Activity of Natural Carboxylic Acids

Subjects: Food Science & Technology | Nutrition & Dietetics

Contributor: Aleksandra Golonko, Beata Godlewska-Żyłkiewicz, Świsłocka Renata, Monika Kalinowska, Świderski Grzegorz, Edyta Nalewajko-Sieliwoniuk, MONIKA NAUMOWICZ, Wlodzimierz Lewandowski

Natural carboxylic acids described in this paper are plant-derived compounds having biological activity. The aim of this review is to summarize and evaluate the physicochemical properties of selected compounds naturally occurring in plants, their potential of microbiological and anticancer activity. In order to create targeted modifications of the structure enhancing its activity, it is; therefore, necessary to thoroughly understand the mechanisms of action of a given molecule under systemic conditions.

Keywords: phenolic acids ; natural carboxylic acids ; structure-activity relationship ; hydroxyl groups ; antibacterial ; antioxidant ; cytotoxic activity

1. Introduction

The chemical structures of the reviewed natural carboxylic acids are presented in Figure 1. Benzoic acid (BA) is the simplest aromatic monocarboxylic acid comprising a benzene ring core with a carboxylic acid substituent. Cinnamic acid (CinA) ((E)--3-phenylprop-2-enoic acid) is an unsaturated monocarboxylic acid comprising an acrylic acid bearing a phenyl substituent at the 3-position. It occurs as both *cis* and *trans* isomer, although the *trans* form is more common. It is a precursor for the synthesis of a huge number of other more complex phenolic compounds. *p*-coumaric acid (p-CA) (4-hydroxycinnamic acid) is one of the three hydroxyl derivatives of cinnamic acid that differ by the position of the hydroxy substitution of the phenyl group. Caffeic acid (CFA) ((E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid, 3,4-dihydroxycinnamic acid) is also a hydroxyl derivative of CinA in which the phenyl ring is substituted by hydroxyl groups at positions 3 and 4. It exists in *cis* and *trans* forms, although the latter is more common. CFA is the building block of a variety of the plant metabolites from the simple monomers to multiple condensation products giving a variety of caffeic acid derivatives. Rosmarinic acid (RA) is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid and its chemical structure contains five hydroxyl groups. Chicoric acid (ChA) (also known as cichoric acid) ((2*R*,3*R*)-2,3-bis[[(E)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]oxy]butanedioic acid) is a tartaric acid ester of two caffeic acids. It possesses six hydroxyl groups in the structure; its most abundant natural form is L-chicoric acid.

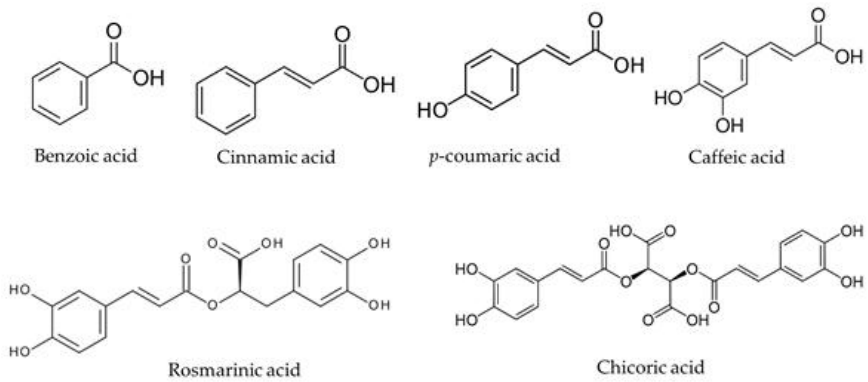

Figure 1. Chemical structures of reviewed natural carboxylic acids (NCA): benzoic acid (BA), cinnamic acid (CinA), *p*-coumaric acid (*p*-CA), caffeic acid (CFA), rosmarinic acid (RA), and chicoric acid (ChA).

Natural carboxylic acids can be found in all plant tissues, including edible parts such as fruits, seeds, leaves, stems, and roots. BA and CinA are naturally present in fruits, vegetables, nuts, herbs, spices, as well as fungal and animal tissues. BA can be also produced by microorganisms during food processing. *Cinnamomum cassia* (L.) J. Presl–called chinese cinnamon-is the richest natural sources of BA (0.336 mg/g) and CinA (0.01–1.91 mg/g) [1]. The content of BA in sage (*Salvia officinalis*), thyme (*Thymus vulgaris*), and nutmeg is in the range of 0.015–0.05 mg/g. Other spices, such as turmeric, coriander, laurel, paprika, and white and black pepper contain lower amounts of this compound (0.001–0.005 mg/g) [2]. CinA can be also found in citrus fruits, grapes, tea, cocoa, spinach, celery, and brassicas vegetables [3]. Phenolic

acids, such as *p*-coumaric, caffeic, and rosmarinic acids occur in small amounts in almost all green plants: fruits, vegetables, herbs, grains, and mushrooms. They are frequently present in herbs and spices, such as rosemary, thyme, oregano, sage, cinnamon, cumin, and bay. *p*-CA serves as a precursor of other phenolic compounds and exists either in free or conjugated forms in plants. It forms conjugates with mono-, oligo-, and polysaccharides, alkyl alcohols, organic acids, amine, and lignin. The content of free *p*-CA is very high in some mushroom species (traditional Chinese medicines) and vary from several milligrams per gram to nearly a thousand times higher than that in fruits and herbs [4][5]. The level of *p*-CA determined in cinnamon, thyme, oregano, and rosemary was in the range 0.0022–0.0096 mg/g of dry weight (DW). CFA is widely distributed in plant tissues. Coffee is the primary source of CFA in the human diet. Other edible plants that have been found to contain CFA include sweet potatoes and artichoke. This polyphenol is present in many other food sources, including blueberries, apples and cider, olive oil, and many culinary herbs: caraway, thyme, oregano, and rosemary. The high content of CFA and *p*-CA was found in sage (1.215 mg/g DW) and oregano (2.148 mg/g DW) [6]. Lower amounts are present in bay, marjoram, and cinnamon [7]. RA is naturally occurring in several plants of the Lamiaceae family, including rosemary, from which it was originally isolated, sage and Spanish sage, basil, oregano, marjoram, and lemon balm. In lower amounts it was found in bay, cinnamon, and cumin [8]. ChA is most often reported in the family *Asteraceae* (Aster family), or the family *Dryopteridaceae* (Wood fern family). *Cichorium intybus* and *Echinacea purpurea* (L.) *Moench.* are well-known for their ChA production. But it was identified also in other plants (25 families, 63 genera and species) [9].

2. Antimicrobial Properties of NCA

NCA have proven antimicrobial and antioxidant effects, which is why some of them have found application in food preservation, for example benzoic acid (E210), which occurs naturally in cranberry or cinnamon and propyl gallate (E310) synthesized from propanol and gallic acid. The antimicrobial potential of phenolic acids is associated with their chemical structure and depends on the number of hydroxyl (-OH) and methoxy (-OCH_3) groups [10]. As antimicrobial compounds, they are often described as weak organic acids that diffuse across the cell membrane, acidify the cytoplasm and lead to cell death [11]. Therefore, pKa and lipophilicity are important parameters in the initial assessment of their bactericidal properties [10]. For example, caffeic acid as a hydroxycinnamic acid has a propene side chain, which makes it much less polar than, for example, protocatechuic acid. Therefore, caffeic acid as a less polar compound also exhibits higher lipophilicity, which may contribute to increase of cell membrane permeability [12] (Figure 2).

In studies conducted by Stojković et al. [13] it was observed that phenolic compounds such as caffeic acid, *p*-coumaric acid, and also rutin retain their antioxidant properties in situ in food. Among the mentioned acids, caffeic inhibited the growth to the greatest extent of *Staphylococcus aureus* developing in a food product. Analysing the antimicrobial activity of phenolic acids, it was found that hydroxycinnamic acids have comparable or better properties than hydroxybenzoic acids with the same number of hydroxyl groups. In addition, the antibacterial properties of hydroxybenzoic acids decrease as the number of -OH groups increases [13]. It was also observed that the longer side chains in the alkyl esters of caffeic acid showed better activity against Gram-positive bacteria, and the average chain length determined better activity against Gram-negative bacteria. The activity of the esters formed is directly related to lipophilicity, which affects the sensitivity of bacteria, the physicochemical properties of the bacteria and the integrity of cell membranes [14]. Generally, the structure of the cell wall of Gram-positive bacteria allows the penetration of hydrophobic molecules into the cell, while the membrane surrounding the wall of Gram-negative bacteria is virtually impermeable to them. Small hydrophilic compounds are able to penetrate the transmembrane channels; however, Gram-negative bacteria are usually more resistant to the action of antibiotics and hydrophobic toxins [15]. Higher lipophilicity enables the penetration of the acid molecule through the cell wall and membrane, where it disrupts the structure of individual layers of lipopolysaccharides, fatty acids and phospholipids and permeabilize them.

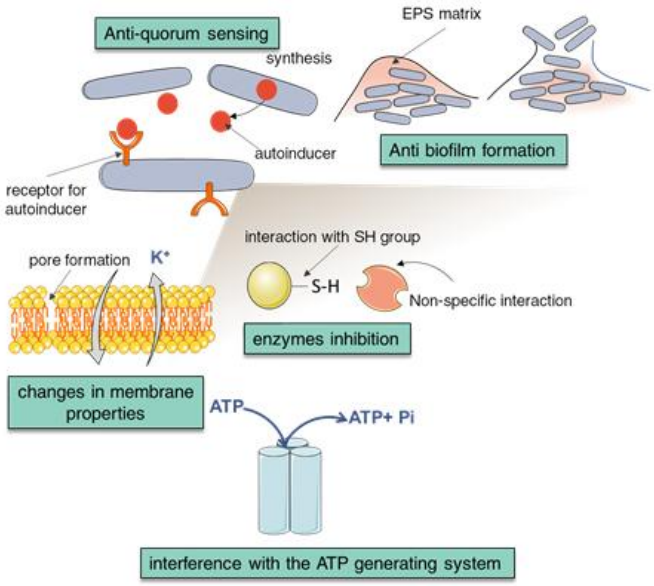

Figure 2. Selected mechanism of antimicrobial action of plant-derived carboxylic acids. [Based on [16]] Anti-quorum sensing. The quorum-sensing communication system can be inhibited in several different ways: Inhibition of autoinducers synthesis and transport, antagonist activity for autoinducers-receptors, and also direct reaction or inhibition of autoinducer activity. Changes in membrane properties. Phenolic acids (especially hydrophobic compounds) affect the properties of cell membranes (charge, permeability) through changes in hydrophobicity, reduction of negative surface charge, and the formation of pores in the membranes and leakage of intracellular components [17][18]. Anti-biofilm formation. Limiting the formation of biofilm by phenolic acids involves limiting cell adhesion to the surface and inhibiting biofilm maturation, indirectly through anti-quorum sensing action and inhibition of the expression of genes involved in biofilm formation [19][20]. Interference with the ATP generating system. Phenolic acids, by increasing the permeability of cell membranes, leak ions and partially inhibit the activity of ATPase [21] and other proteins, including enzymatic (enzymes inhibition). Acids with strong nucleophilic properties (e.g., CA) can donate an electron pair to electrophilic functional group of plasma membrane proteins and lipids leading to the membrane destabilization [22].

3. Anticancer Activity of NCA

For many years, natural compounds of plant origin were the main source of oncological drugs, which over time underwent the necessary structural modifications to enhance their activity, bioavailability, and specificity [23][24]. Although experimental studies in cell or animal models have shown a positive relationship between the presence of phenolic compounds of natural origin and inhibiting the development of cancer cells, it is very difficult to extrapolate the results of these studies to cancer prevention or therapy in humans. One reason is that studies are often carried out at doses or concentrations far beyond those that can be achieved in patients. Available literature on the beneficial effects of polyphenols in human diets is based on in vitro or animal model experiments, but at concentrations far above those available in food sources. Mainly aglycons or conjugated forms are studied, most often without taking into account the active forms of metabolites, which does not provide complete information on the activity of these compounds in the body [25].

In population studies, Russo et al. [26] observed a relationship between the consumption of phenolic acids and the risk of developing prostate cancer. It turned out that patients consumed less caffeic and ferulic acid than healthy men (CA: 2.28 Vs. 2.76 mg/day, ferulic acid: 2.80 Vs. 4.04 mg/day). This may suggest that a sufficient level of phenolic acids in the diet reduces the risk of developing prostate cancer. The effect of phenolic acid depends on the type of cancer. High and moderate coffee consumption, up to 5 cups a day, appears to be associated with significantly smaller sizes of oestrogen receptor alpha positive (ER+) invasive breast cancer, but no significant association with ER-type cancers was observed. In vitro tests have shown that exposure to caffeic acid is followed by a 50% reduction in MCF-7 cell proliferation and a 30% decrease in IGFIR levels. In addition, women with ER+ tumours drinking more than two cups of coffee a day during tamoxifen therapy showed reduced cancer recurrence compared to patients with low daily coffee intake [27]. Therapeutical potential of plant phenolic acids in prostate and breast cancer was also described, inter alia, in [28][29][30] and in recent review published by Abotaleb et al. [31]. In addition, caffeic acid has the property of reducing the mutagenic potential of sodium azide or nitrofurylacrylic acid by 20–35% [32]. Chicoric acid had no antimutagenic effect. It al4so prevents chromosomal aberrations and doxorubicin-induced cardiotoxicity in rats [33][34]. The rosmarinic acid also has an interesting profile of anti-cancer properties. Zhang et al. [35] observed that RA induces apoptosis and inhibits the migration of ovarian

cancer cells and modulates the expression of Malat-1–long non-coding RNA associated with,among other, tumour metastasis. Other in vivo studies in xenograft mice indicate that RA also inhibits the growth of such pancreatic cells, where it increases expression of miR-506 while inhibiting MMP2/16 and Ki-67 [36].

Natural carboxylic acids, especially phenolic acids, are most often described in the context of antioxidant properties, but the mechanism of their action is very wide, not limited to reducing ROS. Small molecules can interact with receptors, nucleic acids and proteins that act as transcription factors and enzymes (Figure 3).

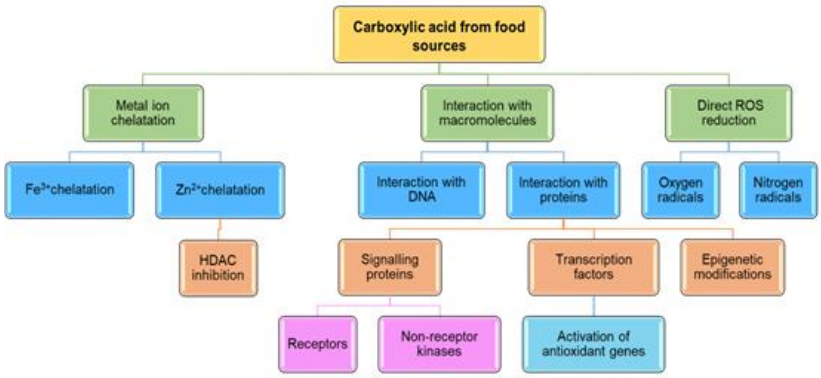

Figure 3. Selected molecular mechanisms of action of carboxylic acids from food sources. (HDAC—histone deacetylase).

Therefore, these compounds affect signal transduction pathways (e.g., redox sensitive Keap1/Nrf2/ARE system) and modifications of the chromatin structure, thus regulating gene expression, including those whose products are proteins involved in antioxidative defence and cell cycle regulation [37]. It has been proved that cinnamic acids, especially dihydroxycinnamic (caffeic) acid, have the ability to interact with HDAC2 (histone deacetylase 2), inhibiting its activity ex vivo and in vitro and inducing apoptosis of colon and cervical cancer cells [38]. It is worth noting that HDAC inhibitors are known potential anti-cancer drugs, among which there are inhibitors with a high affinity for zinc ions located in active deacetylase centres (e.g., hydroxamic acid and compounds having a benzamide group [39][40]. Due to the fact that carboxylic acid derivatives, also phenolic acids, possess chelating properties of metal ions (also Zn^{2+}), they are potential HDAC inhibitors, which was confirmed by in silico and in vitro tests [41].

In the prevention of colon cancer, a large role is played by the products of the metabolism of the intestinal microbiome, which in addition to butyric acid and short-chain fatty acids are phenolic acids, e.g., *trans*-cinnamic acid formed in the process of deamination of phenylalanine [42]. The products of microbiome metabolism often have much better health-promoting properties than parent compounds, and in most cases biotransformation by microflora is necessary to ensure the bioavailability of phenolic acids. Only part of the phenolic compounds consumed in the form of glycosides is hydrolysed and absorbed in the small intestine. Ultimately, they undergo metabolism in the liver to conjugate forms—sulphates or glucuronides. Non-absorbed glycosides pass into the colon, where they are metabolized by the intestinal microbiome (e.g., flavonoids combined with rhamnose are hydrolysed by α-rhamnosidases produced by *Bifidobacterium dentium* [43][44]. Hence the final effect caused by phenolic acids in the body will depend on the content of phenolic compounds in food, their chemical form and the composition of the intestinal microflora. Although the activity of these acids is low compared to conventional inhibitors, this result indicates that the metabolic product of microorganisms inhabiting the gastrointestinal tract has antitumor potential. In studies published by Zhu et al. [45], it was noted that the administration of *trans*-cinnamic acid to rodents at a concentration of 1 and 1.5 mmol/kg body weight inhibited the growth of colon cancer xenografts, and the mechanism of action of this compound was partly due to HDAC inhibition in cancer cells. Phenolic acids also have direct antioxidant potential, protecting, among others before lipid peroxidation building biological membranes. Cancer cells are often characterized by elevated levels of ROS compared to healthy cells, but due to the inadequate bioavailability of phenolic compounds, their antioxidant intra-systemic activity is controversial.

Studies of Zambonin et al. [46] showed that phenolic acids (caffeic, syringic, and protocatechuic) reduce ROS and act antiproliferative and proapoptotic in leukaemia (HEL) cell lines, without causing any (antioxidant and toxic) effect on healthy cells (HUVEC). According to Wang and Yi [47] there are two opposing cancer therapy strategies based on the redox status of cancer cells. On the one hand, antioxidant therapy can effectively inhibit cell proliferation and neovascularization, which is a process in which free radicals participate, and also prevent the accumulation of mutations leading to genomic instability. At the same time, pro-oxidative therapy aimed at sufficiently increasing the concentration of free radicals in cancer cells may be a signal of initiation of apoptosis [48]. The biological properties of phenolic phytochemicals depend; however, on the amount of metabolized compound and the concentration obtained in the body. Ferulic and caffeic acids-the most common phenolic acids, after absorption undergo intensive metabolic processes, and some of these metabolites still retain strong antioxidant properties in vivo. In human plasma, both acids occur almost

exclusively as conjugated forms—glucoronates and sulphates, and in addition synergistic effects in the presence of other products of metabolic processes are not excluded [49]. These compounds can also act indirectly on the reduction of free radicals by stimulating the synthesis of antioxidant enzymes—SOD (superoxide dismutase), CAT (catalase), and GPx (glutathione peroxidase) [50][51].

4. Summary

In this review, we analysed the physicochemical and biological properties of the natural carboxylic acids series naturally occurring in aromatic plants and spices—benzoic acid, cinnamic acid, and its hydroxyl derivatives (*p*-coumaric and caffeic acids)—and selected esters (rosmarinic and chicoric acids). Cinnamic acid is a precursor for the synthesis of various derivatives having hydroxyl groups as well as different esters. An example of such compounds are chicoric acid (a derivative of caffeic and tartaric acid) and rosmarinic acid (an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid). An additional hydroxyl groups and two carboxyl groups of the tartaric moiety present in the structure of chicoric acid may improve its solubility and chelating capacity.

In the case of antimicrobial properties, structure-activity relationships are not easy to observe as they closely depend on the experimental conditions and the microbial strain. There are a lot of mechanisms in the case of antibacterial action: From lowering the pH of the cytosol, chelating essential transition metal ions, disrupting quorum-sensing intercellular communication, to disturbing the integrity of cell membranes and efflux of cytoplasmic constituents and release of intracellular K^+ ions (Figure 2). Phenolic acids also inhibit the activity of bacterial enzymes, disrupting their metabolism and depriving the substrates necessary for growth. In the case of hydroxycinnamic acids, a higher ion leakage and a greater influx of protons into the cells is observed than in hydroxybenzoic acids [52].

Current reports on the anti-cancer properties of phenolic acids focus on explaining the mechanism of their action. It was found, inter alia, that acids, in addition to their anti-radical activity, can bind to specific cellular proteins, acting as inhibitors (e.g., inhibition of MAPK4 by rosmarinic acid in cancer cells [53] or inhibition of phosphatase in pathogenic bacteria YopH by chicoric acid on the basis of allosteric inhibition [54]). Some processes are closely related and ROS-dependent signalling pathways are particularly sensitive to the presence of antioxidants as phenolic acids [55]. It seems that hydroxyl groups are particularly important, not only in the reduction of free radicals, but also in intermolecular interactions and shaping the cytotoxic potential, while the carboxyl group participates in the chelation of endogenous transition metal ions acting as, for example, HDAC inhibitors [39]. The studies conducted in the biological systems are extremely important, as other constituents present is biological environment may influence the stability and activity of such compounds.

References

1. † Zhen-Dan He; † Chun-Feng Qiao; † Quan-Bin Han; † Chuen-Lung Cheng; † Hong-Xi Xu; ‡ Ren-Wang Jiang; ‡ Paul Pui-Hay But; ‡ Pang-Chui Shaw; Authentication and Quantitative Analysis on the Chemical Profile of Cassia Bark (Cortex Cinnamomi) by High-Pressure Liquid Chromatography. *Journal of Agricultural and Food Chemistry* **2005**, *53*, 2424-2428, 10.1021/jf048116s.
2. Ana Del Olmo; Javier Calzada; Manuel Nuñez; Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: Uses, exposure, and controversy. *Critical Reviews in Food Science and Nutrition* **2015**, *57*, 3084-3103, 10.1080/10408398.2015.1087964.
3. Juan David Guzman; Natural Cinnamic Acids, Synthetic Derivatives and Hybrids with Antimicrobial Activity. *Molecules* **2014**, *19*, 19292-19349, 10.3390/molecules191219292.
4. Kehan Pei; Juanying Ou; Junqing Huang; Shiyi Ou; p-Coumaric acid and its conjugates: dietary sources, pharmacokinetic properties and biological activities. *Journal of the Science of Food and Agriculture* **2016**, *96*, 2952-2962, 10.1002/jsfa.7578.
5. A Wojdylo; J Oszmianski; R Czemerys; Antioxidant activity and phenolic compounds in 32 selected herbs. *Food Chemistry* **2007**, *105*, 940-949, 10.1016/j.foodchem.2007.04.038.
6. Bin Shan; Yizhong Z. Cai; Mei Sun; Harold Corke; Antioxidant Capacity of 26 Spice Extracts and Characterization of Their Phenolic Constituents. *Journal of Agricultural and Food Chemistry* **2005**, *53*, 7749-7759, 10.1021/jf051513y.
7. Caroline Magnani; V. L. B. Isaac; M. A. Correa; Hérida Regina Nunes Salgado; Caffeic acid: a review of its potential use in medications and cosmetics. *Analytical Methods* **2014**, *6*, 3203-3210, 10.1039/c3ay41807c.
8. Anna Vallverdú-Queralt; Jorge Regueiro; Miriam Martínez-Huélamo; José Fernando Rinaldi Alvarenga; Leonel Neto Leal; Rosa Lamuela-Raventós; A comprehensive study on the phenolic profile of widely used culinary herbs and

spices: Rosemary, thyme, oregano, cinnamon, cumin and bay. *Food Chemistry* **2014**, *154*, 299-307, 10.1016/j.foodchem.2013.12.106.

9. Jungmin Lee; Carolyn F. Scagel; Chicoric acid: chemistry, distribution, and production. *Frontiers in Chemistry* **2013**, *1*, 1-17, 10.3389/fchem.2013.00040.
10. Naresh Kumar; Nidhi Goel; Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnology Reports* **2019**, *24*, e00370, 10.1016/j.btre.2019.e00370.
11. Irvin N. Hirshfield; Stephanie Terzulli; Conor O'byrne; Weak Organic Acids: A Panoply of Effects on Bacteria. *Science Progress* **2003**, *86*, 245-270, 10.3184/003685003783238626.
12. Małgorzata Kępa; Maria Miklasińska-Majdanik; Robert Dariusz Wojtyczka; Danuta Idzik; Konrad Korzeniowski; Joanna Smoleń-Dzirba; Tomasz J. Wąsik; Antimicrobial Potential of Caffeic Acid againstStaphylococcus aureusClinical Strains. *BioMed Research International* **2018**, *2018*, 1-9, 10.1155/2018/7413504.
13. Dejan Stojković; Jovana Petrović; Marina Soković; Jasmina Glamočlija; Jelena Kukić-Marković; Silvana Petrović; In situantioxidant and antimicrobial activities of naturally occurring caffeic acid,p-coumaric acid and rutin, using food systems. *Journal of the Science of Food and Agriculture* **2013**, *93*, 3205-3208, 10.1002/jsfa.6156.
14. Mafalda Andrade; Sofia Benfeito; Pedro Soares; Diogo Magalhães E Silva; Joana Loureiro; Anabela Borges; Fernanda Borges; Manuel Simões; Fine-tuning of the hydrophobicity of caffeic acid: studies on the antimicrobial activity against Staphylococcus aureus and Escherichia coli. *RSC Advances* **2015**, *5*, 53915-53925, 10.1039/c5ra05840f.
15. Filomena Nazzaro; Florinda Fratianni; Laura De Martino; Raffaele Coppola; Vincenzo De Feo; Effect of Essential Oils on Pathogenic Bacteria. *Pharmaceuticals* **2013**, *6*, 1451-1474, 10.3390/ph6121451.
16. Lynda Bouarab-Chibane; Valérian Forquet; Pierre Lantéri; Yohann Clément; Lucie Léonard-Akkari; Nadia Oulahal; Pascal Degraeve; Claire Bordes; Antibacterial Properties of Polyphenols: Characterization and QSAR (Quantitative Structure–Activity Relationship) Models. *Frontiers in Microbiology* **2019**, *10*, 829, 10.3389/fmicb.2019.00829.
17. Anabela Borges; Carla Ferreira; Maria J. Saavedra; Manuel Simões; Antibacterial Activity and Mode of Action of Ferulic and Gallic Acids Against Pathogenic Bacteria. *Microbial Drug Resistance* **2013**, *19*, 256-265, 10.1089/mdr.2012.0244.
18. Omar Aldulaimi; General overview of phenolics from plant to laboratory, good antibacterials or not. *Pharmacognosy Reviews* **2017**, *11*, 123-127, 10.4103/phrev.phrev_43_16.
19. Lívia Slobodníková; Silvia Fialová; Katarína Rendeková; Ján Kováč; Pavel Mučaji; Antibiofilm Activity of Plant Polyphenols. *Molecules* **2016**, *21*, 1-15, 10.3390/molecules21121717.
20. Naybi Muñoz-Cazares; Rodolfo García-Contreras; Macrina Pérez- López; Israel Castillo-Juárez; Phenolic Compounds with Anti-virulence Properties. *Phenolic Compounds - Biological Activity* **2017**, *March*, 139-167, 10.5772/66367.
21. E. Rico-Munoz; E.E. Bargiota; P.M. Davidson; Effect of selected phenolic compounds on the membrane-bound adenosine triphosphatase of Staphylococcus aureus. *Food Microbiology* **1987**, *4*, 239-249, 10.1016/0740-0020(87)90006-2.
22. Maria Miklasińska-Majdanik; Małgorzata Kępa; Robert D. Wojtyczka; Danuta Idzik; Tomasz J. Wąsik; Phenolic Compounds Diminish Antibiotic Resistance of Staphylococcus Aureus Clinical Strains-18. *International Journal of Environmental Research and Public Health* **2018**, *15*, 1-18, 10.3390/ijerph15102321.
23. Marei Sammar; Basheer Abu-Farich; Ibrahim Rayan; Mizied Falah; Anwar Rayan; Correlation between cytotoxicity in cancer cells and free radical-scavenging activity: In﷿vitro evaluation of 57 medicinal and edible plant extracts. *Oncology Letters* **2019**, *18*, 6563-6571, 10.3892/ol.2019.11054.
24. Shao-Xing Dai; Wen-Xing Li; Fei-Fei Han; Yi-Cheng Guo; Jun-Juan Zheng; Jia-Qian Liu; Qian Wang; Yue-Dong Gao; Gong-Hua Li; Jing-Fei Huang; et al. In silico identification of anti-cancer compounds and plants from traditional Chinese medicine database. *Scientific Reports* **2016**, *6*, 1-11, 10.1038/srep25462.
25. Massimo D'Archivio; Carmelina Filesi; Rosaria Varì; Beatrice Scazzocchio; Roberta Masella; Bioavailability of the Polyphenols: Status and Controversies. *International Journal of Molecular Sciences* **2010**, *11*, 1321-1342, 10.3390/ijms11041321.
26. Giorgio I. Russo; Daniele Campisi; Marina Di Mauro; Federica Regis; Giulio Reale; Marina Marranzano; Rosalia Ragusa; Tatiana Solinas; Massimo Madonia; Sebastiano Cimino; et al. Dietary Consumption of Phenolic Acids and Prostate Cancer: A Case-Control Study in Sicily, Southern Italy. *Molecules* **2017**, *22*, 2159, 10.3390/molecules221221599.
27. Ann H Rosendahl; Claire Perks; L. Zeng; Andrea Markkula; Maria Simonsson; Carsten Rose; Christian Ingvar; Jeff M. P. Holly; Helena Jernström; Caffeine and Caffeic Acid Inhibit Growth and Modify Estrogen Receptor and Insulin-like Growth Factor I Receptor Levels in Human Breast Cancer. *Clinical Cancer Research* **2015**, *21*, 1877-1887, 10.1158/1078-0432.ccr-14-1748.

28. Davaasambuu Ganmaa; Walter C. Willett; Tricia Y. Li; Diane Feskanich; Rob M. Van Dam; Esther Lopez-Garcia; David J. Hunter; Michelle D. Holmes; Coffee, tea, caffeine and risk of breast cancer: A 22-year follow-up. *International Journal of Cancer* **2008**, *122*, 2071-2076, 10.1002/ijc.23336.

29. Gianfranco Alicandro; Alessandra Tavani; Carlo La Vecchia; Coffee and cancer risk. *European Journal of Cancer Prevention* **2017**, *26*, 424-432, 10.1097/cej.0000000000000341.

30. Siv Kjølsrud Bøhn; Rune Blomhoff; Ingvild Paur; Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. *Molecular Nutrition & Food Research* **2013**, *58*, 915-930, 10.1002/mnfr.201300526.

31. Mariam Abotaleb; Alena Liskova; Peter Kubatka; Dietrich Büsselberg; Therapeutic Potential of Plant Phenolic Acids in the Treatment of Cancer. *Biomolecules* **2020**, *10*, 221, 10.3390/biom10020221.

32. Lucia Birosova; Maria Mikulasova; Stefania Vaverkova; ANTIMUTAGENIC EFFECT OF PHENOLIC ACIDS. *Biomedical Papers* **2005**, *149*, 489-491, 10.5507/bp.2005.087.

33. Ersin Fadillioglu; Emin Oztas; Hasan Erdogan; Murat Yagmurca; Sadik Sogut; Muharrem Ucar; M Kemal Irmak; Protective effects of caffeic acid phenethyl ester on doxorubicin-induced cardiotoxicity in rats. *Journal of Applied Toxicology* **2004**, *24*, 47-52, 10.1002/jat.945.

34. Denise Crispim Tavares; Walclécio Lira; Camila Santini; Catarina Satie Takahashi; Jairo Bastos; Effects of Propolis Crude Hydroalcoholic Extract on Chromosomal Aberrations Induced by Doxorubicin in Rats. *Planta Medica* **2007**, *73*, 1531-1536, 10.1055/s-2007-993737.

35. Yan Zhang; Min Hu; Liu Liu; Xiao-Ling Cheng; Jing Cai; Jian Zhou; Tao Wang; Anticancer effects of Rosmarinic acid in OVCAR-3 ovarian cancer cells are mediated via induction of apoptosis, suppression of cell migration and modulation of lncRNA MALAT-1 expression.. *Journal of B.U.ON. : official journal of the Balkan Union of Oncology* **2018**, *23*, 763-768, .

36. Yongguang Han; Ligang Ma; Le Zhao; Weisheng Feng; Xiaoke Zheng; Rosmarinic inhibits cell proliferation, invasion and migration via up-regulating miR-506 and suppressing MMP2/16 expression in pancreatic cancer. *Biomedicine & Pharmacotherapy* **2019**, *115*, 108878, 10.1016/j.biopha.2019.108878.

37. Ergul Belge Kurutas; The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutrition Journal* **2015**, *15*, 1-22, 10.1186/s12937-016-0186-5.

38. Preethi G. Anantharaju; Deepa B. Reddy; Mahesh A. Padukudru; Ch. M. Kumari Chitturi; Manjunath G. Vimalambike; SubbaRao V. Madhunapantula; Induction of colon and cervical cancer cell death by cinnamic acid derivatives is mediated through the inhibition of Histone Deacetylases (HDAC). *PLoS ONE* **2017**, *12*, e0186208, 10.1371/journal.pone.0186208.

39. Lei Zhang; Jian Zhang; Qixiao Jiang; Weiguo Song; Zinc binding groups for histone deacetylase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry* **2018**, *33*, 714-721, 10.1080/14756366.2017.1417274.

40. Edward Seto; Minoru Yoshida; Erasers of Histone Acetylation: The Histone Deacetylase Enzymes. *Cold Spring Harbor Perspectives in Biology* **2014**, *6*, 1-26, 10.1101/cshperspect.a018713.

41. Gamze Bora-Tatar; Didem Dayangaç-Erden; Ayhan S. Demir; Sevim Dalkara; Kemal Yelekçi; Hayat Erdem-Yurter; Molecular modifications on carboxylic acid derivatives as potent histone deacetylase inhibitors: Activity and docking studies. *Bioorganic & Medicinal Chemistry* **2009**, *17*, 5219-5228, 10.1016/j.bmc.2009.05.042.

42. Markus Waldecker; Tanja Kautenburger; Heike Daumann; Cordula Busch; Dieter Schrenk; Inhibition of histone-deacetylase activity by short-chain fatty acids and some polyphenol metabolites formed in the colon. *The Journal of Nutritional Biochemistry* **2008**, *19*, 587-593, 10.1016/j.jnutbio.2007.08.002.

43. Giulio Maria Pasinetti; Risham Singh; Susan Westfall; Francis Herman; Jeremiah Faith; Lap Ho; The Role of the Gut Microbiota in the Metabolism of Polyphenols as Characterized by Gnotobiotic Mice. *Journal of Alzheimer's Disease* **2018**, *63*, 409-421, 10.3233/jad-171151.

44. Sumanto Haldar; Sze Han Lee; Jun Jie Tan; Siok Ching Chia; Christiani Jeyakumar Henry; Eric Chun Yong Chan; Dose-Dependent Increase in Unconjugated Cinnamic Acid Concentration in Plasma Following Acute Consumption of Polyphenol Rich Curry in the Polyspice Study. *Nutrients* **2018**, *10*, 934, 10.3390/nu10070934.

45. Bingyan Zhu; Boyang Shang; Yi Li; Yongsu Zhen; Inhibition of histone deacetylases by trans-cinnamic acid and its antitumor effect against colon cancer xenografts in athymic mice. *Molecular Medicine Reports* **2016**, *13*, 4159-4166, 10.3892/mmr.2016.5041.

46. Laura Zambonin; Cristiana Caliceti; Francesco Vieceli Dalla Sega; Diana Fiorentini; Silvana Hrelia; Laura Landi; Cecilia Prata; Dietary Phenolic Acids Act as Effective Antioxidants in Membrane Models and in Cultured Cells, Exhibiting Proapoptotic Effects in Leukaemia Cells. *Oxidative Medicine and Cellular Longevity* **2012**, *2012*, 1-12, 10.1155/2012/839298.

47. Jie Wang; Jing Yi; Cancer cell killing via ROS: To increase or decrease, that is the question. *Cancer Biology & Therapy* **2008**, *7*, 1875-1884, 10.4161/cbt.7.12.7067.
48. Muhammad Hassan Raza; Sami Siraj; Abida Arshad; Usman Waheed; Fahad Aldakheel; Shatha Alduraywish; Muhammad Arshad; ROS-modulated therapeutic approaches in cancer treatment. *Journal of Cancer Research and Clinical Oncology* **2017**, *143*, 1789-1809, 10.1007/s00432-017-2464-9.
49. A. Piazzon; U. Vrhovsek; D. Masuero; F. Mattivi; F. Mandoj; M. Nardini; Antioxidant Activity of Phenolic Acids and Their Metabolites: Synthesis and Antioxidant Properties of the Sulfate Derivatives of Ferulic and Caffeic Acids and of the Acyl Glucuronide of Ferulic Acid. *Journal of Agricultural and Food Chemistry* **2012**, *60*, 12312-12323, 10.1021/jf304076z.
50. Silvio José Valadão Vicente; Emília Yasuko Ishimoto; Robison José Cruz; Camilo D. Seabra Pereira; Elizabeth A. F. Da S. Torres; Increase of the Activity of Phase II Antioxidant Enzymes in Rats after a Single Dose of Coffee. *Journal of Agricultural and Food Chemistry* **2011**, *59*, 10887-10892, 10.1021/jf202390x.
51. Chi-Tai Yeh; Gow-Chin Yen; Induction of Hepatic Antioxidant Enzymes by Phenolic Acids in Rats Is Accompanied by Increased Levels of Multidrug Resistance–Associated Protein 3 mRNA Expression. *The Journal of Nutrition* **2006**, *136*, 11-15, 10.1093/jn/136.1.11.
52. F.M. Campos; J.A. Couto; A.R. Figueiredo; I.V. Tóth; A.O.S.S. Rangel; T.A. Hogg; Cell membrane damage induced by phenolic acids on wine lactic acid bacteria. *International Journal of Food Microbiology* **2009**, *135*, 144-151, 10.1016/j.ijfoodmicro.2009.07.031.
53. Saleha Anwar; Anas Shamsi; Mohd Shahbaaz; Aarfa Queen; Parvez Khan; Gulam Mustafa Hasan; Asimul Islam; Mohamed F. Alajmi; Afzal Hussain; Faizan Ahmad; et al. Rosmarinic Acid Exhibits Anticancer Effects via MARK4 Inhibition. *Scientific Reports* **2020**, *10*, 1-13, 10.1038/s41598-020-65648-z.
54. Alicja Kuban-Jankowska; Kamlesh K. Sahu; Magdalena Gorska; Jack A. Tuszynski; Michal Wozniak; Chicoric acid binds to two sites and decreases the activity of the YopH bacterial virulence factor. *Oncotarget* **2016**, *7*, 2229-2238, 10.18632/oncotarget.6812.
55. Prashant Deshmukh; Sruthi Unni; Gopinatha Krishnappa; Balasundaram Padmanabhan; The Keap1–Nrf2 pathway: promising therapeutic target to counteract ROS-mediated damage in cancers and neurodegenerative diseases. *Biophysical Reviews* **2016**, *9*, 41-56, 10.1007/s12551-016-0244-4.

Retrieved from https://encyclopedia.pub/entry/history/show/6190