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

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Table 1. Summary of *in vitro* and *in vivo* studies in colorectal cancer models of the main bioactive compounds in coffee

Experimental model	Dose/intervention	Biological effect	Ref.
In vitro HCT116 p53 +/+ cells CCD-18Co cells	2 mM caffeine for 3 h	**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 h	All 35 compounds induced apoptosis at 5 x IC_{50}, while at 1 x 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 h + 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 h 20 μM caffeine 2 h + 80 μM paclitaxel 48 h	**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 RKO cells Cocultured with PBMCs	Caffeine: 25, 75, and 225 μg/ml for 24 h	No effect on cell proliferation No effect IL-1β or IL-6 levels ↓ TNFα 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	(Bessler et al., 2012)

		and 225 µg/ml caffeine)	
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 ↓ COX-2 expression ↓ metallothionein expression ↑ lipid peroxidation levels	(Soares et al., 2019)

In vitro Caco-2 cells	Chlorogenic acids (CGA): 100, 250, 500, and 1000 µM for 24 h	↑ apoptosis ↑expression in caspase-3 (with 500 and 1000 µM only) ↑ LDH release (250 µM, 12.2%, 500 µM, 22.5%, and 1000 µM, 39.2%). ↓ cell proliferation (500 µM, 42.5%; 1000 µM, 60.4%) ↓ cells in G0/G1 phase (≥ 250 µM) ↑ cells in S phase (≥ 250 µM)	(Sadeghi Ekbatan et al., 2018)
In vitro HCT116 cells HT-29 cells	CGA: 0, 125, 250, 500, and 1000 µM for 24 to 72 h	↓ cell viability ↑ ROS production S-phase arrest on both cell lines ↓ p-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 h	↓ cell proliferation (IC_{50} 1.87 mM) ↓ 46% growth rate (with 1 mM)	(Nam et al., 2017)
In vitro HT-29 cells	Methyl 3,5-dicaffeoyl quinate (MDQ): 0, 6.25, 12.5, 25, 50, 100, 200 ug/ml for 24, and 48 h	↓ cell viability ↑ apoptosis Cell cycle arrest at G0/G1 ↓ p-ERK ↓ NFκβ nuclear levels	(Hu et al., 2011)
In vitro RKO cells HT-29 cells	CGA, quinic acid, caffeic acid, dicaffeoylquinic acids (diCQAs): 1, 50, 100, and 200 µM for 24 h	**With all compounds:** ↓ NO production and 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	(Puangpraphant et al., 2011)

		μM) No effect on CCD-33Co cells ↑ apoptosis ↓ NFκβ nuclear levels	
In vivo C57BL/6 mice (DSS-induced colitis)	Treatment groups: Control UC group (induced by DSS) UC + chlorogenic acid low dose group (CGA-L): 30 mg/kg/day chlorogenic acid for 10 days UC + chlorogenic acid middle dose group (CGA-M): 60 mg/kg/day chlorogenic acid for 10 days UC + chlorogenic acid high dose group (CGA-H): 120 mg/kg/day chlorogenic acid 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 ↓ PAF, PGE2, and MPO expression ↑ SOD expression ↑ Bcl-2 expression ↑ Bax expression ↑ cleaved caspase 3 ↓ ERK1/2, p-ERK, p38, p-p38, 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, Scharf, et al., 2002)
In vivo F344 mice	Treatment groups: Control diet Kahweol : cafestol (1:1), 0.2%	↑ 25% GST-CDNB in colon	(Huber, Prustomersky et al., 2002)
In vitro HCT116 cells SW480 cells CCD-18Co	Kahweol: 0, 12.5, 25, and 50 µM for 24 and 48 h	**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 h and 48 h ↑ p-ERK1/2, p-JNK, and p-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 h and 48 h **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 h	**In all cells:** ↑ cleaved PARP (with 25 and 50 µM) ↑ 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.