Review Article

Anticancer Properties of Phenolic Acids in Colon Cancer – A Review

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Abstract

Consumption of fruits and vegetables is associated with lower risk of several cancers, particularly colorectal cancer, which is mainly associated to their phytochemical content. A diverse range of phytochemicals, especially phenolic compounds, has been reported to possess important biological properties such as anticancer, antiviral, antioxidant and anti-inflammatory activities. Several factors contribute to the development of colorectal cancer. The scientific evidences support the genetic predisposition, diet, and lifestyle as some of the major contributing factors for colorectal cancer development. In this sense, this review aims to summarize the anticancer activities and the proposed mechanisms of action of phenolic acids with an emphasis in colon cancer through *in vitro* evidences. The evidences supports the theory of anticancer properties of phenolic acids, although the mechanisms are still not fully understood, but may include scavenging free radicals, induction of enzymes involved in the metabolism of xenobiotics, regulation of gene expression, modulation of cellular signaling pathways including those involved in DNA damage repair, cell proliferation, apoptosis and invasion.

Keywords: Cancer; Phenolic acids; Colon; Bioactive compounds; Functional food; Caffeic acid

Introduction

In the last few years, some studies have reported that the diet possesses an important role in the etiology of colorectal cancer. Epidemiological evidences suggest that diets rich in fruits and vegetables, which have high contents of phytochemical compounds, may contribute to reduce the risk of certain cancers. Regarding the colon cancer, the influence of antioxidant compounds present in foods is one of the factors with extensive discussion in the literature [1].

A wide variety of bioactive compounds, especially phenolic compounds have been reported to possess important biological properties such as anticancer, antiviral, antioxidant and anti-inflammatory activities. The potential biological effects of various constituents of fruits and vegetables suggested a plausible mechanism for protective effects, such as by reducing oxidative damage of DNA or increasing the activity of enzymes able to detoxify carcinogens [2,3].

Phenolic acids are import constituents of plants found in a wide range of commonly consumed plant foods such as fruits, vegetables, cereals, legumes and beverages. The main functions of phenolic acids in plants are pigmentation, growth, reproduction and resistance to pathogens [4].
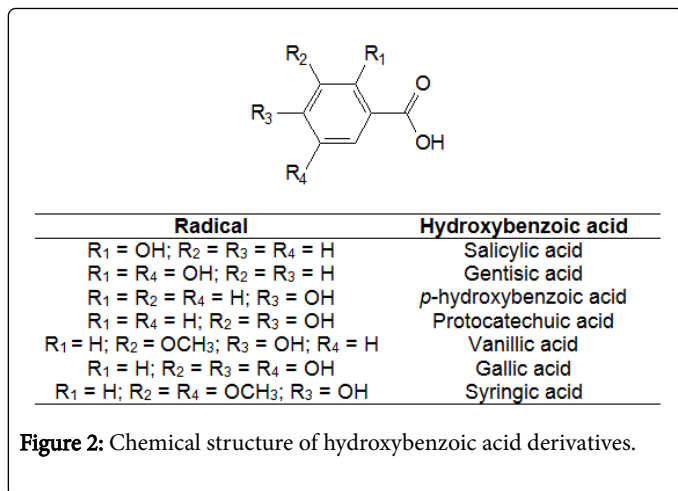
In plants, phenolic acids are derived from an ortho oxygenation and subsequent methylation substitution of cinnamic acid. These gives rise to the most common hydroxycinnamic acids, namely: p-coumaric, caffeic, ferulic and sinapic acids (Figure 1). These are often considered as intermediates of lignin biosynthesis. However, they are also the important building blocks of many other natural products and are often found as specific esters (e.g. chlorogenic acid) [5].
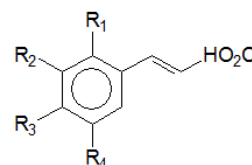
Radical	Hydroxycinnamic acid
$R_1 = R_2 = R_3 = R_4 = H$	Cinnamic acid
$R_1 = R_2 = R_4 = H; R_3 = OH$	p-Coumaric acid
$R_1 = R_2 = H; R_3 = R_4 = OH$	Caffeic acid
$R_1 = R_2 = H; R_3 = OH; R_4 = OCH_3$	Ferulic acid
$R_1 = H; R_2 = R_4 = OCH_3; R_3 = OH$	Sinapic acid

Figure 1: Chemical structure of hydroxycinnamic acid derivatives.

Hydroxybenzoic acids can be formed directly from intermediates early in the shikimate pathway. However, in plants they are more frequently formed by degradation of C_6C_3 cinnamic acid derivatives. Commonly found examples are p-hydroxybenzoic protocatechuic, vanillic and syringic acids (Figure 2). Less abundant are hydroxyphenylacetic acids (the C_6C_2 derivatives). Generally, they are observed to have the same substitution pattern as observed for the hydroxybenzoic and hydroxycinnamic acids, but the direct route to their biosynthesis is unclear. Phenolic acids can be found in plants not only in their free form but also conjugated (predominantly by esterification) to a variety of molecules including simple sugars, organic acids and plant polymers [5].

Figure 2: Chemical structure of hydroxybenzoic acid derivatives.

Radical	Hydroxybenzoic acid
R_1 = OH; R_2 = R_3 = R_4 = H	Salicylic acid
R_1 = R_4 = OH; R_2 = R_3 = H	Gentisic acid
R_1 = R_2 = R_4 = H; R_3 = OH	p-hydroxybenzoic acid
R_1 = R_4 = H; R_2 = R_3 = OH	Protocatechuic acid
R_1 = H; R_2 = OCH$_3$; R_3 = OH; R_4 = H	Vanillic acid
R_1 = H; R_2 = R_3 = R_4 = OH	Gallic acid
R_1 = H; R_2 = R_4 = OCH$_3$; R_3 = OH	Syringic acid

This review aims to summarize the anticancer activities and the proposed mechanisms of action of phenolic acids in cell lines and animal models of colon cancer through *in vitro* evidences.
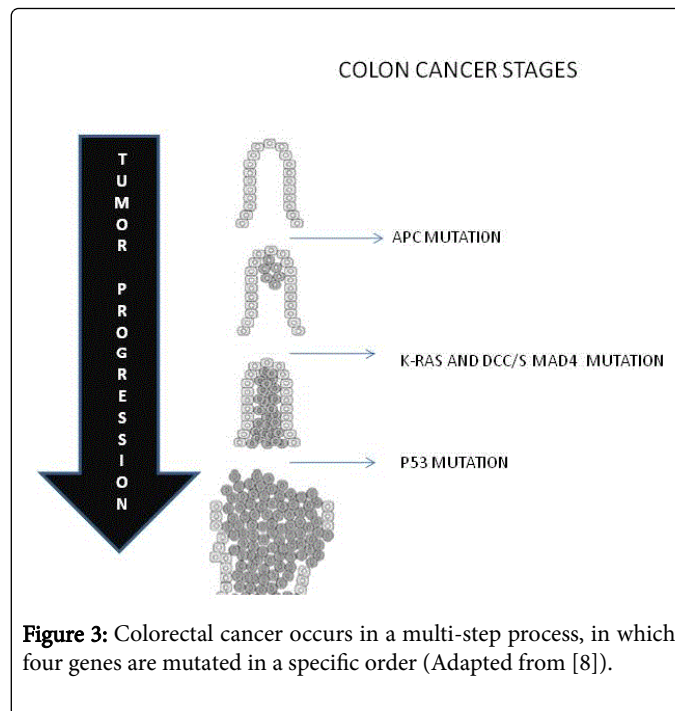
Colon cancer

More than 1 million new cases of colorectal cancer (CRC) are diagnosed worldwide each year. CRC is the third most common malignancy and fourth most common cause of cancer mortality worldwide [6].

Development of CRC results from the accumulation of mutations or epigenetic changes that leads to transformation of normal colonic mucosa into colonic adenocarcinoma and subsequent carcinoma [7]. This mutational event is the initiating step in a pathway termed the adenoma-carcinoma sequence and involves genes such as APC (Adenomatous Polyposis Coli), K-ras, DCC (Deleted in Colorectal Cancer) and p53 (Figure 3), and is characterized by three stages: i.) initiation involving exposure to or uptake of carcinogens resulting in permanent DNA damage; ii.) Promotion involving a lengthy process of abnormal cell replication forming a preneoplastic lesion, and iii.) Progression of tumorigenesis involving gradual conversion of preneoplastic cells to malignant cells [2,8].

The colon epithelial cells are exceptionally fast proliferating and are chronically exposed to potentially mutagenic and carcinogenic food residues and bacterial metabolites [9]. There is increased scientific interest in the potential of dietary substances for prevention of colon cancer. The colonic microflora has been suggested to play a critical role in maintaining a healthy bowel and lowering the risk of colorectal cancer. The interaction between the diet and the microbiome is complex. Bacteria can influence cancer risk by metabolizing dietary components and dietary components can influence the composition and activity of the microbiome [10].

Several factors contribute to the development of colorectal cancer. There is hard evidence that genetic predisposition, diet, and lifestyle are some of the major contributing factors for colorectal cancer development [11].

A healthy lifestyle and diet can reduce the risk of developing cancer as stated by the World Cancer Research Fund/American Institute for Cancer Research in 2007. Dietary fiber is an important component in a healthy diet, and a strong association between its intake and decreased incidence of colon cancer has been evidenced in several studies [12].

Figure 3: Colorectal cancer occurs in a multi-step process, in which four genes are mutated in a specific order (Adapted from [8]).

Chemotherapy is an effective way to treat many types of cancers, but the cost of treatment is a major public health concern in developing countries. Anti-cancer drugs used to treat patients often are expensive, and most of them cause negative side effects, especially to normal cells that have a high proliferation rate, affecting most cancer patients [3].

Of course, developing new chemotherapeutic is an enormous undertaking. There is another popular source of therapeutics used to treat cancer that is often overlooked by natural medicine. This might be considered understandable given the area of alternative medicine is obviously a controversial one. However, understanding that there are many strategies available to researchers for discovering new molecules that may be viable drug candidates is very relevant to this review.

Role of phenolic acids on colon cancer

A range of evidence supports the theory of anticancer properties of phenolic acids, although the mechanisms are still not fully understood, but may include scavenging free radicals, induction of enzymes involved in the metabolism of xenobiotics, regulation of gene expression, modulation of cellular signaling pathways including those involved in DNA damage repair, cell proliferation, apoptosis and invasion.

One important aspect of carcinogenesis is recognized to be the involvement of inflammation. For instance, prostaglandins are mediators of inflammation and chronic inflammation predisposes to carcinogenesis. The over-expression of inducible cyclooxygenases (COX-2), the enzyme which catalyzes a critical step in the conversion of arachidonic acid to prostaglandins and is induced by pro-inflammatory stimuli, including mitogens, cytokines and bacterial lipopolysaccharide (LPS), is believed to be associated with colon, lung, breast and prostate carcinogenesis [13].

Cell/ Animal model	Phenolic acids and derivatives	Anticarcinogenic activities	Reference
Caco-2	3-O-Methylgallic acid; gallic acid	$\downarrow$ cell viability; induce apoptotic cell death; (-) G_0/G_1 phase; $\downarrow$ S-phase; (-) NF-kB; (-)AP-1 (activator protein-1); (-) STAT-1 and (-)OCT-1	[14]
Caco-2	Ferulic acid; p-coumaric acid	$\downarrow$ cell viability $\downarrow$ G1 phase; $\uparrow$ S and G_2 phase	[9]
Caco-2	Ferulic acid; p-coumaric acid	regulation cell proliferation; regulation cell cycle	[12]
HT-29	5-Caffeoylquinic acid; caffeic acid	$\downarrow$ cell viability; $\uparrow$ G_0/G_1phase; $\downarrow$ G_2/M phase; $\uparrow$ apoptosis	[16]
HT-29	Caffeic acid; coumaric acid; ferulic acid	(-) cell proliferation; (-) superoxide anion production; (-) cell adhesion	[29]
HCT15	Caffeic acid	(-) cell growth; (-) colony formation; $\downarrow$ forward scatter; $\uparrow$ side scatter; $\uparrow$sub-G_1 phase; $\uparrow$ ROS; $\uparrow$ apoptosis	[18]
HCT116	3,4-Dihydroxyphenylacetic acid	$\downarrow$ proliferative activity	[21]
HCT116	Caffeic acid esters; ferulic acid esters	(-) cell proliferation; (-) COX-1 and COX-2; (-) peroxidation *in vitro*	[24]
HCT116	Caffeic acid phenethyl ester; caffeic acid phenylpropyl ester	Cell cycle arrest G_0/G_1 phase; (-) D1 cyclin; (-) PCNA; (-) NF-kB	[22]
HCT116	Caffeic acid phenyl ester	$\uparrow$ G0/G1 phase cells; $\downarrow$ S phase ratio; $\uparrow$apoptosis; (-) cell proliferation	[19]
HCT116 SW480	Caffeic acid phenethyl ester	(-) cell growth; $\uparrow$ apoptosis; $\uparrow$ G_0/G_1 phase; $\downarrow$ mRNA expression; $\downarrow$ D1 and c-myc protein	[27]
SW-480	Caffeic acid phenethyl ester; caffeic acid phenylpropyl ester	Cell cycle arrest G_0/G_1 phase; (-) D1 cyclin and PCNA; (-) expression of NF-kB	[22]
HT 29 HCT-15	p-Coumaric acid	(-) cell growth; (-) colony formation; $\uparrow$ sub-G_1phase; $\uparrow$ apoptosis and $\uparrow$ROS	[25]
RKO HT-29	3,4-, 3,5- and 4,5-dicaffeoylquinic fraction	$\uparrow$ ratio Bax:Bcl-2 protein expression; $\uparrow$ apoptosis; $\uparrow$ activation of caspase-8; (-) cell proliferation	[26]
SW480 SW620	Cycloartenyl ferulate	(-) cell growth; $\uparrow$ apoptosis	[31]
SW480	p-Coumaric acid; caffeic acid; ferulic acid	(-) viable cells; (-) colony formation	[30]
DLD-1	Dicaffeoylquinic acid from sweet potato leaf	(-) cell growth;	[17]

		(-) cell proliferation	
CT26	Caffeic acid phenyl ester	(-) cell invasion; ↓ MMP-2 and MMP-9; ↓ VEGF	[33]
mouse xenograft model with colorectal tumor	Caffeic acid phenethyl ester; caffeic acid phenylpropyl ester	↓ growth of colorectal tumors; (-) PCNA, FASN and MMP-9	[22]
SW480 xenograft in nude mice	Cycloartenyl ferulate	induce significant regression of tumor	[31]
F344 rats	Ferulic acid and its geranylated derivative 3-(4′-geranyloxy-3-methoxyphenyl)-2-propenoate	(-) effects on aberrant crypt foci (ACF); (-) aberrant crypts (AC) development; (-) cell proliferation; (-) cells in S-phase	[32]

Table 1: Effects of phenolic acids in different colon cancer cell lines and animal models, Legend: (-) inhibition, suppression.

Phenolic acids have been reported to inhibit transcription factors linked to inflammation, pro-inflammatory cytokines, COX-2, lipoxygenases (LOX), inducible nitric oxide synthase (iNOS). These evidences are described below and summarized in Table 1.

Forester et al. [14] demonstrated that 3-O-Methylgallic acid (Megal) reduced cell viability in SW-480 cells; they also reported that Megal and gallic acid (Gal) have the capacity to induce apoptotic cell death and decrease Caco-2 cell viability. This decrease was mostly due to the capacity of Megal and Gal to inhibit cell cycle at the G0/G1 phase. Additionally, Megal and Gal inhibited transcription factors NF-kB, AP-1, STAT-1, and OCT-1 which are known to be activated in CRC. The capacity of these compounds to inactivate transcription factors could in part mediate the anti-carcinogenic actions of Megal and Gal.

NF-κB signaling was shown to contribute to cancer progression by controlling epithelial to mesenchymal transition and metastasis. The latter is often associated with an up-regulation of matrix metalloproteinases loosening the extracellular matrix for an evasion of cancer cells, NF-κB can also contribute to tumor progression by controlling vascularization of tumors via upregulation of VEGF (vascular endothelial growth factor) and its receptors [15].

Murad et al. [16] evaluate the cellular uptake of Caffeic Acid (CA) and 5-caffeoylquinic acid (5-CQA) and their effects on cell viability, cell cycle, and apoptosis in human colon adenocarcinoma cells (HT-29) in different concentrations and times. After treatment with 5-CQA their cellular uptake was observed in all treatment times (0.5 h to 96 h) with a large variety, being the maximum uptake (46.0 ± 0.01 mg/g) 2 hr after incubation. 3-CQA and 4-CQA, the major isomers of 5-CQA, were detected in the intracellular medium in almost all treatment times. Three phenolic compounds, CA, dihydrocaffeic acid and 2,4-dihydroxybenzoic acid were identified and quantified in HT-29 cells after treatment with CA, being CA rapidly increase in the intracellular medium in the first 2 hr. CA and 5-CQA showed inhibitory effects on cell growth, suggesting a modulation of the cell cycle with an increase in apoptosis in human colon adenocarcinoma cells.

Kurata et al. [17] isolated dicaffeoylquinic acids (diCQA) from sweet potato leaf and investigated the suppression of the proliferation in human colon cancer cell (DLD-1). They showed that diCQA depressed cell growth in a dose-dependent manner.

The effects of CA were also evaluated [18] in human colon cancer cells (HCT 15). CA inhibited colony formation and the growth of HCT 15 cells in a dose-dependent manner with an IC50 of 800 μM, decrease in the mean forward scatter and an increase in mean side scatter in a time dependent manner while comparing with the untreated cells grown for 48 h. This may be attributed to the apoptosis induced by CA. They had found increasing accumulation of cells at sub-G1 phase and significant increase in the reactive oxygen species (ROS) levels after CA treatment. ROS generation is involved in the apoptosis of many anticancer agents.

Several studies have demonstrated that Caffeic acid phenyl ester (CAPE) has anti-proliferative effect and apoptosis inducing against various tumors cell lines. Wang et al. [19] investigated the effect of CAPE on the proliferation, cell cycle and apoptosis of CRC HCT116 cells and demonstrated that treatment with CAPE was associated with a strong inhibition of proliferation in a dose- and time-dependent manner, along with induction of G0/G1 arrest and apoptosis.

During aerobic metabolism a cell naturally produces ROS; however tumors require a higher amount of energy to support their increased rate of cellular activity. As a consequence the neoplastic phenotype of many tumors is associated with an increased production of ROS. During aerobic metabolism, electrons can escape from the mitochondrial electron transport chain, especially complexes I and III, and react with molecular oxygen to form the superoxide radical. This superoxide radical is then converted into hydrogen peroxide by superoxide dismutase 2. As superoxides are constantly produced during respiration, and are converted into other ROS, mitochondria are considered a major source of cellular ROS in cancer [20].

Gao et al. [21] observed that 3,4-dihydroxyphenyl acetic acid (3,4DHPAA) was the only phenolic acid that exhibited a considerable antiproliferative effect in LNCaP prostate cancer and HCT116 colon cancer cells, which also was found in literature.

The effects of ferulic acid (FA) and p-coumaric acid (p-CoA) were investigated on proliferation and cell cycle phase distribution of the colon cancer cell line Caco-2. When the cells were treated with 1500 μM of FA, the cell number was reduced to 75% and 43% of control after 2 and 3 days of treatment, respectively. Similarly, when Caco-2 cells were treated with 1500 μM of p-CoA for 2 and 3 days, the cell number was 74% and 55% of control, respectively. The decrease in the G1 phase was reflected in an increased in S-phase population after 1

day of treatment and an increased in G2 phase population after 2 and 3 days of treatment with both phenolic acids. Neither FA nor p-CoA treatment had any significant effect on the proportion of cells in the sub-G1 phase [9].

Additionally, Janicke et al. [12] have investigated the effects of FA and p-CoA treatment on global gene expression in Caco-2 colon cancer cells. They have found that FA and p-CoA treatment delayed cell cycle progression and the expressions of a number of genes involved in centrosome assembly, such as RABGAP1 and CEP2, were upregulated by FA treatment as well as the gene for the S phase checkpoint protein SMC1L1 regulation, a total of 517 genes were significantly affected by FA and 901 by p-CoA.

Chiang et al. [22] showed that both caffeic acid phenylpropyl ester (CAPPE) and Caffeic acid phenethyl ester (CAPE) promoted significantly inhibition on the proliferation of human CRC HCT-116 and SW-480 cells. Both compounds significantly induced cell cycle arrest at the G0/G1 phase in a dose-dependent manner and also inhibited the expression of the cyclin D1 protein and NF-kB, as well suppressed the expression of proliferating cell nuclear antigen (PCNA) protein in CRC cells.

In the same study Chiang et al. [22] showed that CAPPE and CAPE significantly inhibited the growth of colorectal tumors in a mouse xenograft model, suppressed the expression of malignant biomarker proteins, such as PCNA and fatty acid synthetase (FASN) in tumor tissues and matrix metallopeptidase 9 (MMP-9).

The deregulation of cyclin D1 will not only promote mitogen-independent proliferation, but may also affect other cellular processes, both directly and indirectly, in ways that have potentially oncogenic consequences. These consequences include angiogenesis, through the regulation of VEGF expression, centrosome duplication and the DNA damage response. Nuclear cyclin D1 (but not cyclin D2) is rapidly degraded after DNA damage or replication stress as part of the S phase DNA damage checkpoint, but the remaining low levels contribute to efficient DNA repair. High levels of cyclin D1 prime cells for an enhanced DNA damage response, perhaps acting as a 'safety net' for rapidly proliferating cells, but sustained cyclin D1–CDK4 activity following DNA damage leads to the inappropriate re-replication of DNA and chromosomal damage. Collectively, these observations raise the question of which molecular functions of cyclin D1 are crucial during oncogenesis [23].

Jayaprakasam et al. [24] synthesized a series of ferulic and caffeic acid esters and tested for tumor cell proliferation, cyclooxygenase enzymes (COX-1 and -2) and lipid peroxidation inhibitory activities *in vitro*. In tumor cell proliferation inhibitory assays, caffeic acid esters were more active than the ferulates. For example, dodecyl and hexadecyl caffeates inhibited colon cells by 89% and 88%, respectively, at 20 µg/ml. However, they did not observe much difference in the activity profile for ferulic and caffeic acid esters in your study. Both ferulic and caffeic acid esters inhibited COX-1 and -2 enzymes and lipid peroxidation *in vitro*, although ferulic acid did not inhibit COX enzymes, caffeic acid showed specific COX-2 inhibition .

Events associated with the apoptotic effect of p-coumaric acid in human colorectal carcinoma (HCT-15 and Ht-29) cells were also investigated. Antiproliferative test showed that p-coumaric acid has an inhibitory effect on HCT-15 and HT-29 cells with an IC50 value of 1400 µmol/L and 1600 µmol/L, respectively. Colony forming assay revealed the time-dependent inhibition of HCT-15 and HT-29 cells subjected to p-coumaric acid treatment. Propidium iodide staining of treated HCT-15 cells showed increasing accumulation of apoptotic cells at sub-G1 phase of the cell cycle after p-coumaric acid treatment. HCT-15 cells observed with photomicrograph and scanning electron microscope showed the signs of apoptosis like blebbing and shrinkage after p-coumaric acid exposure. A fall in mitochondrial membrane potential and increasing ROS generation was observed in the p-coumaric acid treated cells. Further apoptosis evaluated by YO-PRO-1 staining also showed the time-dependent increase of apoptotic cells after treatment [25].

Puangpraphant et al. [26] isolated and purify diCQAs from yerba mate tea leaves and assess their anti-inflammatory and anti-cancer capabilities *in vitro* and explored their mechanism of action. After purified resulted in two fractions one containing 3,4- and 3,5- diCQAs. The diCQA fractions inhibited human colon cancer cells RKO and HT-29 cell proliferation by inducing apoptosis in a time- and concentration-dependent manner, but did not affect the protein levels of p21, p27, p53, and Bax: Bcl-2 ratio in RKO cells. In HT-29 cells, however, the diCQA fractions increased Bax: Bcl-2 ratio. The diCQA fractions increased the activation of caspase-8 leading to cleavage of caspase-3 in both RKO and HT-29 colon cancer cells. These results suggest that diCQAs in yerba mate could be potent anti-cancer effect and could mitigate other diseases also associated with inflammation.

Xiang et al. [27] investigated the effect of CAPE on the growth, cell cycle and apoptosis of colon cancer cells and demonstrate that CAPE treatment was associated with a strong inhibition of growth in a dose- and time-dependent manner, along with induction of G0/G1 arrest and apoptosis in both HCT116 and SW480 colon cancer cells. CAPE also reduced the expression of cyclin D1 and C-MYC in a dose and time dependent manner.

The C-MYC oncogene has been highlighted as a key element in the tumorigenesis of various human cancers. Recent evidence reinforces the direct and indirect participation of the C-MYC protein in cell cycle regulation, differentiation, metabolism, cell growth, apoptosis, genomic instability, immortality and angiogenesis. New efforts have focused on the identification of target genes regulated by C-MYC and explaining the molecular mechanisms involved in neoplastic cell transformation. However, the greatest challenge is the development of tools capable of modulating the interaction between the C-MYC protein and its molecular targets, thereby revealing potential therapeutic approaches [28].

The effect of three phenolic acids (caffeic, coumaric and ferulic) were examined on superoxide anion production, adhesion and migration of colon adenocarcinoma (HT29-D4) cancer cell lines. Proliferation of tumor cells was inhibited by caffeic, coumaric and ferulic acids also significantly inhibited superoxide production in HT29-D4 cells. Superoxide anion production decreased by 77% at the highest tested concentration (200 mM) of caffeic acid in HT29-D4 cell line. Furthermore, HT29-D4 cell adhesion was reduced by 79.8% at the higher tested concentration ferulic acid (200 mM) [29] (Figure 4).

Hudson et al. [30] investigated the potential colon tumor suppressive properties of rice, testing the hypothesis that rice contains phenols that interfere in cell proliferation or colony-forming ability of colon cells. Eight hydroxycinnamic acids, including p-coumaric, caffeic, ferulic, sinapic, vanillic and methoxycinnamic acids were identified in the extracts of two different types of rice (bran and brown extract). Bran extract decreased the numbers of viable colon-derived SW480 cells and human colonic epithelial cells. It also reduced colony formation of SW480 cell line and MDA-MB-468 breast cancer cells.

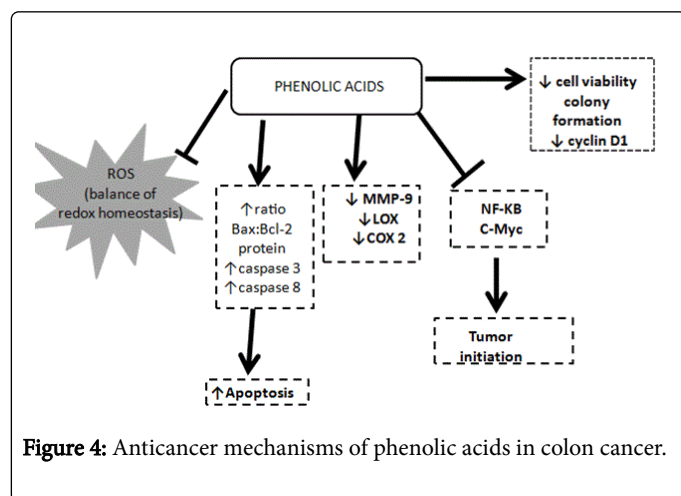CA (50 μM) decreased the number of viable cells in all cancer cell lines studied, in this study except HBL 100.

Figure 4: Anticancer mechanisms of phenolic acids in colon cancer.

Human CRC cells (480 and SW620), were incubated with cycloartenyl ferulate (CF) for 72 hr. Among the phenolic compounds tested in another moment, CF showed the most prominent growth inhibition on the CRC cells, the cancer cell growth was inhibited by 62% and 31 % of their control levels, respectively. Among the CRC cells, SW480 was found to be the most responsive cell line for the CF treatment with dose-dependent growth inhibition and induce apoptosis. The anticancer effect of CF was further confirmed with nude mice transplanted with SW480 solid tumor, administrations with CF (1.6 and 32 mg/kg) for 10 consecutive days reduced the tumor weight by 43 and 47% of the control level, respectively [31].

The inhibitory influence of FA, and its geranylated derivative 3-(4′-geranyloxy-3-methoxyphenyl)-2-propenoate (EGMP) on the post-initiation stage of azoxymethane (AOM)-induced colon carcinogenesis was studied in male F344 rats. The of aberrant crypt foci (ACF) and aberrant crypts (AC) per rat in the group given 0.2% FA were significantly decreased as compared to the AOM alone group. Furthermore, the amount of ACF and AC per rat fed the 0.2% and 0.1% EGMP were significantly reduced. Colonic epithelial cells in S-phase, in rats fed EGMP were significantly decreased in the 0.2 and 0.1% The results indicate that FA and EGMP have inhibitory effects on ACF and AC development, EGMP being more potent, possibly due to stronger suppressive effects on cell proliferation, suggesting that EGMP and FA, especially the former, might have potential as chemopreventive agents against colon tumor development [32].

Phenolic acids have been a prime source for the treatment of many forms of cancer, many of which are consumed daily in the diet. They provide significant protection against various cancers and many other diseases. The antioxidant potential of phenolic acids prevent from the cancer and other diseases by protecting cells from damage.

Following much time, money and effort invested in initial studies, many more years of clinical trials are required to ascertain a potential drug's effectiveness and safety in human patients. In an ideal situation, therapy would be tailored to suit the individual at the outset; this is unlikely at least for the very near future, despite rapid progress in pharmacogenomics. In the meantime, a better understanding of the mechanisms of resistance will at least allow the physician to modulate the therapy on a need to do basis. Phenolic acids have contributed a rich health of human beings. Plant extracts containing phenolic acids, which are responsible for anticancer activity; have to be screened for their valuable information.

Conclusion

In conclusion, this review found that phenolic acids could inhibit colon cancer cell proliferation and induce cancer cell apoptosis in part through oxidant-mediated mechanisms. However, additional studies are necessary to investigate which mechanisms and signal transductions are responsible for the regulation of cell cycle and apoptosis after treatment with phenolic acids and are required to clarify the mechanisms and to evaluate the bioavailability and metabolism of phenolic acids before it can be determined that intake can reduce colon cancer risk.

Acknowledgement

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