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Review Article

Immunomodulatory And Carcinopreventer Activities of Coffee and Caffeine

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Received date: September 18, 2023; Accepted date: September 29, 2023; Published date: October 09, 2023

Citation: Meir Djaldetti, (2023), Immunomodulatory and Carcinopreventer Activities of Coffee and Caffeine, *J, Biotechnology and Bioprocessing*, 4(6); **DOI:10.31579/2766-2314/120**

Abstract

The energizing effect of a cup of coffee combined with its distinctive flavor and test are well known and highly regarded. These coffee characteristics are due to a number of polyphenols, the principal one being caffeine. The usefulness of coffee as a potential adjuvant in medicine is increased when the health benefits of coffee drinking are added to a list of chronic disorders, such as the prevention of cancer and chronic inflammation. Consideration is warranted given the importance of chronic inflammation as a heralder of cancer development and the immunomodulatory effects of caffeine and coffee on immunological and cancer cells. In this regard, caffeine's ability to alter the release of inflammatory cytokines by cancer cells as well as peripheral blood and tumor microenvironment mononuclear cells plays a critical role in the tumor development. The ways coffee or caffeine may exert carcinoprevention and particularly their impact on the cross talk between immune and cancer cells is the purpose of the present review.

Key Words: coffee; caffeine; immunity; cytokines; cancer; chemoprevention

Introduction

The world's widespread use of coffee can be easily explained by the aroma, the taste, and the comfort it brings after drinking. Furthermore, coffee's health advantages have long been known to exist. In addition to providing pleasure, coffee has beneficial effects on the progression of chronic diseases such type II diabetes, cardiovascular, gastrointestinal, and liver ailments as well as chronic inflammation [1,2]. Coffee drinkers showed lower levels of inflammatory markers such as CX3CL1, CCL4/MIP-1β, IFNγ and FGF-2 [3]. Caffeine (CA) is the most significant of the several polyphenols found in coffee; there fore investigations are typically conducted using CA alone or in combination with other polyphenols or medications. Treatment of PBMC with CA reduced T-cell proliferation and suppressed IL-2, IL-4, IL-5, IL-10 and IFNγ production [4]. Those and other studies [5] indicate that CA exerts a significant anti-inflammatory activity. In addition, frequent coffee consumption was associated with a decreased death rate and a lower risk of cancer in a large sample of both men and women. [6]. Comprehensive meta-analyses showed that 3-4 cups of coffee consumption per day is linked with a decreased risk of breast, colorectal, endometrial and prostate cancer [7, 8]. However, according to some studies the relationship between coffee and cancer prevention is less evident with the exception of hepatocellular carcinoma and the risk of breast cancer in postmenopausal women mostly in those carrying a BRCA1 mutation. [9, 10]. The type and method of coffee beans cultivation, the time of coffee brewing, the amount of beverages consumed daily, the duration of its use, and individual behaviors could all be factors in the disparity in the studies' findings. Given the close link between chronic inflammation and the development of cancer, the protective impact of coffee drinking on reducing the risk of cancer deserves attention [11]. Reviewing the link between the immunomodulatory capacity of coffee and CA and their carcinopreventive effect was the goal of the current study.

Anti-inflammatory and immunomodulatory effects of CA

Despite the fact that there have been many in vitro studies exploring the immunomodulatory effects of CA, investigations using both animal models and humans are infrequent [5]. In two out of five studies of coffee trials reviewed by Pavia et al. [12] CA increased the anti-inflammatory IL-10 production. Notably, the mode and the degree of PBMC stimulation affect the impact of CA on cytokine generation. Thus, non-stimulated PBMC incubated with CA did enhance IL-1 production but not that of IL-6, IL-10, or TNF, whereas PBMC stimulated by co-incubation with HT-29 or RKO colon cancer cells significantly raised the production of all of them, including IL-1ra and IFN [13]. CA induced a decreased secretion of IL-1β and IL-18 secretion in LPS stimulated human monocytic leukemia derived macrophages due to inhibited NLRP3 inflammasome activation [14].

Macrophages stimulated with conditioned medium of mesenchymal stem cells treated with CA showed increased phagocytic capacity, inhibited ROS and NO expression compared to macrophages treated with conditioned medium alone [15]. Six mg/kg body mass of CA supplemented to athletes before exercise increased plasma concentration of IL-6, IL-10 and IL-12 levels without having any impact on PBMC production of theses cytokines [16]. Interestingly, different subpopulations of human macrophages respond in a different way to coffee and CA. In contrast to macrophages activated by GM-CSF, coffee was able to promote the secretion of IL-8, IL-6, and IL-1β in macrophages treated with macrophage colony-stimulated factor. TNF-generation, however, was reduced in both cell types [17]. It appears that how coffee is brewed and consumed affects its ability to reduce inflammation. According to Castaldo et al. [18], brewed coffee contains more polyphenols and has higher anti-oxidant activity on HT-29 cells after simulated gastrointestinal intake, than non-digested samples. Additionally, the expression of the NF-kB p65 subunit and the pro-inflammatory cytokine IL-6 were inhibited by digested coffee samples, whereas the production of the anti-inflammatory cytokine IL-10 was increased. Notably, higher CA doses suppress the macrophage and NK cells immune activity by a decreased synthesis of the anti- inflammatory cytokines, as well as TLR1, TLR2, and TLR4 receptors, while lower doses promoted their secretion [5]. One cup of coffee's worth of CA exposure to PBMC caused a downregulation of the inflammatory pathways STAT1, TNF, and IFN as well as lower levels of several pro-inflammatory cytokines. [19].

Caffeine and cancer development

Coffee and its polyphenols gained the title of chemopreventers by modulating the immune system, the course of chronic inflammation and the production of anti-inflammatory cytokines. Montenegro et al. [20] reported that coffee prompted prostate cancer prevention by lowering the production of the inflammatory mediators IL-6, IL-8, TNFα, C reactive protein, and modulation of the NF-kB pathway. In a carcinogen-induced model, CA was found to inhibit immunological mechanisms that contribute to the development of cancer by increasing the infiltration of CD8+T lymphocytes while decreasing that of CD+CD25+ regulatory cells. The PD-1 activity decreased in each group. IFNγ- and IL-6 production was boosted by CA combined with anti-PD1mAb and increased anti-tumor activity against B16F10 melanoma cells [21]. Acting on cytokine receptors, CA amplified the antitumor properties of CD4+ and CD8+ T lymphocytes, and increased the activity of macrophages and natural killer cells, thus reducing the development of colorectal cancer cells [22]. The production of the pro-inflammatory cytokines IL-6, IL-12, and TNFα was found to be reduced in a mouse colon carcinogenesis model when CA and its ester, chlorogenic acid, were administered together as opposed to when the coffee polyphenols were given alone. Additionally, the production of non-coding miR molecules was modified, thus reducing cancer development [23]. Tryptophan-induced coffee extracts prevented the production of IL-8, IL-12, TNFα and IL1-β in colon carcinoma HT-29 cells [24]. CA affects cancer cells in a variety of ways, including mitotic arrest, autophagocytosis, enhanced macrophage phagocytosis, and necrosis as depicted in Figure. 1.

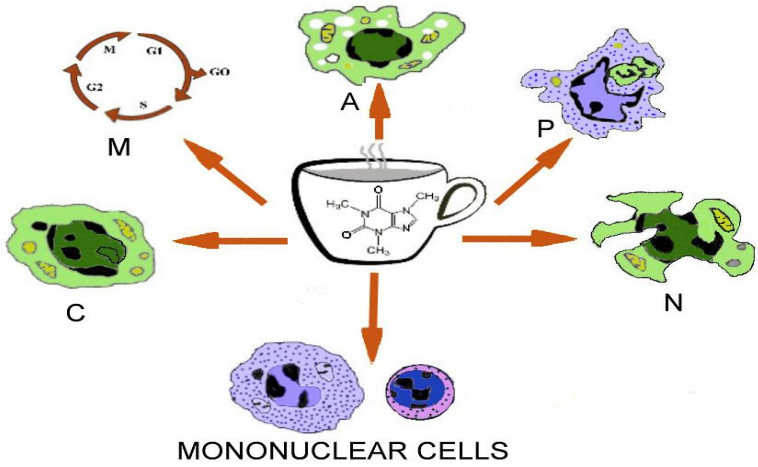

Figure 1: Caffeine affects the proliferation and viability of cancer cells (C) by a mitotic cycle arrest (M), increased apoptosis (A) and phagocytosis (P) and necrosis (N). In addition it modulates the immune activity of the mononuclear cells.

Digestive tract cancers

Esophageal cancer

The effect of CA on the digestive tract malignancies has attracted researchers' attention, but it appears that CA's efficacy in preventing esophageal cancer is uncertain. In a retrospective analysis of patients with Barrett's esophagus, CA was found to be a risk factor for developing into esophageal cancer along with other factors like age and abdominal obesity [25]. In vitro studies have shown that CA inhibits the proliferation rate of esophagus squamous carcinoma KYSE-30 cells in a dose-dependent matter [26]. On the other hand, a meta-analysis of a large sample of coffee drinkers revealed that East Asians, but not Euro-Americans, were protected from esophageal cancer by coffee [27].

Gastric cancer

The prevalence of coffee consumption raises the potential of a connection between coffee intake and the risk of gastric cancer. Studies on the subject failed to demonstrate an association between coffee beverage and carcinogensis [28]; moreover, reports suggested that coffee polyphenols and in particular CA may lower the risk of gastric cancer development [29,30]. CA treatment of MGC-803 and SGC-7901 gastric cancer cells resulted in lowered growth and enhanced apoptosis due to activation of the caspase-9/-3 pathway, enzymes actively involved in the apoptotic progression [31]. In the same type of cells CA suppressed cell proliferation and migration and prompted autophagy trough PTEN activation and PI3K/Akt/mTOR pathway inhibition [32]. CA had the ability to boost the effectiveness of gastric anti-cancer medications. The combination of CA with cisplatin significantly improved cisplatin cytotoxicity on STKM-1 gastric cancer cells [33] and the survival time of STKM-1 cancer bearing mice compared to the effect of each of the substances alone [34].

Colorectal cancer

Coffee intake was found to be inversely associated with progression and metastasis of colorectal cancer [35] and with a reduced the risk of its

development by about 13% [23]. According to prospective studies, drinking 2-4 cups or more per day dramatically reduced stage III colorectal cancer risk and mortality [36-38]. CA's effect on the proliferation and apoptosis of the malignant cells of colorectal cancer bearing mice was greatly enhanced when combined with another coffee polyphenol, i.e. chlorogenic acid [23]. Emile et al. [39] conclude that further research is needed to determine whether coffee drinking has any influence on colorectal cancer in a recent review that included 14 systematic studies on the topic.

Hepatocellular carcinoma

Hepatocellular carcinoma risk has been shown to be decreased by coffee drinking [40- 42]. CA supplementation significantly increased the apoptotic effect of 5-fluorouracil and decreased the growth of malignant cells, which was attributed to the activation of the pro-apoptotic Bcl-2 and Bcl-xL proteins and amplified PARP enzyme cleavage [43]. A further route by which CA reduces hepatocellular carcinoma cells is PI3K/Akt inhibition [44]. Incubation of HrpG2 and Huh7 hepatocellular carcinoma cells with CA at doses 0-600 μM reduced proliferation, migration and invasion via Akt signaling pathway. When HrpG2 carcinoma bearing mice were fed with CA the number and progression of the tumors was reduced [45].

Breast cancer

There isn't much clear evidence from studies on the role of coffee and CA in preventing breast cancer. Analyses on a large number of patients failed to demonstrate an association between coffee consumption and incidence of invasive cancer risk in postmenopausal women [46-48]. Lafraconi et al. [49] reported that four cups of coffee a day may reduce the incidence of breast cancer in those patients by 10%. Treatment of MCF-7 and MDA-MB-231 breast cancer cells with various doses of CA caused an inhibited cell proliferation and viability, as well as a burst of oxidative stress. The generated reactive oxygen species (ROS) damaged the DNA in the MCF-7 cells but not in those of the MDA-MB-231 line indicating that the toxicity of CA varied depending on the subtype of cancer cells [10,50].

Genital tract cancers

Although research on the impact of CA on the development of genital tract cancer is, at best, classified as unreliable [51,52] , it has been found that overall CA consumption from coffee and tea was associated with a lower risk of ovarian cancer in a case-control study done in Denmark [53]. Four cups of coffee per day were linked to a 20% lower risk of endometrial cancer, according to a meta-analysis on the topic [49]. Other cohort studies and meta-analyses support these observations [54,55]. These and additional reports [7,54] indicate that the relationship between CA and the development of genital cancer is still uncertain and additional research is advised to elucidate the situation. Likewise, the reports as for the effect of CA on ovarian cancer development are rather inconclusive. In an analysis of data comprising 44,062 individuals, Ong et al. [56] concluded that there was no link between coffee consumption and the risk of epithelial ovarian cancer, findings supported by other studies [57,58]

Lung cancer

Considering the habit of coffee drinking with cigarette smocking the association of CA intake with lung cancer development is difficult to assess. Guertin at al. [59], based on a sizable group of individuals have concluded that six cups of coffee per day was positively associated with the occurrence of lung cancer. However an adjustment regarding smocking attenuated the linkage between coffee consumption and cancer development. Studies done in vitro showed more encouraging results. In NCI-H23 lung cancer cells, p-FaK and p-Akt kinase activity were reduced, metastasis-promoting integrins were downregulated, and the cell cycle was arrested at the G0/G1 phase [60]. Claudin-2, a protein that is abundantly expressed in A549 lung cancer cells, was significantly downregulated by CA together with Nrf 2 factor. Additionally, CA boosted the doxorubicin cytotoxicity [61]. CA alone and in combination with artemisinin, a product of Artemisia annua, caused an attenuation of the tumor lesions in several organs in mice with dimethyl-benzene-anthracene induced cancer by reducing P53 expression and nitric oxide levels [62].

Prostate cancer

There is conflicting evidence about CA's relationship to the risk of prostate cancer. Prostate cancer cells PC-3 and DU145 that have been treated with CA had significantly less ability to proliferate and spread. Additionally, cohort studies conducted concurrently with the in vitro tests found that men who drank more than three cups of coffee per day had a 53% lower risk of developing prostate cancer than those who drank 0–2 cups. [63]. In a population case control study, Geybels et al. [64] attained comparable outcomes. Notably, when combined with atorvastatin, the effect of CA on the migratory capacity, invasion, and death of prostate cancer cells was dramatically enhanced [65]. A combination of CA and atorvastatin decreased the activity of phosphorylated Akt and Erk1/2, two proteins crucial for the survival of prostate cancer cells, and increased the anti-apoptotic gene Bcl-2. [65].

Malignant melanoma

Patients studies revealed that high coffee consumption or CA intake - $\geq$ 393 mg/day as opposed to <60 mg/day was negatively associated with the risk of malignant melanoma [66], data that were later supported by case control analyses [67,68]. Administration of 100 mg/kg./body weight of CA to mice bearing B16F10 melanoma tumors with lung metastases showed a definitive reduction of spreading and tumor volume [69]. Tyrosinase expression, a prerequisite for the synthesis of melanin, was reduced in melanoma-initiating cells treated with CA, as was the secretion of the cytokines IL-1, IL- 10, MIP-1, and IMP-1, which are known to promote inflammation [70]. Synergistic treatment of B16F10 melanoma cells with doxorubicin and CA resulted in a significant reduced tumor growth most likely by inhibiting the adenosine-A2A receptor pathway that controls inhibitory cytokines [71], indicating that A2A receptor antagonists may be another approach for preventing the development of cancer [72].

Other cancers

Although it has been advised to further examine the potential benefit of coffee as a preventer of renal cancer, based on meta-analyses [73], earlier studies have revealed that consumption of coffee was inversely associated with the incidence of renal carcinoma [74,75].

CA affects the cross between immune and cancer cells.

The monocytes/macrophages and lymphocytes with all their subtypes in the peripheral blood and the tumor microenvironment play a crucial role in maintaining chronic inflammation prior to carcinogenesis. In this regard the role of inflammatory cytokines in the proceeding of caner development has been thoroughly studied [76]. It has been demonstrated that TGF-β, TNF, and a number of interleukins, including IL-6, IL-10, IL-12, IL-17, and IL-23, are involved in the growth and proliferation of cancer cells [77]. Certain interleukins such as IL-5, IL-6 and IL-27 enhance cancer spread and suppress apoptosis [78]. Cytokines generated by tumor cells may promote tumor development and migration as well to stimulate tumor microenvironment for production of pro-inflammatory cytokines such as IL-6 and IL-8 [79]. Tumor cell-produced TGF, TNF, IL-6, and IL-12 may stimulate the generation of pro- and anti-inflammatory cytokines by macrophages and mononuclear cells [76], inciting the existence of an immune cross-talk between cancer, innate immune cells and those in the tumor microenvironment [78,80, 81]. Chen et al. [82] reported that MDA-MB-231, MCF-7, T-47D and BT-474 human breast cancer cells release a great number of inflammatory cytokines resulting in a cross-talk between immune and cancer cells. Some of them, such as IL-1β are closely connected with the spreading capacity of breast cancer cells to the bones that could be inhibited by drug administration [83]. Alteration of the cross-talk between immune and cancer cells induced by CA has been reported by Bessler et al. [13].

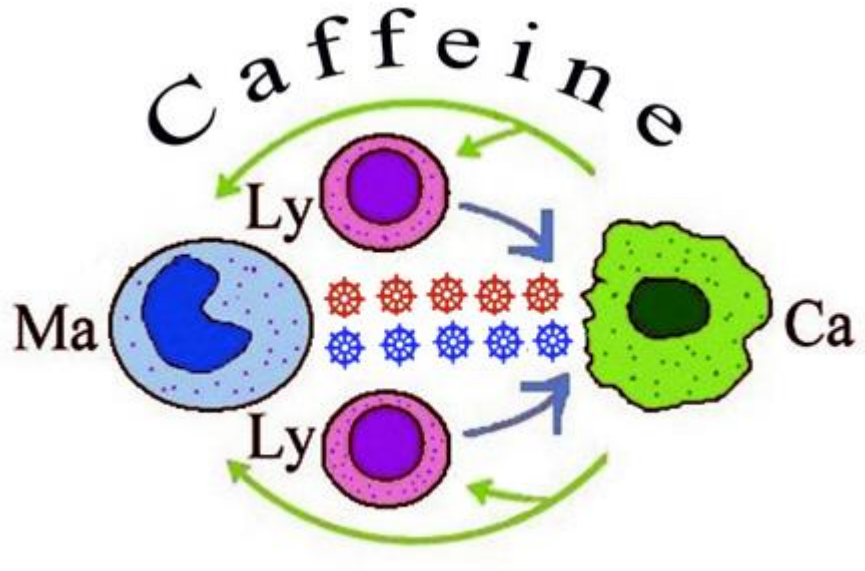

Figure 2: Caffeine affects the cross-talk between macrophages (Ma) and lymphocytes (Ly) and cancer cell Ca) stimulating the cells for pro-inflammatory (red stars) and anti-inflammatory (blue stars) cytokine production.

Figure. 2 illustrates the crucial interactions between mononuclesrs and cancer cells. TGF-β performs two functions in cancer development: in the early stages of it induces apoptosis and interact with the cell cycle; in the later stages, it stimulates tumor migration and metastasis [84, 85]. Studies have shown that CA may impair tumor progress by modulating immune responses through inhibition of cAMP–phosphodiesterase, inhibition of adenosine receptors and modulation of HIF-1α, IL-8 and VEGF expression by cancer cells [86]. CA decreased tumor incidence and growth by inhibition of PD1 receptors in CD4+CD5+ regulatory T lymphocytes [21].

Conclusion

Taken together, the findings from meta-analyses, prospective and laboratory research indicate that coffee and CA exert a protective effect against significant types of malignancies through a variety of molecular mechanisms. Immunomodulation expressed by decreased pro-inflammatory interleukins production and enhanced activity of the anti-inflammatory ones is a key factor in the regulation of tumor microenvironment and cancer development [23]. Moreover, it has been proposed that CA may act as an additive to anticancer medications by targeting the pro-inflammatory cytokines [87]. The data presented support the assertion made in the majority of publications on the subject that further research is required to elucidate the mechanisms of CA carcinopreventer effect and to introduce it as an important adjuvant to anticancer drugs.

Conflicts of interest:

none

Ethical approval:

not applicable

Funding:

none

List of Abbreviations

A2aR: protein recognition adenosine receptor

BCL-2: cell cycle regulator

CX3CL1: transmembrane adhesion protein

FGF: fibroblast growth factor

GM-CSF: granulocyte macrophage colony stimulating factor

HIF-1α Hypoxia-inducible factor 1-alpha,

MIP: macrophage inflammatory proteins

mTOR: mammalian rapamycin target

NLRP: pattern recognition adapter

NO: nitric oxide

Nrf2: nuclear factor erythroid 2 related factor

pAk7: protein kinase

PARP: poly(ADP-ribose) polymerase

PBMC: peripheral blood mononuclear cells

pFaK: focal adhesion kinase

PI3K: Akt phosphoinositide 3-kinase

PTEN: phosphatase tensin homologue

ROS: reactive oxygen species

STAT: Signal transducers and activators of transcription

TLR: immune recognition receptor

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DOI:10.31579/2766-2314/120