INTRODUCTION

Caffeine or better known popularly by the name of coffee, is a xanthine alkaloid compound. This compound is found in all types of commercials under the name Arabica coffee, which is distributed 60% and Robusta coffee which is distributed 40% in the world. The differences between these two types include the place where the climate grows, physical aspects, chemical composition, and characteristics. Arabica coffee is known for its aroma while Robusta has a stronger taste with solutes that are richer in antioxidants. Caffeine was first purified by a German chemist, Friedrich Ferdinand Runge, in 1819. The term “caffein” was coined to refer to the chemical compound in coffee. Caffeine is called teina when found in tea, equally referring to the same chemical compound and is found naturally in foodstuffs such as coffee beans, cocoa and tea leaves.1

Unlike other psychoactive, caffeine is legal and not regulated by law in almost all jurisdictions in the world and is on the WHO’s list of essential drugs.2 Coffee is the most consumed drink globally, having an effect on human metabolism at extracellular and intracellular levels. Caffeine or trimethylxantine in intracellular has potential as an agent for antiviral and anticancer. Treatment with caffeine will affect the mechanism of DNA repair enzymes and induce premature chromatin condensation (PCC), which organizes the occurrence of mitosis at rudimentary cell cycle phase S which makes DNA integrity unattainable, and cells become apoptosis. Studies have already been conducted observing the effects of caffeine at the cellular level, by reacting Escherichia coli (E.coli) or mammalian cells to reactions that disrupt cell cycles such as arsenualysis, exposure to UV radiation, x-ray induced, and starvation with nothing to consumed accept of purines derivatives including caffeine. The result of caffeine treatment on E.coli and mammalian cells on UV radiation and arsenolysis least affected was inosine, acting as an inhibitor, which then can be concluded that caffeine and inosine have almost the same physiological function as substrates for substitution reactions by the most reactive cell metabolism compared to hypoxanthine, xanthine, adenine, and guanine. Additional studies explained caffeine on mammalian cells was not affecting mammalian DNA replication but only made it shorter in replication length there for giving a promised future impact for interfering mechanism of caffeine as DNA repair substrates as beneficial if it is used as a mechanism to interfere with the proliferation of cancer cells and inhibit the spread of viral virions.

A cup of coffee contains chlorogenic acid (CGA), melanoidin, caffeine, trigonelline and diterpenes (cafestol-kaahweol). These compounds are proven in-vivo in the form of antioxidant, chemopreventive, anti hypertensive, hypoglycemic, antiglycative, and anticarcinogenic. Although when passing through the gastrointestinal tract (GIT) not all are absorbed.1 Caffeine is a hydrophobic compound so that it can directly penetrate the cell membrane and react with aryl hydrocarbon receptor (AHR) and cysteine residues from kelch-like associated protein 1 (keap1) which causes the translocation of nuclear factor erythroid 2-related factor (Nrf2) to the nucleus. Mitochondria metabolize caffeine producing reactive oxygen species (ROS). Stress cells produce lower energy and increase concentrations of adenosine monophosphate (AMP) and nicotinamide adenine dinucleotide (NAD+) causing activation of AMP kinases (AMPK) from sirtuin. AMPK degrades anabolic...
AhR is CYP1A2 part of the enzyme superfamily cytochrome P450, is a protein that also regulates immune response KynA, through the agonist effect of AhR, becomes important in stopping the production of cytokines in several cell types including macrophages.

HYPOTHETICAL, EFFECTS OF CAFFEINE AS DNA’S REPAIR SUBSTRATE

Arthur Koch and William Lamont observed the metabolic effects of purines with caffeine as an inhibitor on *Escherichia coli* (*E. coli*). Cells cultured in lactate medium undergo reaction of arsenolysis (Figure 2), then harvested and functioned as growth enzymes in the de novo synthesis of purine grown in adenine and caffeine media as controls. Purine residue was measured by the absorption of UV rays from the arsenolysis reaction. Lysis results were obtained in the form of adenosine and inosine. Results from these experiments with caffeine treatment are the least affected by arsenolysis were inosine, which can then be concluded that caffeine and inosine have almost the same physiological function as substrates for substitution reactions by the most reactive cell metabolism compared to hypoxanthine, xanthine, adenine, guanine, where caffeine is recorded to be more inhibiting.

Grigg and Stuckey observed the growth of prototrophs *E. coli* wild type bacteria (bacteria that are very independent and can eat anything to survive) that stop growing when histidine, the food substrate, is depleted and enter the stationary phase and become cannibals that cause gene mutations. Damage is also done with UV radiation and hampered by caffeine if endonuclease repairs the damage. The incidence of this mutation became a marker for the study, calculated on the mutation rate, if caffeine was added the rate of the mutation immediately decreased. Caffeine has a significant influence as a metabolic substrate, when the bacteria do not take their body’s proteins to survive then mutations do not occur.

Genetic factors can be a dominant consideration, especially to predict potential health effects. Genome-wide association studies (GWAS) of caffeine drinking habits identified variations of cytochrome P450 (CYP1A2) and AHR. CYP1A2 is responsible for ~95% metabolism of caffeine in humans and catalyzes many metabolic reactions of drugs and other cholesterol, steroids and lipid synthesis. While AHR is a protein in humans with the gene code AhR, acts as a regulatory mechanism for basal and substrate conditions including the induction of expression target genes, which include CYP1A1 and CYP1A2, also a transcription factor that regulates gene expression and function as a sensor of xenobiotic chemical compounds.

Figure 1. Caffeine-derived compounds metabolized in-vitro on human liver with demethylation enzyme position N1 (Theobromine), N3 (Paraxantine), N7 (Theophyline), C8 hydroxylation (1-3-7 trimethyluric Acid).

Figure 2. Irreversible enzymatic arsenolysis of purine nucleotides, X = aromatic or unsaturated aliphatic substituents.

Figure 3. Photolyase theory, canonical thymines reversible form cyclobutene thymine dimer induced by UV and absorb blue light photons.
Sancar won the Nobel Prize for Chemistry 2015 for explaining the work of the photolyase enzyme (DNA repair enzyme) on DNA damaged by UV light (Figure 3). Thymine dimer is formed which can react to photolyase in E. coli bacteria. Caffeine inhibits the work of photolyase and does not inhibit photochemical reactions measured with the southern blot method where caffeine inhibits the improvement of DNase in terms of DNA repair. Caffeine inhibits DNase (exonuclease) because of the hydrolysis of the phosphodiester bond that connects the thymine dimer, then intensity of photo reparation is qualified.13,14

On the contrary, the effect of caffeine on mammalian DNA was studied by Lehman on lymphoma rats induced γ-ray. Caffeine does not exert an inhibitory effect on replication, but the size of the resulting DNA becomes smaller, yet not mutagenic but suspected caffeine binds on the repair site and causes premature termination.15 Waldren and Patterson observed the incidence of mammalian DNA Chinese hamster ovary cells (CHOK1), being exposed to UV rays and damaged. Caffeine that is attached to the area of purine nucleotide biosynthesis would undergo such repairs, including the defect location of the purine-requiring needs, if purines are not available the damage becomes even worse.16

**EXISTING MEDICATIONAL USE OF ANALOG PURINE PYRIMIDINE**

Inosine pranobex (IP) commonly known by the names of inosine acedoben dimepranol, isoprinosine and methisoprinol (Figure 4), has been shown to have a positive effect on the host’s immune system by strengthening the proliferation of T-cell lymphocytes and NK activity, increasing the level of pro-inflammatory cytokines, that is overcoming the deficit response of immunocompromised patients. Inosine exerts an effect on viral RNA by inhibiting its growth. It has been used since 1971 against viral infections such as subacute sclerosis panencephalitis, herpes simplex virus, human papillomavirus, human immunodeficiency virus, influenza, and acute infections respiratory, cytomegalovirus, Epstein-Barr.17

Other example of purin and pyrimidine analog effecting purine biosynthesis is Allopurinol as inhibitor of xanthine oxidase enzyme that catalyses purine derivative to uric acid which is used as solution in gout therapy. Also, Fluorocytosine as an antimicrobe and Fluorouracil as chemotherapy agent, for the capability to inhibit the formation of thymidin monophosphate (TMP) and cell become apoptosis.18

**CAFFEINE POTENTIAL AS ANTIVIRAL**

Caffeine is an inhibitor of DNA repair and repair checkpoint. Caffeine also inhibits retroviral transduction in dividing cells by inhibiting the post-integration phase. The cellular target of this mechanism is through kinase ataxia telangiectasia mutated (ATM) and rad3-related (ATR) kinase. Researchers observed reduced transduction of caffeine-administered cells, at the growth-arrested stage and terminal differentiation stages, of human nerve cells and macrophages. The experiment was carried out by observing and comparing caffeine and nocodazole as cell cycle inhibitors, the results of caffeine efficiently reduced HIV-1 transduction and the transduction effect was also observed in human macrophage cells. It was obtained that caffeine did not cause negative effects on host cells. Transduction deficiency is also observed in human immunodeficiency virus type 1 (HIV-1) which does not have a vector Vpr, indicating this effect is independent of the presence of infecting viral proteins. HIV-1 transduction of nocodazole-arrested cells is reduced which expresses the dominant-negative ATR protein and that residue from transduction from ATRkd-expressing cells is relatively resistant to caffeine. The effect of caffeine on HIV-1 transduction was mediated by inhibition of the ATR pathway and did not depend on the host cell’s checkpoint. HIV-1 DNA integration is critical in viral replication. The mechanism of cellular host protects the integrity of chromosomes. Surveillance is carried out by monitoring the integrity of the genome, detection of DNA array damage will coordinate the control point path and DNA repair path. The activation of this DNA repair pathway results in a control point of stopping the cell cycle to allow time for repair. Caffeine is a chemical compound that very strongly enhances the reactivity effect of cells from radiation ionization and is also an agent that causes damage from other DNA in insignificant amounts in the initial cell. Caffeine disrupts DNA repair control points, eliminating P53 activation, G1 termination, G2/M termination, and delaying S phase in response to DNA damage. The path of DNA repair control points is regulated by 2 related kinases ATM and ATR, which are part of the family of phosphatidylinositol-3 kinase. ATMs are activated by the double chain fracture of DNA while ATR also responds to the stress of replication process, they play a direct role at the point of DNA repair. Caffeine affects the ATM ATR response by inhibiting its activities directly. Caffeine inhibits transduction from retrovirus splitting cells (mitosis) because without having ATR protein, or ATRdk (dead kinase) it would become apoptosis. In cells with the expression ATRdk, the reduction in transduction efficiency is associated with the purpose of apoptosis. Caffeine cancels the cell cycle control point, explaining that activation from that cell cycle control point is needed for retrovirus DNA integration. It was proven that caffeine also inhibits the transduction of retroviruses in cells under the influence of drug nocodazole on cells that naturally do not divide. The effect of caffeine on the performance of ATR at the control point of the cell cycle is not affected by the activation and the cancellation of the cell cycle, which leads to the storage of ATR serves for the integration of repairs after repair on dividing cells or also on

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**Figure 4.** Inosine.
non-dividing cells. Interesting results were observed phosphorylation of histone H3 ser10, where this process is closely related to mitosis. 19,20

Another study has shown that caffeine and other methylxanthine derivatives suppress replication of HIV by suppressing the replication of the host cell cycle, which will make a promising therapy for HIV. This time the experiment was carried out by infecting monocyte cells with HIV and giving P24 antigen assay and was observed how the antigen levels of the virus decreased. It concluded caffeine inhibits the development of the virus. Further experiments were conducted by observing specific RNA splicing with the addition of caffeine and a decreased amount for the integration of viral DNA in the specimen. In HIV-1, DNA integration is an essential stage for viral replication. At this stage, the life cycle of HIV-1 triggers cellular DNA damage response and requires cellular DNA repair proteins. These proteins include DNA-dependent protein kinase (DNA-PK), ATR and ATM. 21 The effect of caffeine in ATM ATR phosphorylation, etoposide as a control, observed p53 levels of phosphorylated in serine 15 residues in infected cells are targets of ATM ATR kinases. This figure can come from the inefficient viral-host DNA merger and requires ATR, where the response of damaged DNA and ATR deficiency makes caffeine perform its function in the formation of chromatin and continues with inhibition of viral-host DNA integration. In immunodeficiency cases, ataxia-telangiectasia often combines with various symptoms, for example, Chédiak- Higashi syndrome, Wiskott-Aldrich and DiGeorge syndrome. Ataxia-telangiectasia is an autosomal recessive disorder characterized by ataxia, vascular malformations telangiectases, neurological deficits, increased incidence of tumors and immunodeficiency. This immunologic defect is an additional variable and affects both B and T cells. Common humoral immune defects are IgA and IgG2 deficiencies, which may be due to the important role of ATM proteins in the combination of antibody class changes. This T cell defect is associated with thymic hypoplasia or compromised thymus, recurrent infections of the airways, autoimmune phenomena and increasing cases of cancer with age. The gene that causes this event is located on chromosome 11 and encodes ATM protein which is structurally related to phosphatidylinositol 3-kinase which is a protein kinase. ATM proteins can activate cell cycle burst and apoptosis in response to double-stranded DNA rupture and contribute to the stability of DNA complexes during V(D)J recombination. Due to the weakening of DNA repair contribution, antigen receptors also became abnormal. DNA repair during class change not only involves non-homologous end-joining pathways but also requires ATM proteins, meiotic recombination 11 proteins (MRE11) and Nijmegen breakpoint syndrome 1 proteins (NBS1). Patients with mutation from the ATM encoding gene often experience decreased levels of IgG, IgA, and IgE. Caffeine suppresses HIV-1 replication on this ATM ATR phosphorylation mechanism. 22

Further studies show caffeine's effects on viral DNA and RNA. It was shown that HSV-1 (Herpes Simplex) levels decreased with caffeine treatment, polio was slightly affected, and Influenza did not give results. It concluded that not all types of viruses are affected by caffeine. 23

CAFFEINE POTENTIAL AS ANTICANCER

Micro RNA (mir) is an arrangement of nucleotides of 19-20 pairs of bases, which can be used for diagnosis and early phase detection of cancer. This study proved that caffeine lowers the expression of mir-423-3p. Mir-423 has been reported to regulate hepatocellular carcinoma, in the cell cycle phase of G0/G1. AdipoR2 is also a target of mir-423, which produces cytokines for glucose and fat metabolism and the development of cancer. 24 Caffeine has been considered as a potential anticancer drug which can override the control point of the cell cycle which is indeed weak in each cancer cell. Caffeine mimics adenine 2 adenosine, which inhibits the activity of guanine nucleotides from a regulator of chromatid condensation 1 protein (RCC1) and the kinase activity of ATR. 25-27 ABCG2 is an ATP-binding-cassette (ABC) transporter that alters to multidrug resistance (MDR) resistance of tumors cells by interfering with chemotherapeutic agents. Suppression of expression and function of ABCG2 has been part of the efficacy improvement of improving cancer therapy. The group of xanthine including caffeine, and theophylline, can lower ABCG2 protein in cells that have a content of BeWo (placental choriocarcinoma cell line) or high MCF-7/MX100, (breast cancer drug-resistant cell subline). Down-regulation of this time-dependent, dose-dependent, and reversible, using lysosomal inhibitors, found that xanthon lowers ABCG2 by inducing internalization and lysosome degradation. As a result, caffeine treatment significantly decreased the ABCG2 substrate in the MCF-7/MX100. In conclusion, xanthin can be used as an anticancer agent with ABCG2 substrate. It shows that caffeine inhibits ABCG2 expression which is beneficial for tackling the problem of chemotherapeutic resistance cancers. 28

CONCLUSION

Caffeine or trimethylxantine is directed as an agent for antiviral and anticancer. Related to how it affects the cell, if located intranuclear which affects the performance of the repair of the cell cycle, cell processes to maintain the integrity of DNA. This mechanism is utilized to inhibit the spread of virions and cancer proliferation, by inducing the incidence of PCC, this compound is targeted to inhibit DNA repair for apoptosis. Authors recommend further research on caffeine's effects on the nervous system on dividing and growing neuron cells at a young age when DNA replication is rapidly occurring.

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