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A review of the chemopreventive effects of the main bioactive compounds in coffee in colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is a public health problem worldwide, and despite technological advances in diagnosis and treatment, its incidence and mortality continue to increase. In recent decades, considerable efforts have been made in evaluating natural dietary compounds as chemopreventive agents that help reduce the risk of cancer development, progression, or recurrence. Coffee is of particular interest as it has a high content of bioactive compounds, and there is strong epidemiological evidence that it has a protective effect against CRC. Here, we review the most abundant phytochemicals found in coffee [caffeine, chlorogenic acids (CGAs), cafestol, and kahweol] and their contribution to chemoprevention of CRC, as reported in *in vitro* studies and in animal studies. The literature shows that the chemopreventive effect of coffee is largely attributed to CGAs and cafestol/kahweol, rather than caffeine, although caffeine may have a small cumulative effect.

INTRODUCTION

According to the International Coffee Organization (www.ico.org), in 2019, 164.487.000 60 kg bags of coffee beans were sold worldwide, making it one of the most widely sought-after beverages. Interestingly, meta-analyses show that coffee consumption significantly reduces all-cause mortality, as well as reducing the risk of developing cardiovascular disease, several different types of cancer, and metabolic and liver conditions (Poole *et al*., 2017). Specifically, there is great interest in the effect of coffee on the incidence, severity, and response to treatment of colorectal cancer (CRC), as this is one of the most prevalent types of cancer worldwide, and the colon is directly exposed to the bioactive compounds in coffee when it is ingested. A literature review of epidemiological studies, as well as experimental *in vitro* and *in vivo* studies, has compiled evidence showing that coffee has a chemopreventive effect against CRC (Moreno-Ceballos *et al*., 2019).

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Coffee beans contain multiple phytochemicals such as caffeine, chlorogenic acids (CGAs), cafestol, and kahweol, to which many of these health effects can be attributed. Caffeine is the most commonly recognized compound present in coffee. This alkaloid and the metabolites derived from it have been shown to exhibit antioxidant, antiproliferative, and anti-inflammatory effects (Cui *et al*., 2020). Kahweol and cafestol are two diterpenes in the lipid fraction of the coffee bean, which are particularly interesting as they have been shown to induce apoptosis of malignant cells *in vitro* (Lee *et al*., 2012), reduce cell proliferation and migration (Moeenfard *et al*., 2016), and counteract oxidative stress (Lee *et al*., 2007). One of the main components of coffee is CGAs. This abundant group of polyphenols are esters formed between caffeic and quinic acids, of which 5-caffeoylquinic acid (5-CQA) is the main CGA present in coffee (Perrone *et al*., 2010). Evidence shows that CGAs also have antioxidant and anti-inflammatory activities (Liang and Kitts, 2015).

In this paper, we will review the effects of the main bioactive compounds in coffee : caffeine, CGAs, cafestol, and kahweol, in cell and animal models of CRC, in order to provide a clearer picture of how these phytochemicals contribute to the chemopreventive properties of coffee in CRC.

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Literature search

Results of the literature search are shown in Table 1. Studies were initially screened in order to eliminate review articles. After this screening, the remaining studies were assessed for eligibility independently by the authors in order to determine which ones were within the scope of this review. Bioinformatics and epidemiological studies were excluded, as well as studies with whole plant extracts, when it was not possible to determine if the effect was due to a specific component. For the case of cafestol and kahweol, all studies with cafestol included kahweol, so the studies were repeated when searching individually.

Bioactive compounds in coffee

The green coffee bean is composed of carbohydrates, lipids, proteins, alkaloids, minerals, and phenolic and aliphatic acids (see Fig. 1). The concentration of these components in the coffee bean varies according to variety and origin (altitude, climate, etc.). The toasting process, in particular, changes the chemical profile of the coffee bean, resulting in a decrease in total protein, reduction in CGAs, and a reduction in carbohydrates as these undergo a process of pyrolysis in which melanoidins are formed.

Table 1. Results of the literature search.

MeSH Terms	Database	Number of Records	Studies Included
(colorectal cancer OR colon) AND caffeine	Pubmed	25	8
(colorectal cancer OR colon) AND chlorogenic acid	Pubmed	26	7
(colorectal cancer OR colon) AND cafestol	Pubmed	12	6
(colorectal cancer OR colon) AND kahweol	Pubmed	15	

PARP = Poly (ADP-ribose) polymerase; NFkB = Nuclear factor kB; iNOS = inducible nitric oxide synthase; Cox-2 = cyclooxygenase-2; PAf = Platelet-activating factor; PGE2 = Prostaglandin E2; MPO = Myeloperoxidase; SOD = Superoxide dismutase; JNK = c-Jun N-terminal kinase; GSkB = Glycogen synthase kinase; ATF3 = Activating Transcription Factor 3

Although all of these components are integral to the aroma and flavor of the coffee we consume, the health benefits of coffee have been mainly attributed to alkaloids (caffeine), diterpenes in the lipid fraction (cafestol and kahweol), and CGAs (Sarraguça *et al*., 2016). In the literature, we find ample evidence as to the chemopreventive and bioactive activities of these substances against the hallmarks of cancer (Gaascht *et al*., 2015); thereby we will only focus on these components in the next sections.

Caffeine

Caffeine (1,3,7-trimethylxanthine) is an alkaloid from the xanthine group (see Fig. 1), naturally present in tea leaves, coffee beans, cocoa beans, and cola seeds, among others. Coffee beans contain less than 3% caffeine depending on species, origin, and roasting times (Górecki and Hallmann, 2020). It is the most well-known bioactive compound present in coffee and is mainly recognized as a central nervous system stimulant. There are many studies that report a protective effect of coffee consumption on the colon (Moreno-Ceballos *et al*., 2019); however, it is not altogether clear to what extent caffeine contributes to this effect. *In vitro* and *in vivo* studies of caffeine in CRC models are summarized in Table 2.

In a study in which colorectal carcinoma (HCT116) and normal colon (CCD-18co) cells were treated with 2 mM of

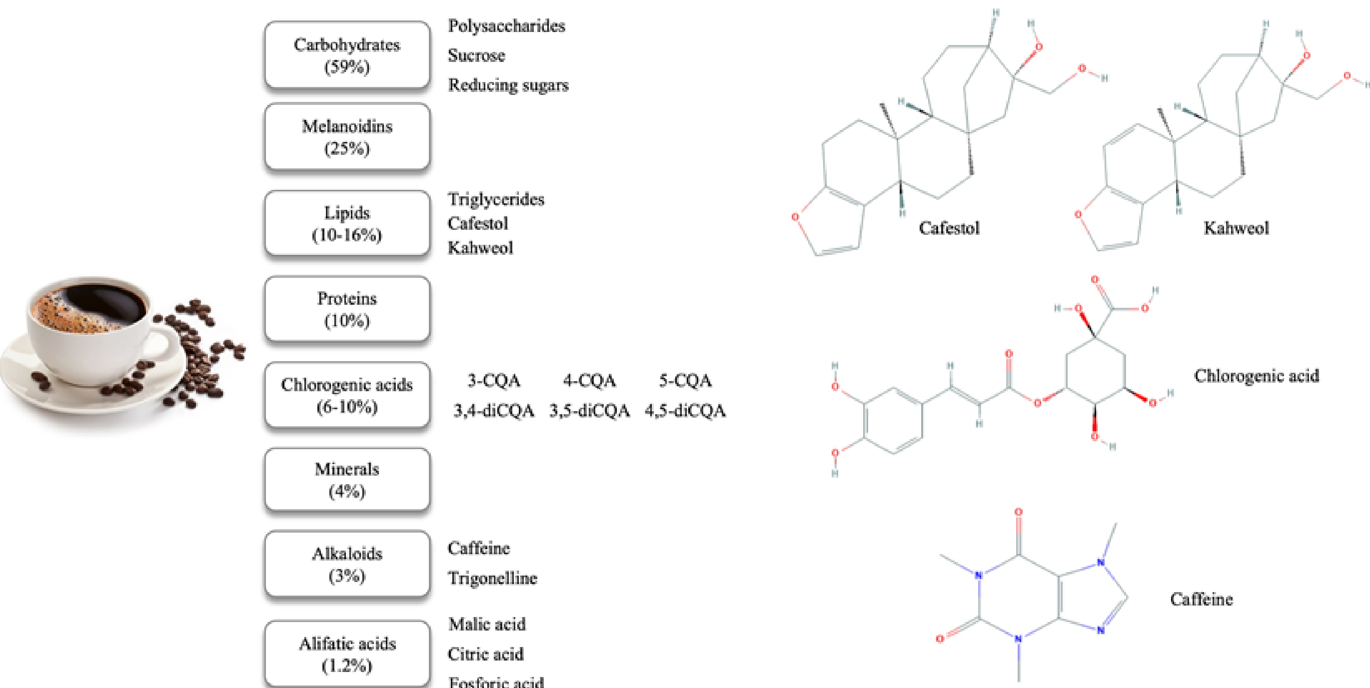

Figure 1. Main components in coffee beans. Percentages correspond to the contribution of each component to the total dry weight. Melanoidins are only present in the roasted coffee bean. 3-Caffeoylquinic acid (3-CQA), 4-caffeoylquinic acid (4-CQA), 5-caffeoylquinic acid (5-CQA), 3,4-dicaffeoylquinic acid (3,4-diCQA), 3,5-dicaffeoylquinic acid (3,5-diCQA), and 4,5-dicaffeoylquinic acid (4,5-diCQA). Chemical structures were taken from PubChem. Cup of coffee: Deman/Shutterstock.com.

Table 2. Summary of *in vitro* and *in vivo* studies in CRC models of the main bioactive compounds in coffee.

Experimental model	Dose/intervention	Biological effect	References
In vitro HCT116 p53 +/+ cells CCD-18Co cells	2 mM caffeine for 3 hours	**HCT116 p53 +/+ cells:** ↓ 14% cells phase G2/M ↑ 2.77-fold apoptosis **CCD-18Co cells**: ↓ 4.05% cells phase G2/M ↑ 0.23-fold apoptosis	(Saito *et al*., 2003)
In vitro HCT116 p53 +/+ cells HCT116 p53 −/− cells	35 different caffeine-hydrazones: 0 to > 25 µM for 24 hours	All 35 compounds induced apoptosis at 5 × IC_{50}, while at 1 × IC_{50} only hydrazones 23, 32, and 35	(Kaplánek *et al*., 2015)
In vitro HCT116 p53 +/+ cells HCT116 p53 −/− cells	2 mM caffeine for 2 hours + 100 nM doxorubicin for 5 days	**HCT116 p53 +/+ cells:** ↓ 3-fold SA-β-Gal activity ↓ 3.9-fold cell granularity **HCT116 p53 −/− cells:** ↓ 2-fold SA-β-Gal activity ↓ 1.8-fold cell granularity **Both:** ↑ 3-fold cell proliferation	(Strzeszewska *et al*., 2018)
In vitro Colo205 cells	0–20 µM caffeine for 2 hours 20 µM caffeine 2 hours + 80 µM paclitaxel 48 hours	**Caffeine alone:** No effect on apoptosis **Pretreatment with caffeine followed by paclitaxel:** ↑ 2-fold Mcl-1 expression ↑ 1.3-fold GRP78 expression ↓ 2-fold paclitaxel-induced apoptosis	(Mhaidat *et al*., 2014)
In vivo Male F344 rats	Rats were treated with three cycles of PhIP/HF diet: PhIP 50 mg/kg every day for 2 weeks followed by 4 weeks on HF diet with no PhIP Rats were then assigned to treatment groups: 0.065% caffeine or citrate buffer (controls) as sole source of drinking fluid for 1 year	**Caffeine group:** ↓ survival to 1 year (18% *vs.* 32% control) ↑ colon tumor incidence (73.3% *vs.* 41.6% control) ↑ 1.8-fold increase in tumor volume ↑ frequency of β-catenin mutations (79% *vs.* 36% control) ↑ c-myc mRNA ↑ cell proliferation in the colonic crypt ↓ apoptosis ↓ cleaved caspase-3	(Wang *et al*., 2008)
In vitro HT-29 cells rectal carcinoma cell line (RKO) cells Cocultured with peripheral blood mononuclear cells (PBMCs)	Caffeine: 25, 75, and 225 µg/ml for 24 hours	No effect on cell proliferation No effect IL-1β or IL-6 levels ↓ TNF-α production (30%, 41%, and 66% with HT-29) (21%, 45%, and 70% with RKO) ↓ IFNγ production (35%, 69%, and 83% with HT-29) (30%, 63%, and 84% with RKO) ↓ IL-1ra production (11%, 16%, and 17.5% with HT-29) (16.3%, 18%, and 29.3% with RKO) ↓ IL-10 production (only with 75 and 225 µg/ml caffeine)	(Bessler *et al*., 2012)
In vivo Male WT Balb/c mice	Treatment groups: Control Colitis (induced by DSS) CAC (induced by DSS and AOM) Colitis + caffeine 2.5 mmol/l CAC + caffeine 2.5 mmol/l	↓ tumor incidence (25% in CAC + caffeine *vs.* 75% in CAC) ↓ inflammation in colitis + caffeine vs. colitis ↓ CHI3L1 expression with caffeine ↓ 8-OHdG expression with caffeine	(Ma *et al*., 2014)
In vivo Male Wistar rats	Treatment groups: Control rats treated with caffeine (5.4 mg/kg) Carcinogen exposed rats (MNNG) treated with caffeine (5.4 mg/kg)	**In MNNG + caffeine** ↓ phosphorylation of histone γH2AX ↓ cyclooxygenase-2 (COX-2) expression ↓ metallothionein expression ↑ lipid peroxidation levels	(Soares *et al*., 2019)
In vitro Caco-2 cells	CGAs: 100, 250, 500, and 1,000 µM for 24 hours	↑ apoptosis ↑expression in caspase-3 (with 500 and 1,000 µM only) ↑ LDH release (250 µM, 12.2%, 500 µM, 22.5%, and 1,000 µM, 39.2%). ↓ cell proliferation (500 µM, 42.5%; 1,000 µM, 60.4%) ↓ cells in G0/G1 phase (≥ 250 µM) ↑ cells in S phase (≥ 250 µM)	(Sadeghi Ekbatan *et al*., 2018)

(Continued)

Experimental model	Dose/intervention	Biological effect	References
In vitro HCT116 cells HT-29 cells	CGA: 0, 125, 250, 500, and 1,000 µM for 24 to 72 hours	↓ cell viability ↑ ROS production S-phase arrest on both cell lines ↓ p-extracellular signal-regulated kinase (ERK)	(Hou *et al*., 2017)
In vitro HT-29 cells	CGA: 0, 0.01, 0.05, 0.1, 0.25, 0.5, 1, 2.5, and 5 mM for 48 hours	↓ cell proliferation (IC$_{50}$ 1.87 mM) ↓ 46% growth rate (with 1 mM)	(Nam *et al*., 2017)
In vitro HT-29 cells	MDQ: 0, 6.25, 12.5, 25, 50, 100, 200 ug/ml for 24, and 48 hours	↓ cell viability ↑ apoptosis Cell cycle arrest at G0/G1 ↓ p-ERK ↓ nuclear factor kappa beta (NFκβ) nuclear levels	(Hu *et al*., 2011)
In vitro RKO cells HT-29 cells	CGA, quinic acid, caffeic acid, diCQAs: 1, 50, 100, and 200 µM for 24 hours	**With all compounds:** ↓ NO production and inducible nitric oxide synthase (iNOS) expression ↓ proinflammatory markers PGE$_2$ and COX-2 **With diCQAs:** ↓ cell viability of RKO (IC$_{50}$ 180–190 µM) and HT-29 (IC$_{50}$ 280–300 µM) No effect on CCD-33Co cells ↑ apoptosis ↓ NFκβ nuclear levels	(Puangpraphant *et al*., 2011)
In vivo C57BL/6 mice (DSS-induced colitis)	Treatment groups: Control UC group (induced by DSS) UC + CGA low dose group (CGA-L): 30 mg/kg/day CGA for 10 days UC + CGA middle dose group (CGA-M): 60 mg/kg/day CGA for 10 days UC + CGA high dose group (CGA-H): 120 mg/kg/day CGA for 10 days	No significant results with CGA-L or CGA-M **CGA-H group:** ↓ CMDI ↓ IL-1*β*, IL-6, and TNF-*α* expression ↑ IL-10 expression ↓ platelet-activating factor (PAF), prostaglandin E2 (PGE2), and myeloperoxidase (MPO) expression ↑ superoxide dismutase (SOD) expression ↑ Bcl-2 expression ↑ Bax expression ↑ cleaved caspase 3 ↓ ERK1/2, p-ERK, p38, p-p38, c-Jun N-terminal kinase (JNK), p-JNK, p-I*κ*B, and p-p65	(Gao *et al*., 2019)
In vivo C57BL/6 mice (DSS-induced colitis)	Treatment groups: Control UC group (induced by DSS) UC + CGA 100 mg/kg UC + CGA 200 mg/kg	↓ p-ERK1/2 protein levels **In CGA 200 mg/kg:** ↓ nuclear and cytoplasmic NF-κB p65 ↓ AKT and p-AKT ↓ STAT3 and p-STAT3 ↓ Cox-2, NF-κB p65, and TNF-α	(Vukelić *et al*., 2018)
In vivo F344 mice	Several treatment groups including: Standard diet + kahweol : cafestol (1:1) 0.2% for 10 days and treated with PhIP	↓ 54% PhIP-DNA adduct formation in colon	(Huber *et al*., 1997)
In vivo F344 mice	Treatment groups: Control diet Kahweol : cafestol (1:1), 0.2%, 0.1%, 0.04%, and 0.02% for 10 days Cafestol, 0.2%, 0.1%, 0.04%, and 0.02% for 10 days	↑GSH and GCS in colon (K:C 0.1 and 0.2%) ↑↑↑GSH and GCS in liver	(Huber *et al*., 2002b)
In vivo F344 mice	Treatment groups: Control diet Kahweol : cafestol (1:1), 0.2%	↑ 25% GST-CDNB in colon	(Huber *et al*., 2002a)

(Continued)

Experimental model	Dose/intervention	Biological effect	References
In vitro HCT116 cells SW480 cells CCD-18Co	Kahweol: 0, 12.5, 25, and 50 µM for 24 and 48 hours	**HCT116 cells:** ↓ cell proliferation 16% and 48% at 12.5 mM, 28% and 69% at 25 mM, and 53% and 99% at 50 mM for 24 hours and 48 hours ↑ p-ERK1/2, p-JNK, and p-glycogen synthase kinase (GSKb) ↑ p-cyclin D1 (Thr286) **SW480 cells:** ↓ cell proliferation 8% and 12% at 12.5 mM, 19% and 38% at 25 mM, and 38% and 89% at 50 mM for 24 hours and 48 hours **CCD-18Co cells:** No effect on proliferation **In both:** ↓ cyclin D1 protein levels No change in cyclin D1 mRNA levels	(Park *et al*., 2016)
In vitro HCT116 cells SW480 cells LoVo cells HT-29 cells	Kahweol: 12.5, 25, and 50 µM for 24 hours	**In all cells:** ↑ cleaved poly (ADP-ribose) polymerase (PARP) (with 25 and 50 µM) ↑ activating transcription factor 3 (ATF3) protein and mRNA levels ↑ ATF3 promoter activity	(Park *et al*., 2017)
In vitro HT-29 cells	Kahweol: 0, 10, 25, and 50 µM	↓ cell proliferation (IC_{50} 61 ± 17 µM) ↓ number of colonies (50 µM) ↑ apoptosis (25 µM) Cell cycle unchanged	(Cárdenas *et al*., 2014)
In vitro HT-29 cells	Kahweol: 0, 10, 50, 100, and 200 µM	↓ cell proliferation and viability (50% at 200 µM) ↑LDH release (5-fold increase at 200 µM) ↑ caspase-3 and cleaved PARP ↓ Bcl-2 and p-Akt ↓ Hsp70	(Choi *et al*., 2015)

AOM = azoxymethane; CAC = colitis-associated carcinoma; CGA = chlorogenic acid; CMDI = colon mucosal damage index; DSS = dextran sodium sulfate; GCS = γ-glutamylcysteine synthetase; GSH = glutathione; GST = glutathione S-transferase; LDH = lactate dehydrogenase; MNNG = N-methyl-N-nitrosoguanidine; NO = nitric oxide; PhIP = 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine; ROS = reactive oxygen species.

caffeine for 3 hours, a selective effect of caffeine was reported on apoptosis and cell cycle in HCT116 cells (Saito *et al*., 2003). In terms of apoptosis, this increased 2.77-fold in treated HCT116 cells, but only 0.23-fold in CCD-18co cells. Cell cycle analysis revealed a 14% reduction of HCT116 cells in the G2/M phase 72 hours after treatment and a 4.05% reduction of CCD-18co cells in the G2/M phase. In another study in which 35 synthetic caffeine-hydrazones were tested on several types of cell lines, including human colorectal carcinoma HCT116 cells and HCT116 p53−/− cell lines, it was reported that all the compounds induced apoptosis at concentrations ranging between 0.34 and 25 µM in both cell lines (Kaplánek *et al*., 2015).

These results are contradicted by a study in which HCT116 cells were pretreated for 2 hours with 2 mM caffeine and afterward treated with 100 nM doxorubicin for 5 days (Strzeszewska *et al*., 2018). This study showed that when cells were pretreated with caffeine, the activity of SA-β-Gal reduced between 2- and 3-fold and cell granularity was reduced between 1.8- and 4-fold. SA-β-Gal is a biomarker of cellular senescence, while cell granularity is a phenotypic marker of cellular growth arrest or death (Haynes *et al*., 2009), so this study showed that treatment with caffeine reduces cell cycle arrest and cell death caused by doxorubicin. These results were reflected in a 3-fold increase in cell proliferation when cells were pretreated with caffeine.

Another report, which is in accord with the results published by Strzeszewska, described that when human colon cancer cells Colo205 were treated with different doses of caffeine ranging from 0 to 20 µM, there was no effect on apoptosis (Mhaidat *et al*., 2014). Moreover, when cells were pretreated with 20 µM caffeine, followed by treatment with paclitaxel, cells were significantly protected from the paclitaxel-induced apoptosis that is normally observed. This antiapoptotic effect seems to be due to increased activation of the ERK1/2 survival pathway by caffeine. The effect of caffeine on several cell survival mediators was analyzed by Western Blot, showing that treatment of cells with caffeine induced a 2-fold increase in Mcl-1, an antiapoptotic member of the BCL-2 family, as well as a slight (approximately 1.3-fold) increase in GRP78, a chaperone protein which responds to endoplasmic reticulum stress.

In an *in vivo* model of male F344 rats treated with PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine) to induce the formation of intestinal tumors, followed by 0.065% caffeine as a sole source of fluid intake, only 18% of rats survived to 1 year, which was lower than the PhIP control group (32% survival) (Wang *et al*., 2008). There was also an increase in the incidence of colon tumors in rats treated with caffeine versus the controls (73.3% *vs*. 41.6%) and in tumor volume (1.8-fold). However, caffeine showed a protective effect on other organs,

as the incidence of all noncolon tumors in the rats treated with caffeine was significantly lower than the controls (PhIP/HF + caffeine 13.3% *vs.* PhIP/HF controls 69.5%). There was a higher frequency of β-catenin mutations in caffeine-treated animals (79% *vs.* 36% in controls), as well as increased levels of expression of c-myc. This was reflected in an increase in cell proliferation and reduction of apoptosis in colonic crypts, as measured by cleaved-caspase three staining in the group treated with caffeine.

It has been shown that caffeine can have an effect on inflammation. In a study where PBMC cells were cocultured with HT-29 and RKO cells with 0, 25, 75, and 225 µg/ml caffeine for 24 hours, there was a dose-dependent effect of caffeine on the production of proinflammatory cytokines Tumor necrosis factor alpha (TNF-α) and IFNγ, as well as of anti-inflammatory cytokines IL-1ra and IL-10 by PBMC (Bessler *et al*., 2012). These results were confirmed by an animal study of colitis and colitis-associated carcinoma (CAC). In this *in vivo* study, WT Balb/c mice were treated with saline (control), dextran sodium sulfate (DSS) to induce colitis, or DSS followed by azoxymethane (AOM) in order to induce CAC (Ma *et al*., 2014). In the CAC group, when mice were also treated with caffeine, tumor incidence reduced 3-fold (25% in CAC + caffeine versus 75% in CAC). In the colitis group, inflammation was greatly reduced when mice were also treated with caffeine. This was confirmed by results that showed reduced expression of CHI3L1 in all groups treated with caffeine. This is significant as CHI3L1 has a role in inducing proinflammatory and protumorigenic and angiogenic factors that promote tumor growth and metastasis (Libreros *et al*., 2013). A widely used biomarker for oxidative stress, 8-OHdG, was also measured and showed reduced expression in the colon when mice were treated with caffeine.

In rats exposed to carcinogen N-methyl-N-nitro-N-nitrosoguanidine (MNNG) followed by daily oral gavage of caffeine, it was found that in the rats treated with caffeine there was a reduction in phosphorylation of histone γH2AX, which is an early cellular response to DNA damage, as well as a reduction in the expression of Cox-2, an enzyme involved in the production of prostaglandins during inflammation (Soares *et al*., 2019). This shows that caffeine reduces DNA damage and inflammation caused by MNNG. However, this same study showed conflicting results, as the treatment with caffeine post MNNG caused an increase in lipid peroxidation and a reduction in metallothionein expression, which is involved in protecting the cell against oxidative stress.

CGAs

CGAs are the most abundant phenolic acids found in green coffee extracts and tea, formed by the esterification of caffeic acid and quinic acid (see Fig. 1). They are divided into caffeoylquinic acids (CQAs: 3-CQA, 4-CQA, and 5-CQA), dicaffeoylquinic acids (diCQAs: 3,4-diCQA, 3,5-diCQA, and 4,5-diCQA), and feruloylquinic acids (FQAs: 3- FQA, 4- FQA, and 5-FQA). The content of these CGAs is approximately 10% of the dry weight of the coffee bean, although this varies according to species, origin, and roasting time (Ludwig *et al*., 2014). Many therapeutic properties have been ascribed to CGAs such as antioxidant, antibacterial, hepatoprotective, cardioprotective, and anti-inflammatory activities, among others (Naveed *et al*., 2018). *In vitro* and *in vivo* studies of CGAs in CRC models are summarized in Table 2.

A study in which Caco-2 cells were treated with 100–1,000 µM CGA for 24 hours showed an increase in cytotoxicity and apoptosis which brought about a decline in cell proliferation (Sadeghi Ekbatan *et al*., 2018). Cell membrane damage (cytotoxicity) was measured by the lactate dehydrogenase (LDH) assay, showing a dose-dependent effect of CGA on the release of intracellular LDH into the culture medium: 250 µM (12.2%), 500 µM (22.5%), and 1,000 µM (39.2%). There was also an increase in caspase-3 expression, which is one of the main proteins involved in the initiation of apoptosis, when cells were treated with concentrations of 500 and 1,000 µM CGA. As expected, this effect was also observed when measuring cell proliferation, with a significant reduction of 42.5% and 60.4% when cells were treated with 500 and 1,000 µM CGA. In terms of cell cycle, there was a significant reduction in the number of cells in the G0/G1 phase and an increase in cells in S phase, when treated with 250 µM of CGA or higher.

Similar doses of CGA (100–1,000 µM) were evaluated in HCT116 and HT29 cells, showing a dose-dependent effect on cell viability, with a 50.1% and 55.2% reduction at 1,000 µmol/l for HCT116 and HT29 (Hou *et al*., 2017). Induction of reactive oxygen species (ROS) production and S-phase arrest was also observed in both cell lines. The authors evaluated the activation of the mitogen-activated protein kinase (MAPK)/ERK pathway, which plays an important role in cell proliferation, and reported that treatment with CGA reduces ERK phosphorylation, suggesting an inactivation effect of CGA over the MAPK/ERK pathway. In another study with very similar results, the inhibition of HT-29 cell survival was evaluated when treated with doses of CGA from 0.01 to 5 mM, resulting in a significantly decreased growth rate of the cells (52% at 1 mM) (Nam *et al*., 2017).

The chemopreventive potential of CGA derivatives has also been of interest in the context of CRC. A study into the antiproliferative and proapoptotic effect of methyl 3,5-dicaffeoyl quinate (MDQ) in HT-29 cells found that MDQ reduces cell viability and induces apoptosis in a dose and time-dependent manner. When the molecular basis of this was effect was analyzed, it was found that MDQ modulates the mitochondria-dependent pathway of apoptosis by upregulating caspase-3 and cleaved PARP levels, altering the mitochondrial membrane potential and the Bcl-2/Bax ratio, which altogether results in cytochrome c release into the cytosol (Hu *et al*., 2011). This study also revealed that treatment with MDQ reduced ERK phosphorylation and NFκβ nuclear levels, thus confirming that the antiproliferative effects of these components are related to the MAPK/ERK and NFκβ pathways.

In another study with different CGA derivatives, known as diCQAs, the anticarcinogenic potential was explored in RKO and HT29 cells (Puangpraphant *et al*., 2011). The results demonstrate that these molecules inhibited cell proliferation and induced apoptosis in the colorectal carcinoma cell lines, with no effect over normal human colon fibroblasts. The anti-inflammatory potential of these diCQAs was evaluated by measuring nitric oxide (NO) and PGE2 production and the expression of iNOS and COX-2 on lipopolysaccharide-induced RAW 264.7 cells. All the compounds tested reduced NO production and iNOS expression, as well as proinflammatory markers and nuclear NFκβ levels.

In a DSS-induced ulcerative colitis mouse model, several dosages of CGA were used in order to evaluate if CGA

could mitigate the damage caused by DSS in colon tissue (Gao *et al*., 2019). Low and medium doses of CGA had no significant effect; however, a high dose of 120 mg/kg/day CGA for 10 days inhibited the inflammatory reaction, reduced oxidative damage, and decreased apoptosis. The colon mucosal damage index was evaluated and treatment with CGA was shown to reduce the presence of ulcers, inflammation, and adhesions. This was further confirmed, as the levels of proinflammatory factors IL-1β, IL-6, and TNF-α were reduced, while anti-inflammatory cytokine IL-10 was increased by CGA. Oxidative damage caused by DSS was also improved by CGA, shown by a reduction in the expression of oxidative stress-related factors PAF, PGE2, and MPO, while levels of the antioxidant protein SOD increased. Apoptosis of intestinal tissue cells was also reduced by CGA, as seen by increased levels of Bcl-2, Bax, and reduced caspase 3. It appears that the protective effect of CGA is mediated by modulation of the MAPK/ERK/JNK pathway, as protein levels of ERK1/2, p-ERK, p38, p-p38, JNK, p-JNK, p-IκB, and p-p65 were reduced by CGA. These conclusions are supported by a previous study that used the same ulcerative colitis mouse model (Vukelić *et al*., 2018). This group of authors also reported that CGA decreased the expression of p-ERK1/2, as well as of other key players such as AKT, p-AKT, STAT3, and p-STAT3. Inflammatory proteins Cox-2, NF-κB p65, and TNF-α also reduced when mice were treated with CGA.

Cafestol and kahweol

Within the lipid fraction of the coffee bean, we find two important diterpenes, which are specific to coffee: cafestol and kahweol. Cafestol is found in both *Coffea arabica* and *Coffea canephora*, while kahweol is only found in *C. arabica* (de Toledo Benassi and Dias, 2015). In their structure and function, they are very similar, differing only by a double bond between the C1 and C2 carbon atoms (see Fig. 1). A range of biological effects with potential for cancer prevention and/or treatment have been reported for these two diterpenes (Cavin *et al*., 2002). *In vitro* and *in vivo* studies of cafestol and kahweol in CRC models are summarized in Table 2.

In one of the first studies with cafestol and kahweol, mice were pretreated with kahweol : cafestol (1:1) 0.2% for 10 days, followed by PhIP exposure, which is known to induce colon tumors in mouse models, and results showed a 54% reduction of PhIP-DNA adduct formation in the colon (Huber *et al*., 1997). Due to this promising result, the authors followed up with another study published in 2002 in which mice were treated with kahweol : cafestol (1:1) in concentrations of 0.2%, 0.1%, 0.04%, and 0.02% for 10 days or with cafestol alone at the same concentrations (Huber *et al*., 2002b). When treated with the combination of cafestol and kahweol, glutathione (GSH) levels and γ-glutamylcysteine synthetase (GCS) activity slightly increased in colon tissue at the higher doses (0.1% and 0.2%), effect which was much more prominent in the liver. GSH is a potent antioxidant, and GCS catalyzes the rate-limiting reaction in GSH biosynthesis, so this helps explain the protective role of cafestol and kahweol on the colon. The detoxification enzyme glutathione S-transferase (GST) is also increased with kahweol : cafestol (1:1) in the concentration of 0.2% (Huber *et al*., 2002a).

In human CRC cells HCT116 and SW480 and normal colon cells CCD-18co, treated with varying concentrations of kahweol, there was a dose-dependent decrease in cell proliferation in HCT116 and SW480 cells, but not in CCD-18co (Park *et al*., 2016). In order to explore the role of kahweol a bit further, levels of cyclin D1, an important regulator of cell cycle progression, were measured, and it was found that mRNA levels of cyclin D1 remained unchanged while protein cyclin D1 levels reduced noticeably. This indicated that kahweol could be promoting cyclin D1 proteasomal degradation, which was confirmed by pretreating cells with a proteasome inhibitor which blocked the kahweol-induced decrease of cyclin D1 protein levels. Threonine-286 (Thr286) phosphorylation of cyclin D1 has been reported to be associated with its proteasomal degradation, and increased levels of p-cyclin D1 (Thr286) by kahweol were confirmed. Similar to CGAs, kahweol also induced the phosphorylation of ERK1/2, JNK, and GSKb.

A study with HCT116, SW480, LoVo, and HT-29 cell lines showed an increase in cleaved PARP and ATF3 expression when treated with 25 and 50 µM of kahweol, although the effect was much more noticeable with 50 µM, so all subsequent experiments were carried out at this concentration (Park *et al*., 2017). In order to explore the role of kahweol-mediated ATF3 expression in apoptosis, ATF3 overexpression was induced in cells treated with kahweol and this increased cleaved PARP levels even more, while silencing of ATF3 drastically reduced cleaved PARP. Kahweol enhanced ATF3 promoter activity and thus ATF3 mRNA levels, and these levels were reduced when cells were treated with inhibitors of ERK1/2 and GSK3β, indicating that these are the upstream kinases involved in kahweol-mediated ATF3 expression.

In a study with several types of cell lines treated with kahweol, HT-29 cells exhibited reduced cell proliferation and a decreased number of colonies when treated with a concentration of 50 µM (Cárdenas *et al*., 2014). Apoptosis was increased at 25 µM; however, cell cycle analysis revealed no changes in the distribution of cells. A further study into the effect of kahweol on HT-29 cells showed that treatment with 200 µM kahweol significantly reduced cell proliferation and viability (50% at 200 µM) (Choi *et al*., 2015). LDH release increased 5-fold at 200 µM, confirming this cytotoxic effect. Levels of the proapoptotic protein caspase-3 noticeably increased in a dose-dependent manner, and cleaved PARP appeared with as low a concentration of kahweol as 10 µM. On the other hand, levels of antiapoptotic proteins, Bcl-2, and p-Akt decreased, thus confirming the proapoptotic effect of kahweol on these cells. Hsp70 was also diminished by treatment with kahweol which is significant as Hsp70 is often overexpressed in cancer cells, participating in the promotion of oncogenesis and resistance to chemotherapy (Boudesco *et al*., 2018). Overexpression of Hsp70 reduced kahweol-induced cytotoxicity, as well as levels of caspase-3 and cleaved PARP, and increased Bcl-2 and p-AKT, while an HSP70 inhibitor increased kahweol-induced cytotoxicity, indicating that this protein has a central role in the kahweol-mediated effect.

CONCLUSION

The effects of caffeine on many aspects of human physiology are well described; however, evidence regarding the potential chemopreventive effect of this compound on the colon is conflicting. Some *in vitro* studies report that caffeine induces cell cycle arrest and increases apoptosis in colorectal carcinoma cell

lines, while other studies report no effect on cell cycle, increased cell proliferation, and protection from chemotherapy-induced apoptosis. Evidence from *in vivo* studies is also not clear, as one study described that treatment of mice with caffeine reduced animal survival in a CRC model, while another indicated a greatly reduced number of tumors and inflammation due to caffeine. These conflicting results could be due to the fact that there are not many studies available that look into the effect of caffeine on the colon, at a cellular and molecular level; however, it seems that the chemopreventive effect of coffee is likely to be attributed in a larger degree to other compounds, rather than caffeine, although caffeine may have a small cumulative effect.

On the other hand, results from different *in vitro* and *in vivo* studies with CGA or its derivatives were consistent, reporting cell cycle arrest, cytotoxicity, and reduced cell viability, as well as increased apoptosis. Additionally, anti-inflammatory properties were observed for these compounds, and the results suggest that this protective effect could be related to the modulation of the MAPK/ERK/JNK and NFκβ pathways.

In vitro results of kahweol consistently report a chemopreventive effect on the colon. All studies available in colorectal adenocarcinoma cell lines agree that kahweol increases cytotoxicity, reduces cell proliferation, and increases apoptosis. It appears that, similar to CGA, the protective effect of kahweol is mediated by the MAPK/ERK/JNK pathway. There are no *in vitro* studies of cafestol in colon-derived cell lines, most likely due to the fact that cafestol and kahweol are very similar in structure and function. Studies of cafestol and kahweol in a CRC animal model show that these compounds increase the expression of antioxidant and detoxification enzymes, contributing to colon health.

It is seen that often results from *in vitro* studies are not well supported in animal models. This is most likely due to the fact that all *in vitro* studies reported in this review use the traditional monolayer approach to cell culture, which does not reflect the three-dimensional structure of the colon or of a tumor. Cell–cell and cell–matrix interactions that occur *in vivo*, as well as limited diffusion of the compound through the tumor mass, are not taken into account in most *in vitro* studies. Therefore, it is important to migrate to three-dimensional culture models that mimic the microenvironment and cell heterogeneity of colon tumors more closely.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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