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An assessment of caffeine as a multifunctional alkaloid: Biological, medical, and environmental perspectives

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Abstract

Caffeine has become a defining feature of modern lifestyles. Caffeine is valued for its role as the world's most widely consumed psychoactive stimulant. Naturally present in coffee, tea, and cocoa, and synthetically incorporated into pharmaceuticals and personal care products, caffeine is a nitrogen-based alkaloid found in plant leaves and seeds. In plants, it functions as a defense mechanism, deterring herbivores and pathogens, also influencing allelopathy by suppressing competing vegetation. Remarkably, caffeine can enhance pollination, improving memory in pollinators such as bees and encouraging repeated visits to flowers. For humans, caffeine plays a dual role. It stimulates metabolic pathways like glycolysis and lipolysis, mobilizing energy reserves. Despite its classification as a potentially addictive stimulant, it is recognized by the World Health Organization on its Model List of Essential Medicines, underscoring its importance in treating conditions such as neonatal apnea. Caffeine has environmental consequences. High consumption leads to its presence in aquatic systems, where it acts as an emerging pollutant. Meanwhile, intensive sun-grown coffee farming contributes to soil degradation, biodiversity loss, and elevated carbon emissions. Large-scale deforestation for monoculture plantations further destroys habitats, threatening species essential to ecosystem balance.

Keywords: Secondary metabolite, plant defense, human metabolism, allelopathy, lipolysis

Introduction

Caffeine is a plant-derived secondary metabolite (An alkaloid) functioning primarily as a natural pesticide and defense mechanism against herbivores and pathogens. Produced by plants like *Coffea*, it renders tissues unpalatable, while being consumed by humans as a stimulant that acts as a competitor to adenosine receptors. (Kolb *et al.* 2021, Santos *et al.* 2016) ^[10, 11] Caffeine (1, 3, 7-trimethylxanthine) is a xanthine alkaloid that is derived from plants. It was first isolated from coffee seeds by German scientists Runge and Von Giese in 1820. Owing to its multifaceted biological effects, caffeine has been found widespread use in everyday life, as well as in the food and medical industries. (Socala *et al.* 2022, Tao *et al.* 2021) ^[12].

In the food industry, caffeine is used as a natural additive in various products, such as chocolate, tea, and cola. Not only does it significantly improve the taste of food but it also can alleviate fatigue and improve sustained attention. Numerous studies have shown that moderate caffeine consumption can obviously promote diuresis improve memory, increase anticancer effects (Fredholm *et al.* 1999, Meeusen *et al.* 2013) ^[1, 2], decrease blood pressure lower the risks of type 2 diabetes, and delay aging (Ruggiero *et al.* 2022) ^[16]. In the medical field, caffeine is primarily used as a stimulant (Sharman *et al.* 2016) ^[7] and an analgesic adjuvant (WHO 2023, Derry *et al.* 2012, Fison *et al.* 2004) ^[36, 14, 13]. Moreover, caffeine has been identified as a potential biomarker for disease detection, especially in the case of Parkinson's disease (Tej *et al.* 2018, Fujimaki *et al.* 2018) ^[5, 15]. Apart from these applications, the cosmetics industry has also developed caffeine-based products for weight loss and beauty care. (Herman *et al.* 2013) ^[18] Caffeine can promote skin blood microcirculation, prevent fat accumulation, and provide antioxidant benefits (Bartolomen 2022, Marx *et al.* 2016, Cheng *et al.* 2016) ^[6, 3, 4].

However, the use of caffeine also poses severe environmental challenges. For example, the production of coffee and tea generates millions of tons of agricultural and industrial refuse annually. (Asihara *et al.* 2017) ^[19] As a result, the scientific community and the public are highly concerned about the environmental impact from caffeine and its biodegradation.

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Although there have been some reports on the metabolic pathways of caffeine in microorganisms, a comprehensive summary is currently lacking. In this review, we mainly focus on the metabolic pathways of caffeine degradation in bacteria and fungi, and we summarize the structures and gene sequences of related enzymes. (Vega *et al.* 2021, Thathola *et al.* 2021) ^[27, 28].

Caffeine was first detected in coffee and tea plants, and it has been identified in more than 100 plant species. In particular, some *Camellia* and *Coffea* species possess relatively high levels of caffeine. For example, *Coffea arabica* and *Camellia sinensis* contain 1-2% and 2-5% caffeine, respectively. Other plants, such as *Theobroma cacao*, *Cola acuminata*, *Ilex paraguariensis*, and *Paullinia cupana*, contain 0.03%, 1.5%, 0.7%, and 4% caffeine, respectively (Anaya *et al.* 2006, Koshishi *et al.* 2001) ^[21, 20]. The daily average consumption of caffeine for humans ranges from 80 to 400 mg/person. Excessive intake of caffeine can lead to various health problems, such as insomnia, anxiety, osteoporosis, and fetal weight loss. Even low doses of caffeine can affect the quality of sleep and have harmful effects on individuals with heart disease and on pregnant women. Caffeine is also considered an addictive substance (Ngueta *et al.* 2020; Nihlig *et al.* 2010) ^[9, 8], and its withdrawal can cause adverse reactions, such as headache, fatigue, apathy, and drowsiness. Moreover, caffeine is recognized as an environmental pollutant and the problem of how to remove it has garnered increasing attention from the scientific community (Kim *et al.* 2008) ^[24].

Currently, traditional methods are used globally for caffeine removal, including water extraction, adsorption, supercritical CO₂ extraction, microwave-assisted extraction, ultrasound-assisted extraction, and membrane filtration. However, these methods often come with issues, e.g., high costs, toxicity, or a lack of specificity for caffeine. Instead, caffeine biodegradation provides a safe and inexpensive alternative to physical and chemical methods. It mainly consists of two methods, that is, the microbial and enzymatic methods. The microbial method is more economical and eco-friendly in treating sewage and other waste containing caffeine and is preferred due to its safety and nontoxicity. (Mazzfera *et al.* 1996). Transgenic methods are being explored to produce strains that can remove caffeine, but this topic is relatively sensitive, and additionally, whether it can be utilized remains to be discussed. Enzymatic degradation of caffeine is mainly used in food applications and the production of specific intermediates, such as theophylline, 7-methylxanthine, and paraxanthine. Enzymatic degradation has the advantage of specifically removing methylxanthine, thus preserving the unique flavor and aroma compounds in coffee and tea, and avoiding an impact on the taste of food. However, caffeine-degrading enzymes are not stable in the environment, and their production and development costs are very high, leading to rare usage (Sugiyama 2002, Dash *et al.* 2008) ^[26, 30].

Caffeine, which is also widely present in aquatic environments, has been found to possess negative impacts on aquatic organisms, including oxidative stress, lipid peroxidation, neurotoxicity, energy reserve, and metabolic disorders, and meanwhile, it causes adverse effects on their reproduction, and development, and even causes mortality in some cases. Therefore, caffeine is now considered a new type of pollutant. Although caffeine generally exhibits high removal efficiency in wastewater treatment processes, the increasing consumption of coffee and other caffeinated beverages has led to a higher input of caffeine into aquatic systems than its degradation amount.

Given the concerning levels of caffeine concentration in biotic and abiotic samples from related studies, it is important to develop suitable treatment methods and effective removal technologies to eliminate or significantly limit caffeine and its derivatives in aquatic systems. (Asano *et al.* 1994). Currently, *Pseudomonas* has been demonstrated to have good tolerance to caffeine and the ability to completely degrade caffeine in wastewater treatment. Therefore, the application of *Pseudomonas* for caffeine degradation in sewage treatment will significantly improve the issue of damaged ecological environments and provide a new method for sewage purification. (Loos 2009, Kolpin 2002, Kim 2020, Gluck 1988) ^[48, 46, 47].

Key Aspects of Caffeine as a Secondary Metabolite

Caffeine is a purine alkaloid secondary metabolite that plays a crucial ecological role in plants, functioning as a defense compound against herbivores, pathogens, and competing species. It is stored mainly in young leaves and flowers, and also exhibits allelopathic effects by inhibiting the growth of neighboring plant. It acts as a natural pesticide, protecting plants from herbivore predation and inhibiting pathogens. Caffeine is a nitrogen-containing alkaloid belonging to the methylxanthine family, commonly found in leaves and seeds. (Gracia 2015) ^[39].

In humans, caffeine is metabolized in the liver primarily by the enzyme CYP1A2, which converts it into three major metabolites: paraxanthine, theobromine, and theophylline. Roughly 80% of this metabolism occurs through N³-demethylation to form paraxanthine. Once in circulation, caffeine acts as a stimulant by binding to adenosine receptors, blocking the signal that normally promotes drowsiness and fatigue. Several factors influence the rate of caffeine metabolism, including genetics, liver enzyme activity, smoking, pregnancy, and certain medications such as oral contraceptives (AMR 2022) ^[38]. Chemically, caffeine (trimethylxanthine) is a purine alkaloid and functions as a secondary metabolite in plants like coffee (*Coffea*) and tea (*Camellia sinensis*). Unlike primary metabolites, which are essential for growth and survival, secondary metabolites provide ecological advantages. (ICO 2023) ^[37].

Key roles of caffeine in plants

Chemical Defense: Caffeine acts as a natural insecticide and deterrent against generalist herbivores, protecting young plant tissues from damage. It is toxic to many pests and can kill snails and slugs. It inhibits the growth of bacteria and fungi, acting as a pathogen defense mechanism. Plants release caffeine into the soil (e.g., via fallen leaves) to inhibit the germination and growth of neighboring competitive plants. In some species, low doses of caffeine in nectar can improve pollinator memory, helping them return to that plant species. It can influence the behavior of insects, for example, by reducing the feeding efficiency of herbivores.

Caffeine is toxic and undesirable to insects. It can block the development of mosquito larvae (*Aedes aegypti*), repel insects like moths and beetles, and inhibit feeding in tobacco hornworms. (Hollingsworth *et al.* 2002) ^[25]. It functions by causing neurotoxic reactions and interfering with neurotransmitter release in insects. Low levels of endogenous caffeine can stimulate a plant's self-defense system. Transgenic plants expressing caffeine genes showed enhanced resistance to viruses, bacteria, and insects, likely because the plant interprets its own caffeine as a threat and activates defense-related genes, increasing production of salicylic acid. Caffeine has dual-track effects, inhibiting

pathogens while also fostering the growth of beneficial microorganisms like *Trichoderma* fungi, which protect the plant roots, a concept known as "caffeine fostering"

Allelopathy: Caffeine released from fallen leaves and fruit can inhibit the germination and growth of surrounding plants, reducing competition for resources. Caffeine, a purine alkaloid, reduces the growth of weeds, which makes it a useful component of coffee infusion residues for managing weed infestation. High concentrations (e.g., 1000 ppm) have been shown to significantly inhibit the radicle growth and reduce the biomass of target weeds. Seedlings exposed to high doses of caffeine often display stunted growth, twisted forms, and a lower biomass yield. Caffeine is actively secreted into the soil through the primary roots of coffee plants. It alters the microbial community, specifically enriching it with, "killer" fungi like *Trichoderma*, which help protect the plant by destroying harmful phytopathogens, reduces the size of primary roots and slows shoot growth, which decreases a plant's ability to absorb water and nutrients.

Phytotoxicity and necrosis: Exposure can cause abnormal, twisted seedling growth and tissue necrosis (death) at high doses. High doses of caffeine significantly inhibit germination. Seeds treated with higher concentrations (such as 1.75% or higher) often show little to no germination. It is known to interfere with mitosis (cell division) and cell plate formation in rootlets, leading to abnormal, stunted, and twisted roots. **Pollination Enhancement:** In small doses, caffeine in nectar can improve a pollinator's memory, encouraging repeat visits to the same plant species. While

coffee grounds are popular in compost, direct application of high-caffeine mixtures can damage sensitive plants. Low concentrations of caffeine present in floral nectar have been shown to enhance pollinator memory, thereby increasing the likelihood of repeated visits to the same plant species and improving reproductive success. This adaptive mechanism benefits plants by reinforcing pollinator fidelity. However, while coffee grounds are commonly incorporated into compost where microbial activity reduces caffeine content, the direct application of high-caffeine solutions to soil or plants can be phytotoxic. Elevated caffeine levels may impair seed germination, inhibit root development, and disrupt the soil microbial community, ultimately compromising plant health (Summers 2012) ^[35].

Biosynthesis in plants

Caffeine is synthesized through a four-step core pathway, primarily starting from the precursor xanthosine: or caffeine synthase). In humans, caffeine is metabolized in the liver, primarily by the enzyme CYP1A2. This process yields several "secondary" metabolic products such as Paraxanthine. It Stimulates lipolysis (fat breakdown) in cells. Another metabolic product is Theobromine. It acts as a vasodilator and diuretic. Another metabolic product is Theophylline. It Relaxes smooth muscle in the bronchi, often used to treat asthma. Caffeine is a secondary metabolite acting primarily as a natural pesticide, herbivore repellent, and allelopathic agent in plants. It protects young leaves, flowers, and seeds from pathogens and insects, while also inhibiting the growth of competing plants through soil-leached inhibition of root development. (Yu *et al.* 2009) ^[34].

Table 1: Comparison of Caffeine in Popular Plants

Features	Tea	Coffee
Main Accumulation	Young leaves and buds	Mature beans/seeds
Content (% Dry Weight)	~2-5%	~1-2%
Biosynthesis Site	Primarily in chloroplasts	Primarily in the cytoplasm
Pesticide Role	Repels leaf-feeding insects	Protects beans from seed-boring pests

Environmental impacts

Emerging contaminant: Caffeine is a human stimulant and a plant defense compound. It is increasingly recognized as an emerging contaminant in the environment. Because it is widely consumed and excreted, it often ends up in wastewater and surface waters, (Sim 2011) ^[51] where it can have ecological consequences. Caffeine pollution is more complex than just residues in water it spans from coffee farming practices that drive deforestation and carbon emissions to subtle but cascading effects on aquatic ecosystems and even potential risks for human drinking water. (Mazzafera 1996, Buerge *et al.* 2003) ^[29, 50] Recent studies highlight bioaccumulation in food chains, (Facozio 2008) ^[49] synergistic toxicity with other pollutants, and the absence of regulatory standards as major emerging concerns. (Ashihara *et al.* 2017, Vieira *et al.* 2022, Edwards 2015) ^[19, 45, 40].

Due to high human consumption, significant amounts of caffeine enter aquatic environments through sewage, acting as a persistent pollutant. It have adverse effects on aquatic organisms, causing oxidative stress, changing metabolic activity, and impacting reproduction in fishes and bivalves. (Kuo essar 2024, Li 2020) ^[44, 43] Caffeine synthesis genes can be upregulated in plants in response to environmental stressors such as drought or intense light. Fish exposed to caffeine show increased metabolic rates, forcing them to expend more energy, which reduces survival chances in stressful environments (Mohd W 2020) ^[42].

Daphnia (water fleas) exhibit altered reproduction and mobility, which can destabilize food chains (Pierce 2016) ^[41] Predators consuming contaminated prey may accumulate higher caffeine levels, amplifying ecological stress. (Bioaccumulation). Further Caffeine can interact with pharmaceuticals and personal care products in water, intensifying harmful effects. No global standards exist for caffeine levels in water, leaving a blind spot in environmental and public health policy. (Hollingsworth *et al.* 2002s) ^[25].

Conclusion: Intensive sun-grown coffee farming has significant ecological downsides. By clearing shade trees and relying heavily on chemical inputs, it accelerates soil erosion, diminishes wildlife habitats, and contributes to higher greenhouse gas emissions Shade-grown coffee protects ecosystems, but its decline since the 1970s has worsened habitat destruction. Roasting, brewing, and transporting caffeinated products are energy-intensive, adding to climate change. Trace caffeine has been detected in municipal supplies. While levels are low, vulnerable groups (pregnant women, children, caffeine-sensitive individuals) may face risks. Coffee's lifecycle from farming to brewing adds significantly to greenhouse gas emissions. Intensive sun-grown coffee farming is eroding our planet's resilience. By stripping away shade trees, it accelerates soil degradation, destroys vital biodiversity, and drives up carbon emissions. This model of production prioritizes

short-term yields over long-term sustainability, leaving farmers and ecosystems vulnerable. Advanced filtration and bioremediation methods are needed to remove caffeine residues.

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