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

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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 vitro, 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](image_url)

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.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors / reference</th>
<th>Sample size</th>
<th>Experimental period (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Scheller et al. (37)</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>1993</td>
<td>Frenkel et al. (38)</td>
<td>104</td>
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</tr>
<tr>
<td></td>
<td>Rao et al. (18)</td>
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<td>1995</td>
<td>Rao et al. (39)</td>
<td>90</td>
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</tr>
<tr>
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<td>Huang et al. (40)</td>
<td>28</td>
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<td>Matsushige et al.(41)</td>
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<tr>
<td></td>
<td>Mitamura et al. (42)</td>
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<tr>
<td>1998</td>
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</tr>
<tr>
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<td>2001</td>
<td>Kimoto et al. (36)</td>
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### Chart 2: Authors, year of publication, reference, sample size and experimental period of the studies published from 2002 to 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors / reference</th>
<th>Sample size</th>
<th>Experimental period (weeks)</th>
<th>Year</th>
<th>Authors / reference</th>
<th>Sample size</th>
<th>Experimental period (weeks)</th>
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<td>2002</td>
<td>Suzuki et al. (47)</td>
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<td>Liao et al. (48)</td>
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<td>Orsolić et al. (15)</td>
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<td>Sugimoto et al. (49)</td>
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<td>El-khawaga et al. (19)</td>
<td>20</td>
<td>4</td>
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<td>Orsolić &amp; Basić (52)</td>
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<td>Messerli et al. (66)</td>
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<td>Cole et al. (13)</td>
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<td>Cavalcante et al.72</td>
<td>42</td>
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<td>Dornelas et al.78</td>
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<td>Sulaiman et al. (82)</td>
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<td>Huang et al. (80)</td>
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<td>Sequetto et al. (88)</td>
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<td>Lirdprapamongkol et al. (85)</td>
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<td>Motallebnejad et al. (92)</td>
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<td>Orsolić et al. (86)</td>
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<td>2014</td>
<td>Munari et al. (93)</td>
<td>40</td>
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<td></td>
<td>Díaz-Carballo et al. (89)</td>
<td>125</td>
<td>40</td>
<td></td>
<td>Pinheiro et al. (94)</td>
<td>90</td>
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<tr>
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<td>69</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lisičić et al. (91)</td>
<td></td>
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</tbody>
</table>
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].

<table>
<thead>
<tr>
<th>Authors, year of publication and reference</th>
<th>Main objectives and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iljazović et al. (2006) (95)</td>
<td>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.</td>
</tr>
<tr>
<td>Abdulrhman et al. (2012) (96)</td>
<td>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.</td>
</tr>
<tr>
<td>Ishikawa (2012) (97)</td>
<td>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</td>
</tr>
<tr>
<td>Tomaževič &amp; Jazbec (2013) (98)</td>
<td>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.</td>
</tr>
<tr>
<td>Noronha et al. (2014) (99)</td>
<td>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.</td>
</tr>
</tbody>
</table>
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, 112, 113, 116, 121). The following compounds were also frequently found: chrys, in 21 articles (3, 4, 6, 7, 53, 54, 76, 83, 85, 88, 144, 150, 157, 190, 209, 210, 211, 212, 213, 214); artepelin-c, in 15 articles (8, 33, 36, 43, 57, 58, 65, 66, 122, 129, 137, 173), 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 chemopreventive 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

<table>
<thead>
<tr>
<th>Period</th>
<th>Number of articles</th>
<th>Smaller number of animals 5 to 70 (n, %)</th>
<th>Larger number of animals 71 to 300 (n, %)</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988 to 2001</td>
<td>4 (5.6%)</td>
<td>8 (11.3%)</td>
<td>12 (16.9%)</td>
<td></td>
<td>0.025</td>
</tr>
<tr>
<td>2002 to 2014</td>
<td>40 (56.3%)</td>
<td>19 (26.8%)</td>
<td>59 (83.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44 (62%)</td>
<td>27 (38%)</td>
<td>71(100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Period</th>
<th>Number of articles</th>
<th>Shorter length of time Up to 12 weeks</th>
<th>Longer length of time 13 to 60 weeks</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988 to 2001</td>
<td>4 (5.6%)</td>
<td>8 (11.1%)</td>
<td>12 (16.7%)</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>2002 to 2014</td>
<td>48 (66.7%)</td>
<td>12 (16.7%)</td>
<td>60 (83.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52 (72.2%)</td>
<td>20 (27.8%)</td>
<td>72(100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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
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 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 Kummarr 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.

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Evaluation of genotoxicity and antigenotoxicity of artipillin C in V79 cells by comet and micronucleus assays.


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