Review Article

The Anticancer Activity of Caffeine - A Review

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Abstract

The cancer burden statistics have been on the rise between the years 2008 and 2018. There has been an increase in the incidence and mortalities of cancers within this period. These statistics justify the sustained increase in the study and exploration of more agents with significant anticancer activity. Compounds of natural origin, such as caffeine, a widely known member of the xanthine family of purines fall under this category. It is a popular component of beverages and medications used in contemporary times. This review aims to elucidate on the anticancer activities attributed to caffeine. Caffeine consumption has been shown to have anticancer benefits from epidemiological evidences. It prevents the initiation of carcinogenesis and has antitumor activity. Caffeine also has significant anticancer activity against animal and cultured cell line models of cancer. The cytotoxic effects of some anticancer drugs have also been improved by combination with caffeine. Furthermore, caffeine and related xanthine derivatives have also been applied in experimental chemotherapy. Some molecular pathways have been implicated in these activities related to apoptosis and DNA damage repair pathways. These studies outline the beneficial anticancer effects of caffeine against the different stages of cancer development.

Keywords: Caffeine; Cell Line Models; Experimental Animal Models; Cancer Epidemiology; Molecular Pathways; Anticancer activity

1. Introduction

Cancer is a genetic disease that is caused by cellular genomic alterations which include insertions, deletions and chromosomal aberrations. These cellular alterations

can lead to uncontrolled cell growth that is evident in tumors [1]. According to Alberts, et al. [2], tumor growth is accompanied by invasion and spread of cells from the origin of the cancers to other sites in the body through a process known as metastasis. The classes include carcinomas (they occur in epithelial cells), sarcomas (they develop from connective or muscle tissue, cancer of the nervous tissue, leukaemia and lymphomas (they derive from white blood cells) [2]. Furthermore, poor prognosis, diagnosis, and therapies of cancer could be attributed to their variation of severities, location, resistance against drugs amongst others [3]. The increase in incidence of cancer can be attributed to factors such as aging of the population, smoking, obesity, late age at first birth, poor diet and physical inactivity [4]. In 2008, there were about 12.7 million cancer incidences and 7.6 million cancer mortalities. The global incidence of cancer is most common in less developed countries, with 56% new cancer cases and 63% cancer deaths recorded [5]. Surprisingly, the incidence increased over the next decade, with 18.1 million new cancer cases and 9. 6 million cancer deaths recorded [6]. This shows both an increase in incidence and mortality of cancers. Hence, a signal for continued pursuit for research into both prevention, therapy and discovery of novel anticancer compounds. Caffeine is one of the most-studied food substance and it has been recorded to be safe with no adverse health implications when consumed in moderation [7]. It is an alkaloid that is found naturally in fruits, leaves, and beans of plants. It can be found in over 60 plants in varying quantities. The common sources of caffeine include: cacao bean (Theobroma cacao), kola nut (Cola acuminate), Guarana berries (Paullinia cupana), and Yerba mate (Ilexparaguariensis sp). However, the world's main sources of dietary caffeine are tea leaves (Camelia siniensis) and roasted coffee beans (Coffea Arabica and Coffea robusta) [8]. Coffee has a wide range of health benefits [9]. It reduces risks of Alzheimer's and Parkinson's disease, diabetes, liver disease, and depression [10-13]. The consumption of 2-5 cups of coffee (16-40 Oz) daily and the intake of caffeine (400 mg/day) have been suggested to be safe, and it has been associated with reduced risks to major disease conditions [14, 15]. In fact, coffee is a natural source of compounds that target the hallmarks of cancer [16, 17]. Caffeine (1, 3, 7-trimethylxanthine), a purine alkaloid gotten naturally from plants can be used to make beverages such as tea and coffee, and it is also used in the production of many soft drinks [18]. There is inadequate evidence to suggest that coffee drinking can cause carcinogenicity in humans, and this was seen from a combination of studies on different types of cancer, including liver cancer, female breast cancer, uterine endometrial cancer, prostate cancer, and pancreatic cancer [19]. As we will see recent studies have shown the epidemiological anticancer effects of the consumption of caffeine. Additionally, caffeine has a demonstrated anticancer activity on animal models and cancer cell lines, both individually and in combination with anticancer drugs.

2. The biological effects of caffeine and related xanthine-based compounds

According to Sultani, et al. [20] purines are promulgated to be an essential category of biochemically important nucleotides; as well as pyrimidines. Xanthines are a group of compounds which are part of the catabolic pathway of purines in humans. There are three pharmacologically important xanthine compounds and they include caffeine, theophylline, and theobromine. They occur naturally in certain plants and they are popularly consumed as beverages (infusions or decoctions) obtained from these plants [21]. Xanthines, methylxanthines, or xanthine derivative compounds are

a particularly interesting category of drugs because they have diverse pharmacological properties. The xanthines are mostly central nervous system stimulating agents, however, they do not all possess this property. The mechanism of stimulation is derived from the methyl xanthines' ability to function as an antagonist of adenosine, a compound that is inborn in human cells [21]. The adenylate cyclase signalling system can be sabotaged by the methylated purine derivatives caffeine, theophylline-used in asthma treatment [22], and theobromine (found in chocolate) and so they function as stimulants. Xanthine and related analogues have biological activity through the inhibition of phosphodiesterase, antagonism of adenosine receptors, sensitization of calcium release ryanodine-sensitive channels in the sarcoplasmic and endoplasmic reticulum to action by calcium and antagonism of GABA receptors [23, 24]. They antagonize adenosine receptors that act through inhibitory G proteins [25]. This antagonism results in an increase in intracellular camp concentration. Aspirin, which is frequently combined with is applied to the treatment of headaches. They are easily absorbed through the rectal and oral routes. Although these agents like theophylline can be administered by injection, it is only used in premature infants suffering from status asthmaticus and apnoea [21]. Theophylline is often administered as a bronchodilator for the treatment of asthmatic conditions. It is also administered as a soluble salt of ethylenediamine, aminophylline. It helps in alleviation of the paroxysmal dyspnoea that is related to left heart failure. Theophylline has been shown to be beneficial in treating neonatal apnoea syndrome and increases myocardial contractile force [21]. Methylxanthines, including theophylline and aminophylline have been used for the management of chronic obstructive pulmonary disease and asthma for over fifty years [26]. The xanthines have their associated toxicities which include nervousness, insomnia, and in extreme situations, delirium. Extreme respiratory stimulation may happen wherein which dress may be apparent. The intravenous administration of aminophylline (or theophylline) may cause adverse effects if the drug is administered too quickly. Adverse effects that may manifest include headache, hypotension, and palpitation [21]. Theophylline has a marginal therapeutic range and unevenness in disposition. These properties make dosing hard to prognosticate and toxicity hard to proscribe. Furthermore, theophylline may become lethal in children and adults likewise if it is not administered with appropriate control. More so, other symptoms of toxicity comprise agitation, tachycardia, severe restlessness, vomiting and convulsions [27].

3. Epidemiological studies on the anti-cancer effects of caffeine and caffeine containing substances

A study was conducted to assess the carcinogenicity of coffee in liver cancer, female breast cancer, uterine endometrial cancer, prostate cancer, and pancreatic cancer. They discovered a negative correlation for liver and endometrial cancers. Furthermore, the evidence other sites that were reviewed was insufficient. These facts led to the finalization that there is insufficient information in humans to support that coffee drinking can lead to carcinogenesis [19]. An early research conducted by Schairer, et al. [28] showed that there was a negative relationship, especially in women diagnosed for breast cancer aged beyond 50. This negative correlation was elucidated when they investigated the association between breast cancer and methylxanthine intake with the use of data from a case-control study. Lubin, et al. [29]. In their study analyzed the intake of methylxanthines in patients suffering from malignant breast cancer in comparison to those patients of the

benign breast cancer variety. They performed the analysis through adjusting by age and ethnic group and there was a reduced risk for developing the malignant phenotype. Another study provided proof that the inverse relation between coffee and Hepatocellular Carcinoma (HCC) is significant, however, inference on causality is still open to further discussions [30].

In subgroup analyses, Dong, et al. [31], showed that coffee consumption was strongly correlated with a reduction in the risk of incidences of pancreatic cancer in men. Moreover, among women in that population, an association was not observed. Several studies from the Asia-Pacific region, Europe, and North America also reported similar results. These results suggest coffee drinking and risk of pancreatic cancer have an inverse association. Another epidemiological study was conducted by Beehler, et al. [32] with participants, including 1932 breast cancer patients and 1895 controls with neoplastic conditions. They discovered a protective effect of coffee intake and not black tea intake on premenopausal breast cancer risk, however, the effect was not observed in postmenopausal breast cancer risk. Meta-analysis of case studies done by [33]. Product results that show that intake of coffee greatly reduces the risks of development of colorectal and colon cancers. The results were most pronounced in Europe and in the female population. Daily caffeinated coffee consumption was greatly correlated with a dose-dependent decrement in the widespread presence of nonmelanoma skin cancer in Caucasian women. In a variation to caffeinated coffee consumption, the consumption of decaffeinated coffee on a daily basis was negatively associated with a remarkable difference in nonmelanoma skin cancer incidences reported by Caucasian women [34].

In a study done on 9650 subjects that gave information about their drinking habits in 1982–1984, it was discovered that consumption of caffeine and the normal ground coffee was linked to a reduced incidence of chronic liver disease. Hence, consumption of tea and coffee lowers the risk of developing chronic liver disease [35]. The effect of coffee (and other methylxanthines sources) on Type I vs Type II endometrial cancer (EC) risk have not been previously investigated until Uccella, et al. [36] did so. In the study that was conducted on 23,356 women that are past their menopause. The cases of Type I and Type II endometrial cancer cases were 471 and 71 respectively. These results imply that coffee may have a protective effect against Type I EC in postmenopausal obese women. Additionally, coffee have been linked with reduced risk of prostate cancer, breast cancer, endometrial cancer, colon cancer, and colorectal cancer [37] and inversely associated with mortality from all-sites cancers [38]. Molecules that contain nitrogen and are sourced from marine and terrestrial organisms have been studied for the past few years to test their antitumor activity. These molecules comprise 1, 3, 7-trimethylxanthine (caffeine), and its several derivatives, referred to as 1, 3, 7- trialkylxanthines [20]. Besides, a study has shown caffeine's inhibition of tumourigenic growth induced by carcinogens. [39]. Results of a study done on female Sprague-Dawley rats showed that prolonged consumption of caffeine can lead to the significant inhibition of benign mammary gland tumorous development in DMBA-treated rats [40]. Caffeine has also been shown to be involved in the prevention of skin cancer induced by sunlight in both mice and humans. It does this by protecting against DNA damage, which is the major mutagenic outcome of UV radiation [34, 41]. The consumption of caffeinated coffee daily has been associated with a decreased prevalence of nonmelanoma skin cancer in Caucasian

women, and it is dose-related. When compared with caffeinated coffee, it was observed that the consumption of decaffeinated coffee daily did not result in a significant change, and was consequently, not associated with nonmelanoma skin cancer for Caucasian women [34]. The intake of caffeine and regular ground coffee was linked to reduced incidence of chronic liver disease, and this was recorded from a detailed drink information in 1982-1984 gotten from 9650 participants. Therefore, drinking of tea and coffee reduces the risk of developing chronic liver disease [35].

4. The individual effects of caffeine on cancer cell lines and animal models of cancer

Molecules that contain nitrogen and are sourced from marine and terrestrial organisms have been studied for the past few years to test their antitumor activity. These molecules comprise 1, 3, 7-trimethylxanthine (caffeine), and its several derivatives, referred to as 1, 3, 7-trialkylxanthines [20]. Besides, a study has shown caffeine's inhibition of tumorigenic growth induced by carcinogens [39]. Results of a study done on female Sprague-Dawley rats showed that prolonged consumption of caffeine can lead to the significant inhibition of benign mammary gland tumorous development in DMBA-treated rats [40]. Caffeine has also been shown to be involved in the prevention of skin cancer induced by sunlight in both mice and humans. It does this by protecting against DNA damage, which is the major mutagenic outcome of UV radiation [34, 41]. The intake of caffeine at higher levels have been associated with some beneficial effects along with some health implications in pregnant women and children [7]. Treatment with caffeine greatly reduced the expression levels of hepatocarcinogenic markers than curcumin. This shows that when compared with curcumin, caffeine could serve as a more effective compound for the prevention of hepatocarcinogenesis in DEN-induced rats [42]. Another study observed a hepatoprotective effect against fibrosis in the groups receiving conventional coffee and 0. 1% caffeine, it was also observed that groups receiving instant coffee and 0. 1% caffeine had the greatest effects against liver carcinogenesis [43]. Eini, et al. [44] showed for the first time that treatment with caffeine can lead to an effective anti-tumor immune response promotion during the initiation of tumor, partly through the antagonism of the A2AR adenosine receptor. In a work done by Lou, et al. [45], caffeine at a concentration of 0.44 mg/ml was administered to lab mice for a period of 18 to 23 weeks as a component of the singular drinking fluid source. Ultraviolet light (UVB) was also concurrently applied as a carcinogen and the development of malignant and non-malignant tumors were prevented as a result of the caffeine treatment. The treatment also caused a decrease in the tumor size of another control group of mice. They concluded that their results show that caffeine essentially contributes to green and black tea's inhibition of the carcinogenic effects of UVB. Chung, et al. [46] studied caffeine and black tea's activity on lung tumorigenesis in F344 rats. The tumour was affected by the nicotine-sourced carcinogen, 4-(methylnitrosamino) -l-(3-pyridyl) -l-butanone (NNK) in a two-year study of biological activity. This study demonstrated for the first time that lung tumorigenesis as prevented in the subjects of study and this caffeine was responsible for this protection to a significant extent because it is a major component of tea. In the study by Huang, et al. [47], they found out that UVB-induced carcinogenesis was significantly inhibited by the administration of caffeine alone orally. Furthermore, the incorporation of caffeine to the decaffeinated teas instituted their inhibitory effects on UVB-induced carcinogenesis in the skin of SKH-1 mice. Caffeine and theobromine had an

inhibitory effect on the doxorubicin efflux from tumor cells (Ehrlich ascites carcinoma cell), increased the concentration of doxorubicin in a tumor, and enhanced doxorubicin antitumor-effect [48]. It was found that the combination atorvastatin and caffeine downregulated the levels of Phospho-Erk1/2, phospho-Akt, Survivin, and anti-apoptotic Bcl-2 protein [49]. In vitro studies showed that a number of compounds, including caffeine and kahweol, we're able to reduce the growth of human colorectal cancer cell lines, primarily by cell phase arrest and increasing apoptosis. It is of importance to establish the in vitro setting of the studies, as there is need to investigate the complexity of the organism as a whole [50]. Caffeine reduced the invasion in human glioblastomas LN229, U-87MG and GBM8401 cells [51]. Chen, Hwang [52] suggested a new mechanism of caffeine on glioma, by decreasing HDAC1 activity and/or by increasing p300 activity, caffeine could increase the death glioma cell. The loss of RT2 glioma cells seemed to occur after changes in HDAC1 and p300 activities. Motegi, et al. [39] found out that caffeine or theophylline administration along with DXR generated a synergistic anticancer effect in canine hemangiosarcoma cell line. Saito, et al. [53] showed that the combination of caffeine and adenovirus-mediated transfer of PTEN (Ad-PTEN) caused a synergistic suppression of cell growth and an induction of apoptosis in colorectal cancer cells. Guaraná (A highly caffeinated food and caffeine inhibited some MAPKs proteins (p-HSP27 and p-p38) in MCF-7 breast cancer cell lines [54]. Additionally, guaraná inhibited mTORC2 (p-AKT) and mTORC1 (p-S6K) in MCF-7 cells, but only mTORC1 in HT-29 colorectal cell lines. Caffeine only inhibited the mTOR pathway in MCF-7 breast cancer cell lines. There is a notable paucity of research done on with caffeine on animal models of cancer [40, 45, 46, 55-60] relative to the cell line models. The recent work was done by Higuchi, et al. [56] on Synovial sarcoma (SS), a recalcitrant neoplasm with low chemosensitivity in patient-derived orthotopic xenograft (PDOX) mouse model. Their results suggested that combining oral rMETase (recombinant methioninase) and caffeine together with first-line chemotherapy can be greatly efficient for SS and has clinical potential for this unmanageable disease. Furthermore, they posited that caffeine boosts the effectiveness of anticancer drugs by affecting cell-cycle arrest induced by drugs and intensifying successive apoptosis which is buttressed by studies by Wang, et al. [61] in lung cancer cells, Wang, et al. [49] in prostate cancer cells and by Bode, Dong [62] in their review. An early study by wolfram, et al. [40] showed that prolonged consumption of caffeine can lead to the significant inhibition of benign mammary gland tumorous development in DMBA-treated female rats. A genome-wide study by Bartkova, et al. [63] with the use of allelic imbalance assessment, showed that human cells activate an ATR/ATM-regulated DNA damage response network early in tumorigenesis (before genomic instability and malignant conversion), and those that delays or prevents cancer. A study was done on an experimental model of pancreatic carcinogenesis, pancreatic intraepithelial lesions in mice was induced using DMBA [55]. In this study, an association between caffeine and pancreatic cancer was not observed, the results also showed that the caffeine group (15%) had a similar relative frequency of invasive adenocarcinoma to that of the water group (16. 6%). Another study showed that the invasion of glioma cells and tumor growth was reduced by caffeine through ROCK-cathepsin B/FAK/ERK signalling pathway in orthotopic xenograft animal model, and this study supports the possible anti-cancer effect of caffeine in glioma therapy [51].

5. The combined effects of caffeine and chemotherapeutic agents on cancer cell lines and in chemotherapy

Tomita, Tsuchiya [64] stated that reports have shown that caffeine, which seems to have an inhibiting effect on DNA repair actually enhances the cytotoxicity of DNA damaging agents (Example ultraviolet light and alkylating agents) on cancer cell lines. They studied the effects of several combinations of several anticancer agents (including cisplatin, 4-hydroxyperoxycyclophophamide, mitomycin C, adriamycin, vincristine and methotrexate) with caffeine against cultured human sarcoma cells. Furthermore, they suggested that cisplatin, cyclophosphamide, mitomycin C and Adriamycin had their DNA-damaging effects enhanced by caffeine. Cisplatin was shown to possess the most synergistic effects of the DNA synthesis-inhibiting drugs. When 4 mg of caffeine was given once a day for three days after the administration of cisplatin, marked regression of the sarcoma was observed in groups treated with 5 or 10 mg/kg of cisplatin, without significant weight loss. These results indicate that caffeine enhances the antitumor effect of cisplatin on transplanted osteosarcoma in BALB/C athymic mice [65]. Caffeine boosts the effectiveness of anticancer drugs by affecting cell-cycle arrest induced by drugs and intensifying successive apoptosis [56]. A contrasting result was found in Mohammadrezaei, et al. [66] when they showed that low-dose doxorubicin induced senescence in MCF-7 cell breast cancer cells via ATM and chk2 activation. However, the sensitivity of the cells to doxorubicin-induced senescence could not be increased by caffeine, chk2 inhibitor and a combination of chk2 inhibitor, caffeine and doxorubicin. A very early work by Tsuchiya, et al. [67] on thirty-six patients with histologically high-grade soft-tissue sarcomas were treated with caffeine-potentiated chemotherapy with standard drugs doxorubicin and cisplatin and conservative surgery. Furthermore, nine patients had stage III disease, of which eight patients died of metastatic disease within two and a half years from the beginning of the treatment. They concluded that caffeine-potentiated chemotherapy and limb-sparing surgery produced beneficial results for stage II nonmetastatic soft-tissue sarcomas. However, the problem of treatment for stage III metastatic soft-tissue sarcomas remained unsolved. Kimura, et al. [68] reported results of caffeine-potentiated chemotherapy for patients with osteosarcoma with pulmonary metastases and discovered that there was prolonged survival of patients in the experiment. Nakata, et al. [69] used caffeine with ifosfamide, and using a novel drug delivery system with Span 80 nano-vesicles, the tumor-specific caffeine-potentiated chemotherapy for murine osteosarcoma was administered. The result showed significant antitumor effects, as well as limited adverse effects. Another study by Karita, et al. [70] used liposomes containing polyethylene glycol encapsulated cisplatin (CDDP-L) as the drug delivery system. In osteosarcoma bearing rats administered with CDDP-L, it was observed that the antitumor effect was not only improved by the caffeine co-administration but also by the increasing the dosing period of caffeine. The effect of caffeine-potentiated chemotherapy for clear cell sarcoma in five patients was reported in this study [71]. Four patients responded to preoperative chemotherapy. Out of the five patients, only one underwent local recurrence. Development of new distant metastasis was observed in one patient. All five patients survived. Treatment with caffeine-potentiated chemotherapy can be effective for clear cell sarcoma not only as initial therapy, but also as salvage therapy. Paclitaxel (Taxol) is a chemotherapeutic agent that exists naturally and is isolated from the bark of the Pacific Western yew. Gururajanna, et al. [72] showed that both Caffeine and

Taxol are efficient in triggering of cell growth inhibition, cell cycle arrest and eventually leads to the death of pancreatic adenocarcinoma cells. The study showed that these effects were less in cells with the p53 mutation cells and more in cells containing the wild-type p53, and this suggests an essential role of p53 in determining the effects of these agents in pancreatic cancer cells. Three categories of purine antagonists have been shown to be applied in cancer chemotherapy. Thiopurines, 6-thioguanine (6-TG) and 6-mercaptopurine (6-MP) were applied in the treatment of leukaemia in the early 1950s. However 6-mercaptopurine is an acceptable drug for the perpetuation of recovery in acute childhood lymphocytic leukaemia when combined with methotrexate [73]. Both 6-MP and 6-TG inhibit new purine bases, production and they are integrated into the DNA strand [74]. In a work done by Motegi, et al. [39], xanthine derivatives in combination with doxorubicin and without doxorubicin were applied to canine hemangiosarcoma cell lines. The anticancer properties were elucidated by evaluating the growth of tumor cells, cytotoxic effects on cancer cells and apoptosis (through measurement of annexin V or caspase 3/7 protein gene expression). According to their study, xanthine derivatives (theophylline and caffeine) induced apoptosis in the cancer cell lines and after treatment, annexin V and caspase 3/7 expressions were observed; they also showed that the xanthine derivatives increased the cytotoxic effects of doxorubicin. Another xanthine derivative, 1-methyl-3-propyl-7-butylxanthine (MPBX) was shown to improve the antitumor activity of idarubicin against P388 leukemia cells; suppression of bone marrow was also observed by Sadzuka, et al. [75]. Caspase-3 activation studies on CRL5985 and HTB182 lung cancer cell lines showed that treatment with caffeine augments the apoptotic effects of cisplatin on the cells [61].

6. Molecular pathways implicated in the anticancer activity of caffeine

6.1 Caffeine's involvement in the cellular DNA damage related pathway

It is well known that DNA damage response (DDR) involves two major kinases the Rad3-related (ATR) and Ataxia Telangiectasia mutated (ATM) [76, 77]. The protein kinases Rad3-related (ATR) and Ataxia Telangiectasia mutated (ATM) are members of the Phosphatidyl inositol 3-kinase-like family (PIKKs). They are involved in an essential role regarding the response of cells to damage of the DNA [78-80]. Caffeine has been shown to abolish the G_2/M DNA damage checkpoint of mammals through the inhibition of Ataxia-Telangiectasia-mutated (ATM) Kinase activity [81-83]. It was further shown that the checkpoint is accompanied by Cdc25c phosphorylation in the nucleus after of cells exposure to gamma radiation [81] this implies that damaged cells have a marked increase in phosphorylation of Cdc25c. In human cells, the damage-induced delay in G2 is mostly due to the inhibitory phosphorylation of Cdc2 [84]. Furthermore, Chk2/Cds1 protein localizes in the nucleus and phosphorylates Cdc25C as part of the cascade of cell arrest in response to damage. In the experiment by Zhou, et al. [81], it was found that treatment of gamma irradiated cells with caffeine inhibited the activation of Chk2/Cds1. They further suggested that ATM is a direct kinase for Chk2/Cds1 which suggests that caffeine can inhibit cell cycle arrest by inhibiting the phosphorylation of Chk2/Cds1 by ATM. A study also reported that caffeine inhibits ATM kinase activity directly in vitro [84]. Sarkaria, et al. [85] stated that the radio sensitizing effects of caffeine are linked to the inhibition of the protein kinase ATM and ATR activities and that both proteins are significant targets for the development of novel anticancer agents. Treatment with

caffeine treatment led to the rapid loss, by proteasomal degradation, of both Dna2, a nucleus that facilitates one of two extensive resection pathways, and Sae2, a nucleus that plays a role in the early steps of resection [86]. In human fibroblasts that express telomerase, caffeine was also able to overturn the G2 and S responses which are dependent on ATM and S checkpoint response that is dependent on ATR. The damages were induced Ionizing Radiation and Ultraviolet radiation, respectively [87].

6.2 Caffeine's induction of apoptosis

Cisplatin is an example of an alkylating agent that damages DNA and so it is applied in cancer chemotherapy. Unfortunately, cisplatin's anticancer activity reduces rapidly as the cancer cells become resistant to the drug and consequently results in an unsuccessful chemotherapeutic regimen. Caspase-3 activation studies on CRL5985 and HTB182 lung cancer cell lines showed that treatment with caffeine augments the apoptotic effects of cisplatin on the cells [61]. Liu, et al. [88] examined the anticancer effects of caffeine on gastric cancer cells in vitro. They determined the association of the apoptosis-related caspase-9/-3 pathway with these anti-cancer properties. They also studied the continuous anti-proliferative activity of caffeine on the gastric cancer cell lines. Results from this study revealed that caffeine notably inhibited the growth of the gastric cancer cell lines and caused apoptosis through the activation of the caspase-9/-3 pathway. The treatment with caffeine caused an increase in the activation of caspase-9 and -3 and an increase in the levels of expression of Cyt-c in the gastric cancer cell line, compared with the control group. Moreover, caffeine's anticancer effects seemed to be continuous because the caspase-9/-3 pathway maintained its activity even after the withdrawal of caffeine. A contrasting result was stipulated by pre-treatment of CRC cells with caffeine, the levels of the antiapoptotic Bcl-2 family member, Mcl-1 was increased, thereby resulting in a significant inhibition of paclitaxel-induced cytotoxicity. Saito, et al. [53] implicated the abrogation of G(2)/M arrest, down regulation of the Akt pathway, and modulation of the p44/42MAPK pathway in the synergistic effects of caffeine against colorectal cancer cell lines. Horrigan, et al. [89] demonstrated that the camp/PKA pathway mediates the effect of suppression caffeine has on LPS-induced TNF-α production, possibly due to the inhibition of camp-phosphodiesterase. The derivatives of Methylxanthine (caffeine and theophylline) can effectively induce apoptosis and autophagy in gastric cancer cell by activation of PTEN and suppression of PI3K/Akt/mTOR pathway [90]. Caffeine significantly reduced the expression levels of HIF-1α and VEGF in glioblastoma cells exposed to hypoxia. The mediation of this effect is achieved through the inhibition of MAPK/ERK and PI3K/Akt signalling pathways [91]. Jia, et al. [92] found that splicing factor SRp20 (SFRS3) is over expressed in cancers. Furthermore, RNAi-mediated reduction of SRp20 expression in cancer cells caused them to show G2/M arrest, apoptosis and growth retardation. Lu, et al. [93] showed that a higher caffeine dose downregulated SRSF3 and p53α, and thus suggest the active functions of p53 in stimulation of caffeine. Caffeine has also been shown to have a potential role in regulating the initiation, progression and maintenance of tumors, by downregulating the proto-oncogene SRSF3 [92, 94]. Lu, et al. [95] found out that caffeine application can boost UVB-induced increases in apoptosis by p53- and Bax-independent pathways. Dubrez, et al. [96] reiterated the independence of caffeine to cell-cycle related activities and caffeine synergizes with p53 for inducing cell death through a cell cycle-independent mechanism. This mechanism involves the mitochondrial translocation and

conformational change of BAX protein. The invasion of glioma (Brain tumor) cells was decreased by caffeine through the ROCK-cathepsin B/FAK/ERK signalling pathway [51]. Another work also showed that caffeine was also prevented the progression glioma cells through induction of apoptosis, caused higher expression levels of FoxO1 gene and as well proapoptotic target Bim [97].

3. Other implicated molecular pathways in caffeine's anticancer activity

Lastly, another caffeine-induced effect is mediated through the inhibition of adenosine receptors. This effect may alter HIF1 alpha stability in addition to the expression levels of VEGF and interleukin-8 in tumor cells, which could directly influence the neovascularization of human tumors [98]. Another mechanism of caffeine seems to involve the inhibition of the extracellular signal-regulated kinase 1/2 (ERK1/2), p38, and Akt, which then leads to a marked decrease in the accumulation of adenosine-induced HIF-1α, activation of VEGF transcription, and accumulation of VEGF and IL-8 protein [99]. Research by Dong, et al. [100] showed that caffeine may stop the growth of Human Hepatocellular Carcinoma via the Akt signalling pathway. Caffeine also improved the autophagic flux in hepatic stellate cells, which was caused by Endoplasmic reticular stress via the IRE1-α signalling pathway [101].

7. Conclusion

Caffeine has been shown to have activity at all stages of cancer development. These include preventing initiation of carcinogenesis, induce apoptosis abolish checkpoint of DNA damage, inhibit angiogenesis, possess antitumor activity in vivo and enhance the chemotherapeutic effects of anticancer drugs. It has also been shown to be used in experimental chemotherapy as well as its fellow xanthine analogues. Epidemiological evidence also points towards the recommendation of its consumption as a result of beneficial anti-cancer activity. Caffeine has shown promise as a very good anticancer agent and more translational research experiments could be conducted to discover novel insights about its activity. This review has presented clearly about current literature on the landscape of the anticancer activity of caffeine as stated.

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Enoma D. O was responsible for defining the content of the work, and major contribution of materials in the subject area. Dokunmu T. O was responsible for providing general oversight, direction, content addition and proof reading the contributions added to the work. Obi P. O. Was responsible for adding content to the work and also working on the grammar and plagiarism of the work.

Conflicts of interest

There are no conflicts of interest declared in the completion of this work.

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