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REVIEW / PRACA POGLĄDOWA

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BIOLOGICAL AND ANTICANCER ACTIVITY OF SELECTED NATURAL PRODUCTS

BIOLOGICZNA I ANTYRAKOWA AKTYWNOŚĆ WYBRANYCH NATURALNYCH PRODUKTÓW

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S u m m a r y

Cancer continues to be one of the major causes of death worldwide. In recent years, the concept of cancer chemoprevention and treatment with natural occurring agents has evolved greatly. In this review work the biological activity and protective effects against cancer of some natural products - coffee, caffeic acid, caffeic acid phenethyl ester **(**CAPE), chlorogenic acid, quercetin and curcumin are presented. It seems that the most natural products with anticancer activity act as strong antioxidants and/or modify the activity of one or more protein kinases involved in cell cycle control. The results of *in vitro* and *in vivo* studies showed that some of them may be useful as potential chemotherapeutic or chemopreventive anticancer drugs or adjuvants in complex anticancer therapy.

S t r e s z c z e n i e

Rak pozostaje jedną z głównych przyczyn zgonów na świecie. W ostatnich latach obserwuje się znaczny wzrost zainteresowania chemoprewencją i wykorzystaniem naturalnych produktów w leczeniu schorzeń nowotworowych. W prezentowanej pracy przeglądowej opisano aktywność biologiczną i działanie ochronne przed rakiem wybranych naturalnych produktów, jak: kawa, kwas kawowy, fenylowy ester kwasu kawowego (CAPE), kwas chlorogenowy, kwercetyna i kurkumina. Liczne dane naukowe potwierdzają ich silne działanie przeciwnowotworowe jako przeciwutleniaczy i/lub substancji modyfikujących aktywność kinaz białkowych i wpływających na kontrolę cyklu komórkowego. Wyniki badań *in vitro* i *in vivo* wykazały, że niektóre z nich mogą być przydatne jako potencjalne chemioterapeutyki lub leki chemoprewencyjne w złożonej terapii przeciwnowotworowej.

Key words: cancer, chemoprevention, natural agents, coffee, caffeic acid, CAPE, chlorogenic acid, quercetin, curcumin

Słowa kluczowe: rak, chemoprewencja,naturalne produkty,kawa,kwas kawowy, CAPE, kwas chloro genowy, kwercetyna, kurkumina

INTRODUCTION

Cancer is a multifactorial disease that requires treatments able to target multiple intracellular components and signalling pathways [1]. Many factors including life style, genetic variation, virus infection and chronic inflammation may affect the susceptibility to cancer [2]. Nowadays, although a lot of

chemotherapeutic agents have been developed for cancers, the treatment efficacy of many anticancer drugs is still limited or unsatisfactory [3].

Throughout history, natural products have afforded a rich source of compounds that have found many applications in the fields of medicine, pharmacy and biology [4]. More than half of currently available drugs [5] are natural compounds or are related to them. Over 70% of anticancer compounds are either natural products or substances derived from natural products [6]. In the past 5 decades, a series of natural products with the capability to regulate physiological functions have been isolated and exploited from plants, animals and microorganisms, and most of them have revealed obvious anticancer activity [3]. Natural products that enriched flavonoids from fruits have confirmed their anti-carcinogenic, anti-proliferative, co-chemotherapeutic and estrogenic effects through various mechanisms such as modulating cell cycles, inducing apoptosis, inhibiting ERK phosphorylation, and so on [7].

Cancer chemoprevention by either natural or synthetic agents is a promising route towards lowering cancer incidence. In addition to synthetic compounds, many natural products have been found to be able to inhibit carcinogenesis, at least in animal models. There are many ongoing clinical trials to test the safety and efficacy of natural agents in preventing or treating cancer [2].

Natural compounds are expected to become potential effective drugs for the prevention and treatment of cancers in the future. *In vitro* and *in vivo* studies have shown that many dietary agents from fruits, tea and some herbs with both medicinal and food functions are able to fight against and prevent cancers *via* regulating cellular fate through apoptosis and autophagy [3, 8-13].

In this review work the biological activity and protective effect against cancer some of natural agents is presented.

BIOLOGICAL AND ANTICANCER ACTIVITY OF COFFEE, CAFFEIC ACID, CAPE, CHLOROGENIC ACID, QUERCETIN AND CURCUMIN

COFFEE

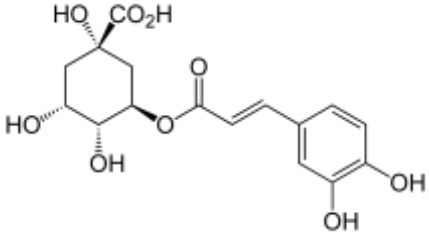
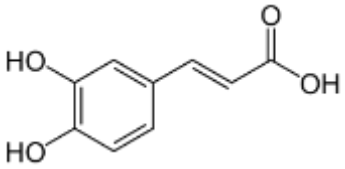
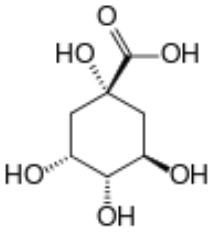
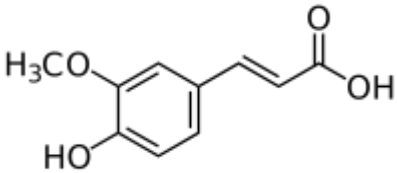
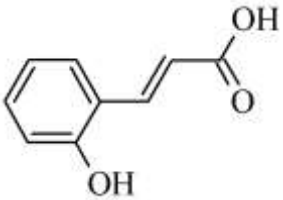
Coffee which is one of the most widely consumed beverages worldwide contains a wide variety of phytochemicals, many of which are antioxidants [14]. The coffee tree belongs to the *Rubiaceae* family, genus *Coffea*. Although more than 80 coffee species have been identified worldwide, only two are economically important. *Coffea arabica*, also known as *Arabica coffee*, is responsible for approximately 70% of the global coffee market, and *Coffea canephoraor Robusta* coffee (commercial name of one of the main *C. canephoracultivars*) accounts for the rest. Coffee has been the most commercialized food product and most widely consumed beverage in the world for decades. Since the opening of the first coffee house in Mecca at the end of the fifteenth century, coffee consumption has greatly increased all around the world. In 2010, coffee production reached 8.1 million tons worldwide. This represents more than 500 billion cups, with the United States, Brazil, Germany, Japan, and Italy being the major consumer countries. However, *per capita* consumption in North European countries such as Finland, Norway, Denmark, and Sweden may reach 8 kg/year, more than twice as much as in the United States or Brazil [15-17].

In 2004 year Bøhn et. al., found that coffee, due to the widespread consumption, is the single greatest contributor to redox-active compounds in the diet, contributing to more than 60% of the total dietary antioxidants [14]. Known constituents of coffee include caffeine, diterpenes (coffee lipids), phenolic acids, and melanoidins, N-methylpyridinium, and acrylamide produced during roasting of coffee beans. The major polyphenols in coffee are the chlorogenic acids and metabolites including quinic acid, caffeic acid, ferulic acid, and coumaric acid [18–23].

Over eleven hundred publications reporting anticancer activities of polyphenols have appeared in the peer-reviewed literature. In addition, a search of the PubMed database using ‘polyphenols – cancer – review’ as keywords produced over 667 hits for review articles (February 2015). Polyphenol anticancer activities include, among others, anti-oxidative, pro-apoptotic, DNA damaging, anti-angiogenic, and immunostimulatory effects. Targeting specific protein kinases to combat cancer represents a major focus of oncology research within the so-called targeted therapy approach [24]. The chemical structures and the sources of main biologically active polyphenols and metabolites in coffee are presented in Table 1.

Growth condition, the sort of coffee plant (usually Robusta and Arabica), sorting procedure, removal of flesh, fermentation, washing and drying of the beans, as well as the roasting and brewing processes all affect the quality, composition, and biological abilities of the

Table I. *The chemical structures of main biologically active polyphenols and metabolites in coffee*

Polyphenols	Chemical structure	The sources
Chlorogenic acid		➢ in bamboo, ➢ as well as in many other plants, ➢ in peach, ➢ in prunes, ➢ in green coffee bean extract.
Caffeic acid		➢ in the bark of *Eucalyptus globulus*, ➢ in the freshwater fern *Salvinia molesta*, ➢ or in the mushroom *Phellinus linteus*, ➢ in coffee, ➢ in argan oil, ➢ in barley grain.
Quinic acid		➢ cinchona bark, ➢ coffee beans, ➢ and other plant products
Ferulic acid		in the seeds of : ➢ coffee, ➢ apple, ➢ artichoke, ➢ peanut, ➢ and orange, as well as in both seeds and cell walls of commelinid plants, such as: ➢ rice, ➢ wheat, ➢ oats, ➢ the Chinese water chestnut (*Eleocharis dulcis*) ➢ and pineapple).
Coumaric acid. There are three isomers of coumaric acids - *o*-coumaric acid, *m*-coumaric acid, and *p*-coumaric acid- that differ by the position of the hydroxy substitution of the phenyl group.	 *o*-coumaric acid	➢ *o*-Coumaric acid can be found in vinegar, ➢ *m*-Coumaric acid can be found in vinegar, ➢ *p*-Coumaric acid can be found in *Gnetum cleistostachyum*, *p*-Coumaric acid can be found in a wide variety of edible plants such as: ➢ peanuts, ➢ navy beans, ➢ tomatoes, ➢ carrots, ➢ garlic, ➢ wine, ➢ vinegar, ➢ in barley grain, ➢ *p*-Coumaric acid from pollen is a constituent of honey.

coffee. The degree and methodology of roasting that create unique coffees with regard to appearance and taste and chemical profile seems to be particularly important for the biological effects of coffee in a clinical trial and in experimental systems. For example, recent studies clearly demonstrate that the degree of roasting differentially affects biological activities, such as gene expression and antioxidant defence, protection against DNA oxidative damage (*in vitro* and *ex vivo* genoprotective effects) [25-30].

Table II. *The biological effect of coffee compounds in relation to different cancer sites (Based on Bøhn et. all., 2014 [14]*

Cancer	Biological effect of coffee	References
Breast	➢ There seems to be no association between the overall risk of breast cancer and coffee intake ➢ recently, Simonsson et al., 2013 observed that moderate (two to four cups per day) to high (five or more cups per day) coffee consumption was associated with significantly decreased risk for early events in tamoxifen-treated breast cancer patients. ➢ emerging evidence point toward an inverse association between breast cancer and coffee intake, particularly for subgroups of estrogen receptor negative cancers, brest cancer type 1 mutation carriers, postmenopausal women, as well as tamoxifen-treated breast cancer survivors.	[31] [32], [33], [34], [31]
Prostate	➢ the current evidence shows no clear association between overall prostate cancer risk and consumption of coffee. ➢ however, an inverse association between the intake of coffee and both lethal and advanced prostate cancers was found In the large cohort from the 'Health Professionals Follow-up Study' and in the 'Cancer of the Prostate in Sweden' cohort. ➢ Geybels et al., 2013 also recently observed that higher prediagnostic coffee consumption is associated with a lower risk of prostate cancer recurrence/progression. Thus, new evidence may suggest an inverse association between subgroups of prostate cancers such as lethal and advanced prostate cancer, and recurrence/progression in prostate cancer survivors. These possible beneficial effects deserve further investigation.	[14] [35], [36] [37]
Liver	➢ the accumulating evidence provided by epidemiological studies consistently point toward protective effects of coffee for risk of liver cancer.	[14]
colorectal	➢ Wang et al., 2013 found a U-shaped response curve for the relationship between coffee and colorectal cancer, with significantly decreased risk up to three cups of coffee per day in a Japanese population. ➢ similarly, another Japanese study found decreased risk of colorectal cancer with a moderate coffee intake in women. ➢ the accumulating evidence provided by epidemiological studies thus point toward protective effects of coffee for risk of colorectal cancers.	[38] [39] [14]

Many coffee compounds have the potential to induce biological effects. Caffeine, chlorogenic acid, kahweol, and cafestol are so far the most studied in the perspective of cancers. Potential mechanisms for chemopreventive effects of coffee phytochemicals include inhibition of oxidative stress and oxidative damage, regulation of DNA repair, phase II enzymatic activity, apoptosis, inflammation, as well as having antiproliferative, antiangiogenetic effects and antimetastatic effects [14]. Table 2 presented the biological effect of coffee compounds in relation to different cancer sites.

CAFFEIC ACID (CA) AND CAFFEIC ACID PHENETHYL ESTER (CAPE)

Caffeic acid (CA; 3,4-dihydroxycinnamic) is one of the hydroxy-cinnamate metabolites universally present in plant tissues. CA is found in many food sources, including coffee drinks, blueberries, apples and cider. Besides acting as a cancer inhibitor [40, 41], it also possesses anti-oxidant and anti-bacterial activities *in vitro* and can contribute to the prevention of atherosclerosis and other cardiovascular diseases (CVDs) [42]. In the latest work of Búfalo M. C. and Sforcin J. M., 2015 [43] caffeic acid downregulated TLR-2 and HLA-DR expression and inhibited cytokine production, whereas it upregulated the fungicidal activity of monocytes, without affecting cell viability. Caffeic acid exerted an immunomodulatory action in human monocytes in the evaluated parameters depending on concentration, with no cytotoxic effects.

Caffeic acid phenethyl ester (CAPE) (Fig. 1), a lipophilic derivatives of caffeic acid and a phenolic antioxidant , is a natural bioactive compound extracted from honeybee hive product propolis. It occurs in many plants. It is acquired from propolis obtained through extraction from honeybee hives. The chemical name of CAPE is 2-phenylethyl (2E)-3-(3,4-dihydroxyphenyl) acrylate. It is also termed as phenylethyl caffeate or phenethyl caffeate. Its molecular formula is $C_{17}H_{16}O_4$. CAPE is a polyphenol with hydroxyl groups within the catechol ring which is responsible for its crucial role in many biological activities. The available studies narrate it as an effective moiety against various pathologies such as infections, oxidative stress, inflammation, cancer, diabetes, neurodegeneration, and anxiety. Large number of studies have been conducted on various features of the biological and pharmacological activities of CAPE and its mode of action [44-54].

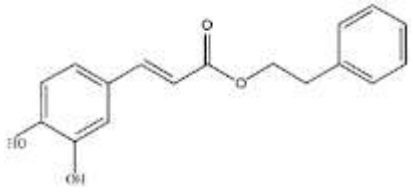


Fig. 1. *Structure of caffeic acid phenethyl ester (CAPE)*

Table III. *Some of the main biological activities of CAPE and its potential mechanisms of the anti-cancer activity (Based on 51-54)*

Biological activity	Targets for CAPE	Effects of CAPE
Antimicrobial	DNA, RNA, cellular proteins	- antimicrobial activity againts *Enterococcus faecals, Listeria monocytogenes, Staphylococcus ureus, Haemophilus influenzae,Escherichia coli DH5α,* -CAPE is useful for the treatment of sore throat, common cold and wound, -fungicidal activity on fungi infecting tomato without causing any harm to the fruit, - CAPE has been proposed as a valuable inhibitor of HIV-1 integrase; therefore, this polyphenol is believed to be a potential anti-HIV therapy. - CAPE and its esters, in a concentration range of 1.0 to109.6mM, have also been tested In an HCVreplicon cell line of genotype 1b and found effective against replication of hepatitis C virus suggesting it a promising anti-HCV compound,
Antioxidant	ROS	- Oxidative stress is also suggested to be a major cause of cellular injuries in carcinogenesis. The results showed that CAPE and its related polyphenolic acid esters elicited remarkable inhibitory effects on erythrocyte membrane lipid peroxidation, cellular DNA stand breakage, and protein fragmentation.
Anti-inflammatory activity	- Pro-inflammatory enzymes: COX -1, COX-2, - Pro-inflammatory mediators: PGE2, TNF-α, IL1β, IL6, IL8, IL10, MCP-1, - Transcription factors: NF-κB, -Upstream signaling molecules: TLR 4, JNK.	- The mode of anti-inflammatory activity of CAPE involves the inhibition of arachidonic acid release from the cell membrane; it, in return, inhibits the COX-1 and COX-2 activity as well as suppresses the activation of gene responsible for COX-2 expression. In carrageenin-induced inflammation, CAPE suppresses both exudate volume and leukocytes relocation, - immunosuppressive behavior of CAPE has been evaluated in T-cells. This discovery revealed the CAPE-mediated inhibition of initial and late steps in T-cell receptor-mediated T-cell activation and thus proposed the mechanistic basis for the immunomodulatory and anti-inflammatory activities of CAPE, - CAPE inhibits of both interleukin- (IL-) 2 gene transcription and the IL-2 synthesis In stimulatedT-cells, - the CAPE-mediated inhibition of the production of TNF-*α*and IL-6 factors. The attenuation of phosphorylation potentials of ERK1/2 and JNK was also observed, - in CAPE-treated gastric epithelial cell line (AGS), an obstruction was observed in cytokine- and mitogenprovoked NF-κB and AP-1 expression. Additionally, CAPE inhibited theH. pylori-provoked cell proliferation, *H. pylori*-induced COX-2 expression, and synthesis of the cytokines, TNF-a, and IL-8. These results are potential insights into the anticancer and anti-inflammatory activities of CAPE.
Anticarcinogenic	CAPE modulates the activity of the main signaling molecules of: -metastasis suppression (MMP-2, MMP-9, VEGF, TGF- β phosphorylation), Induction of apoptosis (Bax, Bak, JNK, P42/44ERK, P53, P38 MAPK, Fas, cytochrome C release, caspase activity, NF-κB, Bel-2, Mel-1, glutatione xanthione oxidase, ROS, cAIP – 1, cIAP, Induction of cell cycle arrest (cyklin D1, cyklin E, cyklin B1, c-myc, nu clear β-catenin, hyperphosphorylated of Rb)	-CAPE can induce apoptosis, -G1 or G2 cell cycle arrest and necrosis while it can reduce motility and invasiveness in cancer cells depends on the concentration of CAPE being used and the types of cancer cells being treated. -CAPE also suppresses development, growth and metastasis of tumors in animal models. These observations suggest that CAPE might be a potential therapeutic agent for cancers.

Abbreviations: ROS - Reactive oxygen species; HIV - Human immunodeficiency virus; HCV - Hepatitis C virus; COX – Cyclooxygenase; PGE2 – Prostaglandin E2; MCP-1 - Monocyte Chemoattractant Protein-1; TLR4 - Toll-like receptor 4 (protein); ERK1/2 - Extracellular-signal-regulated kinases; IL – Interleukin; NF-Kb - Nuclear factor kappa; JNK - c-Jun NH2-terminal kinase; TNF – Tumor necrosis factor; MMP-2, MMP-9 - Matrix Metalloproteinases; VEGF - Vascular Endothelial Growth Factor, TGF – β - *Transforming Growth Factor beta*; Bax - Apoptosis regulator; Bak - is a pro-apoptotic member of the Bcl-2 gene family which is involved in initiating apoptosis; P42/44 ERK – kinase; P38 MAPK - P38 mitogen-activated protein kinases; Fas – protein; Mcl-1 - Induced myeloid leukemia cell differentiation protein; Bcl-2- protein; cIAP - cellular inhibitor of apoptosis; cAIP - cellular apoptosis inhibitor protein; P16, P21, P27 – 16, 21, 27 protein; c-myc – regulator gene; Rb – protein - a *tumor suppressor*.

CAPE has been reported to inhibit transformation of normal cells to cancer cells. Different cancer cell lines showed different sensitivity to CAPE treatment. CAPE treatment suppresses proliferation of several human cancer cell lines. Non-cancer cells, such as human immortal lung fibroblast WI-38 cells, Human Normal Umbilical Vein Epithelial Cells (HUVEC), or Human Normal Oral Fibroblast (NHOF) cells are much more resistant to CAPE treatment, indicating potential selective cytotoxic effect against cancer cells of CAPE treatment [53].

CAPE specifically inhibits NF-κB (nuclear factor-kappa B). It exhibits antioxidant, anti-inflammatory, antiproliferative, cytostatic, and most importantly, antineoplastic properties [54]. CAPE (50-80 μM) specifically inhibits the activation of nuclear

transcription factor NF-κB induced by Tumor Necrosis Factor (TNF) and inflammatory agents as well as prevented the translocation of p65 unit of NF-κB. CAPE inhibits the binding between NF-κB and DNA but has no effect on other transcription factors. CAPE is also a strong antioxidant [49-54].

An extensive literature is available regarding cytotoxicity studies of CAPE. In the presence of CAPE, human pancreatic and colon cancer cells undergo apoptosis. The *in vitro* and *in vivo* studies reveal the growth inhibition of C6 glioma cells by CAPE. There are many evidences which elaborate the antiproliferation activity of CAPE. The antitumor activity of CAPE has been investigated to reveal its influence on cancer development including angiogenesis, tumor invasion, and metastasis. CAPE can induce apoptosis, G1 or G2 cell cycle arrest and necrosis, while it can reduce motility and invasiveness in cancer cells depends on the concentration of CAPE being used and the types of cancer cells being treated. CAPE also suppresses development, growth and metastasis of tumors in animal models. These observations suggest that CAPE might be a potential therapeutic agent for cancers. The achievable concentration of CAPE in human serum is around 5.0 μg mL^{-1} (17 μM). This concentration (17 μM) is not enough to eradicate all types of cancer cells. However, CAPE can be used in combination with current standard treatments. Several studies indicate that CAPE may be an alternative, safe and effective adjuvant therapy for several types of cancer with little or no side effect. CAPE has shown promising efficacy in preclinical settings including neuroprotective, hepatoprotective and cardioprotective effects. Large research has been done to assess antioxidant role of CAPE. The evidences show that CAPE is potent antioxidant which can scavenge ROS and protect the cell membrane against lipid peroxidation. Some other studies elaborate immunomodulator, antihepatotoxic, antiosteogenic, and antiatherosclerotic role of CAPE [45-54]. Some of the main biological activities of CAPE and its potential mechanisms of the anti-cancer activity are presented in Table III.

CHLOROGENIC ACID

Chlorogenic acid (CGA) is a natural chemical ester composed of caffeic acid and (-)-quinic acid, and is further metabolized into active compounds in the living body. Chlorogenic acid (CGA) holds promise as a physiologically active substance; its properties are attributable to the phenolic hydroxyl group(s) and it is characterized by relatively low toxicity and side effects. CGA is a natural phenolic compound commonly found in apples, coffee beans, grapes, pulp, peel, plum, and tea leaves. Chlorogenic acid has antibacterial, antiviral, clear free radicals, and antitumor effects [55]. In recent years, the effective anticancer activity and low toxicity of chlorogenic acid were constantly confirmed and draw scientists' attention [56–58]. Kurata et al. [59]showed that the inhibition of tumor cell proliferation effect of chlorogenic acid was enhanced with increasing dose; they speculated that this inhibition of tumor cell proliferation may be obtained by enhancing the activity of the DNA ladder and caspase-3 as well as increasing the expression of c-Jun. Gmnado and Feng et al. showed that the in vitro experiments show that the anticancer mechanism of CGA contains inhibition of cell growth, regulation of cell cycle, and induction of apoptosis pathways, such as: to reduce ROS expression to reduce cell growth/reproduction signal transduction pathway of NFκB,AP-l, and MAPKs to reduce cancer cell viability; to improve the activity of the NAD(P)H and GST; to inhibit the expression of tetradecanoyl method wave alcohol acetate (TPA), in order to reduce the c-Jun NH2-terminal kinase, p38 kinase, and MAPK kinase-4 to present cancer transformation, and to stimulate the expression of NF-E2-related factor and the activity of GST regulated by Nrf2 downstream cascade links antioxidant response element (ARE) to inhibit the growth of cancer cells [60, 61]. Chlorogenic acid is considered to be an effective cancer chemical repellent because of its significant inhibitory effect on colorectal cancer, liver cancer, and laryngeal [62].

QUERCETIN

For several decades, naturally occurring flavonoids have received widespread attention due to a remarkable scope of health benefits. Results from cell culture and animal models reveal that flavonoids exert positive preventive effects in carcinogenesis and neurodegenerative disorders essentially because of their antioxidant activity, their capacity to affect the expression of several detoxifying enzymes, and their ability to modulate protein signalling cascades. Flavonoids can interfere with specific stages of the carcinogenic process, and can inhibit cell proliferation and induce apoptosis in several types of cancer cells. Meanwhile, the antiproliferative effects of flavonoids

are considered to be among the most therapeutically utilizable of bioactivities [63-65].

Quercetin (3,5,7,3´,4´-pentahydroxy flavone) is one of the most abundant bioflavonoids. It is present in edible fruits and vegetables. It consists of two aromatic rings A and B, linked by an oxygen containing heterocyclic ring C (Fig.2) [65].

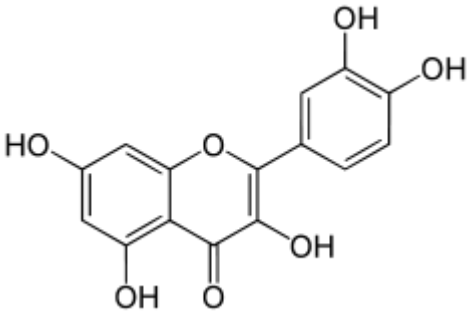
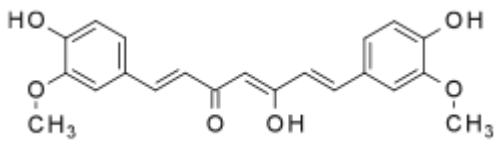


Fig. 2. *The chemical structure of quercetin (Que)*

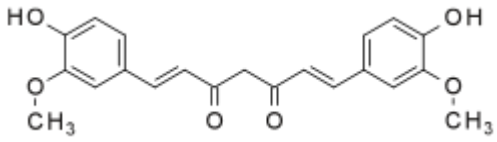
Numerous studies have described the cancer preventive effects and molecular mechanisms of quercetin, which has been shown to be one of the major flavonoids with antiproliferative efficacy on a wide range of cancer cells. For example, quercetin was shown to inhibit the growth of acute lymphoid and myeloid leukemia cells. It was also reported to have growth-inhibitory effects on human gastrin and colon cancer cells by inhibiting cell cycle progression at the G1-S boundary. These diverse antitumor activities of quercetin make it a lead compound for the development of new effective cancer preventive or therapeutic agents [62, 66-67].

CURCUMIN

Curcumin or diferuloylmethane (Fig. 3) is a yellow spice that is used in curry. It is extracted from the rhizome of the plant, *Curcuma longa*, and has been used for centuries in Ayurvedic, Chinese and Hindu traditional medicines as a potent anti-inflammatory agent. Research over the last 50 years established that curcumin appears both as a preventive and therapeutic agent able to reverse, inhibit or prevent the development of cancer by inhibiting specific molecular signalling pathways involved in carcinogenesis, as reported in in vitro, in vivo and in clinical studies. The chemistry of curcumin induces biological effects that allow it to influence multiple cell signalling pathways, giving it anti-inflammatory, antioxidant, chemo-preventive, chemotherapeutic, anti-mutagenic, anti-metastatic and anti-angiogenic properties in the micromolar concentration range in several cancer cell types [68-76].



Enol form



Keto form

Fig. 3. *The chemical structure of curcumin*

At the molecular level there is evidence that curcumin inhibits the growth of a variety of human cancer cell lines in vitro by cell cycle arrest and induction of apoptosis through inhibition of several protein and/or pathways such as cyclin, cyclin-dependent kinase, NF-κB, protein kinase C and mitogen-activated protein kinase (MAPK). It also suppresses pro-inflammatory signalling by inhibiting the expression and activity of cyclooxygenase-2 (COX-2). Curcumin has been reported to have anti-prostate cancer activity in vitro and in vivo in both androgen-dependent and androgen-independent prostate cancer. Curcumin was demonstrated to have a wide spectrum of pharmacological properties with an absence of systemic toxicity [77-89].

Curcumin has poor bioavailability, which has been determined in both animal and human models, limits its clinical application as a potential anticancer agent. This limitation has led researchers to develop a variety of synthetic analogues of curcumin with similar safety profiles and increased activity, but improved bioavailability. Several analogues of curcumin with different bioactivities through modification of the molecular structure have resulted in the development of potential anti-cancer candidates that target various cancers [90-98].

It seems that most dietetic products with anticancer activity act as strong antioxidants and/or modify the activity of one or more protein kinases involved in cell cycle control. Kinases such as protein kinase A, protein kinase B, protein kinase C, JNK-1, CDK-2, and CDK-4 are either activated or deactivated by these antioxidants, as shown in Fig. 4. This can happen directly or indirectly through activation of some transcription factors such as NF-IL6 or tumor suppressor genes such as $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ [99-101].

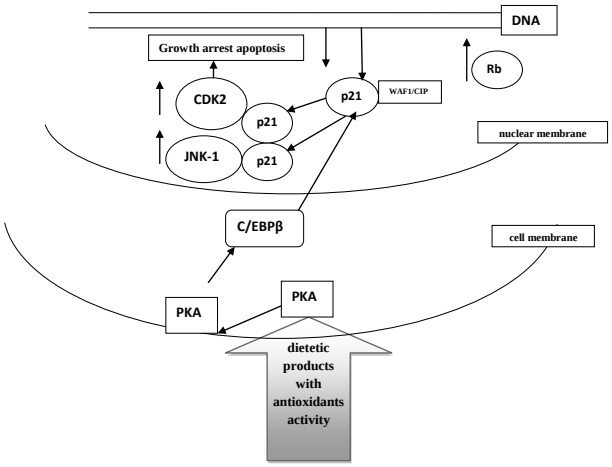


Fig. 4. *Schematic mechanism of presentation of signal transduction cascades modified by some dietetic antioxidants. Products with antioxidants activity reduce protein kinase A (PKA). The reduced form of PKA translocates to the membrane where it phosphorylates transcription factor C/EBPβ. C/EBPβ then translocates to the nucleus where it induces the transcription of p21 $^{WAF1/CIP1}$ in a p53-independent way. Induction of p21 $^{WAF1/CIP1}$ results in inhibition of CDK-2 and growth arrest of cells in G 1 phase. p21$^{WAF1/CIP1also}$ binds to JNK-1 and inactivates this stress-activated protein kinase (SAPK). Rb - protein is a tumor suppressor, which plays a pivotal role in the negative control of the cell cycle and in tumor progression; p53 – tumor suppressor protein; p21 $^{WAF1/CIP1}$ - cyclin-dependent kinase inhibitor 1 or CDK-interacting protein 1; CDK-2 - Cyclin-dependent kinase 2; JNK-1 - c-Jun N-terminal protein kinase 1(Based on 99-101)*

CONCLUSIONS

About 12.5% of the 422,000 plant species of higher plants are known as medicinal plants and constitute a principal source of bioactive molecules. About 25% of drugs in the modern pharmacopoeia are derived from plants, and many others are synthetic analogues built on prototype compounds isolated from plants. Up to 60% of prescribed drugs in the Western world contain plant products or their derivatives.

Natural products have been a prime source for the treatment of many forms of cancer, many of which are consumed daily with the diet. They provide significant protection against various cancers and many other diseases.

Although a number of natural compounds have been reported to possess anticancer properties, their mechanisms of action are not well understood. Additionally, the poor bioavailability of them is the main limitation of their application as a potential anticancer agent. Extensive literature is available on some research areas, but still some areas are very much less or not explored; therefore, further investigations to use natural compounds for the best therapeutic treatment are required.

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