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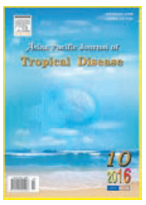

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Influence of coffee and its components on breast cancer: A review

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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 diterpines (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 27 323 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-α from cancer-associated fibroblasts. Moreover, caffeine also diminishes the concentration of the key myo-fibroblasts markers, α-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 α-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 α-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 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