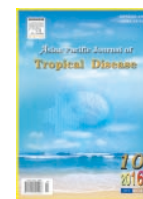




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## Influence of coffee and its components on breast cancer: A review

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## ABSTRACT

Amongst females, breast cancer is one of the major culprits for cancer death. Consequently, many scientists have focused their researches to delineate the novel alternative strategies to cure or to reduce the outgrowth of this disease. Amongst the beverages, coffee is widely available and one of the most popular non-alcoholic drink worldwide. Due to the widespread usage of coffee in adults, scientists are trying to delineate its beneficial and harmful influences on human health and diseases. Evidences from an amount of researches have outlined the possible role of coffee and its components as chemoprotective agents against specific carcinogens as well as suppressors for tumorigenesis. Furthermore, some studies tried to elucidate the relationship amid coffee intake and suppression of carcinogenesis in breast tissues. The present review is an effort to highlight the consequence attributable to the intake of coffee and its key chemical components (caffeine, caffeic acid, kahweol and cafestol) upon breast cancer developmental process.

## 1. Introduction

Breast cancer is still one of the major causes for the morbidity and the 2nd main reason of demise in females internationally and it is also the 5th most common cancer globally[1,2]. The progression of breast cancer is an intricate phenomenon that includes the functional modifications in epithelial cells and their microenvironments together[3-5].

A number of hereditary variations foster the growth and advancement of carcinogenesis. For example, the altered expression of oncogenes (up-regulation) and tumor suppressor genes (down-regulation) cascades are favorable for the expansion of neoplastic tissues. The cancer cells basically lost the regulation on signals for cell division and development, consequently abnormal proliferation of cells, which, at the same time, may also escape from apoptosis[6].

Cancerous tissue is an intricate unit which consists of various cell lineages that cooperate to empower tumorigenesis. Therefore, an effective treatment strategy should focus to support the non-carcinogenic supportive cells, while creating the hindrance for

tumorigenesis. Subsequently, the molecules which can interrupt the cross talk of cancer stroma via regularizing the constituents of the tumour microenvironment may help the tumour cell directed therapy[3-6].

Coffee is one of the most commonly consumed beverages in the world. It is the primary source of caffeine ingestion amid adults worldwide. The biological and chemical impact of coffee is not restricted to the consequences of caffeine but it may have significant impact due to other components of the coffee also[7]. It is believed that coffee consumption reduces the jeopardy of various chronic diseases[3-5]. For example, the beneficial health impacts of coffee may include the reduced risk of depression[8], reduced threat of the diseases related to central nervous system which includes Parkinson's disease[9-11] and Alzheimer's dementia[12,13], prevention of gallbladder stone formation[14] and defense against few infectious and malignant ailments of the liver[15-17]. Furthermore, some studies suggested that coffee might improve asthma symptoms, as caffeine is believed to be a methylxanthine bronchodilator[18,19].

In addition to aforementioned diseases, coffee consumption has also been associated with breast cancer. Studies on coffee consumption or on exposure to its phytochemicals have variable results on the process of carcinogenesis.

## 2. Phytochemicals in coffee

Coffee is a complex drink consisting thousands of biologically

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effective compounds. Several of its ingredients could potentially modify cancer risks via regulating various cell signalling cascades of carcinogenesis. Coffee consists of many components including caffeine, caffeic acid, cafestol, kahweol, chlorogenic acid, hydroxyl hydroquinone and antioxidants. Many of the components of coffee have been studied along with the diterpenes (cafestol and kahweol) for their anti-carcinogenic properties[3,4].

### 3. Effect of coffee on breast cancer

The study of Simonsson *et al.* showed that the consumption of moderate to high quantities of coffee was linked to significantly diminish the risk for the early events in tamoxifen-treated patients and it modified the hormone receptor status. While observing survival analyses, Simonsson *et al.* initially analyzed the cytochrome P genotypes against the different concentrations of coffee intake as independent variables. Further, two interaction variables were analyzed by them to determine whether there is any gene environment interaction between low coffee consumption and consisting at least one minor allele on the risk for the early events. The other tumor characteristics were not significantly concomitant with coffee consumption. The key observation of their research revealed that coffee intake was associated with a significantly diminished risk for early breast cancer proceedings in tamoxifen-treated patients having tumors[5].

Bhoo Pathy *et al.* reported that the risk of breast cancer does not have statistically significant relationship between coffee or tea consumption observed in 27323 females. Their results were alike for lean and overweight females even when restricting analysis to the cases in postmenopausal females having breast cancers[2].

Isshiki *et al.* observed that coffee constituents induced the breast cancer resistance protein (BCRP) via nuclear factor kappa B activation in human colorectal cancer cell line cells. Coffee up-regulated the BCRP gene expression in colorectal cancer cell line cells in concomitant with coffee concentration. This study suggests that everyday intake of many cups of coffee would up-regulate the BCRP expression in the gastrointestinal tract. The BCRP up-regulation would reduce the bioavailability of drugs and environmental chemicals including carcinogens, which are substrates for BCRP. This modification of the BCRP activity by coffee might be associated to the results of epidemiological studies, which proposes the relationship of coffee intake with a reduced risk of certain types of cancers[20].

### 4. Effect of caffeine on breast cancer

Caffeine is the most observed constituent of coffee, and it is the most suggested culprit for the characteristically habit-forming nature of coffee consumption[7]. Coffee accounts for 71% of caffeine intake among American[21]. The caffeine content in coffee beverage is variable, even though if we obtain it from the same café-outlet. An 8-ounce cup of brewed coffee can contain variably 95–200 mg and brewed decaffeinated coffee can contain around 5–15 mg of caffeine, while the maximum outlets serve in larger volume which further increase the caffeine content accordingly as well[22,23].

Caffeine (1,3,7-trimethylxanthine), a natural purine alkaloid, is the most widely disbursed psychoactive substance that has different pharmacological actions. Various researches described the anti-carcinogenic feature of caffeine via the up-regulation of apoptosis and down-regulation of cell proliferation in many cancer types[20,24–30].

Roughly, 100 mg of caffeine is present in a single cup of coffee[31], which signifies that the persons who drink coffee every day may have micromolar concentrations of caffeine in their blood circulation. Furthermore, it has been observed that approximately after 30 min of caffeine intake by any sources, the peak plasma concentration reaches up to 15.9–18.7 mg/mL, which suggests the prompt absorption of caffeine (5 mg/Kg) via oral route. Additionally, the half-life of caffeine in plasma varied from 2.7 to 9.9 h, which specifies the considerable inconsistency in caffeine disposal in different persons[32]. The aforesaid phenomenon may possibly help to achieve a physiologically active concentration of caffeine in blood circulation after the intake of moderate quantity of caffeine sources.

Caffeine suppresses the expression/secretion of stromal-derived factor-1, matrix metalloproteinase-2 and transforming growth factor- $\alpha$  from cancer-associated fibroblasts. Moreover, caffeine also diminishes the concentration of the key myo-fibroblasts markers,  $\alpha$ -smooth muscle actin, and sturdily inhibits the cancer-associated fibroblasts migration and invasion towards other cells. The above mentioned impacts are mediated via the inhibition of extracellular signal regulated kinases-1/2 and  $\alpha$ -serine/threonine protein kinases. This inhibitory property relies on the augmentation of phosphatase and tensin homolog proteins, which is a common inhibitor for both extracellular signal regulated kinases-1/2 and  $\alpha$ -serine/threonine protein kinases[3,4,24,33].

Al-Ansari *et al.* demonstrated in their study that active breast stromal fibroblast cells can return to normal and down-regulate the pro-carcinogenic and metastatic properties after the ingestion of caffeine. The aforesaid down-regulation is administered via the augmented expression of vital tumour suppressor proteins (p16, p21, p53 and Cav-1), which suppress the release of several pro-carcinogenic cytokines[4].

Niknafs' study also emphasized that caffeine is an inhibitor of the inositol triphosphate kinase of the human breast cancer cell line. This study showed that caffeine and cisplatin caused some human breast cancer cell line cells to detach from the attachment surface, while the cells that resisted to the drug treatment remained attached. The detached cells showed different stages of apoptotic and non-apoptotic cells. Caffeine, as an inositol triphosphate inhibitor, induces apoptosis by the intra-cellular release of  $\text{Ca}^{2+}$ . According to this study, it is beneficial to use caffeine with the anticancer drug, cisplatin, to induce cancer cell death[34].

### 5. Effect of caffeic acid on breast cancer

The well-recognized phenolic phytochemical caffeic acid (3,4-dihydroxycinnamic acid) exists in several diets including coffee. The caffeic acid and their esters have been broadly observed to explicate its beneficial health impact. In recent times, many scientists are exploring the anti-carcinogenic properties of caffeic acid phenethyl

ester (CAPE) as a probable therapeutic agent[35-37].

Wu *et al.* have shown various anti-tumorous properties of CAPE, which was derived from propolis (a honeybee product, not from coffee) in pre-clinical models of human breast cancer. They observed that CAPE inhibits the development of breast cancer and preserve non-tumorigenic mammary epithelia cells at the same time[35].

Beauregard *et al.* elucidated that CAPE and its derivatives efficiently diminish the viability of breast cancer cells. They further observed that few of the CAPE esters presenting better inhibitory properties than CAPE and its amide analog on michigan cancer foundation-7 (MCF7) breast cancer cell growth[38]. The aforesaid observations they derived from their experiments on apoptotic markers caspase-3 and caspase-7 as cancer cell growth and tumor cell survival induced by defective apoptosis signaling cascade. The results of the experiments showed that CAPE and its derivatives up-regulate the caspase-dependent apoptotic cascade for caspase-3, -7 apoptosis activity in MCF7 breast cancer cells. Other studies also demonstrated the effectiveness of CAPE as an apoptotic activator[36,38-42].

Furthermore, Beauregard *et al.*[38] tried to explore the effectiveness of CAPE and its derivatives on p53-mediated apoptotic cascade, which was prior described by Watabe *et al.*[36] and Lee *et al.*[43] with exposure to CAPE only. The p53 is the most extensively studied tumor suppressor and in response to diverse forms of cellular stresses, the activation of p53 receptor takes place which induces apoptosis by multiple pathways in a manner to ensure that the cell death program proceeds efficiently. This p53-dependent apoptotic cascade is potentially very important in dysregulation of cell cycle to promote carcinogenesis. It means whenever the control over the p53 pathway disrupted it helps the tumorigenesis and further metastasize[38,44]. The experimental observations after exposure of CAPE and its derivatives on MCF7 breast cancer cells showed augmentation of p53 expression. While when they tried with MDA-MB-231, p53-mutated breast cancer cells, for their surprise, maximum of the CAPE derivatives, cannot be able to up-regulate the apoptosis except the CAPE itself and one other derivative. Their results are comparable with the study of Nomura *et al.* which elucidated the potential of CAPE to activate the p53-dependent and -independent apoptosis in carcinoma cells[38,45].

## 6. Effect of kahweol on breast cancer

Kahweol is a diterpene presenting in coffee beans with varying concentrations of 0.01–0.40 mg/cup in coffee. Its concentration is relatively high in unfiltered coffee like, espresso, French press, boiled coffees or Turkish coffee/Greek coffee, and low in filtered coffee and instant coffee[46].

Kahweol, an antioxidant diterpene, has been vigorously investigated for its potential anti-cancer, anti-tumor, and anti-inflammatory functions. Kahweol up-regulates the apoptotic cascade and blocks the tumor cell proliferation and metastasis in various types of human carcinoma cells[47-50]. Um *et al.* has observed that kahweol does not affect normal human mesangial cells, while it induces apoptosis in human renal cancer cells via tumor necrosis factor-related apoptosis-inducing ligand-mediated pathway. Their

experimental results demonstrated that the attenuation of B-cell lymphoma 2 (Bcl-2) and cellular FLICE-like inhibitory protein causes the apoptotic impact of kahweol in carcinoma cells via tumor necrosis factor-related apoptosis-inducing ligand-mediated pathway[48]. Choi *et al.* investigated the effect of kahweol in HT-29 human colon adenocarcinoma cells and observed its cytotoxicity properties. They observed that kahweol up-regulates the pro-apoptotic caspase-3 expression, while at the same time attenuating the anti-apoptotic Bcl-2 and phosphorylated Akt expression. Furthermore, kahweol precisely diminishes heat shock protein-70 (HSP70) expression. This diminished expression of HSP70 significantly augmented the kahweol-induced cell apoptosis. Choi *et al.* concluded that kahweol inhibits tumorigenesis via the up-regulation of apoptosis and down-regulation of HSP70 expression in HT-29 human colorectal cancer cells[49].

Cárdenas *et al.* described the effect of kahweol as an inhibitor of tumor cell proliferation and inducer of apoptosis in the estrogen receptor-negative MDA-MB231 human breast cancer cells. They have observed that kahweol upsurges the generation of reactive oxygen species in human breast cancer cells which activates the cytotoxic effect in these cells, while not hampering the normal cells. So, they suggested that along with caspases-3, -7 and -9 activation and cytochrome-c release, the cytotoxic effect due to the upsurge of reactive oxygen species is responsible for antitumor activity of kahweol, which enforces the inhibitory effects on MDA-MB231 breast cancer cells during his experiments[50].

## 7. Effect of cafestol on breast cancer

The concentration of cafestol ranges from 0.04 to 0.80 mg/cup of coffee depending upon types of coffee. Higher concentrations of cafestol exist in unfiltered coffee such as espresso, French press, boiled coffees or Turkish coffee/Greek coffee, while low concentrations are present in filtered coffee and instant coffee[46].

Cafestol, an antioxidant diterpene, has been explored for their potential anti-cancer, anti-tumor and anti-inflammatory activities. Cafestol has been reported to up-regulate the apoptotic cascade while inhibiting the tumorigenesis[47,51].

Lee *et al.*[47] have observed chemotherapeutic effects of cafestol and kahweol in MSTO-211H and H28 cells. Their results suggest the decreased viability of MSTO-211H and H28 cells and increased apoptosis via suppressed specificity protein (Sp1) levels after cafestol and kahweol treatment. When cafestol and kahweol are exposed to human malignant pleural mesothelioma, they modify the Sp1 regulatory gene proteins expression, which comprises cyclin D1, Mcl-1 and survivin along with the promoter activity. They concluded that cafestol activates the apoptotic pathway via cleavages of Bid, Caspase-3, and poly ADP ribose polymerase along with up-regulated Sp1 regulatory gene proteins expression.

Woo *et al.*[51] evaluated the activity of cafestol if it could surpass the inhibitory effect of ABT-737 (BH3 mimetic inhibitor of anti-apoptotic, Bcl-xL, Bcl-2 and Bcl-w) in Mcl-1-overexpressed human renal carcinoma Caki cells. They observed that the ABT-737 inhibitor alone cannot activate apoptosis while when they exposed ABT-737 along with cafestol, this combination evidently up-regulated

the apoptosis in Mcl-1-overexpressed Caki cells, human glioma U251MG cells as well as human breast carcinoma MDA-MB-231 cells. Furthermore, combined exposure of cafestol and ABT-737 significantly diminished the tumorigenesis as compared with ABT-737 or cafestol individually. Woo *et al.* concluded that cafestol attenuates the Mcl-1 protein expression (the causative agent for ABT-737 resistance) via up-regulating the protein degradation along with increased pro-apoptotic Bim protein expression[51].

## 8. Conclusion

For those who consume coffee everyday frequently due to caffeine dependency, the biggest concern is caffeine toxicity. As it is well-known that caffeine behaves as a stimulator for central nervous system, and its consistent intake might cause mild physical dependency as it is demonstrated by the increased tolerance, withdrawal symptoms (headaches, irritability, fatigue, depressed mood, anxiety and difficulty concentrating) and cravings with abstinence[52,53]. But based on the publications we reviewed, it is evident that moderate caffeine consumption of 300 mg/day along with healthy diet and physically active lifestyle is safe and can rather have beneficial health implications at varying levels. Indeed, the tendency for coffee to promote habitual daily consumption may ultimately turn out to be advantageous to decrease the risk of several chronic diseases along with the breast cancers, if the lists of publications we reviewed do not have any fortification of data. Therefore, based on the available ample publications we went through, our concluding remark is that intake of 2 to 4 cups of coffee per day, if tolerable, seems reasonably good to decrease the chances of breast cancer along with some other chronic diseases.

## Conflict of interest statement

We declare that we have no conflict of interest.

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