Polyphenols and Side Effects Induced by Anti-Tumor Drugs

Subjects: Plant Sciences

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Cancer is one of the most widespread diseases globally and one of the leading causes of death. Known cancer treatments are chemotherapy, surgery, radiation therapy, targeted hormonal therapy, or a combination of these methods. Antitumor drugs, with different mechanisms, interfere with cancer growth by destroying cancer cells. However, anticancer drugs are dangerous, as they significantly affect both cancer cells and healthy cells. In addition, there may be the onset of systemic side effects perceived and mutagenicity, teratogenicity, and further carcinogenicity. Many polyphenolic extracts, taken on top of common anti-tumor drugs, can participate in the anti-proliferative effect of drugs and significantly reduce the side effects developed.

Anti-Tumor Drugs Side Effects Polyphenols

1. Introduction

A correct diet, rich in fruits, vegetables, and fibers, with moderate consumption of milk, dairy, meat, and animal products or animal fats plays a protective role in preventing cancer. In particular, the Mediterranean diet, which precisely reflects this nutritional program, is the best food model to reduce the onset of cancer [1][2]. More than 100 natural plant-based compounds possess anti-cancer properties, killing cancer cells without being toxic to healthy cells [3][4]. Most of the molecules with these characteristics belong to the family of polyphenols, a group of natural compounds widely distributed in the plant kingdom; polyphenols are characterized by more than 8000 phenolic structures [5][6]. Polyphenols are made, as the name indicates, from a set of phenolic structures, in which a OH group replaces a benzene hydrogen atom and whose chemical formula is C_6H_5OH. These compounds are secondary plant metabolites and possess countless beneficial activities on human health [7]. Among the beneficial properties of polyphenols, it is appropriate to remember the antioxidant, anti-microbial, anti-inflammatory, anti-cancer, and anti-diabetic properties regulating the intra and intercellular signaling pathways [8]. Following the ingestion, polyphenols are absorbed and transformed into bioactive compounds; initially, the enzymatic splitting of the carbohydrate portion (when present) occurs, and then aglycones enter the epithelial cells of the small intestine by passive diffusion. Polyphenolic compounds that cannot be absorbed or large ones reach the colon, where the microbiota will metabolize them [9]. The aglycones and the final derivatives absorbed (in the small intestine or the colon, respectively) are conjugated by methylation, sulfation, and glucuronidation in the enterocytes and then enter the bloodstream through the portal vein. Then, they reach the liver, where they may be subjected to more phase II

metabolism; they are subsequently transported to the various tissues or secreted in urine. Finally, the unabsorbed metabolites are eliminated via feces [10].

2. Effects of Polyphenols, Contained in Genera *Vaccinium* L., *Citrus* L., *Olea* L., and *Cynara* L, against the Side Effects Induced by Treatment with Selected Anti-Tumor Drugs

When macromolecules, cells, and tissues are exposed to an excess of oxidizing agents and the antioxidant defenses of the cell/organism are insufficient to maintain a redox balance, an oxidative stress state occurs with increased highly reactive unstable chemical species (oxygen and nitrogen free radicals, ROS and RNS, respectively), which can generate metabolic changes, damage, and cell death [11][12]. To date, it is known that oxidative stress is involved in the occurrence of many human pathologies such as metabolic, inflammatory, and neurodegenerative diseases and cancer [13][14][15]. In cancer, on the one hand, the accumulation of oxidative stress is able to contribute, through different mechanisms, to the onset of the disease; on the other hand, the alteration of the redox balance accentuates the proliferation of cancer by the development of chemoresistance [16]. Multiple-drug resistance (MDR) occurs when cancer cells are resistant to chemotherapy drugs and may present as innate or acquired. In innate MDR, cancer cells are already equipped to withstand the anticancer drug used. In contrast, in acquired resistance, cancer cells initially respond to treatment, but subsequently develop extraordinary resistance mechanisms [17]. To date, the development of the acquired resistance to cancer tends to be associated with increased cellular oxidative stress [18]. Processes involved in chemoresistance mediated by oxidative stress include autophagy by endoplasmic reticulum stress, increased progression of the cell cycle, increased number of cancer stem cells, and increased conversion into metastases [19]. In fact, cancer cells that have developed drug resistance have a higher content of reactive oxidizing species than cancer cells that are not resistant to chemotherapeutic agents and are more susceptible to changes in ROS levels. In addition, molecules capable of reducing the generation and accumulation of ROS are potentially useful in the treatment of cancer patients who have developed chemoresistance [20]. To date, it is known that the oxidative stress modulation can be considered a winning strategy to combat MDR, and compounds that reduce cellular ROS levels can increase the death of MDR cancer cells and sensitize MDR cancer cells to certain chemotherapeutic drugs. For this reason, the use of antioxidant compounds of natural origin, such as polyphenols, has become important in order to build a barrier against the generation of reactive oxidant species [21]. The mechanism of action by which polyphenols play antioxidant effects is to be found in the presence of hydroxyl groups linked to the benzene ring that provide the ability to donate a hydrogen atom or electron to free radicals. The consequence is the stabilization of free radicals, which reduces their possibility of damaging cellular components [22].

In order to improve the clinical outcomes of Cisplatin and reduce, at the same time, the side effects caused and the drug resistance, researchers propose the combination of conventional chemotherapy with natural compounds. Ovarian cancer annually causes many deaths worldwide due to the development of resistance to the chemotherapy drugs used. An in vitro study conducted on A2780S and A2780/CP ovarian endometrioid adenocarcinoma cell lines has deepened the effect of oleuropein on cell viability, Cisplatin resistance, and

apoptosis. In particular, oleuropein-treated cell lines showed an increase of expression of p21 and p53, while apoptosis inhibitors Bcl-2 and Mcl1 were reduced [23][24]. As a result, oleuropein was able to induce apoptosis, inhibited cell proliferation, and reduced resistance to cisplatin in ovarian cancer cells. At the same time, oleuropein has been shown to reduce Cisplatin-induced oxidative stress and prevent the development of chemotherapeutic complications including hematological tumors. Geyikoğlu et al. demonstrated these results in an in vivo study conducted on male Sprague Dawley rats [25]. Hydroxytyrosol derives from oleuropein, following a hydrolysis reaction, and has proven to be one of the most powerful compounds with antioxidant action. Frequently, the use of the chemotherapy Cisplatin is reduced due to the induction of inflammation and oxidative stress that facilitate the onset of nephrotoxicity [26][27]. Since hydroxytyrosol has anti-inflammatory and antioxidant effects, it has been tested on the kidney of mice following treatment-induced damage with Cisplatin in an in vitro and in vivo study. The results showed that hydroxytyrosol was able to limit Cisplatin-induced inflammation by reducing the NF-κB activation and the TNF-α and IL-1β levels. In addition, hydroxytyrosol decreased the production of malondialdehyde (MDA) and NO increased by Cisplatin [28]. Luteolin belongs to the large group of flavonoid polyphenols and is present in numerous plants, including pinophyte, pteridophyta, peppermint, thyme, and rosemary; it possesses a variety of pharmacological properties such as anti-inflammatory, antimicrobial, antioxidant, antiallergic, and anticancer activities [29]. Wang et al. demonstrated both in vitro and in vivo that luteolin can enhance the therapeutic potential of Cisplatin in ovarian cancer. The treatment with luteolin alone inhibits cell proliferation, but the co-treatment luteolin-Cisplatin further reduces it [30]. Another in vivo study, highlighting the protective role of luteolin against DNA damage and cisplatin-induced oxidative stress, was conducted by Maatouk et al. The results obtained showed that mice receiving luteolin (40 mg/kg), before treatment with Cisplatin (10 mg/Kg), showed a reduction in levels of MDA, catalase, GPx, SOD, and GSH in the liver, kidneys, brain, and spleen, compared to those induced by treatment with Cisplatin alone. In addition, tissue damage, the genotoxic effect, and the side effects generated by the anticancer drug were reduced [31]. Resveratrol is a polyphenolic phytoalexin found in several different plants in nature and, particularly, in grapes. In addition, resveratrol also belongs to phytochemicals with potent antioxidant activity, which provides preferable efficacy with chemotherapeutics but attenuated toxicity in vital tissue [32].

Literature studies have shown that this natural compound possesses consistent antioxidant properties and that it can emphasize the cytotoxic action of Cisplatin in the testicular cancer of rats [33]. An interesting result was provided by a study [34], which highlighted the effect of resveratrol in limiting the toxicity of Cisplatin, especially when higher doses are needed in particularly aggressive tumors such as those of the head and neck. In particular, the co-treatment with Cisplatin-resveratrol on Fadu cells, a hypopharyngeal cell line carcinoma, induced an increase in the effectiveness of Cisplatin, thanks to an increase in apoptotic death, accompanied by the blocking of the cell cycle in the G0/G1 phase. In addition, resveratrol has reduced the harmful effects induced by Cisplatin. A recent in vitro study on SKOV3 cells, isolated from a female with ovarian adenocarcinoma, showed that treatment with naringin, at different concentrations and for different times, was able to reduce Cisplatin resistance [35].

To date, the use of plant polyphenols is exponentially increasing and is considered an adjuvant therapy in combination with Doxorubicin. Polyphenols have an interesting antioxidant property, and these compounds can prevent tumorigenicity, thanks to their anti-proliferative and cardio-protective effects [36]. Resveratrol, found in large

quantities in red wine, berries, and grapes' skin, can reverse the Doxorubicin-induced cardiotoxicity by reducing oxidative stress and diminishing lipid peroxidation. Polyphenol employment reduces malondialdehyde level and protects the enzyme superoxide dismutase activity [37]. Resveratrol prevents the apoptotic death of cardiomyocytes induced by Doxorubicin, as demonstrated by the reduced expression of the protein p53 and Bax [38] and autophagy dysregulation [39]. Finally, resveratrol can be used in conjunction with Doxorubicin treatment to improve the therapeutic efficiency of chemotherapy while also protecting the heart from cardiotoxicity [40]. Apigenin is a natural flavonoid found in fruits and vegetables with antioxidant, anti-inflammatory, anticancer, and cardioprotective properties [41][42]. Apigenin is a good iron chelator and scavenger of free radicals. It can be used synergistically with Doxorubicin to treat leukemia, causing cell cycle arrest and inducing apoptotic death. In addition, apigenin attenuates Doxorubicin-induced cardiotoxicity by activating a PI3K/Akt/mTOR-dependent pathway and has beneficial action in many cancer models without developing toxicity. Finally, this compound can overcome the chemoresistance to the Doxorubicin, reducing the expression of Nrf2, notoriously involved as a transcriptional regulator of drug resistance [43][44]. The polyphenolic fraction of bergamot (BPF) comes from the pressing of the fruit of the bergamot plant (Citrus bergamia), a plant endemic to the Calabria region (Italy), with a flavonoid and unique glycosidic profile. Carresi and colleagues demonstrated, in an in vivo model of Doxorubicin-induced heart damage, the antioxidant and cardioprotective effects of BPF. The reduction of heart function occurs after 21 days of Doxorubicin treatment, and this adverse effect has been significantly attenuated when animals were co-treated with BPF. BPF's protective effect has also been linked to the activation of an autophagic protective mechanism. [45]. Numerous other polyphenols protect against cardiotoxicity induced by treatment with Doxorubicin, and the use of this drug combined with natural compounds, which increase the death of cancer cells while protecting the heart from cardiotoxicity, is highly recommended [46]. An important and well-organized study by Tavga [47] showed, in an in vivo model, that quercetin was able to induce protection against Doxorubicin-induced cardiotoxicity in rats. The effects were measured on blood samples and levels of troponin, creatine, phosphokinase, C-reactive protein, total antioxidant capacity, lactate dehydrogenase, and total lipid profile were evaluated. The results showed that treatment with Doxorubicin produced a significant increase in the level of troponin, total cholesterol, CRP, low-density lipoprotein, LDH, triglycerides, and atherogenic index of plasma and that quercetin, co-treated with Doxorubicin, reverted these effects, reporting values in a normal range. Histopathological findings were also provided which supported biochemical findings. The cardioprotective effects of quercetin could be attributed to the effects of antioxidant, anti-inflammatory, hypolipidemic and antiatherogenic activity, indicating this natural compound as an excellent therapeutic candidate to be tested in the clinical field.

Luminal breast cancer is an aggressive disease that is resistant to chemotherapy. Numerous studies have shown that oleuropein and olive oil polyphenols exert a strong antitumor activity in multiple human cancers [48][49][50]. For this reason, it was interesting to examine the effect of the combination of oleuropein with tamoxifen chemotherapy. In particular, an in vitro study showed that treatment with oleuropein inhibited the growth of human breast cancer cells BT-474, MCF-7, and T-47D and that the combined treatment oleuropein-tamoxifen led to a synergistic inhibition of the growth of the same cell lines [51]. Recently it has been shown that the flavonoids contained in fruits belonging to the genus *Citrus* (*Citrus reticulata* and *Citrus aurantiifolia*) have anticancer, antiproliferative, and estrogenic effects [52]. In particular, hesperidin, hesperetin, naringenin, tangeretin, nobiletin, and naringin have

inhibiting activity on the growth of some cancer cells through various mechanisms. It has also been shown that these compounds play a synergistic effect with several chemotherapy agents [53]. The mechanisms of action involved include apoptosis, cell cycle modulation, and antiangiogenic effects. Finally, the natural compounds mentioned, in combination with tamoxifen, have demonstrated a synergistic effect on the cell line of human breast cancer MCF-7 [54]. Tamoxifen leads to a strong hepatotoxic and hepatocarcinogenic effect in rats when used at doses comparable to human therapeutic doses. As already mentioned, this drug is metabolized in the liver by the cytochrome P450 family; since there is increasing evidence of the hepatoprotective role of flavonoids, it would be possible to treat breast cancer with Tamoxifen together with these hepatoprotective plant extracts in order to reduce the suffering liver [55][56]. Another plant extract with known hepatoprotective properties is the cynaropicrin, a sesquiterpene lactone extracted from the artichoke plants and the most biologically important class of secondary metabolites of the plants [57][58][59][60][61]. Although no specific studies have been carried out on the use of Tamoxifen and cynaropicrin, it would be interesting to consider the employment of this polyphenol as an adjuvant drug in chemotherapy that induces liver impairment.

The administration of the polyphenol resveratrol (4 mg/kg in 40 mL normal saline, in rabbits) combined with Paclitaxel significantly decreases myelosuppression's degree and duration [62]. The hypersensitivity reactions associated with Paclitaxel include dyspnea, with or without bronchospasm (81%), hives, redness, or erythematous rash (74%), hypotension (41%), and angioedema (18.5%). These side effects occur within the first hour of Paclitaxel infusion and are observed despite premedication with antihistamines and corticosteroids [63]. The concomitant use of certain polyphenols is crucial to preventing or treating this symptomatology. Some polyphenols, such as quercetin, resveratrol, oleuropein, silibinin, and many tannins and carotenoids, exhibit antiallergic effects, including the inhibition of histamine release, reduction of proinflammatory cytokines, and leukocyte production [64]. The mechanisms shown by these natural compounds are that: (a) polyphenols can influence the formation of the allergenic-IgE complex, and (b) polyphenols may delay the binding of this complex to its receptors [65]. Treatment with Paclitaxel can also generate hepatotoxicity; in fact, a clinical study conducted on 402 patients showed elevated bilirubin values and transaminases dysfunction [66]. Recently, an in vitro study of human breast cell lines (MCF7 and MDA-MB231) highlighted that treatment with a polyphenolic fraction of artichoke extract, together with Paclitaxel, managed not only to increase the anti-proliferative effect of the chemotherapy drug but also, at appropriate concentrations, to protect liver cells from Paclitaxel-induced hepatic toxicity [67]. Many chemotherapeutic agents, including Paclitaxel, cause chemotherapy-induced peripheral neuropathy (CIPN), leading to treatment suspension, altering the patient's quality of life and reducing the survival rate. Mechanical and thermal hypersensitivity accompany CIPN and resolves within weeks, months, or years of drug discontinuation. Because the etiology of CIPN has not been fully explained, there is currently no available preventive strategy or effective treatment. However, considerable evidence reveals that free radicals play a role in many neurodegenerative diseases, and recent research has demonstrated the importance of oxidative stress in developing CIPN targeting the overproduction of peroxynitrite for the prevention and reversal of Paclitaxel-induced neuropathic pain [68][69][70]. The bergamot polyphenolic fraction (BPF), a natural derivative antioxidant, can play a crucial role in reducing CIPN. Recent data show that Paclitaxel administration causes mechanical allodynia and thermal hyperalgesia, starting on day seven and ending on day fifteen. In addition, Paclitaxel-induced neuropathic

pain is correlated to protein nitration in the spinal cord, including MnSOD, glutamine synthetase, and the glutamate transporter GLT-1 [71]. Furthermore, some immune system cells, such as mast cells and basophils, seem to be directly involved in CIPN [72][73]. For example, histamine release from mast cells plays a fundamental role in developing thermal hyperalgesia and mechanical allodynia in mice [74]. Furthermore, as mast cells are adjacent to sensory nerves, histamine is released, and neurons participate in spinal nociceptive transmission by releasing neuromediators of pain [75]. Since quercetin, one of the polyphenolic flavonoids distributed in various plants and with biological activity, works specifically as a stabilizer of mast cells and inhibits histamine release, it has been shown that quercetin attenuates Paclitaxel-induced neuropathic pain [76].

References

1. Schwingshackl, L.; Schwedhelm, C.; Galbete, C.; Hoffmann, G. Adherence to Mediterranean Diet and Risk of Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients 2017, 9, 1063.
2. Turati, F.; Carioli, G.; Bravi, F.; Ferraroni, M.; Serraino, D.; Montella, M.; Giacosa, A.; Toffolutti, F.; Negri, E.; Levi, F.; et al. Mediterranean Diet and Breast Cancer Risk. Nutrients 2018, 10, 326.
3. Subramaniam, S.; Selvaduray, K.R.; Radhakrishnan, A.K. Bioactive Compounds: Natural Defense Against Cancer? Biomolecules 2019, 9, 758.
4. Scaria, B.; Sood, S.; Raad, C.; Khanafer, J.; Jayachandiran, R.; Pupulin, A.; Grewal, S.; Okoko, M.; Arora, M.; Miles, L.; et al. Natural Health Products (NHP's) and Natural Compounds as Therapeutic Agents for the Treatment of Cancer; Mechanisms of Anti-Cancer Activity of Natural Compounds and Overall Trends. Int. J. Mol. Sci. 2020, 21, 8480.
5. Drețcanu, G.; Iuhas, C.I.; Diaconeasa, Z. The Involvement of Natural Polyphenols in the Chemoprevention of Cervical Cancer. Int. J. Mol. Sci. 2021, 22, 8812.
6. Mahajan, R.; Attri, S.; Mehta, V.; Udayabanu, M.; Goel, G. Microbe-bio-Chemical Insight: Reviewing Interactions between Dietary Polyphenols and Gut Microbiota. Mini-Rev. Med. Chem. 2018, 18, 1253–1264.
7. Tatipamula, V.B.; Kukavica, B. Phenolic compounds as antidiabetic, anti-inflammatory, and anticancer agents and improvement of their bioavailability by liposomes. Cell Biochem. Funct. 2021, 39, 926–944.
8. Fraga, C.G.; Oteiza, P.I.; Galleano, M. Plant bioactives and redox signaling: (-)-Epicatechin as a paradigm. Mol. Aspects Med. 2018, 61, 31–40.
9. Maiuolo, J.; Gliozzi, M.; Musolino, V.; Carresi, C.; Scarano, F.; Nucera, S.; Scicchitano, M.; Oppedisano, F.; Bosco, F.; Ruga, S.; et al. The Contribution of Gut Microbiota-Brain Axis in the Development of Brain Disorders. Front. Neurosci. 2021, 15, 616883.

10. Doroszkiewicz, J.; Groblewska, M.; Mroczko, B. The Role of Gut Microbiota and Gut-Brain Interplay in Selected Diseases of the Central Nervous System. Int. J. Mol. Sci. 2021, 22, 10028.
11. Zarkovic, N. Roles and Functions of ROS and RNS in Cellular Physiology and Pathology. Cells 2020, 9, 767.
12. Taira, J. Oxidative Stress Modulators and Functional Foods. Antioxidants 2021, 10, 191.
13. Luo, J.; Mills, K.; le Cessie, S.; Noordam, R.; van Heemst, D. Ageing, age related diseases and oxidative stress: What to do next? Ageing Res. Rev. 2020, 57, 100982.
14. García, N.; Zazueta, C.; Aguilera-Aguirre, L. Oxidative Stress and Inflammation in Cardiovascular Disease. Oxid. Med. Cell Longev. 2017, 2017, 5853238.
15. Singh, A.; Kukreti, R.; Saso, L.; Kukreti, S. Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. Molecules 2019, 24, 1583.
16. Klaunig, J.E. Oxidative Stress and Cancer. Curr. Pharm. Des. 2018, 24, 4771–4778.
17. Niedzwiecki, A.; Roomi, M.W.; Kalinovsky, T.; Rath, M. Anticancer Efficacy of Polyphenols and Their Combinations. Nutrients. 2016, 8, 552.
18. Asano, T. Drug Resistance in Cancer Therapy and the Role of Epigenetics. J. Nippon Med. Sch. 2020, 87, 244–251.
19. Cui, Q.; Wang, J.Q.; Assaraf, Y.G.; Ren, L.; Gupta, P.; Wei, L.; Ashby, C.R., Jr.; Yang, D.H.; Chen, Z.S. Modulating ROS to overcome multidrug resistance in cancer. Drug Resist. Updat. 2018, 41, 1–25.
20. Kim, E.K.; Jang, M.; Song, M.J.; Kim, D.; Kim, Y.; Jang, H.H. Redox-mediated mechanism of chemoresistance in cancer cells. Antioxidants 2019, 8, 471.
21. Catalano, A.; Iacopetta, D.; Ceramella, J.; Scumaci, D.; Giuzio, F.; Saturnino, C.; Aquaro, S.; Rosano, C.; Sinicropi, M.S. Multidrug Resistance (MDR): A Widespread Phenomenon in Pharmacological Therapies. Molecules 2022, 27, 616.
22. Nani, A.; Murtaza, B.; Sayed Khan, A.; Khan, N.A.; Hichami, A. Antioxidant and Anti-Inflammatory Potential of Polyphenols Contained in Mediterranean Diet in Obesity: Molecular Mechanisms. Molecules 2021, 26, 985.
23. Heim, K.E.; Tagliaferro, A.R.; Bobilya, D.J. Flavonoid antioxidants: Chemistry, metabolism and structure-activity relationships. J. Nutr. Biochem. 2002, 13, 572–584.
24. Hashemi Sheikhshabani, S.; Amini-Farsani, Z.; Rahmati, S.; Jazaeri, A.; Mohammadi-Samani, M.; Asgharzade, S. Oleuropein reduces cisplatin resistance in ovarian cancer by targeting apoptotic pathway regulators. Life Sci. 2021, 278, 119525.

25. Geyikoğlu, F.; Çolak, S.; Türkez, H.; Bakır, M.; Koç, K.; Hosseinigouzdagani, M.K.; Çeriğ, S.; Sönmez, M. Oleuropein Ameliorates Cisplatin-induced Hematological Damages Via Restraining Oxidative Stress and DNA Injury. Indian J. Hematol. Blood Transfus. 2017, 33, 348–354.
26. Bishr, A.; Sallam, N.; Nour El-Din, M.; Awad, A.S.; Kenawy, S.A. Ambroxol attenuates cisplatin-induced hepatotoxicity and nephrotoxicity via inhibition of p-JNK/p-ERK. Can. J. Physiol. Pharmacol. 2019, 97, 55–64.
27. Crona, D.J.; Faso, A.; Nishijima, T.F.; McGraw, K.A.; Galsky, M.D.; Milowsky, M.I. A Systematic Review of Strategies to Prevent Cisplatin-Induced Nephrotoxicity. Oncologist 2017, 22, 609–619.
28. Chen, C.; Ai, Q.; Wei, Y. Hydroxytyrosol protects against cisplatin-induced nephrotoxicity via attenuating CKLF1 mediated inflammation, and inhibiting oxidative stress and apoptosis. Int. Immunopharmacol. 2021, 96, 107805.
29. Hazafa, A.; Rehman, K.U.; Jahan, N.; Jabeen, Z. The Role of Polyphenol (Flavonoids) Compounds in the Treatment of Cancer Cells. Nutr. Cancer 2020, 72, 386–397.
30. Lopez-Lazaro, M. Distribution and biological activities of the flavonoid luteolin. Mini-Rev. Med. Chem. 2009, 9, 31–59.
31. Maatouk, M.; Abed, B.; Bouhlel, I.; Krifa, M.; Khlifi, R.; Ioannou, I.; Ghedira, K.; Ghedira, L.C. Heat treatment and protective potentials of luteolin-7-O-glucoside against cisplatin genotoxic and cytotoxic effects. Environ. Sci. Pollut. Res. Int. 2020, 27, 13417–13427.
32. Wang, H.; Luo, Y.; Qiao, T.; Wu, Z.; Huang, Z. Luteolin sensitizes the antitumor effect of cisplatin in drug-resistant ovarian cancer via induction of apoptosis and inhibition of cell migration and invasion. J. Ovarian Res. 2018, 11, 93.
33. Hamdy, A.A.; Basma, G. Cisplatin induced testicular damage through mitochondria mediated apoptosis, inflammation and oxidative stress in rats: Impact of resveratrol. Endocr. J. 2020, 67, 969–980.
34. Bostan, M.; Mihaila, M.; Petrica-Matei, G.G.; Radu, N.; Hainarosie, R.; Stefanescu, C.D.; Roman, V.; Diaconu, C.C. Resveratrol Modulation of Apoptosis and Cell Cycle Response to Cisplatin in Head and Neck Cancer Cell Lines. Int. J. Mol. Sci. 2021, 22, 6322.
35. Zhu, H.; Zou, X.; Lin, S.; Hu, X.; Gao, J. Effects of naringin on reversing cisplatin resistance and the Wnt/beta-catenin pathway in human ovarian cancer SKOV3/CDDP cells. J. Int. Med. Res. 2020, 48, 300060519887869.
36. Ventura, G.J. Cardiotoxicity of epirubicin versus doxorubicin: Cost and clinical results. J. Clin. Oncol. 2005, 23, 2873.
37. Ojha, S.; Al Taee, H.; Goyal, S.; Mahajan, U.B.; Patil, C.R.; Arya, D.S.; Rajesh, M. Cardioprotective potentials of plant-derived small molecules against doxorubicin associated

cardiotoxicity, Oxidative Med. Cell. Longev. 2016, 2016, 5724973.

38. Tatlidede, E.; Sehirli, O.; Velioglu-Ogunc, A.; Cetinel, S.; Yegen, B.C.; Yarat, A.; Süleymanoğlu, S.; Şener, G. Resveratrol treatment protects against doxorubicin-induced cardiotoxicity by alleviating oxidative damage. Free Radic. Res. 2009, 43, 195–205.
39. Sharma, P.; Jha, A.B.; Dubey, R.S.; Pessarakli, M. Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. J. Bot. 2012, 2012, 26.
40. Dutta, D.; Xu, J.; Dirain, M.L.; Leeuwenburgh, C. Calorie restriction combined with resveratrol induces autophagy and protects 26-month-old rat hearts from doxorubicin-induced toxicity. Free Radic. Biol. Med. 2014, 74, 252–262.
41. Habauzit, V.; Morand, C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: An update for clinicians. Ther. Adv. Chronic Dis. 2012, 3, 87–106.
42. Zhang, S.; Liu, X.; Sun, C.; Yang, J.; Wang, L.; Liu, J.; Gong, L.; Jing, Y. Apigenin attenuates experimental autoimmune myocarditis by modulating Th1/Th2 cytokine balance in mice. Inflammation 2016, 39, 678–686.
43. Zhang, T.; Yan, T.; Du, J.; Wang, S.; Yang, H. Apigenin attenuates heart injury in lipopolysaccharide-induced endotoxemic model by suppressing sphingosine kinase1/sphingosine 1-phosphate signaling pathway. Chem. Biol. Interact. 2015, 233, 46–55.
44. Gao, A.M.; Ke, Z.P.; Wang, J.N.; Yang, J.Y.; Chen, S.Y.; Chen, H. Apigenin sensitizes doxorubicin-resistant hepatocellular carcinoma BEL-7402/ADM cells to doxorubicin via inhibiting PI3K/Akt/Nrf2 pathway. Carcinogenesis 2013, 34, 1806–1814.
45. Carresi, C.; Gliozzi, M.; Musolino, V.; Scicchitano, M.; Scarano, F.; Bosco, F.; Nucera, S.; Maiuolo, J.; Macrì, R.; Ruga, S.; et al. The Effect of Natural Antioxidants in the Development of Metabolic Syndrome: Focus on Bergamot Polyphenolic Fraction. Nutrients 2020, 12, 1504.
46. Carresi, C.; Musolino, V.; Gliozzi, M.; Maiuolo, J.; Mollace, R.; Nucera, S.; Maretta, A.; Sergi, D.; Muscoli, S.; Gratteri, S.; et al. Anti-oxidant effect of bergamot polyphenolic fraction counteracts doxorubicin-induced cardiomyopathy: Role of autophagy and c-kitposCD45negCD31neg cardiac stem cell activation. J. Mol. Cell Cardiol. 2018, 119, 10–18.
47. Aziz, T.A. Cardioprotective Effect of Quercetin and Sitagliptin in Doxorubicin-Induced Cardiac Toxicity in Rats. Cancer Manag. Res. 2021, 13, 2349–2357.
48. Farinetti, A.; Zurlo, V.; Manenti, A.; Coppi, F.; Mattioli, A.V. Mediterranean diet and colorectal cancer: A systematic review. Nutrition 2017, 43–44, 83–88.
49. Torić, J.; Marković, A.K.; Brala, C.J.; Barbarić, M. Anticancer effects of olive oil polyphenols and their combinations with anticancer drugs. Acta Pharm. 2019, 69, 461–482.

50. Sealy, N.; Hankinson, S.E.; Houghton, S.C. Olive oil and risk of breast cancer: A systematic review and dose-response meta-analysis of observational studies. Br. J. Nutr. 2021, 125, 1148–1156.

51. Ayoub, N.M.; Bakar Siddique, A.; Ebrahim, H.Y.; Mohyeldin, M.M.; El Sayed, K.A. The olive oil phenolic (−)-oleocanthal modulates estrogen receptor expression in luminal breast cancer in vitro and in vivo and synergizes with tamoxifen treatment. Eur. J. Pharmacol. 2017, 810, 100–111.

52. Xu, J.; Guo, Z.; Yuan, S.; Li, H.; Xu, J. BCL2L1 is identified as a target of naringenin in regulating ovarian cancer progression. Mol. Cell. Biochem. 2022, 477, 1541–1553.

53. Meiyanto, E.; Hermawan, A.; Anindyajati, A. Natural products for cancer-targeted therapy: Citrus flavonoids as potent chemopreventive agents. Asian Pac. J. Cancer Prev. 2012, 13, 427–436.

54. Talib, W.H.; Alsayed, A.R.; Barakat, M.; Abu-Taha, M.I.; Mahmod, A.I. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. Biomedicines 2021, 9, 1353.

55. Kumarappan, C.; Vijayakumar, M.; Thilagam, E.; Balamurugan, M.; Thiagarajan, M.; Senthil, S.; Das, S.C.; Manda, S.C. Protective and curative effects of polyphenolicextracts from Ichnocarpus frutescense leaves on experimentalhepatotoxicity by carbon tretrachloride and tamoxifen. Annal. Hepatol. 2011, 10, 63–72.

56. Sinaga, E.; Fitrayadi, A.; Asrori, A.; Rahayu, S.E.; Suprihatin, S.; Prasasty, V.D. Hepatoprotective effect of Pandanus odoratissimus seed extracts on paracetamol-induced rats. Pharm. Biol. 2021, 59, 31–39.

57. Musolino, V.; Gliozzi, M.; Bombardelli, E.; Nucera, S.; Carresi, C.; Maiuolo, J.; Mollace, R.; Paone, S.; Bosco, F.; Scarano, F.; et al. The synergistic effect of Citrus bergamia and Cynara cardunculus extracts on vascular inflammation and oxidative stress in non-alcoholic fatty liver disease. J. Tradit. Complement. Med. 2020, 10, 268–274.

58. Maiuolo, J.; Bava, I.; Carresi, C.; Gliozzi, M.; Musolino, V.; Scarano, F.; Nucera, S.; Scicchitano, M.; Bosco, F.; Ruga, S.; et al. The Effects of Bergamot Polyphenolic Fraction, Cynara cardunculus, and Olea europea L. Extract on Doxorubicin-Induced Cardiotoxicity. Nutrients 2021, 13, 2158.

59. Oppedisano, F.; Muscoli, C.; Musolino, V.; Carresi, C.; Macrì, R.; Giancotta, C.; Bosco, F.; Maiuolo, J.; Scarano, F.; Paone, S.; et al. The Protective Effect of Cynara Cardunculus Extract in Diet-Induced NAFLD: Involvement of OCTN1 and OCTN2 Transporter Subfamily. Nutrients 2020, 12, 1435.

60. De Faria, E.L.P.; Gomes, M.V.; Cláudio, A.F.M.; Freire, C.S.R.; Silvestre, A.J.D.; Freire, M.G. Extraction and recovery processes for cynaropicrin from Cynara cardunculus L. using aqueous solutions of surface-active ionic liquids. Biophys. Rev. 2018, 10, 915–925.

61. Elsebai, M.F.; Mocan, A.; Atanasov, A.G. Cynaropicrin: A Comprehensive Research Review and Therapeutic Potential as an Anti-Hepatitis C Virus Agent. Front. Pharmacol. 2016, 7, 472.
62. Beaver, C.C.; Magnan, M.A. Managing Chemotherapy Side Effects: Achieving Reliable and Equitable Outcomes. Clin. J. Oncol. Nurs. 2016, 20, 589–591.
63. Mansouri, R.; Takiguchi, Y. Monitoring the side effects of cancer chemotherapy. Nihon Rinsho. 2015, 73 (Suppl. 2), 102–106.
64. Dallavalle, S.; Dobričić, V.; Lazzarato, L.; Gazzano, E.; Machuqueiro, M.; Pajeva, I.; Tsakovska, I.; Zidar, N.; Fruttero, R. Improvement of conventional anti-cancer drugs as new tools against multidrug resistant tumors. Drug Resist. Updat. 2020, 50, 100682.
65. Oun, R.; Moussab, Y.E.; Wheate, N.J. The side effects of platinumbased chemotherapy drugs: A review for chemists. Dalton Trans. 2018, 47, 6645–6653.
66. Moghbeli, M. MicroRNAs as the critical regulators of Cisplatin resistance in ovarian cancer cells. J. Ovarian Res. 2021, 14, 127.
67. Gorini, S.; De Angelis, A.; Berrino, L.; Malara, N.; Rosano, G.; Ferraro, E. Chemotherapeutic Drugs and Mitochondrial Dysfunction: Focus on Doxorubicin, Trastuzumab, and Sunitinib. Oxid. Med. Cell Longev. 2018, 2018, 7582730.
68. Xiong, R.; Zhao, J.; Gutgesell, L.M.; Wang, Y.; Lee, S.; Karumudi, B.; Zhao, H.; Lu, Y.; Tonetti, D.A.; Thatcher, G.R. Novel Selective Estrogen Receptor Downregulators (SERDs) Developed against Treatment-Resistant Breast Cancer. J Med. Chem. 2017, 60, 1325–1342.
69. Doyle, T.; Chen, Z.; Muscoli, C.; Bryant, L.; Esposito, E.; Cuzzocrea, S.; Dagostino, C.; Ryerse, J.; Rausaria, S.; Kamadulski, A.; et al. Targeting the overproduction of peroxynitrite for the prevention and reversal of paclitaxel-induced neuropathic pain. J. Neurosci. 2012, 32, 6149–6160.
70. Rafehi, H.; Ververis, K.; Karagiannis, T.C. Mechanisms of action of phenolic compounds in olive. J. Diet. Suppl. 2012, 9, 96–109.
71. Malafoglia, V.; Tenti, M.; Ilari, S.; Balzani, E.; Fanelli, A.; Muscoli, C.; Raffaeli, W.; Bonci, A. Opportunities and challenges for nonaddictive interventions in chronic pain. Curr. Opin. Pharmacol. 2021, 57, 184–191.
72. Lauro, F.; Giancotti, L.A.; Ilari, S.; Dagostino, C.; Gliozzi, M.; Morabito, C.; Malafoglia, V.; Raffaeli, W.; Muraca, M.; Goffredo, B.M.; et al. Inhibition of Spinal Oxidative Stress by Bergamot Polyphenolic Fraction Attenuates the Development of Morphine Induced Tolerance and Hyperalgesia in Mice. PLoS ONE 2016, 11, e0156039.
73. Mileo, A.M.; Di Venere, D.; Mardente, S.; Miccadei, S. Artichoke Polyphenols Sensitize Human Breast Cancer Cells to Chemotherapeutic Drugs via a ROS-Mediated Downregulation of Flap Endonuclease 1. Oxid. Med. Cell Longev. 2020, 2020, 7965435.

74. Chen, L.; Alam, A.; Pac-Soo, A.; Chen, Q.; Shang, Y.; Zhao, H.; Yao, S.; Ma, D. Pretreatment with valproic acid alleviates pulmonary fibrosis through epithelial-mesenchymal transition inhibition in vitro and in vivo. Lab. Invest. 2021, 101, 1166–1175.
75. Bartsch, R. Trastuzumab-deruxtecan: An investigational agent for the treatment of HER2-positive breast cancer. Expert Opin. Investig. Drugs 2020, 29, 901–910.
76. Carthy, E.; Ellender, T. Histamine, Neuroinflammation and Neurodevelopment: A Review. Front. Neurosci. 2021, 15, 680214.