Anticancer Activity of Propolis

Subjects: Nutrition & Dietetics

Contributor: Magdalena Bryś

Propolis is a natural material that honey bees (Apis mellifera) produce from various botanical sources. The therapeutic activity of propolis, including antibacterial, antifungal, and anti-inflammatory effects, have been known since antiquity. Propolis is a rich source of biologically active compounds, which affect numerous signaling pathways regulating crucial cellular processes. The results of the latest research show that propolis can inhibit proliferation, angiogenesis, and metastasis of cancer cells and stimulate apoptosis. Moreover, it may influence the tumor microenvironment and multidrug resistance of cancers.

Keywords: propolis ; propolis compounds ; cancer ; cell proliferation ; cytotoxicity ; apoptosis ; autophagy ; angiogenesis ; metastasis ; cancer therapy

1. Introduction

Propolis is a natural and sticky material, also known as bee glue, that honey bees (*Apis mellifera*) produce from saps, resins, and mucilages collected from various parts of the plant, such as leaves, flower buds, and tree barks, then mixing them with beeswax and several bee enzymes [1][2]. The word propolis originates from ancient Greek, in which "pro" stands for "at the entrance to" and "polis" for "community" or "city", indicating that this natural product is used in hive protection and defense [3][4][5]. Honey bees use this natural material to fix damage in the hive (covering the holes and sealing the cracks in the nest), to refine the internal walls, and to maintain constant humidity and temperature in the hive. Moreover, it is used to defend the colony from pathogen microorganisms, parasites, and predators [1][3][5][6][7]. At elevated temperatures, propolis is soft, pliable, and very sticky, while at low temperatures, it becomes hard and brittle; after cooling, it will remain brittle even at higher temperatures [3]. Propolis is characterized by specific herbaceous aromatic scents with various colors, including brown, yellow, green, and red, depending on the source from which it is obtained and the storage time [1][8].

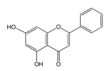
The therapeutic activity of propolis has been extensively explored in traditional medicine throughout centuries and cultures [6]. The ancient Egyptians used it mainly to embalm their cadavers because it prevented bacterial and fungal overgrowth and decomposition [3]. Propolis has been used by humans in different fields, including mainly folk medicine for the treatment of gastrointestinal diseases (i.e., stomach ulcers and buccal infections), wounds, and burns [3][9]. Hippocrates used propolis to cure wounds and external and internal ulcers. Moreover, in the 17th century, British pharmacopoeias listed propolis as an official drug [5]. During World War II, propolis was used as an antibacterial and anti-inflammatory agent [4]. This natural material was also used for other purposes as a constituent of violin varnish by famous Stradivari, Amati, and others [5]. The use of propolis has therefore been developed over time. It reveals biological properties, including antibacterial, fungicidal, antioxidant, immunomodulatory, and anti-inflammatory, among others [6][7][10][11][12][13][14]. Therefore, propolis is currently incorporated into a wide range of complementary health care products, including creams, gels, skin lotions, shampoos, chewing gums, tinctures, throat sprays, cough syrups, lozenges, soaps, toothpaste, and mouthwash preparations [7][15][16].

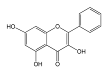
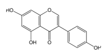
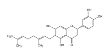
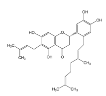
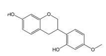
2. Composition of Propolis

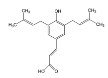
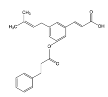
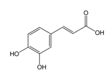
The chemical composition of propolis is diverse and depends on the geographical and botanical origin, i.e., climate factors, plant resources, place of origin, and time in which it was collected by the bees [5][17]. Honey bees collect plant material for propolis production during the warmest hours of sunny days because of the malleability and softness of the resins that are an essential component of propolis. Therefore, in temperate regions, propolis production takes place from late summer until autumn, whereas in tropical regions, honey bees can collect plant material throughout the entire year [6]. The specificity of the local flora is the main factor that determines the chemical composition of propolis and, subsequently, its biological and pharmacological properties [5]. Based on the origin of the propolis plant components, it has been classified into seven major types: 1. poplar (Europe, China, New Zealand, North America, and Southern South America);

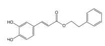
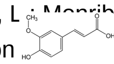
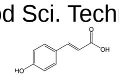
2. birch (Russia); 3. Mediterranean (Sicily, Greece, Crete, and Malta); 4. green (South-eastern Brazil); 5. red (Cuba, North-eastern Brazil, and Southeast Mexico); 6. Clusia (Venezuela and Cuba); and 7. Pacific (Okinawa, Taiwan, Indonesia, and Hawaii) [6][18]. Poplar types propolis originate mainly from the bud exudates of *Populus* spp. and mainly contain flavonoids (flavones and flavanones), phenolic acids (cinnamic acid), and their esters. Birch propolis originates from *Betula verrucosa* Ehrh. and also contains flavones and flavonols but is different from poplar propolis. In the Mediterranean region, honey bees mainly collect the resin of *Cupressus sempervirens*, therefore, Mediterranean propolis is rich in diterpenes. Green propolis contains derivatives of phenylpropanoides and diterpenes, chlorophyll and small amounts of flavonoids collected by bees from young tissues and nonexpanded leaves of *Baccharis dracunculifolia*. Contrary to green propolis, its red type is rich in numerous flavonoids (pinobanksin, quercetin, pinocembrin, daidzein), the source of which are resins of *Dalbergia ecastaphyllum*. The Clusia type of propolis contains benzophenones derivatives and originates from the resin of flowers of *Clusia* sp. Other examples of tropical propolis is Pacific propolis characterized by content of C-prenylflavanones [3][18][19]. The chemical composition and biological activities of propolis extracts depend on the type of solvent used for the extraction. The most commonly used solvent for the extraction of propolis is ethanol (particularly at a concentration of 70–75%) [18][20]. Propolis extracts are also obtained by extraction with solvents such as water, ethyl ether, methanol, hexane, chloroform, glycolic and glyceric solution, and seed oil [18][21]. In fact, in pharmaceutical and health care products, propolis is added in the form of ethanolic and aqueous extracts [21]. The available methods of analyzing the chemical composition of propolis and plant materials included in propolis as well as standardization and quality control methods for industrial applications have been described by Bankova and colleagues [22]. In general, propolis is composed of 50–60% of resins and balms, 30–40% of waxes and fatty acids, 5–10% of essential and aromatic oils, 5–10% of pollen, and about 5% of other substances, such as amino acids, vitamins, macro-, and microelements [5][8][18][23]. According to the literature data, more than 300 compounds have been identified in propolis samples of different geographical origins [15][18][20][23]. The major chemical groups found in propolis are flavonoids, aliphatic and aromatic acids, phenolic esters, fatty acids, alcohols, terpenes, β-steroids, alkaloids that include, but are not limited to chrysin, pinocembrin, apigenin, galangin, kaempferol, quercetin, cinnamic acid, o-coumaric acid, p-coumaric acid, caffeic acid (CA), and caffeic acid phenylethyl ester (CAPE) [3][5][15][24]. Flavonoids are the main substances responsible for the pharmacological properties of propolis, while terpenoids are additionally responsible for the odor of propolis [3]. The biological activities of propolis are the results of the interaction between various compounds. Analysis of the activity of each compound alone allows exploration of the molecular mechanisms underlying the pharmacological properties of propolis [23]. **Table 1** summarizes the results of recent in vitro and in vivo studies on the influence of propolis and its active compounds on the processes related to cancer development.

Table 1. Propolis compounds with anticancer activity (in vitro and in vivo models).

Compound Name, IUPAC Name; Concentration Used	Model	Property	Chemical Structure	Reference
Flavonoids, flavanones, flavones and flavonols				
Chrysin (5,7-dihydroxy-2-phenylchromen-4-one) 50 µM 5, 25, 50, 80 µg/mL	DU145 and PC-3 cells CAL-27 cells	induction of apoptosis		[25][26]

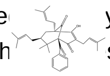
Compound Name, IUPAC Name; Concentration Used	Model	Property	Chemical Structure	Reference
Galangin (3,5,7-trihydroxy-2-phenylchromen-4-one) 0–40 μM 0–40 μM 10, 20 and 30 mg/kg	mice bearing B16F1 TU212, M4e, HBE, HEP-2 RTE, and HHL-5 cells BALB/c nude mice	induction of apoptosis induction of apoptosis and inhibition of migration		[27][28]
Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) 0–120 μM	LNCaP cells; mouse BALB/c 3T3 and SVT2 (SV40-transformed BALB/c 3T3) fibroblasts	inhibition of cell cycle		[3]
Nymphaeol A/Propolin C ((2S)-2-(3,4-dihydroxyphenyl)-6-[(2E)-3,7-dimethylocta-2,6-dienyl]-5,7-dihydroxy-2,3-dihydrochromen-4-one) 5–20 μM 2.5–20 μM	A549 cells A549 and HCC827 cells	anti-angiogenic activity, inhibition of proliferation inhibition of migration and invasion		[29][30]
Nymphaeol C ((2S)-2-[2-[(2E)-3,7-dimethylocta-2,6-dienyl]-3,4-dihydroxyphenyl]-5,7-dihydroxy-6-(3-methylbut-2-enyl)-2,3-dihydrochromen-4-one) 5–20 μM		anti-angiogenic activity, inhibition of proliferation		[29]
Vestitol (3-(2-hydroxy-4-methoxyphenyl)-3,4-dihydro-2H-chromen-7-ol) 0.37, 3.7, 37, and 370 μM	HeLa cells	cytotoxic effect		[31]
Aromatic acids and their derivatives				

Compound Name, IUPAC Name; Concentration Used	Model	Property	Chemical Structure	Reference
Artepillin C ((E)-3-[4-hydroxy-3,5-bis(3-methylbut-2-enyl)phenyl]prop-2-enoic acid) 250 μM 100 μg/mL 0–150 μM	HT1080, A549, and U2OS cells BALB/c nude mice AGP-01 and HeLa cells CWR22Rv1 cells	inhibition of proliferation cytotoxic effect autophagy inhibition		[32][33][34]
Baccharin ((1R,3S,4S,6R,9R,13S,15R,16S,19R,20E,22Z,26R,27S,28S)-16-hydroxy-19-[(1R)-1-hydroxyethyl]-6,15,27-trimethylspiro [2,5,11,14,18,25-hexaoxahexacyclo [2 4.2.1.03,9.04,6.09,27.013,15]nonacosa-20,22-diene-28,2′-oxirane]-12,24-dione) 0–150 μM	CWR22Rv1 cells	autophagy inhibition		[34]
Caffeic acid ((E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid) 50 and 100 μM 65, 130, 190 μg/mL 30 μg/mL, 200 μg/mL 12.5 μM, 1 mM, 50 μM, 100 mg/kg, 20 mg/kg	MDA-MB-231 cells CAL-27 cells Hep3, SK-Hep1, HepG2 cells	cell cycle arrest in a dose- and time-dependent manner apoptosis activation inhibition of angiogenesis, apoptosis activation		[26][35][36]

Compound Name, IUPAC Name; Concentration Used	Model	Property	Chemical Structure	Reference
Caffeic acid phenylethyl ester (2-phenylethyl (E)-3-(3,4-dihydroxyphenyl)prop-2-enoate) 0.005–0.1 mg/mL 0.5–500 µM 10 mg/kg/day 15 mg/kg	AGS, HCT116, HT29, YD15, HSC-4, HN22, MCF-17, MDA-MB-231, MDA-MB-468, A549, HT1080, G361, U2OS, LNCaP, PC-3, DU145, Hep2, SAS, OECM-1, TW01, TW04, SW620, H460 and PANC-1 cells Balb/c nude mice BALB/c AnM-Foxn-1 mice	inhibition of proliferation, migration and invasion, pro-apoptotic activity anti-metastatic activity		[3][35][37][38][39][40][41][42][43][44][45]
Ferulic acid ((E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid) 50, 100, 150 µg/mL	CAL-27 cells	apoptosis activation		[26]
p-coumaric acid ((E)-3-(4-hydroxyphenyl)prop-2-enoic acid) 100 µg/mL 70, 140, 210 µg/mL	AGS-01 and HeLa cells CAL-27 cells	cytotoxic effect apoptosis activation		[26][33]
Other				

References

1. Iqbal, M.; Fan, T.P.; Watson, D.; Alenezi, S.; Saleh, K.; Sahlan, M. Preliminary studies: The potential anti-angiogenic activities of two Sulawesi Island (Indonesia) propolis and their chemical characterization. Heliyon 2019, 5, e01978.
2. Zabaiou, N.; Fouache, A.; Trousson, A.; Buñay-Noboa, J.; Marceau, G.; Sapin, V.; Zellagui, A.; Baron, S.; Lahouel, M.; Lobaccaro, J.M.A. Ethanolic extract of Algerian propolis decreases androgen receptor transcriptional activity in cultured LNCaP cells. J. Steroid Biochem. Mol. Biol. 2019, 189, 108–115.
3. Zabaiou, N.; Fouache, A.; Trousson, A.; Baron, S.; Zellagui, A.; Lahouel, M.; Lobaccaro, J.A. Biological properties of propolis extracts: Something new from an ancient product. Chem. Phys. Lipids 2017, 207, 214–222.
4. Santos, L.M.; Fonseca, M.S.; Sokolonski, A.R.; Deegan, K.R.; Araújo, R.P.C.; Umsza-Guez, M.A.; Barbosa, J.D.V.; Portela, R.D.; Machado, B.A.S. Propolis: Types, composition, biological activities, and veterinary product patent prospecting. J. Sci. Food Agric. 2020, 100, 1369–1382.
5. Stojanović, S.; Najman, S.J.; Bogdanova-Popov, B.; Najman, S.S. Propolis: Chemical composition, biological and pharmacological activity—A Review. Acta Med. Median. 2020, 59, 108–113.
6. Alday, E.; Valencia, D.; Garibay-Escobar, A.; Domínguez-Esquivel, Z.; Piccinelli, A.L.; Rastrelli, L.; Monribot-Villanueva, J.; Guerrero-Analco, J.A.; Robles-Zepeda, R.E.; Hernandez, J.; et al. Plant origin authentication of Sonoran Desert propolis: An antiproliferative propolis from a semi-arid region. Sci. Nat. 2019, 106, 25.
7. Catchpole, O.; Mitchell, K.; Bloor, S.; Davis, P.; Suddes, A. Antiproliferative activity of New Zealand propolis and phenolic compounds vs. human colorectal adenocarcinoma cells. Fitoterapia 2015, 106, 167–174.
8. Doğan, H.; Silici, S.; Ozcimen, A.A. Biological Effects of Propolis on Cancer. Turk. J. Agric. Food Sci. Technol. 2020, 8, 573.
9. Popova, M.; Giannopoulou, E.; Skalicka-Wózniak, K.; Graikou, K.; Widelski, J.; Bankova, V.; Kalofonos, H.; Sivolapenko, G.; Gaweł-Bęben, K.; Antosiewicz, B.; et al. Characterization and biological evaluation of propolis from Poland. Molecules 2017, 22, 1159.
10. Przybyłek, I.; Karpiński, T.M. Antibacterial properties of propolis. Molecules 2019, 24, 2047.
11. Martinello, M.; Mutinelli, F. Antioxidant activity in bee products: A review. Antioxidants 2021, 10, 71.
12. Ripari, N.; Sartori, A.A.; da Silva Honorio, M.; Conte, F.L.; Tasca, K.I.; Santiago, K.B.; Sforcin, J.M. Propolis antiviral and immunomodulatory activity: A review and perspectives for COVID-19 treatment. J. Pharm. Pharmacol. 2021, 73, 281–299.
13. Franchin, M.; Freires, I.A.; Lazarini, J.G.; Nani, B.D.; da Cunha, M.G.; Colón, D.F.; de Alencar, S.M.; Rosalen, P.L. The use of Brazilian propolis for discovery and development of novel anti-inflammatory drugs. Eur. J. Med. Chem. 2018, 153, 49–55.

Compound Name	IUPAC Name	Concentration used	Model	Property	Chemical Structure	Reference
Frondoside A (sodium;[(3R,4R,5R,6S)-6-[(2S,4S,6S,12R,13R,18R)-4-acetyloxy-2,6,13,17,17-pentamethyl-6-(4-methylpentyl)-8-oxo-7-oxapentacyclo[10.8.0.02,9.05,9.013,18]icos-1(20)-en-16-yl]oxy-5-[(2S,3R,4S,5S,6R)-5-[(2S,3R,4S,5R)-4-[(2S,3R,4S,5R,6R)-3,5-dihydroxy-6-(hydroxymethyl)-4-methoxyoxan-2-yl]oxy-3,5-dihydroxyoxan-2-yl]oxy-4-hydroxy-6-methyl-3-[(2S,3R,4S,5R)-3,4,5-trihydroxyoxan-2-yl]oxyoxan-2-yl]oxy-4-hydroxyoxan-3-yl] sulfate)		0.3–1.2 µM	A549 cells	anti-angiogenic activity, inhibition of proliferation		[29]
Nemorosone ((1R,5R,7S)-1-benzoyl-4-hydroxy-6,8-dimethyl-3,5,7-tris(3-methylbut-2-enyl)bicyclo[3.3.1]non-3-ene-2,9-dione)		5–50 µM	HT-29 and THP-1 cells	inhibition of migration and proliferation		[46]

3. The Use of Propolis and Its Components in Cancer Therapy

Numerous studies have evaluated the biological effects of natural products in cancer therapy. Natural substances and their derivatives are used as chemotherapeutic agents, including vincristine, vinblastine, and taxanes (paclitaxel and docetaxel). Moreover, natural compounds may protect healthy cells from the damage caused by chemotherapy and radiotherapy, and limit the more severe effects of anticancer therapy [47].

Motawi and colleagues [48] studied how tamoxifen, CAPE, and their combination effect tumor size, survival time, and life span of Ehrlich tumor-bearing mice. A combination of tamoxifen and CAPE increased the life span of tumor-bearing mice two-fold compared with those treated with tamoxifen or CAPE alone. A combination of studied substances significantly decreased the tumor size and weight compared with the control group and tamoxifen-treated mice [48].

Propolis may also affect the effectiveness of chemotherapy with cytotoxic drugs. Sameni and colleagues showed in a mouse model of colorectal cancer that administration of Iranian propolis extract in combination with 5-fluorouracil (5-FU) significantly reduced the number of azaxymethane-induced aberrant crypt foci compared to 5-FU or propolis alone. Moreover, the propolis combined with 5-FU decreased the expression of Cox-2, iNOS, and β-catenin proteins, which play an important role in the incidences and progression of colorectal cancer [49].

Propolis may also have a positive effect on the efficacy of photodynamic therapy (PDT). PDT is a clinically approved form of therapy involving photosensitizing chemical substances (such as protoporphyrin IX) and a light that activates photosensitizers accumulated in cancer cells. Brazilian green propolis extract significantly enhances the intracellular accumulation of protoporphyrin IX (PpIX) in human epidermoid carcinoma cells A431 and increased PpIX-mediated photocytotoxicity in a xenograft model [50].

Chemotherapy and radiotherapy are the most widely used treatments for human cancer, and both are associated with many side effects [51][52]. Darvishi and colleagues [51] analyzed the antioxidant and anti-inflammatory effects of propolis during a randomized, double-blind clinical trial study on breast cancer patients who revived chemotherapy. In the group of patients taking propolis, in contrast to the placebo group, no increase in the level of proinflammatory cytokines (TNFα, IL-2) and protein carbonyl (biomarker of oxidative stress) was observed [51]. Propolis also shows the radioprotective effects in the case of chemotherapy receiving breast cancer patients undergoing radiotherapy. Moreover, breast cancer patients undergoing radiotherapy and supplemented with propolis had a statistically significant longer median disease-free survival time than the control group (radiotherapy without propolis supplementation) [52].

Oral mucositis is a major side effect of chemotherapy and radiotherapy [53][54]. Piredda and colleagues [54] showed that propolis was safe and well-tolerated by breast cancer patients receiving chemotherapy. Mouth rinsing with dry extract of propolis was effective in the reduction of significant symptoms of oral mucositis in patients with breast cancer during chemotherapy [54]. Similar results were also obtained in patients receiving chemotherapy for head and neck cancer [55].

14. de Mendonça, I.C.G.; de Moraes Porto, I.C.C.; do Nascimento, T.G.; de Souza, N.S.; dos Santos Oliveira, J.M.; dos Santos Arruda, R.E.; Mousinho, K.C.; dos Santos, A.F.; Basílio-Júnior, I.D.; Parolia, A.; et al. Brazilian red propolis: Phytochemical screening, antioxidant activity and effect against cancer cells. BMC Complement. Altern. Med. 2015, 15, 357.

15. Anjum, S.I.; Ullah, A.; Khan, K.A.; Attaullah, M.; Khan, H.; Ali, H.; Bashir, M.A.; Tahir, M.; Ansari, M.J.; Ghramh, H.A.; et al. Composition and functional properties of propolis (bee glue): A review. Saudi J. Biol. Sci. 2019, 26, 1695–1703.

16. Zulhendri, F.; Felitti, R.; Fearnley, J.; Ravalia, M. The use of propolis in dentistry, oral health, and medicine: A review. J. Oral Biosci. 2021.

17. Kubina, R.; Kabała-Dzik, A.; Dziedzic, A.; Bielec, B.; Wojtyczka, R.D.; Bułdak, R.J.; Wyszyńska, M.; Stawiarska-Pięta, B.; Szaflarska-Stojko, E. The ethanol extract of polish propolis exhibits anti-proliferative and/or pro-apoptotic effect on HCT 116 colon cancer and Me45 malignant melanoma cells in vitro conditions. Adv. Clin. Exp. Med. 2015, 24, 203–212.

18. Kocot, J.; Kiełczykowska, M.; Luchowska-Kocot, D.; Kurzepa, J.; Musik, I. Antioxidant potential of propolis, bee pollen, and royal jelly: Possible medical application. Oxid. Med. Cell. Longev. 2018, 2018.

19. Mora, D.P.P.; Santiago, K.B.; Conti, B.J.; de Oliveira Cardoso, E.; Conte, F.L.; Oliveira, L.P.G.; de Assis Golim, M.; Uribe, J.F.C.; Gutiérrez, R.M.; Buitrago, M.R.; et al. The chemical composition and events related to the cytotoxic effects of propolis on osteosarcoma cells: A comparative assessment of Colombian samples. Phytother. Res. 2019, 33, 591–601.

20. De Oliveira Reis, J.H.; de Abreu Barreto, G.; Cerqueira, J.C.; dos Anjos, J.P.; Andrade, L.N.; Padilha, F.F.; Druzian, J.I.; MacHado, B.A.S. Evaluation of the antioxidant profile and cytotoxic activity of red propolis extracts from different regions of northeastern Brazil obtained by conventional and ultrasoundassisted extraction. PLoS ONE 2019, 14, e0219063.

21. Galeotti, F.; Maccari, F.; Fachini, A.; Volpi, N. Chemical composition and antioxidant activity of propolis prepared in different forms and in different solvents useful for finished products. Foods 2018, 7, 41.

22. Bankova, V.; Bertelli, D.; Borba, R.; Conti, B.J.; Cunha, S.; Danert, C.; Eberlin, M.N.; Falcão, I.; Isla, M.I.; Ines, M.; et al. Standard methods for Apis mellifera propolis research. J. Apic. Res. 2019, 8839, 1–49.

23. dos Santos, D.A.; Munari, F.M.; da Silva Frozza, C.O.; Moura, S.; Barcellos, T.; Henriques, J.A.P.; Roesch-Ely, M. Brazilian red propolis extracts: Study of chemical composition by ESI-MS/MS (ESI+) and cytotoxic profiles against colon cancer cell lines. Biotechnol. Res. Innov. 2019, 3, 120–130.

24. Noureddine, H.; Hage-Sleiman, R.; Wehbe, B.; Fayyad-Kazan, A.H.; Hayar, S.; Traboulssi, M.; Alyamani, O.A.; Faour, W.H.; ElMakhour, Y. Chemical characterization and cytotoxic activity evaluation of Lebanese propolis. Biomed. Pharmacother. 2017, 95, 298–307.

25. Ryu, S.; Lim, W.; Bazer, F.W.; Song, G. Chrysin induces death of prostate cancer cells by inducing ROS and ER stress. J. Cell. Physiol. 2017, 232, 3786–3797.

26. Celinska-Janowicz, K.; Zareba, I.; Lazarek, U.; Teul, J.; Tomczyk, M.; Palka, J.; Miltyk, W. Constituents of Propolis: Chrysin, Caffeic Acid, p-Coumaric Acid, and Ferulic Acid Induce PRODH/POX-Dependent Apoptosis in Human Tongue Squamous Cell Carcinoma Cell (CAL-27). Front. Pharmacol. 2018, 9, 336.

27. Benguedouar, L.; Lahouel, M.; Gangloff, S.C.; Durlach, A.; Grange, F.; Bernard, P.; Antonicelli, F. Ethanolic extract of Algerian propolis and galangin decreased murine melanoma tumor progression in mice. Anti Cancer Agents Med. Chem. (Former. Curr. Med. Chem. Anti Cancer Agents) 2016, 16, 1172–1183.

28. Wang, H.X.; Tang, C. Galangin suppresses human laryngeal carcinoma via modulation of caspase-3 and AKT signaling pathways. Oncol. Rep. 2017, 38, 703–714.

29. Nguyen, H.X.; Nguyen, M.T.T.; Nguyen, N.T.; Awale, S. Chemical constituents of propolis from Vietnamese Trigona minor and Their antiausterity activity against the PANC-1 human pancreatic cancer cell line. J. Nat. Prod. 2017, 80, 2345–2352.

30. Pai, J.T.; Lee, Y.C.; Chen, S.Y.; Leu, Y.L.; Weng, M.S. Propolin C inhibited migration and invasion via suppression of EGFR-mediated epithelial-to-mesenchymal transition in human lung cancer cells. Evid. Based Complement. Altern. Med. 2018, 2018, 7202548.

31. Nani, B.D.; Franchin, M.; Lazarini, J.G.; Freires, I.A.; da Cunha, M.G.; Bueno-Silva, B.; de Alencar, S.M.; Murata, R.M.; Rosalen, P.L. Isoflavonoids from Brazilian red propolis down-regulate the expression of cancer-related target proteins: A pharmacogenomic analysis. Phytother. Res. 2018, 32, 750–754.

32. Bhargava, P.; Grover, A.; Nigam, N.; Kaul, A.; Doi, M.; Ishida, Y.; Kakuta, H.; Kaul, S.C.; Terao, K.; Wadhwa, R. Anticancer activity of the supercritical extract of Brazilian green propolis and its active component, artepillin C:

Bioinformatics and experimental analyses of its mechanisms of action. Int. J. Oncol. 2018, 52, 925–932.

The meta-analysis conducted by Kuo et al. [53] confirmed that propolis mouthwash is effective and safe in the treatment of chemo- or radiotherapy-induced oral mucositis in cancer patients.

Multidrug resistance (MDR) is also a significant problem in cancer therapy. MDR is the cellular mechanism by which patients' cancer cells develop resistance to unrelated chemotherapy drugs [56][57]. Doxorubicin (DOX) is one of the drugs commonly used in the treatment of many types of cancer, including breast, lung, ovarian, bladder, gastric, and thyroid cancer [58][59]. Propolis resulted in the inhibition of proliferation of DOX-resistant lung cancer cells (A549) [60]. P-glycoprotein (P-gp) is a multidrug membrane transporter, which effluxes out chemotherapeutic drugs from the cancer cells [56][57]. Kebsa et al. showed that propolis inhibited the P-gp efflux pump in a dose-dependent manner and enhanced the intracellular concentration of DOX [60]. Quercetin, ferulic acid, and CAPE may also influence the MDR of cancer cells by inhibiting P-gp expression [60]. Components of red propolis (propolone B and propolonone A) displayed antiproliferative activities against glioma cells (U-251), breast cancer cells (MCF-7), and prostate cancer cells (PC-3). Propolone B and propolonone A also inhibited the proliferation of multidrug-resistant ovarian cancer cells (NCI-ADR/RES) and were more efficiently than doxorubicin [61]. Frión-Herrera and colleagues discovered the chemosensitizing activity of Cuban propolis (CP) and its main compound (nemorosone) in doxorubicin-resistant colon cancer cells (LoVo). Combination of DOX and propolis extracts or Nem decreased viability of LoVo WT and DOX-resistant cells. All combined treatments increased reactive oxygen species production compared to control and single treatments in wild-type and resistant LoVo cells [59].

Propolis is usually well tolerated by cancer patients in clinical trials. Moreover, the patients appreciated the fact that they use a natural and well-known substance [64]. However, propolis may also be allergenic and may cause gastric problems [54][62]. A certain limitation of the use of propolis is also the highly variable chemical composition, which depends on the botanical origin and extraction methods. As a result, different propolis extracts are characterized by different biological activities [59]. Therefore, it is necessary to develop standarization methods, which will allow to combine the presence of specific compounds with biological activity and to develop recommendations for the use of different types of propolis [63].

33. Arruda, C.; Ribeiro, V.P.; Mejía, J.A.A.; Almeida, M.O.; Goulart, M.O.; Candido, A.C.B.B.; dos Santos, R.A.; Magalhães, L.G.; Martins, C.H.G.; Bastos, J.K. Green propolis: Cytotoxic and leishmanicidal activities of artepillin C, p-Coumaric Acid, and their degradation products. Rev. Bras. Farmacogn. 2020, 30, 169–176.
34. Endo, S.; Hoshi, M.; Matsunaga, T.; Inoue, T.; Ichihara, K.; Ikari, A. Autophagy inhibition enhances anticancer efficacy of artepillin C, a cinnamic acid derivative in Brazilian green propolis. Biochem. Biophys. Res. Commun. 2018, 497, 437–443.
35. Kabała-Dzik, A.; Rzepecka-Stojko, A.; Kubina, R.; Jastrzębska-Stojko, Ż.; Stojko, R.; Wojtyczka, R.D.; Stojko, J. Comparison of Two components of propolis: Caffeic Acid (CA) and Caffeic Acid Phenethyl Ester (CAPE) induce apoptosis and cell cycle arrest of breast cancer cells MDA-MB-231. Molecules 2017, 22, 1554.
36. Monteiro Espíndola, K.M.; Ferreira, R.G.; Mosquera Narvaez, L.E.; Rocha Silva Rosario, A.C.; Machado Da Silva, A.H.; Bispo Silva, A.G.; Oliveira Vieira, A.P.; Chagas Monteiro, M. Chemical and pharmacological aspects of caffeic acid and its activity in hepatocarcinoma. Front. Oncol. 2019, 9, 1–5.
37. Ren, X.; Liu, J.; Hu, L.; Liu, Q.; Wang, D.; Ning, X. Caffeic acid phenethyl ester inhibits the proliferation of HEp2 cells by regulating Stat3/Plk1 pathway and inducing S phase arrest. Biol. Pharm. Bull. 2019, 42, 1689–1693.
38. Gajek, G.; Marciniak, B.; Lewkowski, J.; Kontek, R. Antagonistic effects of CAPE (a Component of Propolis) on the cytotoxicity and genotoxicity of irinotecan and SN38 in Human gastrointestinal cancer cells in vitro. Molecules 2020, 25, 658.
39. Yu, H.J.; Shin, J.A.; Yang, I.H.; Won, D.H.; Ahn, C.H.; Kwon, H.J.; Lee, J.S.; Cho, N.P.; Kim, E.C.; Yoon, H.J.; et al. Apoptosis induced by caffeic acid phenethyl ester in human oral cancer cell lines: Involvement of Puma and Bax activation. Arch. Oral Biol. 2017, 84, 94–99.
40. Wadhwa, R.; Nigam, N.; Bhargava, P.; Dhanjal, J.K.; Goyal, S.; Grover, A.; Sundar, D.; Ishida, Y.; Terao, K.; Kaul, S.C. Molecular characterization and enhancement of anticancer activity of caffeic acid phenethyl ester by γ cyclodextrin. J. Cancer 2016, 7, 1755–1771.
41. Tseng, J.C.; Lin, C.Y.; Su, L.C.; Fu, H.H.; Der Yang, S.; Chuu, C.P. CAPE suppresses migration and invasion of prostate cancer cells via activation of non-canonical Wnt signaling. Oncotarget 2016, 7, 38010–38024.
42. Chung, L.C.; Chiang, K.C.; Feng, T.H.; Chang, K.S.; Chuang, S.T.; Chen, Y.J.; Tsui, K.H.; Lee, J.C.; Juang, H.H. Caffeic acid phenethyl ester upregulates N-myc downstream regulated gene 1 via ERK pathway to inhibit human oral cancer cell growth in vitro and in vivo. Mol. Nutr. Food Res. 2017, 61, 1–30.
43. Chiang, K.C.; Yang, S.W.; Chang, K.P.; Feng, T.H.; Chang, K.S.; Tsui, K.H.; Shin, Y.S.; Chen, C.C.; Chao, M.; Juang, H.H. Caffeic acid phenethyl ester induces N-myc downstream regulated gene 1 to inhibit cell proliferation and invasion of human nasopharyngeal cancer cells. Int. J. Mol. Sci. 2018, 19, 1397.
44. Fraser, S.P.; Hemsley, F.; Djamgoz, M.B.A. Caffeic acid phenethyl ester: Inhibition of metastatic cell behaviours via voltage-gated sodium channel in human breast cancer in vitro. Int. J. Biochem. Cell Biol. 2016, 71, 111–118.
45. Duan, J.; Xiaokaiti, Y.; Fan, S.; Pan, Y.; Li, X.; Li, X. Direct interaction between caffeic acid phenethyl ester and human neutrophil elastase inhibits the growth and migration of PANC-1 cells. Oncol. Rep. 2017, 37, 3019–3025.
46. Frión-Herrera, Y.; Gabbia, D.; Cuesta-Rubio, O.; De Martin, S.; Carrara, M. Nemorosone inhibits the proliferation and migration of hepatocellular carcinoma cells. Life Sci. 2019, 235, 116817.
47. De Giffoni De Carvalho, J.T.; Da Silva Baldivia, D.; Leite, D.F.; De Araújo, L.C.A.; De Toledo Espindola, P.P.; Antunes, K.A.; Rocha, P.S.; De Picoli Souza, K.; Dos Santos, E.L. Medicinal plants from Brazilian Cerrado: Antioxidant and anticancer potential and protection against chemotherapy toxicity. Oxid. Med. Cell. Longev. 2019, 2019.
48. Motawi, T.K.; Abdelazim, S.A.; Darwish, H.A.; Elbaz, E.M.; Shouman, S.A. Modulation of Tamoxifen Cytotoxicity by Caffeic Acid Phenethyl Ester in MCF-7 Breast Cancer Cells. Oxid. Med. Cell. Longev. 2016, 2016.
49. Sameni, H.R.; Yosefi, S.; Alipour, M.; Pakdel, A.; Torabizadeh, N.; Semnani, V.; Bandegi, A.R. Co-administration of 5FU and propolis on AOM/DSS induced colorectal cancer in BALB-c mice. Life Sci. 2021, 276, 119390.
50. Wang, C.C.; Wang, Y.X.; Yu, N.Q.; Hu, D.; Wang, X.Y.; Chen, X.G.; Liao, Y.W.; Yao, J.; Wang, H.; He, L.; et al. Brazilian green propolis extract synergizes with protoporphyrin IX-mediated photodynamic therapy via enhancement of intracellular accumulation of protoporphyrin IX and attenuation of NF-κB and COX-2. Molecules 2017, 22, 732.
51. Darvishi, N.; Yousefinejad, V.; Akbari, M.E.; Abdi, M.; Moradi, N.; Darvishi, S.; Mehrabi, Y.; Ghaderi, E.; Jamshidi-Naaeini, Y.; Ghaderi, B.; et al. Antioxidant and anti-inflammatory effects of oral propolis in patients with breast cancer treated with chemotherapy: A Randomized controlled trial. J. Herb. Med. 2020, 23, 100385.

52. Ebeid, S.A.; Abd El Moneim, N.A.; El-Benhawy, S.A.; Hussain, N.G.; Hussain, M.I. Assessment of the radioprotective effect of propolis in breast cancer patients undergoing radiotherapy. New perspective for an old honey bee product. J. Radiat. Res. Appl. Sci. 2016, 9, 431–440.

53. Kuo, C.C.; Wang, R.H.; Wang, H.H.; Li, C.H. Meta-analysis of randomized controlled trials of the efficacy of propolis mouthwash in cancer therapy-induced oral mucositis. Support. Care Cancer 2018, 26, 4001–4009.

54. Piredda, M.; Facchinetti, G.; Biagioli, V.; Giannarelli, D.; Armento, G.; Tonini, G.; De Marinis, M.G. Propolis in the prevention of oral mucositis in breast cancer patients receiving adjuvant chemotherapy: A pilot randomised controlled trial. Eur. J. Cancer Care 2017, 26.

55. Akhavan-Karbassi, M.H.; Yazdi, M.F.; Ahadian, H.; Sadr-Abad, M.J. Randomized double-blind placebo-controlled trial of propolis for oral mucositis in patients receiving chemotherapy for head and neck cancer. Asian Pac. J. Cancer Prev. 2016, 17, 3611–3614.

56. Ganesan, M.; Kanimozhi, G.; Pradhapsingh, B.; Khan, H.A.; Alhomida, A.S.; Ekhzaimy, A.; Brindha, G.R.; Prasad, N.R. Phytochemicals reverse P-glycoprotein mediated multidrug resistance via signal transduction pathways. Biomed. Pharmacother. 2021, 139, 111632.

57. Mansoori, B.; Mohammadi, A.; Davudian, S.; Shirjang, S.; Baradaran, B. The different mechanisms of cancer drug resistance: A brief review. Adv. Pharm. Bull. 2017, 7, 339–348.

58. Sritharan, S.; Sivalingam, N. A comprehensive review on time-tested anticancer drug doxorubicin. Life Sci. 2021, 278, 119527.

59. Frión-Herrera, Y.; Gabbia, D.; Díaz-García, A.; Cuesta-Rubio, O.; Carrara, M. Chemosensitizing activity of Cuban propolis and nemorosone in doxorubicin resistant human colon carcinoma cells. Fitoterapia 2019, 136, 104173.

60. Kebsa, W.; Lahouel, M.; Rouibah, H.; Zihlif, M.; Ahram, M.; Abu-Irmaileh, B.; Mustafa, E.; Al-Ameer, H.J.; Al Shhab, M. Reversing Multidrug Resistance in Chemo-resistant Human Lung Adenocarcinoma (A549/DOX) Cells by Algerian Propolis Through Direct Inhibiting the P-gp Efflux-pump, G0/G1 Cell Cycle Arrest and Apoptosis Induction. Anticancer Agents Med. Chem. 2018, 18, 1330–1337.

61. Banzato, T.P.; Gubiani, J.R.; Bernardi, D.I.; Nogueira, C.R.; Monteiro, A.F.; Juliano, F.F.; De Alencar, S.M.; Pilli, R.A.; De Lima, C.A.D.; Longato, G.B.; et al. Antiproliferative Flavanoid Dimers Isolated from Brazilian Red Propolis. J. Nat. Prod. 2020, 83, 1784–1793.

62. Nyman, G.; Oldberg Wagner, S.; Prystupa-Chalkidis, K.; Ryberg, K.; Hagvall, L. Contact allergy in western sweden to propolis of four different origins. Acta Derm. Venereol. 2020, 100, 1–5.

63. Toreti, V.C.; Sato, H.H.; Pastore, G.M.; Park, Y.K. Recent progress of propolis for its biological and chemical compositions and its botanical origin. Evid. Based Complement. Altern. Med. 2013, 2013.

Retrieved from https://encyclopedia.pub/entry/history/show/30715