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).

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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 0.33min^{-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.

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