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Antioxidant, antineurodegenerative, anticancer, and antimicrobial activities of caffeine and its derivatives: micro and nano aspects

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ABSTRACT

There are therapeutic and side effects of caffeine. Caffeine as a psychoactive compound can impact the function of the nervous system and lead to alterations in cognitive and physical performance. Therefore, caffeine can be consumed as a nutritional ergogenic aid. However, several side effects including headache and nervousness have been recognized in doses of more than 400 mg daily. In addition, this alkaloid has shown antioxidant, antineurodegenerative, anticancer, and antimicrobial activities. In the case of antioxidant activity, caffeine showed anti-cataract potential and delayed the onset of lens clouding. Recently, for increasing therapeutic effects, numerous organic and inorganic nanomaterials such as cosmeceutical nanogels, lipid-based nanocarrier, hydrogels, protein-polysaccharide nanoconjugates, and cyclodextrin have been employed. This article has tried to cover the antioxidant, antineurodegenerative, anticancer, and antimicrobial activities of caffeine based on recent investigations.

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Introduction

Caffeine (1,3,7-trimethylpurine2,6-dione: $C_8H_{10}N_4O_2$) is an alkaloid related to methylxanthine (methylated xanthine) class and is chemically similar to the guanine and adenine bases (Figure 1) [1]. Caffeine is commonly known as a psychoactive safe drug approved by the US Food and Drug Administration (FDA), which is isolated from the *Coffea* genus of the family Rubiaceae [2]. This alkaloid as a psychoactive agent has variable effects on the function of the nervous system and cognitive and physical performance. Drug addiction and side effects can result from surplus caffeine intake [3]. Caffeine can be consumed as a nutritional ergogenic aid in 2.5-3 mg/kg bw (body weight)/day for children and adolescents, and 400 mg/day for adults [4]. In the case of the food industry, food processing, and operational parameters are critical issues. Caffeine can be degraded by exposure to sunlight and oxygen, and gastrointestinal digestion [5]. In addition, ameliorating the bioavailability of caffeine and other alkaloids is a crucial affair for desirable pharmacokinetic results. In this regard, nanomaterials (NMs) such as liposomes, microemulsions nanoemulsions, pickering emulsions, niosomes, solid lipid nanoparticles (NPs), nanostructured lipid carriers, hydrogels, protein-polysaccharide nanoconjugates, cyclodextrin, silica NPs, and gold NPs may be suitable micro/nano-carriers [6-9]. This purine alkaloid can be combined by coformers to the preparation of cocrystals with desirable stability and solubility [10]. Similar to other bioactive compounds, caffeine may be formulated in micro and nanoscale. Nanotechnology has presented numerous NMs for the encapsulation and loading of active pharmaceutical ingredients [7, 8, 11]. In this mini-review, authors have explained and discussed novel and effective formulas of caffeine.

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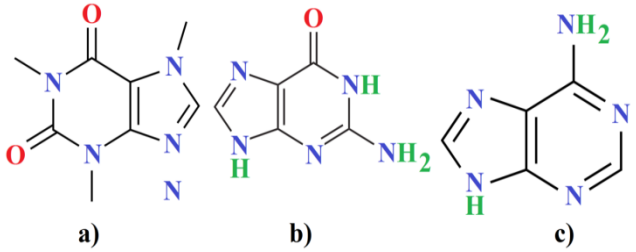

Fig. 1. Chemical structures of caffeine (a), guanine (b), and adenine (c).

Antioxidant

Caffeine in combination with polyphenols such as catechins has antioxidant activity via reducing reactive oxygen species (ROS). However, some foods containing artificial sweeteners or sugars can remarkably reduce the antioxidant effects of caffeine. Caffeine may upregulate the expression of the nuclear factor erythroid 2-related factor 2 (Nrf2) and the hindering of adenosine A_{2A} receptors (Figure 2) [12, 13]. By these mechanisms, caffeine can regulate the inflammatory mediators including phospho-c-Jun n-terminal kinase (p-JNK) and phospho-nuclear factor-kappa B (p-NF-kB). These effects of caffeine are beneficial in neurodegenerative diseases of Alzheimer's and Parkinson's [13]. In a dose-dependent way, this alkaloid in doses of 30-100 mg/kg/day reduces oxidative stress by a decrease in advanced oxidation protein products (AOPP) and malondialdehyde (MDA) amounts [14]. Surgery is the only strategy to treat cataracts, the main cause of blindness worldwide. Caffeine with a strong antioxidant and anti-cataract potential can delay the onset of lens clouding [15]. As the scavenging effect, caffeine can react with the hydroxyl radical [16]. According to cosmetology results, caffeine shows photoaging, thermogenic, and lipolytic properties [17]. However, the cosmetic applications of caffeine have limitations of poor permeability and skin deposition, which can be ameliorated by nanoformulations based on caffeinated hyalurosomes as cosmeceutical nanogels. This formulation composed of f phospholipid vesicles and a hyaluronan polymer in a mean size of 210.10 nm, zeta potential of −31.30 mv, and encapsulation efficiency of 84.60 % exhibited 4.89-fold higher skin accumulation compared to control gel (Carbopol-940 loaded with caffeine) formulation in dorsal rat skin after 24 h incubation [18].

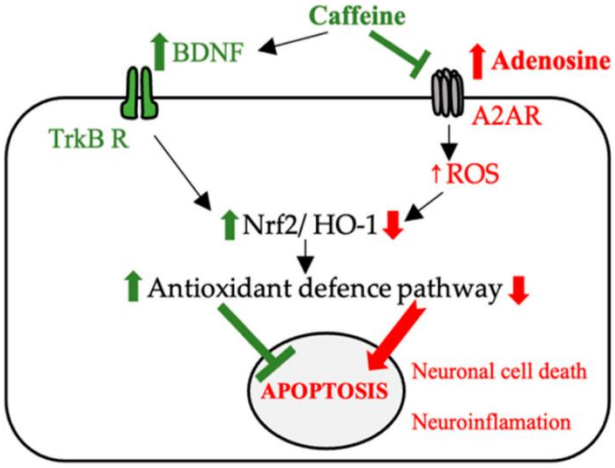

Fig. 2. The possible mechanisms contributed to the antioxidant and neuroprotective effects of caffeine (extracted from [12]).

Anticancer activity

There are many reports about the anticancer activities of caffeine and other methyl xanthines. Anticancer mechanisms of caffeine and its derivatives include transferring the chemotherapeutic drugs to the cancer cells, prevention of cancer formation, inhibition of kinases, effect on DNA repair factors in cancer cells, modulation of the immune system, reduction of the drug toxicity, and increasing the therapeutic effects of drugs. Caffeine and its derivatives can combine with aromatic drugs to deliver chemotherapeutic drugs to the desired tumor cells. A combination treatment based on organometallic platinum(II) terpyridine complexes with a caffeine-derived N-heterocyclic carbene ligand showed a significant anticancer effect on breast adenocarcinoma (MCF-7) cells at sub-cytotoxic concentrations [19]. Caffeine can reduce toxicity (chromosomal aberrations and mitotic index in bone marrow cells) of vinblastine drug against normal cells at a concentration of 100 mg caffeine for 30 h treatment [20]. Caffeine can synergize the anticancer abilities of conventional drugs such as cyclophosphamide, mitomycin C, and adriamycin by synergistic inhibition values of 44.8%, 44.8%, and 27.8%, respectively [21]. Ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3 related (ATR) kinases were inhibited under the effect of caffeine causing sensitizing cancer cells to ionizing radiation [22]. As the major anticancer mechanism, caffeine can bind to adenosine receptors, hinder phosphodiesterases, promote adrenal hormones,

antagonize gamma-aminobutyric acid receptors, and sensitize calcium channels. Signaling pathways such as the mitogen-activated protein kinase (MAPK), the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB)/mammalian target of rapamycin (mTOR), and transforming growth factor β (TGF-β) can be affected by caffeine in colorectal cancer [23]. The inefficiency of immune systems toward cancer cells is limited by the immunosuppression ability of these cells [24]. It should be noted that tumorigenesis or carcinogenesis can be determined by polarization of macrophages (Classically activated (M1; antitumor functions by pro-inflammatory responses such as upregulation of cytokines and chemokines) and alternatively activated (M2) macrophages) [25]. M2-polarized macrophages are associated with tumorigenesis processes including immune suppression, angiogenesis, hypoxia induction, proliferation of cancer cells, and metastasis [26]. Caffeine is an adenosine analog and can be employed remarkably as an adenosine receptor antagonist [27]. For combination therapy with radiotherapy, imiquimod (R837) and caffeine were loaded by a lipid-based nanocarrier as a nano-immunomodulator with size, polydispersity index (PdI), and zeta potential of 154, 0.147, and −23.4, respectively. After the nano-immunomodulator treatment, the expression of iNOS (Nitric oxide synthase) causing tumor cell apoptosis prominently augmented from 19.4% to 96.1% (76.7%) than to the IL-4 (Interleukin 4)-treated control [28]. In another nanoformulation, N-heterocyclic carbene silver complex anchored on Fe_3O_4 NPs functionalized by caffeine metabolite showed significant anticancer activity in magnetic hyperthermia [29].

Antimicrobial activity

Caffeine can form coordinated complexes with metals. Combined caffeine and hexafluorophosphate (PF_6) were used to form complexes with the di-cationic metals of Ni(II), Cu(II), Zn(II), Cd(II), Mn(II), Fe(II), and Co(II). [Cd(caffeine)$_4$ (PF_6)$_2$] showed wider antibacterial activity compared to other complexes. Inhibition zone diameters (IZDs) for this complex were 9, 9, 14, and 9 mm against *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas putida*, and *Klebsiella oxytoca*. A molecular docking study showed higher docking scores of 5.29, 4.79, and 4.72 for $[Ni(caf)4]^{2+}$, $[Zn(caf)4]^{2+}$, and $[Cu(caffeine)_4]^{2+}$, respectively against protein phosphatidylinositol 3-kinase (PI3Kγ) [30]. Caffeine can be employed as active pharmaceutical ingredients to prepare multicomponent cocrystals. The stability of xanthines such as caffeine and theophylline is improved by the formation of COOH$\cdots$ $N_{imidazole}$ and C=O (acid)$\cdots$H$-N_{imidazole}$ synthons [31, 32]. In addition, coformers such as trimesic acid and isophthalic acid can improve the solubility of these cocrystals. Caffeine-trimesic acid, caffeine-isophthalic acid, and theophylline-trimesic acid cocrystals have been synthesized for antibacterial evaluation against Gram-negative and Gram-positive bacteria. In compared to other cocrystals, there were higher zone diameter values of 9.54, 8.54, 9.78, and 8.05 mm for caffeine-isophthalic acid against *Acinetobacter baumannii*, *Escherichia coli*, *K. pneumoniae*, and *Pseudomonas aeruginosa*, respectively [33]. Similar to other natural secondary metabolites [34], caffeine has been exploited for the green synthesis of metallic NPs. For example, green synthesized caffeine/silver (Ag) NPs-triton X-100 with a spherical shape and a mean diameter of 16–24 nm exhibited antibacterial effects on *E. coli* and *S. aureus* in 100 ppm by antibacterial mechanisms including electrostatic interaction with bacterial membrane and cell wall disruption [35].

Conclusions

Caffeine has been well known as a central nervous system stimulant. The increase of the Nrf2 and the blocking of adenosine A_{2A} receptors have been found as possible antioxidant and neuroprotective mechanisms of caffeine. Caffeine in a dose-dependent manner leads to a reduction in AOPP and MDA values. In the case of antioxidant activity, this alkaloid displays anti-cataract activity by delaying the onset of lens clouding. In addition, as the scavenging effect, caffeine reacts with the hydroxyl radical. The cosmetic applications of caffeine can be ameliorated by caffeinated hyalurosomes as cosmeceutical nanogels. As the major anticancer mechanism, caffeine as a purine alkaloid can bind to adenosine receptors, hinder phosphodiesterases, promote adrenal hormones, antagonize gamma-aminobutyric acid receptors, and sensitize calcium channels. Furthermore, important signaling pathways in colorectal cancer cells such as the MAPK, the PI3K/ PKB/mTOR, and transforming growth factor β can be affected by caffeine. By a combination therapy with radiotherapy, imiquimod,

and caffeine were loaded by a lipid-based nanocarrier, and the expression of iNOS prominently augmented by 76.7% compared to the IL-4-treated control. In the case of metal oxide NPs, the N-heterocyclic carbene silver complex anchored on Fe_3O_4 NPs functionalized by caffeine metabolite can hinder cancer cell proliferation in magnetic hyperthermia. In the case of antimicrobial effects, caffeine can be used to green synthesize metal NPs such as AgNPs. These NPs hindered the growth of *E. coli* and *S. aureus* in 100 ppm by antibacterial mechanisms including electrostatic interaction with bacterial membrane and cell wall disruption. Further studies are needed to understand the antioxidant, anticancer, and antimicrobial mechanisms of caffeine alone and in combination therapy for potential clinical applications.

Study Highlights

- Caffeine in a dose-dependent manner leads to a reduction in AOPP and MDA values.
- In the case of antioxidant activity, caffeine displays anti-cataract activity by delaying the onset of lens clouding.
- As the scavenging effect, caffeine reacts with the hydroxyl radical.
- The N-heterocyclic carbene silver complex anchored on Fe_3O_4 NPs functionalized by caffeine metabolite can hinder cancer cell proliferation in magnetic hyperthermia.
- Caffeine can be used to green synthesize metal NPs such as AgNPs.

Abbreviations

AOPP: Advanced oxidation protein products
ATM: Ataxia-telangiectasia mutated
ATR: Ataxia telangiectasia and Rad3 related
FDA: Food and drug administration
IL-4: Interleukin 4
iNOS: Nitric oxide synthase
IZDs: Inhibition zone diameters
M1: Classically activated macrophage
M2: Alternatively activated macrophage
MAPK: Mitogen-activated protein kinase
MDA: Malondialdehyde
mTOR: Mammalian target of rapamycin
PdI: Polydispersity index
PI3K: Phosphatidylinositol 3-kinase
p-JNK: Phospho-c-Jun n-terminal kinase
PKB: Protein kinase B
p-NF-kB: Phospho-nuclear factor-kappa B
ROS: Reactive oxygen species

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Author contributions

All authors: conceptualization, preparing the first draft, and editing.

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