang F, Jin H, Pi J, Jiang JH, Liu L, Bai HH, Yang PH, Cai JY. Anti-tumor activity evaluation of novel chrysin-organogermanium (IV) complex in MCF-7 cells. Bioorg Med Chem Lett. 2013 Oct 15;23(20):5544-51. doi: 10.1016/j.bmcl.2013.08.055.

[211] Li X, Wang JN, Huang JM, Xiong XK, Chen MF, Ong CN, Shen HM, Yang XF. Chrysin promotes tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induced apoptosis in human cancer cell lines. Toxicol In Vitro. 2011 Apr;25(3):630-5. doi: 10.1016/j.tiv.2010.12.013. Epub 2010 Dec 30.

[212] Pichichero E, Cicconi R, Mattei M, Canini A. Chrysin-induced apoptosis is mediated through

p38 and Bax activation in B16-F1 and A375 melanoma cells. Int J Oncol. 2011 Feb;38(2):473-83. doi: 10.3892/ijo.2010.876. Epub 2010 Dec 17.

[213] Woo KJ, Jeong YJ, Inoue H, Park JW, Kwon TK. Chrysin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression through the inhibition of nuclear factor for IL-6 (NF-IL6) DNA-binding activity. FEBS Lett. 2005 Jan 31;579(3):705-11.

[214] Woo KJ, Jeong YJ, Park JW, Kwon TK. Chrysin-induced apoptosis is mediated through caspase activation and Akt inactivation in U937 leukemia cells. Biochem Biophys Res Commun. 2004 Dec 24;325(4):1215-22.

[215] Kumazaki M, Shinohara H, Taniguchi K, Yamada N, Ohta S, Ichihara K, Akao Y. Propolis cinnamic acid derivatives induce apoptosis through both extrinsic and intrinsic apoptosis signaling pathways and modulate of miRNA expression. Phytomedicine. 2014 Jul-Aug;21(8-9):1070-7. doi: 10.1016/j.phymed.2014.04.006. Epub 2014 May 20.

[216] Ha TK, Kim ME, Yoon JH, Bae SJ, Yeom J, Lee JS. Galangin induces human colon cancer cell death via the mitochondrial dysfunction and caspase-dependent pathway. Exp Biol Med (Maywood). 2013 Sep;238(9):1047-54. doi: 10.1177/1535370213497882. Epub 2013 Aug 7.

[217] Zhang W, Lan Y, Huang Q, Hua Z. Galangin induces B16F10 melanoma cell apoptosis via mitochondrial
pathway and sustained activation of p38MAPK. Cytotechnology. 2013 May;65(3):447-55. doi: 10.1007/s10616-012-9499-1. Epub 2012 Sep 22.

[218] Bestwick CS, Milne L. Influence of galangin on HL-60 cell proliferation and survival. Cancer Lett. 2006 Nov 8;243(1):80-9.

[219] Cunha IBS, Sawaya ACHF, Caetano FM, Shimizu MT, Marcucci MC, Drezza FT, Povia GS, Carvalho PO. Factors that Influence the Yield and Composition of Brazilian Propolis Extracts J. Braz. Chem. Soc. 2004 15(6) 964-70.

[220] Bailoo JD, Reichlin TS, Würbel H. Refinement of experimental design and conduct in laboratory animal research. ILAR J. 2014;55(3):383-91. doi: 10.1093/ilar/ilu037.

[221] Disponível em: http://awic.nal.usda.gov/research-animals/institutional-animal-care-and-use-committees Acesso em 09/02/2015

[222] Disponível em: http://www.icmbio.gov.br/ran/images/stories/legislacao/RESOLU%C3%87%C3%83O_NORMATIVA_No-_12_-_20-09-2013.pdf Acesso em 09/02/2015

[223] Bara M, Joffe AR. The ethical dimension in published animal research in critical care: the public face of science. Crit Care. 2014 Jan 14;18(1):R15. doi: 10.1186/cc13694.

[224] Combes RD, Balls M. The three rs - opportunities for improving animal welfare and the quality of scientific research. Altern Lab Anim. 2014 Sep;42(4):245-59.

[225] Bird SJ, Parlee MB. Of mice and men (and women and children): scientific and ethical implications of animal models. Prog Neuropsychopharmacol Biol Psychiatry. 2000 Nov;24(8): 1219-27.

[226] Disponível em: http://www.mct.gov.br/upd_blob/0228/228451.pdf Acesso em 09/02/2015 eutanasia

[227] Dillman RO, Koziol JA.Phase I cancer trials: limitations and implications. Mol Biother. 1992 Sep;4(3):117-21.

[228] Kummar S, Kinders R, Rubinstein L, Parchment RE, Murgo AJ, Collins J, Pickeral O, Low J, Steinberg SM, Gutierrez M, Yang S, Helman L, Wiltrout R,Tomaszewski JE, Doroshow JH. Compressing drug development timelines in oncology using phase '0' trials. Nat Rev Cancer. 2007 Feb;7(2):131-9.

[229] Schutta KM, Burnett CB. Factors that influence a patient's decision to participate in a phase I cancer clinical trial. Oncol Nurs Forum. 2000 Oct;27(9):1435-8.