Biomedicine & Pharmacotherapy 105 (2018) 312–319

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

# Mechanistic considerations in chemotherapeutic activity of caffeine

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ARTICLE INFO

*Keywords:*
Caffeine
G1 phase
G2 phase
Apoptosis
Anti-tumor immune response
Angiogenesis

ABSTRACT

Caffeine (1,3,7-trimethylxanthine) is one of the most commonly consumed food ingredient throughout the world for thousands of years. It is naturally present in beans, leaves, seeds, and fruits of more than 60 plants and the most common sources are cocoa beans, coffee beans, tea leaves, kola nuts, and guarana berries. Several epidemiological studies suggested that consumption of coffee reduces the risk of different types of cancers. Understanding the chemotherapeutic molecular mechanisms of caffeine would facilitate in designing efficacious combination strategies with other anticancer drugs. Therefore, the aim of this review is to identify and highlight all the mechanisms involved in chemotherapeutic activity of caffeine. Mechanistically, caffeine has been shown to affect cell cycle progression at checkpoints, induce apoptosis, and inhibit drug efflux from cells. Caffeine at lower (micromolar) and relatively non-toxic concentrations has been shown to promote anti-tumor immune response (A2 A) and to inhibit tumor angiogenesis (A3) and migration (A2B) by antagonizing adenosine receptors. Considering the fact that a lower (micromolar) and relatively non-toxic concentrations of caffeine are required for its anti-tumor immune response and antiangiogenic activity, developing a combination strategy with immune checkpoint (PD-1 or CTLA-4) inhibitors would represent a novel approach to treat cancer.

## 1. Introduction

Caffeine (1,3,7-trimethylxanthine) is one of the most commonly consumed food ingredient throughout the world for thousands of years. It is naturally present in beans, leaves, seeds, and fruits of more than 60 plants and the most common sources are cocoa beans, coffee beans, tea leaves, kola nuts, and guarana berries [1]. Our understanding on caffeine has boosted its use in variety of commercial food, commercial drinks, and in some medical preparations [1]. Barone and Roberts reported that each cup (150 mL) of coffee contains 64–124 mg of caffeine and the global consumption of caffeine per day corresponds to a single serving of one caffeine beverage per individual [2]. The well-known effects of caffeine are enhancement of mood and alertness [3], improvement of performance during exercise [4], and improvement of cognitive functions such as awareness, reaction time, problem-solving, and decision-making [5]. Caffeine has been shown to reduce the motor and non-motor symptoms associated with Parkinson's disease and play a preventive role in disease onset and progression [6]. Several epidemiological studies suggested that consumption of coffee reduces the risk of cancers of brain [7], endometrium [8], colon [9], skin [10], breast [11], liver [11], and kidney [11]. Even though caffeine was investigated in a variety of disease areas, the focus of this review will be on its ability as an anticancer agent with primary focus on the molecular mechanisms when used alone or in combination with other anticancer agents. In addition, this review emphasizes the relatively unexplored effects of caffeine such as modulation of anti-tumor immune response, in addition to its effect on the process of angiogenesis.

Relevant databases (Google Scholar, PubMed, Science Direct, and Web of science) were searched for peer-reviewed English-language articles. Selected articles (between 1970 to 14 October 2017) that examined the effects of caffeine alone or in combination as a chemotherapeutic agent were analyzed.

## 2. Effect of caffeine on cell cycle progression

The cell cycle of an actively dividing eukaryotic cell consists of four distinct phases such as S phase (DNA synthesis), M phase (DNA separation and cell division), and two gap phases (G1 and G2) whereas, in the absence of mitogenic stimulus, cells stop dividing and enter into a resting state called as G0 phase. G1 is the first gap phase between S phase and G0 phase and the period between S phase and M phase is the G2 phase. The G1/S checkpoint restricts entry to S phase whereas G2/M checkpoint delays the entry into mitotic phase [12]. Dividing cells have the capability to repair DNA damage by pausing or arresting the cell cycle progression at G1/S and G2/M checkpoints [13]. If the damaged DNA is repairable, the cells are subjected to apoptosis under the influence of tumor suppressor protein p53 [14]. Several studies (reviewed in the subsections below) have reported that caffeine alone or in

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https://doi.org/10.1016/j.biopha.2018.05.144
Received 26 February 2018; Received in revised form 28 May 2018; Accepted 28 May 2018
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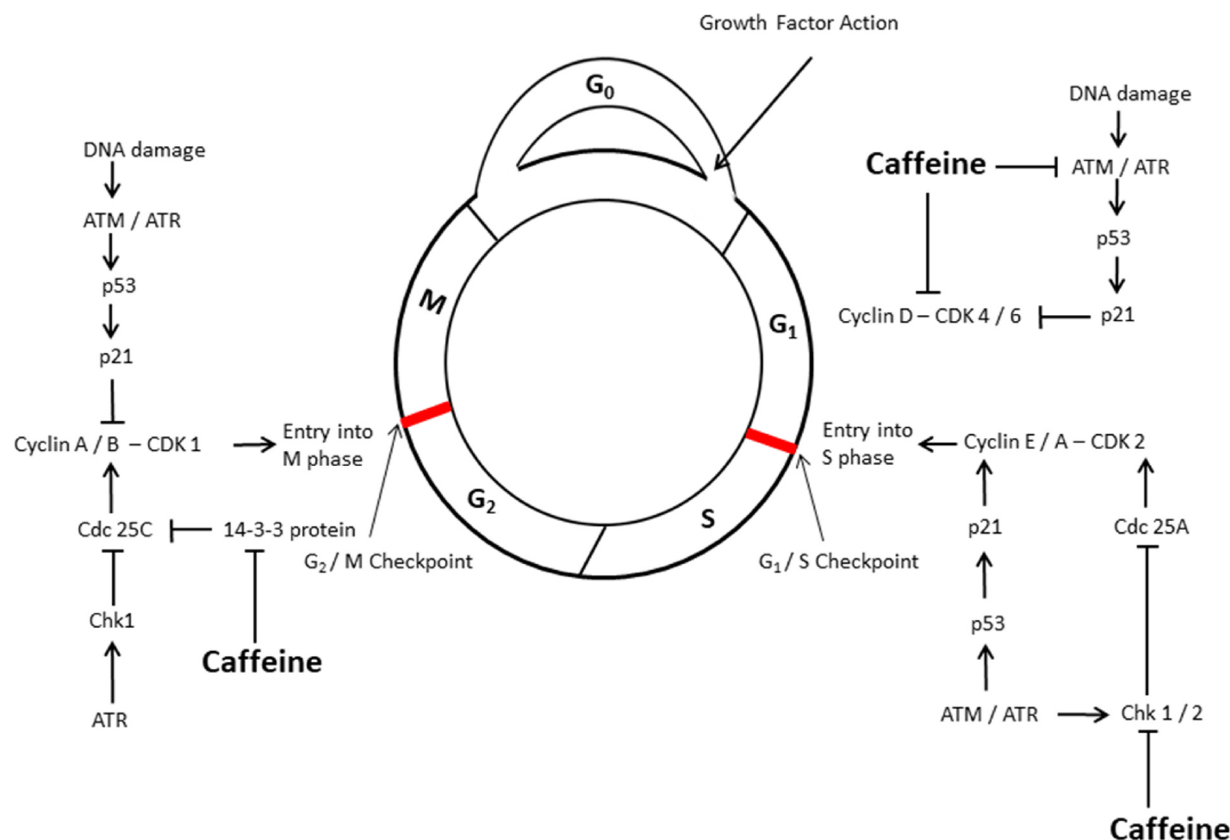


**Fig. 1.** Effects of caffeine on cell cycle progression. Caffeine inhibits the DNA damage induced ATM / ATR kinases and Chk1/2 phosphatases and progress the cell cycle through the G1/S checkpoint without the repair of damaged DNA which ultimately causes apoptosis. Caffeine directly acts on cyclin D – CDK 4/6 complex and arrests the cell in G1 phase. Caffeine prevents the inhibitory binding of 14-3-3 protein with Cdc25c thereby enhancing Cdc25c which in turn activates Cdc2 and progress the cell cycle through the G2/M checkpoint. ATM, ataxia telangiectasia mutated; ATR, ATM- and Rad3-related kinase; CDK, cyclin dependent kinase; Chk, checkpoint kinase.

combination with other anticancer agents acts on the checkpoints and prevent the cell cycle progression.

### *2.1. Effect of caffeine on G1/S checkpoint*

For the first time, Walters and group studied the effects of caffeine (2 mM) on G1/S checkpoint and suggested that caffeine directly induces G1 arrest in a culture of Chinese hamster cells [15]. Later, Tolmach and group reported G1 arrest by caffeine (1 mM) in Hela S3 cells [16]. On the other hand, Kastan and group showed that caffeine (4 mM) blocks both G1 arrest and induction of p53 protein expression in γ-irradiated myeloblastic leukemia cells [17]. Caffeine blocks the induction of p53 expression through the inhibition of ataxia telangiectasia mutated (ATM) and ATM- and Rad3-related (ATR) kinases, leading to apoptosis due to decrease in availability of time for repairing (Fig. 1) [18]. In dividing cells, the activation of ATM and ATR kinases primarily depends on DNA damage [19]. Once activated, the ATM and ATR kinases enhance the phosphorylation of p53 protein leading to accumulation of p53 by reducing its degradation [20]. ATM and ATR kinases has also been implicated in phosphorylation of mouse double minute 2 (MDM2), that disrupts the association of MDM2 with p53 thereby preventing the ubiquitination of p53 and ultimately its degradation [21]. Furthermore, ATM phosphorylates checkpoint regulatory protein chk2, which in turn phosphorylates p53 and prevents the inhibitory binding of p53 with MDM2 [22]. Finally, p53 through activation of p21 protein suppresses the activation of cyclin D/Cdk4/6 and cyclin E/Cdk2 leading to G1 arrest [23,24]. Later, a study conducted by Qi et al. showed that caffeine (5 mM) alone or in combination with γ-irradiation induces p53 independent G1 arrest and cell death in human A549 lung tumor cells [25]. The same study confirmed the p53-independent G1 arrest using p53 deficient human A549 lung tumor cells, suggesting p53 activation is not mandatory for anticancer activity of caffeine. The same researchers observed that caffeine inhibits Cdk2 activity in the p53 deficient human A549 lung tumor cells indicating caffeine-induced G1 arrest depends on the inhibition of cyclin E/Cdk2 complex. When tested at lower concentration (0.5 mM), caffeine alone or in combination with γ-irradiation could not induce G1 arrest indicating a dose-dependent differential effect [25]. But, the γ-irradiation-induced G2 arrest was reversed by caffeine at both 0.5 and 5 mM concentrations [25].

Hashimoto et al. showed that a lower concentration of caffeine (0.25–1 mM) inhibits cell cycle progression at G0/G1 phase in JB6 Cl41 mouse epidermal cells [26]. They observed that caffeine inhibited (IC50 = 0.7 mM) fetal bovine serum-stimulated cell proliferation at G0/G1 phase without cell death. The mechanism by which caffeine caused the G0/G1 phase arrest appeared to be mediated by suppression of cyclin D1/Cdk4 complex activity and subsequent inhibition of retinoblastoma (Rb) protein phosphorylation (Fig. 1) [26]. The role of cyclin D1/Cdk4/6 complex is to phosphorylate and inactive the Rb protein at G0 and G1 phase of the cell cycle. Active Rb forms a complex with E2F transcription factors, and phosphorylation of Rb makes it to release E2F and subsequent activation of genes responsible for cell cycle progression through S phase [27–29]. In the same study by Hashimoto et al., caffeine inhibited the phosphorylation of protein kinase B (Akt) and its substrate, GSK-3β in a time-dependent manner [26]. The role of GSK-3β is to trigger cyclin D1 turnover by phosphorylating it, and thus making the cell to progress through G1 phase [30]. It has been reported that caffeine directly inhibits PI-3 kinase (PI-3 K) activity, which is an upstream activator of Akt/GSK-3β [31]. Hashimoto et al. suggested that

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