Coffee in cancer chemoprevention: an updated review

Coffee in cancer chemoprevention: an updated review.

Introduction: Chemoprevention of cancer refers to the use of natural or synthetic compounds to abolish or perturb a variety of steps in tumor initiation, promotion and progression. This can be realized through different mechanisms, including activation of free radical scavenging enzymes, control of chronic inflammation, and downregulation of specific signaling pathways

Areas covered: The goal of this article is to critically review recent evidence on association between coffee and prevention of different types of cancer, with particular emphasis on the molecular mechanisms and the bioactive compounds involved in its anticancer activity.

Expert opinion: Coffee is a mixture of different compounds able to decrease the risk of many types of cancer. However, its potential anticancer activity is not completely understood. Hundreds of biologically active components such caffeine, chlorogenic acid, diterpenes are contained in coffee. Further research is needed to fully elucidate the molecular mechanisms underlying the anticancer effects of coffee and fully understand the role of different confounding factors playing a role in its reported anticancer activity.

Key words: coffee, caffeine, cancer, chemoprevention, mechanisms of action

List of abbreviations: BCRP, breast cancer resistance protein; CI, confidence interval; diCQA, dicaffeoylquinic acid; EFSA, European Food Safety Authority; FQA, feruloylquinic acid (FQA); HHQ, hydroxyl hydroquinone; IARC, International Agency for Research on Cancer; IC_{50}, half

maximal inhibitory concentration; IL, interleukin; MMP, matrix metalloproteinases; NF, nuclear factor; NOAEL, no observed adverse effect level; PUMA, p53 upregulated modulator of apoptosis; ROS, reactive oxygen species; RR, relative risk; STAT3, transcription factor and signal translation 3; TDI, tolerable daily intake; T_{max} (time of maximum concentration observed).

.

Article highlights box

- Chemoprevention of cancer refers to the use of natural or synthetic compounds to abolish or perturb a variety of steps in tumor initiation, promotion and progression.
- Coffee is one amongst the leading beverages of the world with an estimated global consumption of 165.27million bags for the year 2019-20.
- Chemopreventive effects of coffee have been reported against several forms of cancers. Different cancer inhibitory properties have been proposed including oxidation inhibition, anti-inflammatory effects, and induction of cancer cell death. Chemopreventive properties of coffee are attributed to a variety of compounds including caffeine, chlorogenic acid, diterpenes like kahweol and cafestol.
- Comparing the amount of coffee exhibiting anticancer effects with the maximum daily consumption defined by EFSA, it is quite clear that coffee is able to evoke anticancer effects at amounts below the maximum daily consumption indicated by EFSA.
- Some bioactive compounds of coffee have been found to be genotoxic. However, coffee is devoid of genotoxic effects.
- Human gut flora plays a pivotal role in bioavailability and type of coffee metabolites to which individuals are exposed.

1. Introduction

Chemoprevention of cancer refers to the use of natural or synthetic compounds to abolish or perturb a variety of steps in tumor initiation, promotion and progression. This can be realized through different mechanisms, including activation of free radical scavenging enzymes, control of chronic inflammation, and downregulation of specific signaling pathways [1].

Coffee consumption history dates back to over 1000 year and presently, with an estimated global consumption of 165.27million bags for the year 2019-20, coffee is one amongst the leading beverages of the world (International Coffee Organization 2020). Coffee culture was propagated from Arabia, while most ancient manuscript that mentions coffee as a beverage dates 575 in Yemen. Globally, more than 70 species of *Coffea* L. exist but only two of them i.e., *Coffea arabica* (Arabica) and *Coffea canephora* (Robusta) are considered for coffee production [2]. Chemopreventive effects of coffee against several forms of cancers are under exploration and several models of cancer inhibitory properties have been proposed including oxidation inhibition, anti-inflammatory effects, and induction of cancer cell death. Chemopreventive properties of coffee are attributed to a variety of compounds including caffeine, chlorogenic acid, diterpenes like kahweol and cafestol holding different anticancer mechanisms (Figure 1).

Strong evidence exists suggesting chemopreventive effects of coffee against liver and endometrial cancer, while its inverse association with certain other types of cancers is still under debate [3, 4]. A daily increment in coffee consumption of one cup was reported to reduce cancer risk by 3% in a meta-analysis of 59 studies including 40 independent cohorts [5]. Subgroup analysis of the same study suggested coffee consumption to reduce risk of buccal, pharyngeal, breast, esophageal, hepatocellular, pancreatic, colorectal, endometrial, bladder cancer, and leukemia. Increasing rate of coffee consumption to ≥ 5cups a day was reported to reduce the incidence of all cancer sites and the associated mortality index [6].

A significant amount of epidemiologic literature has been published in the last five years to explore the association between coffee consumption and different types of cancers. This review is a critical appraisal of recent evidence on association between coffee and prevention of different types of cancer. Further, molecular mechanisms of coffee and its bioactive compounds against cancer are also limelight of this review.

2. Biochemistry of Coffee

Coffee has complex nature (Figure 1) with more than 800 volatile compounds. Its composition changes with production and preparation method [7]. Chemical composition of coffee beans depends on type of coffee, coffee cultivar, climatic conditions for coffee cultivation, and processing including roasting and grinding [8]. Approximately 6 – 10% of the green coffee dry weight is constituted by polyphenols including caffeine and chlorogenic acids like caffeic acid and its isomers 5-O-caffeoylquinic, 3-caffeoylquinic and 4-caffeoylquinic [9]. Green coffee contains two-fold higher amounts of 5- caffeoylquinic than observed in roasted coffee beans. Lower concentration of dicaffeoylquinic acid (diCQA) and its isomers 3,4-diCQA, 3.5-diCQA, 4,5-diCQA, feruloylquinic acid (FQA) and its isomers 3-FQA, 4-FQA, 5-FQA, *p*- coumaroylquinic and diferuloylquinic acids has also been reported in green coffee beans [10].

Caffeine is the most consistent compound of coffee beans and its concentration varies between 0.8 – 1.4% and 1.7 – 4.0% for Arabica and Robusta varieties, respectively [2]. Regional variation in caffeine contents of coffee has also been reported by Jeszka-Skowron et al. [11] suggesting Arabica coffee to hold twice as much of the caffeine than in Robusta and its concentration varied from 3.4 to 8.2%. In comparison with caffeine, five times higher concentration of chlorogenic acid – an esterification product of trans-cinnamic acids like *p*-coumaric acid, caffeic acid and ferulic acid was reported in coffee beans i.e., 7 – 12% (w/w) . Arabica coffee also contains higher concentration of lipids, sucrose and trigonelline.

Coffee's distinct flavor, taste and color are referred as an outcome of biochemical changes that emerge with coffee roasting. Green coffee amino acids, sucrose and chlorogenic acids produce melanoidins on roasting that distinctively anticipate typical flavor and color to the coffee [12]. Roasting merges phenolics into melanoidins in condensed form (42 – 62mmol per 100g), while trace amounts of phenolics bind to melanoidins in ester – linked forms (1.1 – 1.6mmol per 100g). Such a degradation of coffee phenolics anticipates approximately 23% loss of chlorogenic acids [13]. Coffee processing like decaffeination has not been reported to affect chlorogenic acids concentration; however, steaming with hot water anticipates significant reduction in 5-O-caffeoylquinic levels [11].

3. Pharmacokinetics of relevant coffee constituents

Pharmacokinetics of coffee components plays a major role in their net biological activity. Although caffeine fate in the human body is well characterized, there are few conclusive studies as to most of other bioactive compounds, particularly with regard to tissue and organ distribution in humans. A brief summary of the pharmacokinetics of selected and relevant constituents, i.e. caffeine, coffee chlorogenic acids, kahweol and cavestol, is reported below and is representative of a wider issue.

The most accurate report on the pharmacokinetic properties of caffeine - from coffee consumption - is a recent meta-analysis [14] which reviewed 43 articles published between 1980 and 2016. Caffeine taken from the oral route is rapidly absorbed in the small intestine raising its maximum availability in 45 minutes (absorption rate constant around $0.33 min^{-1}$) with no significant first pass effect. The volume of distribution ranges between 0.5 and 0.75l/kg and 10–30% of caffeine is bound to plasma-protein; the half-life is around 4 hours, the clearance between 1 and 3mg/kg/min, with an elimination process obeying a first-order kinetics. Caffeine freely crosses blood-brain, placental and testicular barrier and has no specific tissue accumulation. Liver accounts for most of caffeine primary metabolism by cytochrome P450 1A2, while only 3% or less is excreted unchanged in urine. Caffeine is metabolized through phase-I oxidation reactions mainly to the active derivatives paraxanthine, theobromine, and theophylline, followed by phase-II conjugation. 1-Methylxanthine, 1-methyluric acid, 5-acetylamino-6-formylamino-3-methyluracil, and 1,7-dimethyluric acid are the main caffeine metabolites in the urine.

Chlorogenic acids are a family of esters formed between a phenolic acid, e.g. caffeic or ferulic acid, and quinic acid. 5-caffeoylquinic acid is the chlorogenic acid present in higher quantities in coffee; caffeoylquinic, feruloylquinic and dicaffeoylquinic acids are also present in significant amounts. They are absorbed upon habitual coffee consumption giving rise to significantly bioavailable fractions [15].

The rate and extent of the absorption of chlorogenic acids from the gastrointestinal tract depends on their structure, particularly on the presence of an ester moiety that results in lower absorption [15]. Based on animal and *ex vivo* studies, ferulic, caffeic and p-coumaric acids could be absorbed from the stomach, jejunum, ileum and colon. In turn chlorogenic acids esters can be hydrolyzed in the stomach and upper intestine (in dependence of their resistance to pH variations [16], or undergo colonic transformation, which accounts for a significant proportion of their absorption. Indeed, in humans intricate and complex metabolic pathways transform chlorogenic acids

esters into phenolic acids (caffeic, ferulic and isoferulic moieties) and other colonic metabolites (dihydrocaffeic and dihydroferulic acids), which retain valuable bioactivities. Extensive conjugation (glycine, sulfate, glucuronide and methyl) at the level of the intestine and the liver as a result of first-pass metabolism further increases the array of metabolites produced from a single cup of coffee [17]. A significant proportion of these conjugated metabolites have been recently identified, although their validated quantification is yet to be determined.

Thirty percent of ingested chlorogenic acids is absorbed in the small intestine and gives rise to time of maximum concentration observed (T_{max}) plasma concentrations within 1 h. The main circulatory metabolites absorbed in the small intestine are caffeic acid-3′-O-sulphate and ferulic acid-4′-O-sulphate. This latter shows a second T_{max} at 4 h dependent on its relevant and additional colonic absorption "as is". The remaining 70% reaches the colon and may undergo microbial transformation into the hydrolysis by products of caffeic and quinic acids [18]. As it will be discussed in more detail in the "Expert opinion" section, gut microbiota metabolism plays a central role in chlorogenic acid bioavailability.

In general, there is a trend to reach higher plasma chlorogenic acid levels upon consumptions of greater amounts of coffee [18].

Chlorogenic acid metabolites formed by intestinal transformation, e.g., dihydroferulic acid and its conjugates, trigonelline as well as caffeine and its primary metabolites persist in the plasma for a fairly long time, in such a way that their levels are supposed to be hardly cleared during habitual coffee consumption of three cups of coffee per day [17]. Urinary excretion kinetics of chlorogenic acids and their metabolites have been carefully studied by Stalmach et al. [18].

Although its knowledge is still limited, the food matrix - especially the presence of milk proteins - may slightly affect the bioavailability of some coffee phenolic compounds [19].

About 90% of the cafestol and kahweol that enters the small intestine is absorbed there. Absorption of these important coffee diterpenes expressed as a percentage of the amount consumed is about 70%. Most of the other 30% is degraded by gastric juice; only a little fraction (8%) enters the colon; the amount available for the anticarcinogenic effects of coffee diterpenes at the whole-body level is thus very small. Moreover, only a very small amount of the cafestol and kahweol entering the circulation is subsequently excreted as conjugate of glucuronic acid or sulphate in urine. Therefore, the major part of the ingested cafestol and kahweol must be metabolized differently from just glucuronidation or sulphation of the cafestol and kahweol molecules [20].

About 70% of the consumption of cafestol and kahweol can be absorbed in the small intestine [20, 21]. In theory, glucuronidation and sulphation are the major pathways of xenobiotic biotransformation in mammalian species, which occurs largely in the liver, to produce water-soluble products that can be excreted by urine [21]. However, only about 1% or less of cafestol and kahweol consumption was detected to be excreted as conjugate of glucuronic or sulphuric acid in urine in previous studies [21]. It indicates that the major part of the absorbed cafestol and kahweol must be subject to more extensive metabolism, not just by glucuronidation or sulphation. There is evidence that cafestol does not seem to penetrate beyond the enterohepatic axis. Hence cafestol and/or its metabolites largely accumulate in liver and gastrointestinal tract through the enterohepatic cycle [19] triggering a variety of biological effects, including secondary changes in liver metabolism [18]. Secondary modifications in liver metabolism induced by cafestol are likely the cause of its unusually prolonged effect on plasma lipids.

4. Antioxidants in a Cup of Coffee

Coffee consumption delivers a significant amount of phenolics to the consumers and their concentration varies with type and rate of coffee consumption. In western culture, a 7-oz cup of coffee is expected to deliver around 350mg of phenolics to the consumer. People in Mediterranean region drink 2.2 cup of coffee on average while an American coffee cup made with 10g of coffee was reported to deliver 200mg chlorogenic acid [22, 23]. A review on antioxidant and anti-radical activity of coffee had previously reported 200 – 550mg of antioxidant consumption from one cup of coffee [24]. The amount varies with rate of coffee consumption and type of the coffee. A 25ml cup of espresso contains approximately 2.4mg/ml of caffeine, while the same coffee served filtered delivers 1.4mg/ml of caffeine [25].

5. Main Molecular Mechanisms Involved in the Anticancer Activity of Coffee

Development of cancer has various determinants that may be genetic and host-specific or linked to environmental exposure and lifestyle habits, such as alcohol, diet, obesity, physical activity, and certain stress factors like reactive oxygen species (ROS) quite often generated in response to infections [26]. Carcinogenesis is a multistep process that involves DNA mutations. ROS are known

for their essentiality in regulating biological functions such as inflammation, cellular differentiation and proliferation; contrarily, larger amounts of ROS may induce oxidation of cellular lipids and proteins, and generate DNA mutations [27]. Experimental evidence suggests that coffee compounds do not only inhibit DNA mutations but also modulate events involved in cancer development including apoptosis, angiogenesis, and metastasis [28] (Figure 1). Inverse relation between coffee consumption and risk of certain types of cancers is supported by epidemiological studies. Although the molecular mechanisms by which coffee's active ingredients exert anticancer effects are not much clear, there are some studies that report the anticancer mechanisms of coffee compounds [29] (Table 1). An *in vitro* study reported that chlorogenic acid and some metabolites of caffeine are able to inhibit free radicals-associated DNA damage. In particular, chlorogenic acids reduced DNA single-strand breaks on account of their one electron reduction potential well below 1.0 V [29]. Diterpenes of coffee like kahweol and cafestol have been previously reported to reduce carcinogens' activation by the inhibition of cytochrome P450 enzymes [30] and up-regulation of glutathione synthesis pathways [31]. Caffeic acid has also been documented as a potential anticancer compound with well-defined pharmacological mechanisms including inhibition of ROS production and DNA oxidation, reduction of angiogenesis, block of STAT3 (transcription factor and signal translation 3) activation, and suppression of collagenase IV like matrix metalloproteinases (MMP)-2 and MMP-9 [32]. Derivatives of caffeic acid including caffeic acid phenethyl ester and caffeic acid phenylpropyl ester also modulate aberrant AMP-activated protein kinase, mTOR and phosphatidylinositide 3-kinase/Akt signaling pathways, which are involved in cancer progression [33].

6. Activity of Coffee on Different Cancer Types

6.1. Colorectal Cancer

Global cancer statistics rates colorectal cancer as the 3rd most commonly diagnosed cancer and 4th highest death factor in both genders [34]. Colorectal cancer is a heterogeneous disease that generates as an outcome of activities involving epigenetic alterations and genetic mutations of genes implicated in cellular growth and differentiation [35]. It is widely accepted that natural compounds may play a chemopreventive role against different cancer. In this context, the World Health Organization

reported that around 80% of the entire world population depends on dietary-plants-based interventions as a part of primary health care solutions [36].

Sufficient epidemiological evidence highlighted chemopreventive and antitumor potential of coffee against the progression of colorectal cancer [37]. It has been proposed that the anti-carcinogenic effects of coffee consumption could be explained, at least in part, by the fractions of chlorogenic acids, which induce anti-inflammatory effect on intestinal epithelium and attenuates oxidative stress [38]. Multiple *in vitro* and *in vivo* experiments using colorectal cancer models have shown that application of coffee and coffee-derived compounds suppresses cell-cycle progression at the G0/G1 phase, inhibits cell proliferation, and induces apoptosis. Dose-dependent anti-proliferative effects of roasted coffee powder extracts (2.5-5% v/v in DMSO) have been recorded against human colon Caco-2 cells [39]. Induction of microRNA expressions (miR-30c and miR-96) and downregulation of KRAS proto-oncogene (GTPase gene) expression in signal transduction pathways were suggested as molecular mechanisms responsible for this effect. Interestingly, the same study identified that the reduction in KRAS activity was more prominent in Caco-2 cells treated with high-degree roasted coffee beans powder, suggesting that the active compound (melanoidins) emerged during the roasting process.

Isshiki et al. [40] explored the effect of coffee extracts on an intestinal transporter protein namely breast cancer resistance protein (BCRP), using human colorectal cells (Caco-2). Treatment of Caco-2 cells with aqueous extracts of roasted coffee (500µl) induced BCRP gene expression, leading to increased level of BCRP protein and cellular efflux activity. It is worth noting that BCRP protein play a pivotal role in removing food carcinogens from gastro-intestinal tract and favoring their excretion. In this regard, coffee-associated modification of BCRP activity might be associated with reduced risk of cancer progression.

Kahweol, a coffee-specific diterpene, has been proven to induce proapoptotic effect against colorectal carcinoma. Choi and his colleagues [41] treated HT-29 tumor cell lines with indicated concentration (100 µM-200 µM) of kahweol and after six hours observed over-expression of pro-apoptotic factors (caspase-3), down-expression of anti-apoptotic factors (Bcl-2 and phosphorylated Akt) as well as reduction in expression of heat shock protein 70, leading to an increase in apoptosis.

Plausible evidence exists from human studies proving that coffee as a chemopreventive strategy against colorectal cancer. In line with the findings on *in vitro* models, an inverse association

between coffee consumption and risk of colorectal cancer was reported in case-control and prospective observational studies. Coffee consumption was observed to reduce colorectal cancer risk in a dose-response manner with a pooled odds ratio of 0.74 [95% CI (confidence interval), 0.64 – 0.86] [42]. The study also recorded least odds ratio i.e., 0.46 (95% CI 0.39 – 0.54) for risk of colorectal cancer development at ≥2.5 servings of coffee a day. Another prospective study by Hu et al. reported 52% lower risk of colorectal cancer-related mortalities in individuals who maintained more than 4 cups of coffee a day during a median follow up of 7.8 years. Maintaining an intake of more than 2 cups of coffee per day after cancer diagnosis was also recorded to reduce colorectal cancer specific death with an average hazard ratio of 0.63 (95% CI; 0.44 – 0.89) [43]. Ethnicity appeared to be an important variable for identifying the relationship between coffee intake and colorectal cancer. Limited by high degree of heterogeneity and scarce information on the association between genetic make-up and risk of colorectal cancer in coffee consumers, decaffeinated coffee was reported to significantly reduce risk of colon cancer in Asian women (risk ratio 0.73; 95% CI; 0.58-0.88) and distal colon cancer in European men (risk ratio 0.77; 95% CI; 0.57-0.98) [44]. This study also established a weaker protective relationship between decaffeinated coffee consumption and colorectal cancer in USA men and women combined (risk ratio 0.83; 95% CI, 0.72-0.95) and European men (risk ratio 0.85; 95% CI, 0.72-0.99). No-significant relationship was observed in a dose-response analysis of coffee consumption and risk of colorectal and rectal cancers. Interestingly, a sub-group analysis from the same study again suggested a lower risk of colon cancer in Asian non-smokers with a risk ratio of 0.83 (95% CI, 0.71 – 0.97) for ≥ 4 cups of coffee a day [45]. Although the referred study was comprehensive in terms of its approach to exclude potential confounding factors, the authors indicated possible effects of recall bias, residual confounding factors that could not be excluded and red meat consumption to limit the study with no coffee – cancer relationship. A previous meta-analysis of 19 prospective cohorts involving 2,046,575 participants and 22,629 colorectal patients suggested 7% reduced risk of colorectal cancer development at a risk ratio of 0.93 (95% CI, 0.88 – 0.99) in individuals who consumed 4 cups of coffee a day [37]. At apparent, improved quality of research evidence on coffee and colorectal cancer that appeared in the last 5 years suggests coffee to not anticipate risk of colorectal cancers while larger prospective cohorts with better control over highlighted confounding factors and low to moderate heterogeneity may help in establishing a potential inverse relationship between coffee consumption and colorectal cancer.

6.2. Liver Cancer

Inverse association between coffee consumption and risk of liver cancer has been widely recognized in the last decade [28, 46]. Several prospective cohort and case-control studies have reported coffee consumption to protect against liver cancer and cancer-associated mortality [47]. A recent meta-analysis from Japan suggested coffee consumption as a significant contributor to lowering risk of liver cancer mortalities in Japanese populations [48]. Pooled relative risk of liver cancer in the highest coffee consumer group vs the lowest one or no coffee consumption was 0.50 (95% CI, 0.38 – 0.66). Yu et al. [49] in their meta-analysis of 20 prospective cohorts have been previously established a linear dose-response relationship between coffee intake and risk of liver cancer, while relative risk for highest to lowest or no coffee consumption was 0.55 (95% CI, 0.44 – 0.67) under no evidence of publication bias. Protective effect of coffee intake against hepatocellular carcinoma has been observed among more than 215,000 multiethnic cohort of men and women after a mean follow-up of 18 years [50]. Comparing with non-coffee drinkers and regardless of participants ethnicity, ≥ 4 cups of coffee intake per day was observed to reduce risk for hepatocellular carcinoma by 38% at hazard rate ratios of 0.59 (95% CI, 0.35–0.99). Similar beneficial effects with regular coffee intake were observed in a nested case-control study by Aleksandrova et al. [51] suggesting dose-response relationship between coffee consumption and hepatocellular carcinoma. It was observed that 1-2 cups of coffee per day lowered risk of hepatocellular carcinoma at risk ratio of 0.87 (95% CI, 0.77-0.98); however, a significant reduction in risk ratio (0.25) was observed with increasing coffee intake to ≥4 cups (95% CI, 0.11-0.62).

Dose-response relationship between coffee consumption and reduced risk of liver cancer was also reported by Kennedy et al. [52] in their large meta-analysis consisting of 18 cohorts and 8 case-control studies. The study suggested 2 cups of caffeinated or decaffeinated coffee to reduce relative risk of hepatocellular carcinoma by 27% [relative risk (RR) 0.73; 95% CI, 0.63 - 0.85), while reduction in hepatocellular cancer progression was 14% at RR of 0.86 (95% CI, 0.74 - 1.00).

Hepatoprotective effect of caffeinated coffee may be attributed to one of coffee alkaloids, i.e., caffeine that can anticipate an array of biological effects including antioxidant, anti-inflammatory and antiproliferative activities [53]. *In vitro* models with direct application of caffeine (in the range of about 10-1000mM) evidenced an attenuated progression of intrahepatic fibrosis in hepatic stellate cells via intracellular activation of F-actin and cyclic adenosine monophosphate and inhibition of

procollagen type Ic and alpha-smooth muscle actin expression, followed by induction of apoptosis [54]. Likewise, caffeine was also reported to alleviate periportal inflammation, levels of inflammatory cells, and fibrosis in a thioacetamide-induced liver fibrosis rats' model. In a study on two different cell lines (SMMC-7721 and Hep3B), combined treatment with caffeine (0.5mM) and 5-fluorouracil (25, 50μM) significantly (p<0.05) inhibited proliferation and increased apoptosis when compared with control or drug group; interestingly, these *in vitro* findings were also confirmed in nude mice injected subcutaneously with SMMC-7721, where caffeine model, where caffeine + 5-fluorouracil blocked tumor growth [55].

Kahweol has also been reported to exhibit *in vitro* anti-inflammatory activity against C57BL/6 rats-derived primary Kupffer cells and primary hepatocyte cultures [56]. Protective effects of kahweol against liver inflammation were attributed to its ability in inhibiting production of pro-inflammatory cytokines such as interleukin (IL) 1 alpha, IL-1 beta, IL-6, and tumor necrosis factor α, and suppressing NF-κB and STAT3 phosphorylation. Approximately, 91% reduction in tumor growth and tumor volume was recorded in immunodeficient nude mice inoculated intraperitoneally with HepG2 and treated with 60mg/kg b.w. chlorogenic acid for a period of six weeks [57].

6.3. Prostate Cancer

Epidemiological evidence on association between coffee consumption and prostate cancer risk is inconsistent, while *in vitro* and *in vivo* experimentation data presented in this section suggest inhibitory properties of coffee against prostate cancer.

Inhibitory effects of coffee against prostate cancer *in vitro* and animal studies have been associated with the expression of enzymes responsible for androgen metabolism. Prostate cancer's development depends on androgens, and synthesis of androgens depends on the expression of aldo-keto reductase enzymes. Kahweol and cafestol synergistically inhibit proliferation of prostate cancer cells in a dose-dependent manner by reducing androgen receptors, inhibiting epithelial mesenchymal transition, and downregulating chemokine receptor 2 and chemokine receptor 5 [58]. Significant reduction in prostate cancer cells proliferation and metastatic behavior was also recorded by Pounis et al. [59] in different human prostate cancer cell lines treated with caffeine.

A recent meta-analysis on 15 prospective cohort studies recorded reduced risk of prostate cancer with coffee consumption with 0.91 pooled RR at highest level of coffee consumption. A linear trend in risk of prostate cancer reduction was suggested with increment of each cup of coffee per day [60]. A meta-analysis of 14 case control and 14 cohort studies on 42,399 prostate cancer patients had previously reported that coffee consumption does not increase risk of prostate cancer, while an increment in coffee consumption by one cup reduced the risk of localized prostate cancer [61]. A comprehensive meta-analysis of 105 individual prospective studies on coffee consumption and its association with various types of cancer suggested an inverse relation between coffee intake and prostate cancer with a RR = 0.96, 95% CI for increment of two cups of coffee [62]. However, on a large cohort of 142,196 men followed up for a period of 14 years, Sen et al. [63]could not report any association between coffee consumption and prostate cancer risk. Moreover, a non-significant association between low to moderate coffee consumption and disease progression was recorded in cancer patients declaring referred coffee serving as safe in a prospective active surveillance study by Gregg et al. [64].

On the whole, evidence on coffee consumption and risk of prostate cancer are non-conclusive. A clear association between coffee consumption and lower risk of prostate cancer can be achieved by excluding the role of confounding factors. Interfering causality is however difficult to be avoided in observational estimates as have been laid down in the meta-analysis findings. A Mendelian randomization study was carried out by Taylor et al. [65] with genetic variants as proxies for coffee consumption to rule out effects of interfering causality like lifestyle and demographic factors. The results suggested a non-consistent effect of coffee intake either on prostate cancer incidence or its progression.

6.4. Breast Cancer

Breast cancer is the most prevalent gender-specific malignancy accounting for almost 25% cancer cases and is the 2nd leading death cause in women [34]. A prolonged exposure to excessive pituitary as well as sex hormones up-regulates the expression of growth hormone receptors, which stimulate abnormal cell proliferation and establishes malignancy in normal breast tissues [66].

Sufficient lines of evidence have outlined a chemoprotective role of coffee and its bioactive components in reducing the risk of breast cancer progression. However results from epidemiological studies remain controversial and inconsistent [67, 68].

A stratified meta-analysis of 13 prospective studies on coffee and breast cancer appeared in the year 2018 wherein subgroup analysis was performed for estrogen and or progesterone status, body mass index, menopausal status, and smoking as potential confounders. The study reported a non-significant relationship between coffee intake and risk of breast cancer [69]. An inverse association was recorded between highest to lowest coffee intake and breast cancer insurgency when data analysis was limited to post-menopausal women suggesting 10% reduction in cancer risk with ≥4cups of coffee intake per day (RR 0.90; 95% CI, 0.82 - 0.99). Weaker to moderate negative association between coffee consumption and risk of breast cancer has been defined from recent case-control and observational cohort studies. Around 10,812 middle aged Spanish females were followed up for 115,802 person-years to define association between coffee consumption and breast cancer [70]. Even if the study enrolled a fewer number of cases, findings of this small cohort evidenced an inverse association between coffee intake and risk of breast cancer for post-menopausal women who consume more than one cup of coffee per day (hazard risk 0.44; 95%CI, 0.21 – 0.92) compared to those who consume one or less than one cup of coffee a day. A negative association was also recorded between brewed coffee consumption and breast cancer risk (adjusted odd ratio 0.48; 95% CI, 0.28 – 0.82) in a case-control study on Hong Kong Chinese women [71].

Antitumor activities of coffee, its extracts and bioactive components have been reported in *in vivo* and *in vitro* models of breast cancer. In a study focusing on caffeine and caffeic acid, Rosendah et al. [72] reported these two compounds were anti-proliferative, prevented Akt phosphorylation, reduced insulin-like growth factor-I receptor expression, and induced apoptosis in estrogen-receptor positive (MCF-7) and estrogen-receptor negative (MDA-MB-231) breast cancer cells. The cytotoxic effect was higher on MCF-7 as compared to MDA-MB-23 cells after 48 hours treatment with either caffein or caffeic acid.

Kahweol inhibited attachment-independent proliferation and clonogenicity and induced cytotoxicity in various types of human tumor cells. *In vitro* exposure of estrogen receptor-negative MDA-MB231 breast cancer cells to kahweol inhibited their proliferation accompanied by apoptosis induced via caspase (3/7 and 9) activation and cytochrome c release [73]. Additionally, kahweol was

reported to produce ROS including hydrogen peroxide in breast cancer cells and activate cytotoxicity affecting tumor cell growth and survival; however, this response was not monitored in normal breast cancer cells. Hydroxyl hydroquinone (HHQ) is another coffee compound potentially useful for breast cancer treatment. HHQ isolated from coffee inhibited growth of MDA-MB-231 and MCF-7 cells with half maximal inhibitory concentration (IC_{50}) value of 25μM/ml and 50μM/ml, respectively [74]. The study showed that HHQ induced ROS generation as well as compromised the permeability of mitochondria membrane. Furthermore, HQQ upregulated the expression of Bax and caspase-8 levels whereas downregulated phosphoglycerate kinase 1 and pyruvate kinase M2 expression, two proteins suppressing apoptosis.

6.5. Endometrial Cancer

One amongst the most common gynecological malignancies is endometrial cancer that is globally ranked as 14th leading cause of cancer-related mortality among women [34]. Beside genetic predisposition, increased body mass index and reproductive risk factors inducing estrogen excess increase probability of endometrial cancer development [75]. While there are studies claiming inverse association between circulating levels of insulin and coffee consumption, biological and epidemiological evidence suggests caffeinated and decaffeinated coffee consumption to reduce risk of endometrial cancer [76, 77]. In a cohort study on 39,532 Canadian women wherein a 12.2 years follow-up period ascertained 180 endometrial cancer cases, an average hazard ratio per cup increase for total and caffeinated coffee of 0.88 (95% CI, 0.79 - 0.95, 0.80 - 0.96, respectively) was reported, while the average hazard ratio per 100mg increase for caffeine was 0.93 (95% CI, 0.87 – 0.99), suggesting an inverse association between coffee or caffeine and risk of endometrial cancer [78]. A previous meta-analysis of 12 prospective cohort studies observed a dose-dependent reduction of risk of endometrial cancer [69]. While considering body mass index, menopausal status and smoking status as confounding factors, increase in daily coffee consumption up to 4 cups reduced risk of endometrial cancer by 20% at a pooled risk ratio of 0.80 (95% CI). Another dose-response meta-analysis of 13 prospective studies reported 7% reduction in risk of endometrial cancer with each cup of caffeinated or decaffeinated coffee per day, with a risk ratio of 0.66 and 0.77, respectively [79]. Coffee consumption has been reported to exhibit stronger inhibitory properties against endometrial cancer in women with body mass index higher than 25 and those who have never been treated with

hormones [79, 80]. It may be concluded from the findings of the referred studies that coffee consumption may better prevent endometrial cancer insurgency in obese women.

6.6. Lung Cancer

The epidemiological studies, conducted on the association between coffee consumption and lung cancer, led to inconclusive results.

A positive association has been indicated between coffee consumption and lung cancer risk, although not all studies consider the role of confounding factors such as tobacco consumption and smoking, in fact several studies have shown that the consumption of coffee and tea is strongly associated with smoking behavior, and vice [81, 82]. However, an updated meta-analysis of 17 cohort studies with a sum of 1.2 million participants, suggested that a high coffee consumption is associated with an increased risk of lung cancer irrespective of the race and smoking confounders [83]. A significant association of heavy coffee consumption with risk of lung cancer in men (odd ratio 1.41; 95% CI) but not in non-smokers (odd ratio 0.85; 95% CI) has been also reported by Xie et al. [84]. This study, however, recorded a high hazard ratio (HRs) of 1.49; 95% CI with exclusive coffee consumption of 2cups or more per day, in former smokers as compared to non-smokers (1.41; 95% CI). Earlier, a meta-analysis of 13 case control studies and 8 prospective cohorts reported no risk of lung cancer (risk ratio 0.92; 95%CI) in non-smokers while un-adjusted for smoking, the risk ratio increase for 1 cup per day was 1.04, suggesting tobacco as a highly probable confounding factor [85]. Adjusting smoking as potential confounder, an investigative prospective study from Japan Public Health Center found no association between habitual coffee consumption and risk of lung cancer however, despite observing a significant increase in the risk for small cell carcinoma [86].

In vitro and *in vivo* assays on lung cancer inhibitory properties of active ingredients of coffee - including chlorogenic acids and caffeic acid - are well documented and may provide baseline understandings on the molecular mechanism of cancer inhibitory activity of this popular beverage. Chlorogenic acids and caffeic acid significantly affect the expression of apoptosis genes and increase apoptotic response, respectively [87, 88]. Lung cancer inhibitory properties of chlorogenic acid, caffeic acid and caffeine have been causally associated with the reduced gene expression of stem cell markers including POU5F1, SOX2, NANOG, the down-regulating expression of vascular endothelial

growth factor, and the increased expression of p53 upregulated modulator of apoptosis (PUMA) protein, respectively [88, 89]. Chlorogenic acids were also suggested to prevent the development of new tumors in naïve mice and inhibit growth of lung cancer in tumor bearing mice [90].

6.7. Bladder Cancer

With nearly 165,000 per annum deaths worldwide, bladder cancer related fatalities rank seventh amongst cancers [10]. Bladder cancer occurrence is reportedly influenced with major risk factors including male gender, smoking and dietary exposure of chemicals [91]. The first observational study on the association of coffee consumption with bladder cancer was published in 1971; since then several epidemiological researches have been conducted on the topic but, unfortunately, their results are still inconclusive. The first epidemiological studies on coffee and bladder cancer have suggested that men who consume more than 49 cups of coffee a week or more than 7 cups of coffee a day have a high risk of bladder cancer [92]. However, the results obtained from a more recent meta-analysis of 12 cohort studies conclusively indicated that more than 4 cups of coffee, or> 500 ml per day, are associated with a higher risk of bladder cancer in male smokers as compared to non-smokers and females [93]. Such an inconsistency is undoubtedly linked, again, with smoking as residual confounder that had not been taken into account in the previous studies. Subsequent to the year 2016 the International Agency for Research on Cancer declared that coffee consumption was 'not classifiable as to its carcinogenicity to humans' and suggested to conduct larger prospective studies with necessary information on potential confounders: a large prospective cohort study with 469,047 participants and 6012 bladder cancer cases was then conducted in United States [46]. The study reported that the adjustment for smoking and other confounders results in a significant correction of the hazard risk for more than 4 cups per day from 1.91 to 1.18 at 95% CI. While there was positive association between tobacco smoking and coffee drinking, no evidence of association was observed for non-smokers. Similar findings were obtained in a meta-analysis of sixteen prospective studies comprising 2,122,816 participants and 11,848 bladder cancer patients [94]. On the whole, the more recent studies strongly suggest that no positive correlation between habitual intake of coffee and bladder cancer can be established until residual confounders are properly identified, measured and stratified.

6.8. Gastric Cancer

Epidemiology of gastric cancer, although remaining the second leading cause of cancer related mortalities, has quite changed in the last decades showing a significant and consistent decline in incidence. Reduction in gastric cancer-related mortalities is causally related to primary preventive strategies including better and healthier nutrition, well maintained standards of hygiene, and eradication of Helicobacter pylori infection [95]. Despite the experimental observations on the chemo-preventive properties of the bioactive constituents of coffee, epidemiological evidence on its consumption and gastric cancer are still inconsistent. Even if coffee consumption had been reported as an eliciting factor for various gastric disorders (i.e. gastroesophageal reflux, peptic ulcer), the updated literature does not support any association between coffee consumption and gastric ulcer [96]. Mononitrosocaffeidine and dinitrosocaffeidine have been reported as mutagenic *in vitro* [97]: however, six meta-analysis studies during the year 2015-16 collectively suggested the lack of non-linear association between normal coffee intake and risk of gastric cancer. Two of these analyses showed that high levels of coffee consumption, i.e. more than 6.5 cups per day, represent a risk factor for the onset of gastric carcinogenesis [84, 98, 99, 100], while one showed that coffee consumption reduces the risk of gastric cancer at a pooled relative risk of 0.94 for ≤1cup to 3/4 cups per day [84]. Another careful meta-analysis [99] did not support the hypothesis that higher coffee consumption is associated with elevated gastric cancer risk, although subgroup analyses suggested a positive association in the United States population and in the group of equal to or less than 10 years follow-up. The Authors concluded that further studies with larger sample size and longer follow-up times are needed to confirm these subgroup results.

6.9. Leukemia

Leukemia, either lymphoid or myeloid, is an abnormal hyper-proliferation of immature blood cells that may not generate solid tumor masses [101]. Leukemia ranks 13th among all types of cancers and the number of new cases of leukemia recorded in the year 2018 were 437,033 [4]. A number of active coffee constituents may be effective for the treatment of leukemia. Coffee active metabolites including caffeine and the diterpene kahweol are well known for their anti-carcinogenic activity by inducing apoptosis via caspase-3 activation, anti-apoptotic proteins down regulation, increased expression of Bax and mitochondrial cytochrome c release to cytosol [102, 103]. Cafestol – an active

diterpene of coffee - exerted fairly consistent cytotoxic response against leukemia cell lines (HL60 and KG1) by reduction in mitochondrial membrane potential, caspase-3 accumulation, externalization of phosphatidylserine, increase in levels of CD15 and CD11b [104]. Unlike the well documented *in vitro* anti-carcinogenic effects of coffee bioactive compounds, inconsistent and inconclusive findings are available on coffee consumption and its association with leukemia. Contrary to the findings of small epidemiological studies suggesting beneficial effects of coffee consumption against leukemia, regular coffee consumption has neither been supported as ameliorative agent nor as a concausal risk factor for any type of leukemia [105]. Stratified analysis by smoking status has identified relative risk for development of acute myeloid leukemia, thus pointing to the need for good quality observational data with better control over residual confounders [106]. Similar limitations were observed from the findings of Milne et al. (2018) where a positive exposure-correlation between coffee consumption during pregnancy and risk of acute lymphoblastic leukemia was observed pooling data from eight case-control studies. Average odd ratio for none to more than 2 cups of coffee were 1.27 (95% CI; 1.09 – 1.43). A cohort of 95,807 Japanese individuals was investigated for coffee consumption and risk of acute myeloid leukemia [106]. The data stratification by smoking status suggested non-significant association between acute myeloid leukemia and coffee consumption.

The risk assessment for parental coffee consumption and childhood leukemia also needs to be investigated in larger birth cohort studies with more accurate assessment of parental smoking and alcoholism confounders, since these two habits are recognized as possible risk factors for childhood acute myeloblastic leukemia and childhood acute leukemia insurgence [107].

6.10. Pancreatic Cancer

Tobacco smoking, chronic pancreatitis, aging and type 2 diabetes mellitus account for one quarter cases of pancreatic cancer. Approximately 15 – 30% of the pancreatic cancer cases are attributed to tobacco smoking, a modifiable risk factor, while aging is an independent non-modifiable major risk factor [69, 108]. Three meta-analysis reports - appeared in the last five years - found an association between coffee consumption and pancreatic cancer. With the exception of the study by Ran et al. [109], none reported coffee consumption to be associated with reduced risk of pancreatic cancer. Another meta-analysis in the same year reported a weak relationship between coffee consumption and increased risk of pancreatic cancer [110]). Reduced relative risk of pancreatic cancer in low to

high coffee consumers was reported in an interesting prospective cohort of never smoker women (n – 309,797) with an average age of 59.5 years [111]. Dose/response relative risks of coffee consumption adjusted for potential confounders (e.g. alcohol consumption and body mass index) decreased from 1.02 (95%CI; 0.83 – 1.26) to 0.87 (95%CI; 0.64 – 1.18) increasing coffee intake from 1 – 2 cups to ≥5 cups per day. Brewing methods influence likeliness of coffee intake and its level of consumption. Filtered coffee is the most popular brewing method in Scandinavian countries. In a risk assessment study for coffee and its association with cancer in Scandinavian countries [80], the authors found a multivariable adjusted hazard ratio of 0.74 (95%CI; 0.57 – 0.95) in high-filtered coffee consumers (≥4cups daily) when compared with low-filtered coffee consumers (≤ 1 cup daily): however higher coffee intake appeared to be safe when assessed independently of filtration.

7. Conclusion

Despite the limitations discussed above, epidemiological studies and experimental researches suggest that coffee consumption may help to prevent cancer. Similar effects have been found for decaffeinated coffee, suggesting that other components other than caffeine play a role in the cancer protective effects of coffee.

7. Expert Opinion

Coffee is a beverage commonly consumed worldwide. Roasted coffee is a complex mixture of many bioactive compounds, including caffeine, chlorogenic acids, and the diterpenes cafestol and kahweol. A plethora of epidemiological research findings suggests that both caffeinated and decaffeinated coffee consumption could be useful for inhibiting or reducing risk of different types of cancer. This suggests that the protective effects of coffee against cancer are due to other components other than caffeine. Cafestol and kahweol have been found to activate antioxidant pathways and detoxification enzymes and induce apoptosis in animal and *in vitro* experiments [112, 113]. Chlorogenic acid has been reported to induce apoptosis and inhibit hypoxia-stimulated angiogenesis and metastatization in many human cancer cell lines [114, 115, 116]. DiCQAs and caffeic acid exert antiproliferative effects on human oral carcinoma and hepatocellular carcinoma cells [117, 118]

EFSA suggests maximum daily consumption up to 400mg per day of caffeine by healthy adults (that equates to 3 – 6 cups of coffee per day) [119] does not raise concerns for adverse health effects. A study by Derossi et al. [120] suggested that 316 – 336mg of caffeine from one cup of American coffee, three cups of Turkish and five cups of Espresso coffee are well below the maximum allowable level of caffeine. Comparing the amount of coffee exhibiting anticancer effects, it is quite clear that coffee is able to evoke anticancer effects at amounts well below the maximum daily consumption indicated by EFSA.

However, the maximum daily consumption of caffeine for pregnant women determined by EFSA is lower (up to 200mg per day). This is due to the evidence that, during pregnancy, the half-life of caffeine is prolonged (6-16 hours) and returns to a range of 2-8 hours within 4 and 15 weeks after delivery [121]. Caffeine has been reported to cross the placenta and reaches the fetus. Neither fetus nor placenta are able to metabolize caffeine [53]. This evidence together with the prolonged half-life of caffeine during pregnancy leads to the conclusion that fetuses of caffeine-consuming mothers are exposed to caffeine for prolonged time [53].

Some bioactive compounds of coffee like chlorogenic acid and caffeic acid have been found to be genotoxic [122]. It is noteworthy that genotoxic compounds exhibit a dose-response relationship lacking a safe threshold or dose. This means that they can pose a risk even at very low doses. Moreover, the exposure to genotoxic compounds is associated with a broad range of negative effects for human health and in particular with the development of different high-impact diseases including cancer, atherosclerosis, and neurodegenerative diseases [123]. But bioactive compounds of coffee like kahweol and cafestol have been reported to exhibit protective effects against the genotoxicity of aflatoxin B1 in both rat and human cells [30].

Different studies explored the genotoxicity of coffee. Coffee is genotoxic to bacteria, fungi, and mammalian cell cultures. However, its genotoxicity disappears when cells are cultured with liver extracts, which consists of a mixture of metabolic enzymes. As such, *in vivo*, coffee is devoid of genotoxicity [124]. Thanks to the presence of genotoxic and antigenotoxic substances, coffee as a complex mixture may not be genotoxic. Therefore, positive genotoxicity results should take into account the concentration of the toxic component within a mixture, the matrix where the component is contained, and the presence of anti-genotoxic components in the same plant matrix. All these aspects may impact on the whole toxicity of coffee.

In 1991, the International Agency for Research on Cancer (IARC) assessed the carcinogenic effect of drinking coffee. IARC classified coffee as "*possible carcinogenic to humans*'' (Group 2B). After thoroughly analyzing more than 1000 studies in humans and animals, taking into account the impact of confounding factors, measurement errors, sample selection and recall bias [125], IARC established that there is inadequate evidence for the carcinogenicity of coffee drinking overall. Drinking coffee was not classifiable as to its carcinogenicity to humans (Group 3).

From the toxicological point of view, coffee is one of the major sources of acrylamide, a carcinogenic substance [126]. There are many studies in the literature on the carcinogenic effects of acrylamide, mainly on rodents, where acrylamide at doses >0.5mg/kg bw/day has been found to induce the formation of tumors in different tissues, such as mammary gland, ovary, thyroid, testes, skin, stomach [127]. However, the epidemiological data on humans are controversial [128, 129]. A wide range of human studies have been carried out to explore the association between exposure to acrylamide and increased cancer risk, but the results were inconsistent. This can be probably due to the extremely variable occurrence of acrylamide in food. In coffee, in particular, the content of acrylamide is strictly associated with the roasting parameters and the coffee species [130, 131]. As an example, at final temperatures for each level of roasting in the range 215-238°C and roasting times in the range 560-667 s, 100% of samples had levels of acrylamide in the range 170-484µg/kg [132]. Of note, animal toxicological studies identified specific modes of action for acrylamide, which resulted strain- and species-specific, not likely predictive for humans [133]. Moreover, genotoxicity does not represent the key mechanism of action for acrylamide carcinogenicity [134]. This may support an alternative mechanism of action for risk assessment and lead to the definition of a no observed adverse effect (NOAEL) and a tolerable daily intake level (TDI) for acrylamide.

Meanwhile, two recent population-based prospective cohort studies assessed the risk of dietary acrylamide exposure to breast cancer [135] and to endometrial or ovarian cancer in Japanese women [136]: the first study included 48.910 women aged 45-74 years, the second one 47 185 women aged 45-74 years; the intake of dietary acrylamide was calculated using a food frequency questionnaire; the average follow-up period was about 15 years. In these cohorts of Japanese women, no significant association between dietary acrylamide intake and risk of breast, endometrial or ovarian cancer was observed, even when stratified analyses were conducted by coffee consumption.

Despite of the current classification of IARC, and plausible evidences on reduced risk of all kind of mortalities in coffee consumers as have been measured from multination and multiethnic prospective cohorts [137], still coffee consumption and its association with all – sites cancers is controversial. A great deal of interest exists among the potential stakeholders to know about safety of all forms of coffee. Coffee undergoes many chemical reactions from the unroasted green bean, and the type of bean used for preparation of coffee (Arabica versus Robusta), the degree of roasting, and the brewing method within and between populations will impact on the biochemical composition of a cup of coffee. For example, one has to consume five Espresso or three Turkish coffee cups to get the same level of caffeine present in one American cup [138]. Moreover, also human gut flora plays a pivotal role in bioavailability and type of coffee metabolites to which that individuals are exposed [139]. The consumption of coffee (3 cups instant coffee/day for 3 weeks) [140] led to an increase in Bifidobacterium group of gut microbiota. This bacterial group (*Actinobacteria* phylum) has been associated with anti-inflammatory effects, which, in turn, may mitigate local inflammation and inhibit the carcinogenetic process [141].

Most coffee bean components are retained in spent coffee grounds, the residue obtained after brewing. Spent coffee grounds are particularly rich in phenolic compounds, melanoidins and dietary fiber exhibiting antioxidant properties [142]. Fermentation of spent coffee grounds by the human gut flora produced elevated amount of short chain fatty acids, which exert anti-inflammatory activity by suppressing nitric oxide production and cytokine modulation [143].

Dietary polyphenols are mostly utilized by the gut microbiota, since most escape digestion and have low absorption rate in the small intestine [144]. Phenolic compounds feed the human gut microbiota, and microbial metabolites of polyphenols are absorbed in the large intestine and reach the blood stream [145]. There is evidence from cellular, animal, and human studies that administration of coffee induces changes in microbial phyla (Proteobacteria, Actinobacteria, Bacteroidetes, and Firmicutes) and modify the end products of community metabolism [146]. Microbiota alterations may have an important role in the biotransformation of polyphenols, which, in turn, may exert collateral benefits associated with coffee consumption, such as a rise in polyphenol metabolites, which have antioxidant properties [147].

Melanoidins, present in high quantity in roasted coffee, are also able to modify gut microbiota composition, because they act as fiber-like compounds in the intestine gut, and could be considered

a probiotic for improving gut health. The microbial fermentation of these molecules led to an increase of fatty acid production, mainly acetate and lactate, favoring the growth of *Bifidobacterium* and *Faecalibacterium* genera. Furthermore, gut microbiota, by the fermentation of melanoidins, produces phenolics [specially pyrogallol, 2-(3,4-dihydroxyphenyl)acetic and 3-(3,4-dihydroxyphenyl)propionic acids)] [148], compounds with antioxidant activity [144].

In conclusion, recent studies find that coffee may decrease the risk of many types of cancer. However, its potential anticancer activity is not completely understood. Hundreds of biologically active components such caffeine, chlorogenic acid, diterpenes are contained in coffee. Further research is needed to fully elucidate the molecular mechanisms underlying the anticancer effects of coffee and fully understand the role of different confounding factors playing a role in its reported anticancer activity.

Table 1. *In vitro* chemopreventive effects of bioactive compounds of coffee

Compound	Experimental model	Concentrations	Cellular and molecular effects *	Reference
Cafestol	Head and neck squamous carcinoma (SCC25, CAL27 and FaDu cells)	0 - 200 µM	Induction of apoptosis	[149]
Cafestol	Renal cancer (Caki cells)	0 - 40 µM	Inhibition of proliferation, induction of apoptosis, ↑ caspases 2 and 3, cleavage of poly (ADP-ribose) polymerase, ↑ Bim and Bax, ↓ FADD-like IL-1β-converting enzyme)-inhibitory protein, ↓ Bcl-2, ↓ Mcl-1, ↓ Bcl-xL, release of cytochrome c, ↓ Akt phosphorylation	[150]
Cafestol	Leukemia (HL-60 and KG1 cells)	40, 80, and 150 µM	Induction of apoptosis, ↓ clonogenic potential, ↑ caspase 3, ↑ CD11b and CD15 differentiation markers, ↓ ROS generation	[112]
Cafestol + Kahweol	Rat primary hepatocytes	0–8 µg/ml	↓ Aflatoxin B1 metabolites binding on DNA	[30]

Caffeic acid	Irradiated plasmids	20 and 100 µM	↓ DNA single-strand breaks	[29]
Caffeic acid	Breast cancer (MCF-7, MDA-MB-231, Tam-R cells)	0 - 100 µM 0 - 200 µg/ml	Cytotoxicity, inhibition of cell proliferation and migration Cytotoxicity, ↓ p53, ↓ p21 after 1, 2 and 3 h from treatment, ↑ p21 after 48 h from treatment, ↑ Mcl-1	[72, 151, 152]
Caffeic acid	Lung cancer (H1299 and A549 cells)	0 – 800 µM	Induction of apoptosis, ↑ caspases 3 and 9, poly (ADP-ribose) polymerase cleavage, ↑ Bid, ↓ Bcl-xL, ↓ Bcl-2, ↑ phosphorylated ERK1/2 and JNK, inhibition of phorbol-12-myristate-13-acetate-stimulated invasion of A549 cells, ↓ MMP-9, ↓ MAPK and PI3K/Akt signaling, inactivation of NF-κB, activator protein 1, and STAT3, decrease in cell-matrix adhesion	[87, 115]
Caffeic acid	Liver cancer (WCH-17 cells)	1 mM	Inhibition of cell proliferation and survival, ↑ caspase 3/7, disruption of mitochondrial membrane potential	[117]
Caffeic acid and its esters (phenethyl ester and phenylpropyl ester)	Colorectal cancer (HCT-116 and SW480 cells)	0 – 100 µM	Inhibition of cell proliferation through a modulation of the PI3-K/Akt and 5' AMP-activated protein kinase signaling pathways	[33]
Caffeine	Irradiated plasmids	50 – 400 µM	↓ DNA single-strand breaks	[29]
Caffeine	Prostate cancer (PC-3 and DU145 prostate cancer cells)	0.5, 1 and 2 mM	↓ Cell proliferation, inhibition of cell adhesion and motility	[59]

Caffeine	Breast cancer (MCF-7, MDA-MB-231, Tam-R cells)	0 - 5 mM	MCF-7 cells: inhibition of cell proliferation by 80%, induction of cell death, ↓ estrogen receptor, poly (ADP-ribose) polymerase cleavage, ↓ cyclin D1, ↓ Akt, ↓ Bcl-xL, ↑ caspase 7 MDA-MB-231 cells: inhibition of cell proliferation by 40% Tam-R cells: inhibition of cell proliferation by 80%	[72]
Caffeine	Lung cancer (HTB182 and CRL5985 cells)	2 mM	Inhibition of cell proliferation, ↑ PUMA (CRL5985)	[12]
Caffeine	Leukemia (NB4 cells)	0 – 4 mM	Inhibition of cell proliferation, induction of apoptosis, ↑ caspase 3, ↑ Bax, ↑ p21	[103]
Caffeine	Liver inflammation (human hepatic stellate cells)	10 – 1000 mM	↓ Progression of intrahepatic fibrosis, ↑ F-actin and cyclic adenosine monophosphate, ↓ procollagen type Ic and alpha-smooth muscle actin expression, induction of apoptosis	[54]
5-caffeoylquinic acid	Colon cancer (HT-29 cells)	0 - 80 µM	Induction of apoptosis, inhibition of cell proliferation	[153]
Chlorogenic acid	Irradiated plasmids	20 – 200 µM	↓ DNA single-strand breaks	[29]

Chlorogenic acid	Lung cancer (A549 cells)	0 – 5000 µM	Inhibition of cell proliferation, induction of apoptosis, ↓ Bcl-2, ↑ Bax, ↑ Bax/Bcl-2, ↑ p38, ↑ JUN, ↑ caspase 3, ↓ stem cell marker-related genes (CD44, NANOG, POU5F1, and SOX2), inhibition of phorbol-12-myristate-13-acetate-stimulated invasion of A549 cells, ↓ MMP-9, ↓ MAPK and PI3K/Akt signaling, inactivation of NF-κB, activator protein 1, and STAT3, ↓ hypoxia-induced HIF-1α protein level, ↓ transcriptional activity of HIF-1α, ↓ vascular endothelial growth factor	[88, 114, 115, 116]
Chlorogenic acid	Liver cancer (HepG2 cells)	0 – 1000 µM	Inhibition of cell proliferation and colony formation, induction of cell death, inhibition of invasion and migration, ↑ p53, ↑ p21, ↓ DNA methyltransferase 1, ↓ ERK1/2 phosphorylation, ↓ MMP-2/TIMP-2, ↓ MMP-9 expression	[57, 100]
Chlorogenic acid	Leukemia (K562 cells)	5 mM	Generation of hydrogen peroxide, induction of apoptotic topoisomerase−DNA complexes	[114]
Chlorogenic acid	Solid tumor cell lines from hepatoma, lung cancer, glioma, and colon cancer (Huh7, H446 cells, U87MG, M059J, HCT-116, NCI-H358, A549-5FU, SK-LU-1, Bel-7402)	25 and 50 µM	Inhibition of cell proliferation, induction of cell differentiation, ↑ expression of key genes associated with differentiation (e.g. KHSRP, p53, and p21), ↓ expression of genes associated with poor differentiation (e.g. c-Myc and CD44)	[90]
Chlorogenic acid	Human umbilical vein endothelial cells	10 µM	↓ Hypoxia-induced tube formation, ↓ wound cell migration, ↓ cell invasion	[116]

Hydroxyl hydroquinone	Breast cancer (MCF-7 and MDA-MB-231 cells)	0 - 100 µM	Inhibition of cell proliferation and clonogenic survival, induction of apoptosis, ↑ intracellular ROS production, ↑ Bax, ↓ procaspase 8, ↓ phosphoglycerate kinase 1 and tumor specific pyruvate kinase muscle 2	[74]
Kahweol acetate and cafestol	Prostate cancer (NCaP, LNCaP-SF, PC-3, and DU145 cells)	100 µM	Induction of apoptosis, inhibition of epithelial-mesenchymal transition, ↓ nuclear androgen receptor	[58]
Kahweol	Colorectal cancer (HCT116, SW480, LoVo and HT-29 cells)	0 - 200 µM	Induction of apoptosis, ↑ caspase 3, poly (ADP-ribose) polymerase cleavage, ↓ Bcl-2, ↓ phosphorylated Akt, ↑ ATF3 transcription, ↓ heat shock protein 70	[41, 137]
Kahweol	Lung cancer (NCI-H358 and NCI-H1299 cells)	0 - 90 µM	Inhibition of cell proliferation, induction of apoptosis, ↓ basic transcription factor 3, ↓ ERK signaling pathway, ↑ p21, ↓ cyclin D1, ↑ Bax, ↓ Bcl-2 and Bcl-xL	[7]
Kahweol	Liver inflammation (primary Kupffer cells and primary hepatocytes)	40 µM	↓ lipopolysaccharide-induced production of interleukin 1 alpha, interleukin 1 beta, interleukin 6, and tumor necrosis factor alpha; ↓ lipopolysaccharide-stimulated phospho-nuclear factor kappa B and -signal transducer and activator of transcription 3 expression	[56]
Kahweol	Human umbilical vein endothelial cells	1, 5, and 25 µM	Inhibition of cell proliferation, migration, and invasion, inhibition of tubule formation, ↓ MMP-2 expression, ↓ urokinase, ↓ cyclooxygenase-2 and monocyte chemoattractant protein-1	[73]
Kahweol	Leukemia (U937 cells)	0 - 10 µM	Inhibition of cell proliferation, induction of apoptosis, ↑ ROS generation, ↑ caspases 2, 3, 8, and 9, cytochrome c release, ↓ Bcl-2, ↓ Bcl-XL, ↓ Mcl-1, ↓ XIAP, ↑ JNK, ↓ Akt phosphorylation, ↑ JNK pathway	[102]

Trigonelline	Liver cancer (AH109A cells)	0 - 40 µM	↓ Invasive capacity	[154]
Trigonelline	Colon cancer (Caco-2 cells)	100 µM	↓ KRAS	[39]

* See text for abbreviations. ↑ activation/increase, ↓ suppression/decrease

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Legends for figures

Figure 1. Main bioactive compounds and mechanisms of action of coffee involved in its cancer chemopreventive activity.

REFERENCES

1. de Melo FHM, Oliveira JS, Sartorelli VOB, et al. Cancer Chemoprevention: Classic and Epigenetic Mechanisms Inhibiting Tumorigenesis. What Have We Learned So Far? Frontiers in oncology. 2018;8:644. doi: 10.3389/fonc.2018.00644. PubMed PMID: 30627525; PubMed Central PMCID: PMC6309127.
2. Liberto E, Cordero C, Bicchi C. 4(th) Conference on Cocoa Coffee and Tea (CoCoTea 2017) - The world in a cup. Food research international. 2019 Jan;115:302. doi: 10.1016/j.foodres.2018.12.005. PubMed PMID: 30599945.
3. Marko L, Tonje B. Evidence on coffee consumption and pancreatic cancer: not great, not terrible. European journal of epidemiology. 2019 Aug 27. doi: 10.1007/s10654-019-00556-9. PubMed PMID: 31456080; eng.

4. WRCF. 2018 Worldwide cancer data: Global cancer statistics for the most common cancers. . Available at: https://wwwwcrforg/dietandcancer/cancer-trends/worldwide-cancer-data 2020.
5. Yu X, Bao Z, Zou J, et al. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC cancer. 2011 Mar 15;11:96. doi: 10.1186/1471-2407-11-96. PubMed PMID: 21406107; PubMed Central PMCID: PMCPmc3066123. eng.
6. Sado J, Kitamura T, Kitamura Y, et al. Association between coffee consumption and all-sites cancer incidence and mortality. Cancer science. 2017 Oct;108(10):2079-2087. doi: 10.1111/cas.13328. PubMed PMID: 28746796; PubMed Central PMCID: PMC5623740.
** Observational study on the relationship between coffee consumption and reduced incidence of all cancer sites.
7. Jeon JS, Kim HT, Jeong IH, et al. Determination of chlorogenic acids and caffeine in homemade brewed coffee prepared under various conditions. Journal of chromatography B, Analytical technologies in the biomedical and life sciences. 2017 Oct 1;1064:115-123. doi: 10.1016/j.jchromb.2017.08.041. PubMed PMID: 28918319; eng.
8. Belgodoum K, Amira-Guebailia H, Boulmokh Y, et al. HPLC coupled to UV–vis detection for quantitative determination of phenolic compounds and caffeine in different brands of coffee in the Algerian market. J Taiwan Inst Chem Eng. 2014;45:1314-1320.
9. Farah A, de Paulis T, Moreira DP, et al. Chlorogenic acids and lactones in regular and water-decaffeinated arabica coffees. Journal of agricultural and food chemistry. 2006 Jan 25;54(2):374-81. doi: 10.1021/jf0518305. PubMed PMID: 16417293; eng.
10. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210. PubMed PMID: 25220842; eng.
11. Jeszka-Skowron M, Sentkowska A, Pyrzyńska K, et al. Chlorogenic acids, caffeine content and antioxidant properties of green coffee extracts: influence of green coffee bean preparation. European Food Research and Technology. 2016 2016/08/01;242(8):1403-1409. doi: 10.1007/s00217-016-2643-y.
12. Wang X, Lim L-T. Chapter 27 - Physicochemical Characteristics of Roasted Coffee. In: Preedy VR, editor. Coffee in Health and Disease Prevention. San Diego: Academic Press; 2015. p. 247-254.
13. Coelho C, Ribeiro M, Cruz AC, et al. Nature of phenolic compounds in coffee melanoidins. Journal of agricultural and food chemistry. 2014 Aug 6;62(31):7843-53. doi: 10.1021/jf501510d. PubMed PMID: 24998624; eng.
14. Alsabri SG, Mari WO, Younes S, et al. Kinetic and Dynamic Description of Caffeine. Journal of Caffeine and Adenosine Research. 2018;8(1):3-9. doi: 10.1089/caff.2017.0011.
** Accurate description of the pharmacokinetic and pharmacodynamic properties of caffeine from coffee consumption.
15. Farah A, De Paula J. Consumption of Chlorogenic Acids through Coffee and Health Implications. Beverages 2019; 5(1)::11. doi: 10.3390/beverages5010011.
16. Clifford MN, Jaganath IB, Ludwig IA, et al. Chlorogenic acids and the acyl-quinic acids: discovery, biosynthesis, bioavailability and bioactivity. Natural product reports. 2017 Dec 13;34(12):1391-1421. doi: 10.1039/c7np00030h. PubMed PMID: 29160894.
17. Lang R, Dieminger N, Beusch A, et al. Bioappearance and pharmacokinetics of bioactives upon coffee consumption. Analytical and bioanalytical chemistry. 2013 Oct;405(26):8487-503. doi: 10.1007/s00216-013-7288-0. PubMed PMID: 23982107; eng.
18. Stalmach A, Williamson G, Crozier A. Impact of dose on the bioavailability of coffee chlorogenic acids in humans. Food & function. 2014 Aug;5(8):1727-37. doi: 10.1039/c4fo00316k. PubMed PMID: 24947504.
19. Renouf M, Guy PA, Marmet C, et al. Measurement of caffeic and ferulic acid equivalents in plasma after coffee consumption: small intestine and colon are key sites for coffee metabolism. Molecular

nutrition & food research. 2010 Jun;54(6):760-6. doi: 10.1002/mnfr.200900056. PubMed PMID: 19937852; eng.
20. De Roos B, Meyboom S, Kosmeijer-Schuil TG, et al. Absorption and urinary excretion of the coffee diterpenes cafestol and kahweol in healthy ileostomy volunteers. Journal of internal medicine. 1998 Dec;244(6):451-60. doi: 10.1046/j.1365-2796.1998.00386.x. PubMed PMID: 9893098.
21. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. The American journal of clinical nutrition. 2004 May;79(5):727-47. doi: 10.1093/ajcn/79.5.727. PubMed PMID: 15113710; eng.
22. Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. Journal of agricultural and food chemistry. 2001 Jul;49(7):3438-42. doi: 10.1021/jf0101410. PubMed PMID: 11453788; eng.
23. Veronese N, Notarnicola M, Cisternino AM, et al. Coffee Intake and Liver Steatosis: A Population Study in a Mediterranean Area. 2018 Jan 15;10(1). doi: 10.3390/nu10010089. PubMed PMID: 29342916.
24. Yashin A, Yashin Y, Wang JY, et al. Antioxidant and Antiradical Activity of Coffee. Antioxidants (Basel, Switzerland). 2013 Oct 15;2(4):230-45. doi: 10.3390/antiox2040230. PubMed PMID: 26784461; PubMed Central PMCID: PMCPmc4665516. eng.
25. Caporaso N, Genovese A, Canela M, et al. Neapolitan coffee brew chemical analysis in comparison to espresso, moka and American brews. Food research international. 2014;61:152-160. doi: 10.1016/j.foodres.2014.01.020. PubMed PMID: article.
26. Mathers JC, Strathdee G, Relton CL. Induction of epigenetic alterations by dietary and other environmental factors. Advances in genetics. 2010;71:3-39. doi: 10.1016/b978-0-12-380864-6.00001-8. PubMed PMID: 20933124; eng.
27. Liou GY, Storz P. Reactive oxygen species in cancer. Free radical research. 2010 May;44(5):479-96. doi: 10.3109/10715761003667554. PubMed PMID: 20370557; PubMed Central PMCID: PMCPmc3880197. eng.
28. Bøhn SK, Blomhoff R, Paur I. Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. Molecular nutrition & food research. 2014 May;58(5):915-30. doi: 10.1002/mnfr.201300526. PubMed PMID: 24668519; eng.

** Overview on the anticancer mechanisms of coffee.

29. Rathod MA, Patel D, Das A, et al. Inhibition of radical-induced DNA strand breaks by water-soluble constituents of coffee: phenolics and caffeine metabolites. Free radical research. 2013 Jul;47(6-7):480-7. doi: 10.3109/10715762.2013.788167. PubMed PMID: 23521605; eng.
30. Cavin C, Mace K, Offord EA, et al. Protective effects of coffee diterpenes against aflatoxin B1-induced genotoxicity: mechanisms in rat and human cells. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2001 Jun;39(6):549-56. doi: 10.1016/s0278-6915(00)00168-x. PubMed PMID: 11346484; eng.
31. Huber WW, Scharf G, Rossmanith W, et al. The coffee components kahweol and cafestol induce gamma-glutamylcysteine synthetase, the rate limiting enzyme of chemoprotective glutathione synthesis, in several organs of the rat. Archives of toxicology. 2002 Jan;75(11-12):685-94. doi: 10.1007/s00204-001-0295-5. PubMed PMID: 11876501; eng.
32. Espíndola KMM, Ferreira RG, Narvaez LEM, et al. Chemical and Pharmacological Aspects of Caffeic Acid and Its Activity in Hepatocarcinoma. Frontiers in oncology. 2019;9:541. doi: 10.3389/fonc.2019.00541. PubMed PMID: 31293975; PubMed Central PMCID: PMCPmc6598430. eng.
33. Chiang EP, Tsai SY, Kuo YH, et al. Caffeic acid derivatives inhibit the growth of colon cancer: involvement of the PI3-K/Akt and AMPK signaling pathways. PloS one. 2014;9(6):e99631. doi: 10.1371/journal.pone.0099631. PubMed PMID: 24960186; PubMed Central PMCID: PMCPmc4069067. eng.

34. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424. doi: 10.3322/caac.21492. PubMed PMID: 30207593; eng.
35. Mundade R, Imperiale TF, Prabhu L, et al. Genetic pathways, prevention, and treatment of sporadic colorectal cancer. Oncoscience. 2014;1(6):400-6. doi: 10.18632/oncoscience.59. PubMed PMID: 25594038; PubMed Central PMCID: PMCPmc4284625. eng.
36. Calixto JB. Twenty-five years of research on medicinal plants in Latin America: a personal view. Journal of ethnopharmacology. 2005 Aug 22;100(1-2):131-4. doi: 10.1016/j.jep.2005.06.004. PubMed PMID: 16006081; eng.
37. Gan Y, Wu J, Zhang S, et al. Association of coffee consumption with risk of colorectal cancer: a meta-analysis of prospective cohort studies. Oncotarget. 2017 Mar 21;8(12):18699-18711. doi: 10.18632/oncotarget.8627. PubMed PMID: 27078843; PubMed Central PMCID: PMCPmc5386640. eng.
38. Shimizu M. Multifunctions of dietary polyphenols in the regulation of intestinal inflammation. Journal of food and drug analysis. 2017 Jan;25(1):93-99. doi: 10.1016/j.jfda.2016.12.003. PubMed PMID: 28911547; eng.
39. Nakayama T, Funakoshi-Tago M, Tamura H. Coffee reduces KRAS expression in Caco-2 human colon carcinoma cells via regulation of miRNAs. Oncology letters. 2017 Jul;14(1):1109-1114. doi: 10.3892/ol.2017.6227. PubMed PMID: 28693281; PubMed Central PMCID: PMCPmc5494607. eng.
40. Isshiki M, Umezawa K, Tamura H. Coffee induces breast cancer resistance protein expression in Caco-2 cells. Biological & pharmaceutical bulletin. 2011;34(10):1624-7. doi: 10.1248/bpb.34.1624. PubMed PMID: 21963506; eng.
41. Choi DW, Lim MS, Lee JW, et al. The Cytotoxicity of Kahweol in HT-29 Human Colorectal Cancer Cells Is Mediated by Apoptosis and Suppression of Heat Shock Protein 70 Expression. Biomolecules & therapeutics. 2015 Mar;23(2):128-33. doi: 10.4062/biomolther.2014.133. PubMed PMID: 25767680; PubMed Central PMCID: PMCPmc4354313. eng.
42. Schmit SL, Rennert HS, Rennert G, et al. Coffee Consumption and the Risk of Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2016;25(4):634-639. doi: 10.1158/1055-9965.EPI-15-0924. PubMed PMID: 27196095; eng.
43. Hu Y, Ding M, Yuan C, et al. Association Between Coffee Intake After Diagnosis of Colorectal Cancer and Reduced Mortality. Gastroenterology. 2018 Mar;154(4):916-926.e9. doi: 10.1053/j.gastro.2017.11.010. PubMed PMID: 29158191; PubMed Central PMCID: PMCPmc5847429. eng.
44. Sartini M, Bragazzi NL. Coffee Consumption and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. 2019 Mar 24;11(3). doi: 10.3390/nu11030694. PubMed PMID: 30909640.
45. Micek A, Gniadek A, Kawalec P, et al. Coffee consumption and colorectal cancer risk: a dose-response meta-analysis on prospective cohort studies. International journal of food sciences and nutrition. 2019 Dec;70(8):986-1006. doi: 10.1080/09637486.2019.1591352. PubMed PMID: 30922134; eng.
46. Loftfield E, Freedman ND, Inoue-Choi M, et al. A Prospective Investigation of Coffee Drinking and Bladder Cancer Incidence in the United States. Epidemiology (Cambridge, Mass). 2017 Sep;28(5):685-693. doi: 10.1097/ede.0000000000000676. PubMed PMID: 28768299; PubMed Central PMCID: PMCPmc5604321. eng.
47. Salomone F, Galvano F, Li Volti G. Molecular Bases Underlying the Hepatoprotective Effects of Coffee. Nutrients. 2017 Jan 23;9(1). doi: 10.3390/nu9010085. PubMed PMID: 28124992; PubMed Central PMCID: PMCPmc5295129. eng.
48. Tamura T, Hishida A, Wakai K. Coffee consumption and liver cancer risk in Japan: a meta-analysis of six prospective cohort studies. Nagoya journal of medical science. 2019 Feb;81(1):143-150. doi: 10.18999/nagjms.81.1.143. PubMed PMID: 30962663; PubMed Central PMCID: PMCPmc6433635. eng.

49. Yu C, Cao Q, Chen P, et al. An updated dose-response meta-analysis of coffee consumption and liver cancer risk. Scientific reports. 2016 Dec 2;6:37488. doi: 10.1038/srep37488. PubMed PMID: 27910873; PubMed Central PMCID: PMCPmc5133591. eng.
50. Setiawan VW, Wilkens LR, Lu SC, et al. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. Gastroenterology. 2015 Jan;148(1):118-25; quiz e15. doi: 10.1053/j.gastro.2014.10.005. PubMed PMID: 25305507; PubMed Central PMCID: PMCPmc4274222. eng.
51. Aleksandrova K, Bamia C, Drogan D, et al. The association of coffee intake with liver cancer risk is mediated by biomarkers of inflammation and hepatocellular injury: data from the European Prospective Investigation into Cancer and Nutrition. The American journal of clinical nutrition. 2015 Dec;102(6):1498-508. doi: 10.3945/ajcn.115.116095. PubMed PMID: 26561631; PubMed Central PMCID: PMCPmc4658462. eng.
52. Kennedy OJ, Roderick P, Buchanan R, et al. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ open. 2017 May 9;7(5):e013739. doi: 10.1136/bmjopen-2016-013739. PubMed PMID: 28490552; PubMed Central PMCID: PMCPmc5730000. eng.
53. Grosso G, Godos J, Galvano F, et al. Coffee, Caffeine, and Health Outcomes: An Umbrella Review. Annual review of nutrition. 2017 Aug 21;37:131-156. doi: 10.1146/annurev-nutr-071816-064941. PubMed PMID: 28826374; eng.
54. Shim SG, Jun DW, Kim EK, et al. Caffeine attenuates liver fibrosis via defective adhesion of hepatic stellate cells in cirrhotic model. Journal of gastroenterology and hepatology. 2013 Dec;28(12):1877-84. doi: 10.1111/jgh.12317. PubMed PMID: 23808892; eng.
55. Wang Z, Gu C, Wang X, et al. Caffeine enhances the anti-tumor effect of 5-fluorouracil via increasing the production of reactive oxygen species in hepatocellular carcinoma. 2019 Oct 29;36(12):97. doi: 10.1007/s12032-019-1323-8. PubMed PMID: 31664534.
56. Seo HY, Kim MK, Lee SH, et al. Kahweol Ameliorates the Liver Inflammation through the Inhibition of NF-κB and STAT3 Activation in Primary Kupffer Cells and Primary Hepatocytes. Nutrients. 2018 Jul 4;10(7). doi: 10.3390/nu10070863. PubMed PMID: 29973533; PubMed Central PMCID: PMCPmc6073512. eng.
57. Yan Y, Liu N, Hou N, et al. Chlorogenic acid inhibits hepatocellular carcinoma in vitro and in vivo. The Journal of nutritional biochemistry. 2017 Aug;46:68-73. doi: 10.1016/j.jnutbio.2017.04.007. PubMed PMID: 28458139; eng.
58. Iwamoto H, Izumi K. Coffee diterpenes kahweol acetate and cafestol synergistically inhibit the proliferation and migration of prostate cancer cells. 2019 Apr;79(5):468-479. doi: 10.1002/pros.23753. PubMed PMID: 30569541.
59. Pounis G, Tabolacci C, Costanzo S, et al. Reduction by coffee consumption of prostate cancer risk: Evidence from the Moli-sani cohort and cellular models. International journal of cancer. 2017 Jul 1;141(1):72-82. doi: 10.1002/ijc.30720. PubMed PMID: 28436066.
60. Chen X, Zhao Y, Tao Z, et al. Coffee consumption is associated with a lower risk of prostate cancer: a meta-analysis. 2020.
61. Xia J, Chen J, Xue JX, et al. An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer. Urology journal. 2017 Aug 29;14(5):4079-4088. PubMed PMID: 28853102; eng.
62. Wang A, Wang S, Zhu C, et al. Coffee and cancer risk: A meta-analysis of prospective observational studies. Scientific reports. 2016 Sep 26;6:33711. doi: 10.1038/srep33711. PubMed PMID: 27665923; PubMed Central PMCID: PMCPmc5036059. eng.
63. Sen A, Papadimitriou N, Lagiou P, et al. Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. International journal of cancer. 2019 Jan 15;144(2):240-250. doi: 10.1002/ijc.31634. PubMed PMID: 29943826.
64. Gregg JR, Lopez DS, Reichard C, et al. Coffee, Caffeine Metabolism Genotype and Disease Progression in Patients with Localized Prostate Cancer Managed with Active Surveillance. The

Journal of urology. 2019 Feb;201(2):308-314. doi: 10.1016/j.juro.2018.08.048. PubMed PMID: 30179617; eng.
65. Taylor AE, Martin RM, Geybels MS, et al. Investigating the possible causal role of coffee consumption with prostate cancer risk and progression using Mendelian randomization analysis. International journal of cancer. 2017 Jan 15;140(2):322-328. doi: 10.1002/ijc.30462. PubMed PMID: 27741566; PubMed Central PMCID: PMCPmc5132137. eng.
66. Gebre-Medhin M, Kindblom LG, Wennbo H, et al. Growth hormone receptor is expressed in human breast cancer. The American journal of pathology. 2001 Apr;158(4):1217-22. doi: 10.1016/s0002-9440(10)64071-0. PubMed PMID: 11290538; PubMed Central PMCID: PMCPmc1891910. eng.
67. Fagherazzi G, Touillaud MS, Boutron-Ruault MC, et al. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public health nutrition. 2011 Jul;14(7):1315-20. doi: 10.1017/s1368980011000371. PubMed PMID: 21466740; eng.
68. Ganmaa D, Willett WC, Li TY, et al. Coffee, tea, caffeine and risk of breast cancer: a 22-year follow-up. International journal of cancer. 2008 May 1;122(9):2071-6. doi: 10.1002/ijc.23336. PubMed PMID: 18183588; PubMed Central PMCID: PMCPmc4186696. eng.
69. Lafranconi A, Micek A, Galvano F, et al. Coffee Decreases the Risk of Endometrial Cancer: A Dose-Response Meta-Analysis of Prospective Cohort Studies. Nutrients. 2017 Nov 9;9(11):1223. doi: 10.3390/nu9111223. PubMed PMID: 29120352.
70. Sánchez-Quesada C, Romanos-Nanclares A, Navarro AM, et al. Coffee consumption and breast cancer risk in the SUN project. 2020 Jan 18. doi: 10.1007/s00394-020-02180-w. PubMed PMID: 31955220.
71. Lee PMY, Chan WC, Kwok CC, et al. Associations between Coffee Products and Breast Cancer Risk: a Case-Control study in Hong Kong Chinese Women. Scientific reports. 2019 Sep 3;9(1):12684. doi: 10.1038/s41598-019-49205-x. PubMed PMID: 31481730; PubMed Central PMCID: PMCPmc6722060. eng.
72. Rosendahl AH, Perks CM, Zeng L, et al. 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 : an official journal of the American Association for Cancer Research. 2015 Apr 15;21(8):1877-87. doi: 10.1158/1078-0432.ccr-14-1748. PubMed PMID: 25691730; eng.
73. Cárdenas C, Quesada AR, Medina MA. Anti-angiogenic and anti-inflammatory properties of kahweol, a coffee diterpene. PloS one. 2011;6(8):e23407. doi: 10.1371/journal.pone.0023407. PubMed PMID: 21858104; PubMed Central PMCID: PMCPmc3153489. eng.
74. Shashni B, Sharma K, Singh R, et al. Coffee component hydroxyl hydroquinone (HHQ) as a putative ligand for PPAR gamma and implications in breast cancer. BMC genomics. 2013;14 Suppl 5(Suppl 5):S6. doi: 10.1186/1471-2164-14-s5-s6. PubMed PMID: 24564733; PubMed Central PMCID: PMCPmc3852186. eng.
75. Njoku K, Abiola J, Russell J, et al. Endometrial cancer prevention in high-risk women. Best practice & research Clinical obstetrics & gynaecology. 2020 May;65:66-78. doi: 10.1016/j.bpobgyn.2019.12.005. PubMed PMID: 32107136; eng.
76. Giri A, Sturgeon SR, Luisi N, et al. Caffeinated coffee, decaffeinated coffee and endometrial cancer risk: a prospective cohort study among US postmenopausal women. Nutrients. 2011 Nov;3(11):937-50. doi: 10.3390/nu3110937. PubMed PMID: 22254087; PubMed Central PMCID: PMCPmc3257719. eng.
77. Kiyama R. Estrogenic Activity of Coffee Constituents. Nutrients. 2019 Jun 21;11(6). doi: 10.3390/nu11061401. PubMed PMID: 31234352; PubMed Central PMCID: PMCPmc6628280. eng.
78. Arthur R, Kirsh VA, Rohan TE. Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women. Cancer epidemiology. 2018 Oct;56:75-82. doi: 10.1016/j.canep.2018.07.013. PubMed PMID: 30075330; eng.
79. Zhou Q, Luo ML, Li H, et al. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Scientific reports. 2015 Aug 25;5:13410. doi: 10.1038/srep13410. PubMed PMID: 26302813; PubMed Central PMCID: PMCPmc4548216. eng.

80. Lukic M, Guha N, Licaj I, et al. Coffee Drinking and the Risk of Endometrial Cancer: An Updated Meta-Analysis of Observational Studies. 2018 May-Jun;70(4):513-528. doi: 10.1080/01635581.2018.1460681. PubMed PMID: 29708405.
81. Bjørngaard JH, Nordestgaard AT, Taylor AE, et al. Heavier smoking increases coffee consumption: findings from a Mendelian randomization analysis. International journal of epidemiology. 2017 Dec 1;46(6):1958-1967. doi: 10.1093/ije/dyx147. PubMed PMID: 29025033; PubMed Central PMCID: PMCPmc5837196. eng.
82. Freedman ND, Park Y, Abnet CC, et al. Association of coffee drinking with total and cause-specific mortality. The New England journal of medicine. 2012 May 17;366(20):1891-904. doi: 10.1056/NEJMoa1112010. PubMed PMID: 22591295; PubMed Central PMCID: PMCPmc3439152. eng.
83. Zhu J, Zheng W, Sinha R, et al. Abstract 632: Associations of coffee and tea consumption with lung cancer risk: A pooled analysis of 17 cohort studies involving over 1.2 million participants. Cancer Research. 2019;79(13 Supplement):632-632. doi: 10.1158/1538-7445.am2019-632.
84. Xie Y, Qin J, Nan G, et al. Coffee consumption and the risk of lung cancer: an updated meta-analysis of epidemiological studies. European journal of clinical nutrition. 2016 Feb;70(2):199-206. doi: 10.1038/ejcn.2015.96. PubMed PMID: 26081490; eng.
85. Galarraga V, Boffetta P. Coffee Drinking and Risk of Lung Cancer-A Meta-Analysis. Cancer Epidemiol Biomarkers Prev. 2016 Jun;25(6):951-7. doi: 10.1158/1055-9965.epi-15-0727. PubMed PMID: 27021045; eng.
86. Narita S, Saito E. Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study. 2018 Apr 5;28(4):207-213. doi: 10.2188/jea.JE20160191. PubMed PMID: 29151475.
87. Min J, Shen H, Xi W, et al. Synergistic Anticancer Activity of Combined Use of Caffeic Acid with Paclitaxel Enhances Apoptosis of Non-Small-Cell Lung Cancer H1299 Cells in Vivo and in Vitro. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2018;48(4):1433-1442. doi: 10.1159/000492253. PubMed PMID: 30064123; eng.
88. Yamagata K, Izawa Y, Onodera D, et al. Chlorogenic acid regulates apoptosis and stem cell marker-related gene expression in A549 human lung cancer cells. Molecular and cellular biochemistry. 2018 Apr;441(1-2):9-19. doi: 10.1007/s11010-017-3171-1. PubMed PMID: 28875417; eng.
89. Wang G, Bhoopalan V, Wang D, et al. The effect of caffeine on cisplatin-induced apoptosis of lung cancer cells. Experimental hematology & oncology. 2015;4:5. doi: 10.1186/2162-3619-4-5. PubMed PMID: 25937999; PubMed Central PMCID: PMCPmc4417201. eng.
90. Huang S, Wang LL, Xue NN, et al. Chlorogenic acid effectively treats cancers through induction of cancer cell differentiation. Theranostics. 2019;9(23):6745-6763. doi: 10.7150/thno.34674. PubMed PMID: 31660066; PubMed Central PMCID: PMCPmc6815948. eng.
91. Antoni S, Ferlay J, Soerjomataram I, et al. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. European urology. 2017 Jan;71(1):96-108. doi: 10.1016/j.eururo.2016.06.010. PubMed PMID: 27370177; eng.
92. Clavel J, Cordier S. Coffee consumption and bladder cancer risk. International journal of cancer. 1991 Jan 21;47(2):207-12. doi: 10.1002/ijc.2910470208. PubMed PMID: 1988365; eng.
93. Yu EYW, Dai Y, Wesselius A. Coffee consumption and risk of bladder cancer: a pooled analysis of 501,604 participants from 12 cohort studies in the BLadder Cancer Epidemiology and Nutritional Determinants (BLEND) international study. 2020 Jun;35(6):523-535. doi: 10.1007/s10654-019-00597-0. PubMed PMID: 31927701.
94. Dai ZW, Cai KD, Li FR, et al. Association between coffee consumption and risk of bladder cancer in a meta-analysis of 16 prospective studies. 2019;16:66. doi: 10.1186/s12986-019-0390-3. PubMed PMID: 31528185.

95. Sitarz R, Skierucha M, Mielko J, et al. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer management and research. 2018;10:239-248. doi: 10.2147/cmar.s149619. PubMed PMID: 29445300; PubMed Central PMCID: PMCPmc5808709. eng.
96. Shimamoto T, Yamamichi N, Kodashima S, et al. No association of coffee consumption with gastric ulcer, duodenal ulcer, reflux esophagitis, and non-erosive reflux disease: a cross-sectional study of 8,013 healthy subjects in Japan. PloS one. 2013;8(6):e65996. doi: 10.1371/journal.pone.0065996. PubMed PMID: 23776588; PubMed Central PMCID: PMCPmc3680393. eng.
97. Ivankovic S, Seibel J, Komitowski D, et al. Caffeine-derived N-nitroso compounds. V. Carcinogenicity of mononitrosocaffeidine and dinitrosocaffeidine in bd-ix rats. Carcinogenesis. 1998 May;19(5):933-7. doi: 10.1093/carcin/19.5.933. PubMed PMID: 9635885.
98. Deng W, Yang H, Wang J, et al. Coffee consumption and the risk of incident gastric cancer--A meta-analysis of prospective cohort studies. Nutrition and cancer. 2016;68(1):40-7. doi: 10.1080/01635581.2016.1115093. PubMed PMID: 26710312; eng.
99. Li L, Gan Y, Wu C, et al. Coffee consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. BMC cancer. 2015 Oct 19;15:733. doi: 10.1186/s12885-015-1758-z. PubMed PMID: 26481317; PubMed Central PMCID: PMCPmc4615385. eng.
100. Liu H, Hua Y, Zheng X, et al. Effect of coffee consumption on the risk of gastric cancer: a systematic review and meta-analysis of prospective cohort studies. PloS one. 2015;10(5):e0128501. doi: 10.1371/journal.pone.0128501. PubMed PMID: 26023935; PubMed Central PMCID: PMCPmc4449182. eng.
101. Juliusson G, Hough R. Leukemia. Progress in tumor research. 2016;43:87-100. doi: 10.1159/000447076. PubMed PMID: 27595359; eng.
102. Oh JH, Lee JT, Yang ES, et al. The coffee diterpene kahweol induces apoptosis in human leukemia U937 cells through down-regulation of Akt phosphorylation and activation of JNK. Apoptosis : an international journal on programmed cell death. 2009 Nov;14(11):1378-86. doi: 10.1007/s10495-009-0407-x. PubMed PMID: 19768546; eng.
103. Safa M, Bashash D, Hamidpoor M. Induction of cell death and decreased cell proliferation in acute promyelocytic leukemia cells (NB4) by caffeine [Research]. The Scientific Journal of Iranian Blood Transfusion Organization. 2016;12(4):331-339. eng.
104. Higdon JV, Frei B. Coffee and health: a review of recent human research. Critical reviews in food science and nutrition. 2006;46(2):101-23. doi: 10.1080/10408390500400009. PubMed PMID: 16507475; eng.
105. Parodi S, Merlo DF, Stagnaro E. Coffee and tea consumption and risk of leukaemia in an adult population: A reanalysis of the Italian multicentre case-control study. Cancer epidemiology. 2017 Apr;47:81-87. doi: 10.1016/j.canep.2017.01.005. PubMed PMID: 28153669; eng.
106. Ugai T, Matsuo K. Coffee and green tea consumption and subsequent risk of acute myeloid leukemia and myelodysplastic syndromes in Japan. 2018 Mar 15;142(6):1130-1138. doi: 10.1002/ijc.31135. PubMed PMID: 29076523.
107. Orsi L, Rudant J, Ajrouche R, et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study. Cancer causes & control : CCC. 2015 Jul;26(7):1003-17. doi: 10.1007/s10552-015-0593-5. PubMed PMID: 25956268.
108. Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. Nature Reviews Disease Primers. 2016 2016/04/21;2(1):16022. doi: 10.1038/nrdp.2016.22.
109. Ran HQ, Wang JZ, Sun CQ. Coffee Consumption and Pancreatic Cancer Risk: An Update Meta-analysis of Cohort Studies. Pakistan journal of medical sciences. 2016 Jan-Feb;32(1):253-9. doi: 10.12669/pjms.321.8761. PubMed PMID: 27022386; PubMed Central PMCID: PMCPmc4794517. eng.
110. Nie K, Xing Z, Huang W, et al. Coffee intake and risk of pancreatic cancer: an updated meta-analysis of prospective studies. Minerva medica. 2016 Aug;107(4):270-8. PubMed PMID: 27348445; eng.

111. Zhou CD, Kuan AS, Reeves GK, et al. Coffee and pancreatic cancer risk among never-smokers in the UK prospective Million Women Study. International journal of cancer. 2019 Sep 15;145(6):1484-1492. doi: 10.1002/ijc.31994. PubMed PMID: 30426487; PubMed Central PMCID: PMC6767387.
112. Lima CS, Spindola DG, Bechara A, et al. Cafestol, a diterpene molecule found in coffee, induces leukemia cell death. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2017 Aug;92:1045-1054. doi: 10.1016/j.biopha.2017.05.109. PubMed PMID: 28618649.
113. Buldak RJ, Hejmo T, Osowski M, et al. The Impact of Coffee and Its Selected Bioactive Compounds on the Development and Progression of Colorectal Cancer In Vivo and In Vitro. Molecules. 2018 Dec 13;23(12). doi: 10.3390/molecules23123309. PubMed PMID: 30551667; PubMed Central PMCID: PMC6321559.
114. Burgos-Moron E, Calderon-Montano JM, Orta ML, et al. The coffee constituent chlorogenic acid induces cellular DNA damage and formation of topoisomerase I- and II-DNA complexes in cells. Journal of agricultural and food chemistry. 2012 Aug 1;60(30):7384-91. doi: 10.1021/jf300999e. PubMed PMID: 22793503.
115. Tsai CM, Yen GC, Sun FM, et al. Assessment of the anti-invasion potential and mechanism of select cinnamic acid derivatives on human lung adenocarcinoma cells. Molecular pharmaceutics. 2013 May 6;10(5):1890-900. doi: 10.1021/mp3006648. PubMed PMID: 23560439.
116. Park JJ, Hwang SJ, Park JH, et al. Chlorogenic acid inhibits hypoxia-induced angiogenesis via down-regulation of the HIF-1alpha/AKT pathway. Cellular oncology. 2015 Apr;38(2):111-8. doi: 10.1007/s13402-014-0216-2. PubMed PMID: 25561311.
117. Brautigan DL, Gielata M, Heo J, et al. Selective toxicity of caffeic acid in hepatocellular carcinoma cells. Biochemical and biophysical research communications. 2018 Oct 28;505(2):612-617. doi: 10.1016/j.bbrc.2018.09.155. PubMed PMID: 30278886.
118. Iwai K, Kishimoto N, Kakino Y, et al. In vitro antioxidative effects and tyrosinase inhibitory activities of seven hydroxycinnamoyl derivatives in green coffee beans. Journal of agricultural and food chemistry. 2004 Jul 28;52(15):4893-8. doi: 10.1021/jf040048m. PubMed PMID: 15264931.
119. Nawrot P, Jordan S, Eastwood J, et al. Effects of caffeine on human health. Food additives and contaminants. 2003 Jan;20(1):1-30. doi: 10.1080/0265203021000007840. PubMed PMID: 12519715; eng.
120. Derossi A, Ricci I. How grinding level and brewing method (Espresso, American, Turkish) could affect the antioxidant activity and bioactive compounds in a coffee cup. 2018 Jun;98(8):3198-3207. doi: 10.1002/jsfa.8826. PubMed PMID: 29230816.
121. van't Hoff W. Caffeine in pregnancy. Lancet (London, England). 1982 May 1;1(8279):1020. doi: 10.1016/s0140-6736(82)92019-0. PubMed PMID: 6122833; eng.
122. Committee ES, More S, Bampidis V, et al. Genotoxicity assessment of chemical mixtures. EFSA Journal. 2019;17(1):e05519. doi: 10.2903/j.efsa.2019.5519.
123. Fimognari C, Ferruzzi L, Turrini E, et al. Metabolic and toxicological considerations of botanicals in anticancer therapy. Expert opinion on drug metabolism & toxicology. 2012 Jul;8(7):819-32. doi: 10.1517/17425255.2012.685717. PubMed PMID: 22540949; eng.
124. Nehlig A, Debry G. Potential genotoxic, mutagenic and antimutagenic effects of coffee: a review. Mutation research. 1994 Apr;317(2):145-62. doi: 10.1016/0165-1110(94)90022-1. PubMed PMID: 7511793; eng.
125. Loomis D, Guyton KZ, Grosse Y, et al. Carcinogenicity of drinking coffee, mate, and very hot beverages. The Lancet Oncology. 2016 Jul;17(7):877-878. doi: 10.1016/s1470-2045(16)30239-x. PubMed PMID: 27318851; eng.
126. Wang Q, Chen X, Ren Y, et al. Toxicokinetics and internal exposure of acrylamide: new insight into comprehensively profiling mercapturic acid metabolites as short-term biomarkers in rats and Chinese adolescents. Archives of toxicology. 2017 May;91(5):2107-2118. doi: 10.1007/s00204-016-1869-6. PubMed PMID: 27738744.

127. Chain EPoCitF. Scientific Opinion on acrylamide in food. EFSA Journal. 2015;13(6):4104. doi: 10.2903/j.efsa.2015.4104.
*Review on the safety assessment of acrylamide.
128. Hogervorst JGF, van den Brandt PA, Godschalk RWL, et al. Interactions between dietary acrylamide intake and genes for ovarian cancer risk. European journal of epidemiology. 2017 May;32(5):431-441. doi: 10.1007/s10654-017-0244-0. PubMed PMID: 28391539; PubMed Central PMCID: PMC5506210.
129. Je Y. Dietary acrylamide intake and risk of endometrial cancer in prospective cohort studies. Archives of gynecology and obstetrics. 2015 Jun;291(6):1395-401. doi: 10.1007/s00404-014-3595-8. PubMed PMID: 25516180.
130. Bertuzzi T, Martinelli E, Mulazzi A, et al. Acrylamide determination during an industrial roasting process of coffee and the influence of asparagine and low molecular weight sugars. Food chemistry. 2020 Jan 15;303:125372. doi: 10.1016/j.foodchem.2019.125372. PubMed PMID: 31446360.
131. Pugajeva I, Jaunbergs J, Bartkevics V. Development of a sensitive method for the determination of acrylamide in coffee using high-performance liquid chromatography coupled to a hybrid quadrupole Orbitrap mass spectrometer. Food additives & contaminants Part A, Chemistry, analysis, control, exposure & risk assessment. 2015;32(2):170-9. doi: 10.1080/19440049.2014.1000979. PubMed PMID: 25530195.
132. Esposito F, Fasano E, De Vivo A, et al. Processing effects on acrylamide content in roasted coffee production. Food chemistry. 2020 Jul 30;319:126550. doi: 10.1016/j.foodchem.2020.126550. PubMed PMID: 32169765.
** Description of the impact of roasting on the presence of acrylamide in coffee.
133. Maronpot RR, Thoolen RJ, Hansen B. Two-year carcinogenicity study of acrylamide in Wistar Han rats with in utero exposure. Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie. 2015 Feb;67(2):189-95. doi: 10.1016/j.etp.2014.11.009. PubMed PMID: 25553597.
134. Eisenbrand G. Revisiting the evidence for genotoxicity of acrylamide (AA), key to risk assessment of dietary AA exposure. Archives of toxicology. 2020 Sep;94(9):2939-2950. doi: 10.1007/s00204-020-02794-3. PubMed PMID: 32494932; PubMed Central PMCID: PMC7415744.
** Report on the genotoxic and non-genotoxic effects of acrylamide.
135. Kotemori A, Ishihara J, Zha L, et al. Dietary acrylamide intake and risk of breast cancer: The Japan Public Health Center-based Prospective Study. Cancer science. 2018 Mar;109(3):843-853. doi: 10.1111/cas.13496. PubMed PMID: 29288560; PubMed Central PMCID: PMC5834785.
136. Kotemori A, Ishihara J, Zha L, et al. Dietary acrylamide intake and the risk of endometrial or ovarian cancers in Japanese women. Cancer science. 2018 Oct;109(10):3316-3325. doi: 10.1111/cas.13757. PubMed PMID: 30063274; PubMed Central PMCID: PMC6172050.
137. Park SY, Freedman ND, Haiman CA, et al. Association of Coffee Consumption With Total and Cause-Specific Mortality Among Nonwhite Populations. Annals of internal medicine. 2017 Aug 15;167(4):228-235. doi: 10.7326/m16-2472. PubMed PMID: 28693036; eng.
138. Reyes CM, Cornelis MC. Caffeine in the Diet: Country-Level Consumption and Guidelines. Nutrients. 2018 Nov 15;10(11). doi: 10.3390/nu10111772. PubMed PMID: 30445721; PubMed Central PMCID: PMCPmc6266969. eng.
139. Guertin KA, Loftfield E, Boca SM, et al. Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. The American journal of clinical nutrition. 2015 May;101(5):1000-11. doi: 10.3945/ajcn.114.096099. PubMed PMID: 25762808; PubMed Central PMCID: PMCPmc4409687. eng.
140. Jaquet M, Rochat I, Moulin J, et al. Impact of coffee consumption on the gut microbiota: a human volunteer study. International journal of food microbiology. 2009 Mar 31;130(2):117-21. doi: 10.1016/j.ijfoodmicro.2009.01.011. PubMed PMID: 19217682; eng.

* Description of the impact of coffee on the gut microbiota.
141. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World journal of gastroenterology. 2015 Oct 7;21(37):10609-20. doi: 10.3748/wjg.v21.i37.10609. PubMed PMID: 26457021; PubMed Central PMCID: PMCPmc4588083. eng.
142. Campos-Vega R, Oomah BD, Loarca-Piña G, et al. Common Beans and Their Non-Digestible Fraction: Cancer Inhibitory Activity-An Overview. Foods (Basel, Switzerland). 2013 Aug 2;2(3):374-392. doi: 10.3390/foods2030374. PubMed PMID: 28239123; PubMed Central PMCID: PMCPmc5302293. eng.
143. López-Barrera DM, Vázquez-Sánchez K, Loarca-Piña MG, et al. Spent coffee grounds, an innovative source of colonic fermentable compounds, inhibit inflammatory mediators in vitro. Food chemistry. 2016 Dec 1;212:282-90. doi: 10.1016/j.foodchem.2016.05.175. PubMed PMID: 27374534; eng.
144. Selma MV, Espín JC, Tomás-Barberán FA. Interaction between phenolics and gut microbiota: role in human health. Journal of agricultural and food chemistry. 2009 Aug 12;57(15):6485-501. doi: 10.1021/jf902107d. PubMed PMID: 19580283; eng.
145. Russell W, Duthie G. Plant secondary metabolites and gut health: the case for phenolic acids. The Proceedings of the Nutrition Society. 2011 Aug;70(3):389-96. doi: 10.1017/s0029665111000152. PubMed PMID: 21781364; eng.
146. Cowan TE, Palmnäs MS, Yang J, et al. Chronic coffee consumption in the diet-induced obese rat: impact on gut microbiota and serum metabolomics. The Journal of nutritional biochemistry. 2014 Apr;25(4):489-95. doi: 10.1016/j.jnutbio.2013.12.009. PubMed PMID: 24629912; eng.
147. Moco S, Martin FP, Rezzi S. Metabolomics view on gut microbiome modulation by polyphenol-rich foods. Journal of proteome research. 2012 Oct 5;11(10):4781-90. doi: 10.1021/pr300581s. PubMed PMID: 22905879; eng.
148. Pérez-Burillo S, Rajakaruna S, Pastoriza S, et al. Bioactivity of food melanoidins is mediated by gut microbiota. Food chemistry. 2020 Jun 30;316:126309. doi: 10.1016/j.foodchem.2020.126309. PubMed PMID: 32059165; eng.
149. Kotowski U, Heiduschka G, Seemann R, et al. Effect of the coffee ingredient cafestol on head and neck squamous cell carcinoma cell lines. Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]. 2015 Jun;191(6):511-7. doi: 10.1007/s00066-014-0807-x. PubMed PMID: 25575980.
150. Choi MJ, Park EJ, Oh JH, et al. Cafestol, a coffee-specific diterpene, induces apoptosis in renal carcinoma Caki cells through down-regulation of anti-apoptotic proteins and Akt phosphorylation. Chemico-biological interactions. 2011 Apr 25;190(2-3):102-8. doi: 10.1016/j.cbi.2011.02.013. PubMed PMID: 21334318.
151. Kabała-Dzik A, Rzepecka-Stojko A, Kubina R, et al. Caffeic Acid Versus Caffeic Acid Phenethyl Ester in the Treatment of Breast Cancer MCF-7 Cells: Migration Rate Inhibition. 2018 Dec;17(4):1247-1259. doi: 10.1177/1534735418801521. PubMed PMID: 30246565.
152. Rezaei-Seresht H, Cheshomi H, Falanji F, et al. Cytotoxic activity of caffeic acid and gallic acid against MCF-7 human breast cancer cells: An in silico and in vitro study. Avicenna journal of phytomedicine. 2019 Nov-Dec;9(6):574-586. doi: 10.22038/ajp.2019.13475. PubMed PMID: 31763216; PubMed Central PMCID: PMCPmc6823530. eng.
153. Murad LD, Soares Nda C, Brand C, et al. Effects of caffeic and 5-caffeoylquinic acids on cell viability and cellular uptake in human colon adenocarcinoma cells. Nutrition and cancer. 2015;67(3):532-42. doi: 10.1080/01635581.2015.1004736. PubMed PMID: 25803129; eng.
154. Hirakawa N, Okauchi R, Miura Y, et al. Anti-invasive activity of niacin and trigonelline against cancer cells. Bioscience, biotechnology, and biochemistry. 2005 Mar;69(3):653-8. doi: 10.1271/bbb.69.653. PubMed PMID: 15785001.