REVIEW

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Molecular mechanisms of coffee's antidepressant effects in chronic consumption: A context-dependent perspective

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Coffee, one of the most widely consumed beverages, is associated with reduced depression risk in epidemiological studies. However, the relationship between coffee consumption and mental health is more nuanced than a simple antidepressant effect. This review critically examines the molecular mechanisms by which chronic coffee consumption may influence mood, while emphasizing that these effects depend on dose, timing, genetic variability, metabolic status, sleep, and behavioral context. Key bioactive compounds in coffee—including caffeine, chlorogenic acids, trigonelline, and polyphenols—exert effects through adenosine receptor antagonism, monoamine, anti-inflammatory actions, brain-derived neurotrophic factor signaling activation, oxidative stress reduction, hypothalamic-pituitary-adrenal axis modulation, gut-brain axis communication, and metabolic pathway regulation. Importantly, this review distinguishes between coffee-specific effects and those attributable to caffeine alone, recognizing that coffee contains numerous bioactive compounds beyond caffeine that may contribute to its overall biological activity. The review also critically addresses potential adverse effects, including sleep disruption, anxiety exacerbation, and maladaptive coping patterns, particularly in vulnerable populations such as students, shift workers, and individuals with pre-existing anxiety disorders. Genetic polymorphisms in CYP1A2 and ADORA2A are discussed as important moderators of caffeine metabolism and sensitivity. The review concludes that while moderate coffee consumption may offer mood-related benefits under certain conditions, these effects should be interpreted within a conditional risk-benefit framework rather than as a universal antidepressant property.

Key words: chronic coffee consumption, depression, molecular mechanisms, caffeine, context-dependent effects, CYP1A2, ADORA2A, sleep disruption

INTRODUCTION

Coffee, a beverage deeply embedded in global cultural practices, has been the subject of extensive research regarding its potential health effects, including its relationship with mental health outcomes (Fiani et al., 2021). Epidemiological studies have consistently reported an inverse association between coffee consumption and depression risk, suggesting that individuals who regularly consume coffee may experience lower rates of depressive symptoms (Grosso et al., 2016). These observations have prompted investigations into the molecular mechanisms through which coffee might influence mood regulation. However, the translation from epidemiological association to mechanistic explanation requires careful consideration of multiple

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factors, including the distinction between coffee as a complex beverage and caffeine as an isolated compound, the conditional nature of these effects, and the potential for both beneficial and adverse outcomes depending on individual and contextual factors (Hall et al., 2015; Tenore et al., 2015; Fig. 1).

Coffee contains a diverse array of bioactive compounds, including caffeine, chlorogenic acids, trigonelline, melanoidins, quinides, and various polyphenols, each contributing to its overall biological activity (Socała et al., 2020; Liczbiński & Bukowska, 2022). Caffeine, the most extensively studied component, acts primarily as a non-selective adenosine receptor antagonist, influencing neurotransmitter release and neuronal excitability (Fredholm, 1995; Ribeiro & Sebastiao, 2010). However, caffeine is only one component of coffee, and attributing coffee's effects solely to caffeine overlooks the potential contributions of other bioactive compounds that may exert anti-inflammatory, antioxidant, and neuroprotective effects independent of caffeine (Heitman & Ingram, 2017; Socała et al., 2020). This distinction is crucial because many mechanistic studies have employed caffeine in isolation, whereas epidemiological evidence typically examines coffee consumption as a whole beverage. Recent literature has emphasized that coffee and caffeine should not be treated as interchangeable, as the complex matrix of coffee may modulate the effects of caffeine and contribute addi-

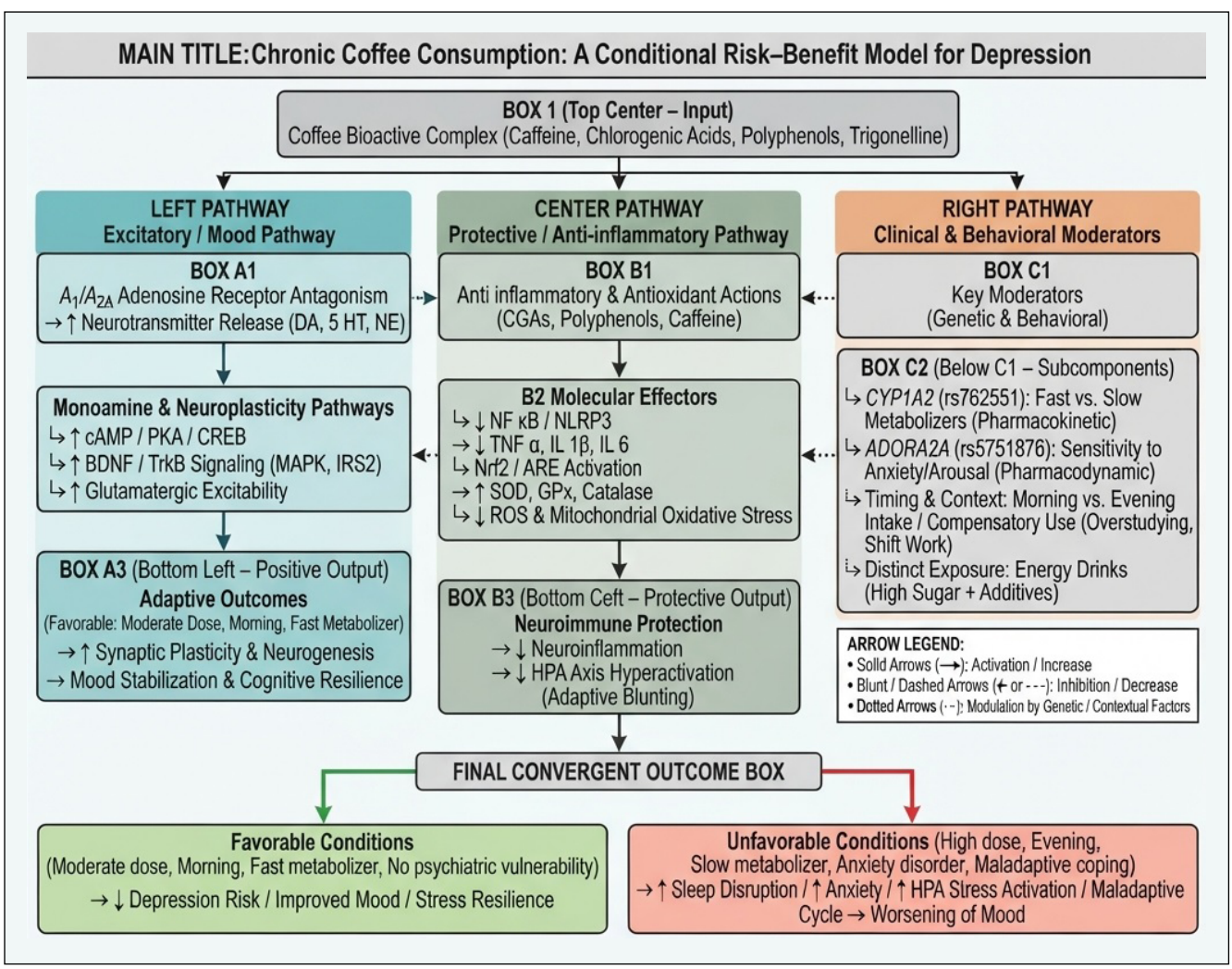


Fig. 1. Schematic of chronic coffee consumption effects on depressionrelevant pathways, emphasizing conditional outcomes. Coffee's bioactive compounds (caffeine, CGAs, polyphenols) act through adenosine antagonism (left), antiinflammatory/antioxidant cascades (center), and are heavily moderated by genetic (CYP1A2, ADORA2A) and behavioral (timing, sleep, coping context) factors (right). The final impact on mood ranges from adaptive resilience (↑ BDNF, ↓ inflammation, moderate monoamine enhancement) under favorable conditions, to maladaptive arousal (↑ anxiety, sleep fragmentation, HPA overactivation) under unfavorable conditions. Thus, the antidepressantlike effects are not universal but strictly conditional. Solid arrows indicate stimulation; blunt arrows indicate inhibition; dashed arrows represent modulation by genetic/contextual factors. CNS, central nervous system; HPA, hypothalamicpituitaryadrenal; ROS, reactive oxygen species; TrkB, tropomyosin receptor kinase B.

tional biological activities (Iriondo-DeHond et al., 2021; Nehlig, 2022).

The concept of coffee as an "antidepressant" requires critical examination. While observational studies consistently show associations between moderate coffee consumption and lower depression risk, these findings do not establish causality (Grosso et al., 2016; Kang et al., 2018). Moreover, the same molecular pathways that may confer mood benefits under some conditions can produce adverse effects under others. Adenosine receptor antagonism, for instance, can acutely enhance alertness and motivation but may also interfere with sleep pressure, increase physiological arousal, and contribute to anxiety, particularly in susceptible individuals (Hughes, 1996; Winston et al., 2005). This duality underscores the need for a conditional risk-benefit model rather than a unidirectional antidepressant framework. Recent research has highlighted that caffeine consumption can function as maladaptive coping behavior, particularly in academic and occupational contexts where it is used to override fatigue, prolong work or study sessions, and regulate negative affect (Kosecka et al., 2025). In such cases, caffeine may reinforce cycles of sleep deprivation, stress, and dependence that ultimately worsen mental health outcomes.

Individual variability significantly influences responses to coffee and caffeine. Genetic polymorphisms in CYP1A2, the primary enzyme responsible for caffeine metabolism, affect the duration and intensity of caffeine exposure (Rodenburg et al., 2012; Low et al., 2024). Individuals who are slow metabolizers (carriers of the CYP1A2*1F variant) may experience prolonged caffeine effects, increasing susceptibility to anxiety, sleep disruption, and cardiovascular activation at lower doses. Conversely, fast metabolizers may consume more caffeine or redose more frequently to maintain stimulation (Tennent et al., 2020). Similarly, polymorphisms in the *ADORA2A* gene, encoding the adenosine A2A receptor, influence sensitivity to caffeine's effects on anxiety, sleep, and arousal (Rogers et al., 2010; Fulton et al., 2018). These genetic factors interact with behavioral context, sleep status, stress levels, and psychiatric vulnerability to determine whether caffeine exposure produces adaptive or adverse outcomes.

Sleep disruption represents a particularly important pathway through which caffeine may influence mental health. Caffeine's adenosine receptor antagonism, while promoting alertness, can significantly impair sleep quality and duration when consumed in the afternoon or evening (Roehrs & Roth, 2008; Clark & Landolt, 2017). Poor sleep is both a symptom and risk factor for depression, anxiety, and emotional dysregulation (Palagini et al., 2019). Therefore, even if caffeine exerts potentially antidepressant molecular effects through dopaminergic, serotonergic, or neurotrophic pathways, these benefits may be offset or reversed when intake disrupts sleep. This bidirectional relationship—where caffeine improves acute alertness at the expense of restorative sleep—is frequently overlooked in mechanistic models that focus exclusively on molecular pathways without considering the broader behavioral and physiological context (Clark & Landolt, 2017).

The timing and dosage of coffee consumption are critical moderators of its effects. Low to moderate doses (approximately 200-400 mg caffeine daily, equivalent to 2-4 cups of coffee) have been associated with positive mood outcomes in many studies, whereas higher doses may produce anxiety, jitteriness, and sleep disturbances (Lieberman et al., 1987; Ruxton, 2008). The timing of consumption relative to circadian rhythms and sleep-wake cycles modulates these effects, with morning consumption aligning with natural cortisol peaks and potentially supporting alertness, while evening consumption may disrupt sleep architecture (Burke et al., 2015; Yin et al., 2023). Additionally, individual tolerance develops with regular consumption, potentially diminishing both beneficial and adverse effects over time (Chou et al., 1985). These considerations underscore the need for personalized recommendations rather than universal guidelines.

This narrative review aims to provide a comprehensive and critical examination of the molecular mechanisms through which chronic coffee consumption may influence mood and depression risk. The review distinguishes between coffee-related and caffeine-related effects, emphasizes the conditional nature of these mechanisms, incorporates genetic and behavioral moderators, and addresses potential adverse outcomes including sleep disruption, anxiety exacerbation, and maladaptive coping.

Our research group has previously investigated the molecular pathways underlying mood and cognitive disorders, with a particular emphasis on neuroinflammation, oxidative stress, and neurotrophic signaling. For instance, Baghcheghi et al. (2024) comprehensively reviewed the molecular mechanisms by which PPARγ agonists modulate memory impairment in neurodegenerative disorders, highlighting the critical roles of synaptic plasticity enhancement, neuroprotection, suppression of neuroinflammation, oxidative stress attenuation, and regulation of amyloidβ metabolism—pathways that are highly relevant to coffee›s potential neuroprotective actions. Hedayati-Moghadam et al. (2026) provided a detailed molecular perspective on diabetesinduced depression, linking metabolic dysregulation to neuroinflammation, HPA axis hyperactivity, and impaired neuroplasticity, which parallels the metabolic and inflammatory context pertinent to

coffee consumption. Mashayekhi-Sardoo et al. (2025) further elucidated the convergent molecular mechanisms of ethanolinduced depression, emphasizing the core pathogenic events of oxidative stress, inflammatory cascades, and BDNF downregulation. Collectively, these studies have established a framework for understanding how extrinsic factors—including dietary components—can modulate depressionrelated molecular networks. In the present review, we build upon this foundation by critically examining the conditional and contextdependent mechanisms through which chronic coffee consumption may influence mood, while integrating genetic and behavioral moderators that determine net outcomes. This review is structured to first present epidemiological evidence, then examine coffee components and bioactive compounds, followed by detailed mechanistic sections that incorporate contextual factors, and concluding with an integrated conditional model of coffee's effects on mental health.

Epidemiological Evidence: Associations and Limitations

Numerous observational studies and meta-analyses have investigated the relationship between coffee consumption and depression risk. A comprehensive dose-response meta-analysis incorporating data from multiple prospective cohort studies reported that each additional cup of coffee consumed daily was associated with a 7% reduction in depression risk, with the strongest protective effect observed at moderate consumption levels (approximately 2-4 cups per day) (Grosso et al., 2016). These findings are supported by large-scale cohort studies, including the Nurses' Health Study, which found that women consuming four or more cups daily had significantly lower depression risk compared to non-consumers, and the Kuopio Ischaemic Heart Disease Risk Factor Study, which reported similar associations in middle-aged Finnish men (Ruusunen et al., 2010; Lucas et al., 2011). However, the evidence base has important limitations that warrant careful interpretation.

The observational nature of these studies precludes causal inference. Confounding by lifestyle factors—such as physical activity, diet quality, socioeconomic status, and social engagement—may explain some or all of the observed associations (Marten & Wilkerson, 2003). Individuals who consume coffee regularly may differ systematically from non-consumers in ways that independently influence depression risk. Furthermore, reverse causality is possible: individuals experiencing prodromal depressive symptoms may reduce coffee consumption due to sleep disturbances, appetite changes, or reduced interest in daily activities. Longitudinal studies with repeated measures of both coffee intake and depressive symptoms provide stronger evidence but remain observational.

Coffee consumption metrics present additional challenges. Epidemiologic studies typically assess consumption in "cups per day," yet caffeine content varies substantially depending on coffee species (Arabica *vs.* Robusta), roasting degree, brewing method (espresso, filter, French press, cold brew), serving size, and preparation practices (Caprioli et al., 2015). A standard cup of coffee may contain anywhere from 50-200 mg of caffeine, representing a fourfold variation that complicates dose-response interpretations. Moreover, other bioactive compounds in coffee, such as chlorogenic acids and trigonelline, vary considerably with processing and brewing methods, and their concentrations are rarely quantified in epidemiological studies (Angeloni, 2019). This imprecision means that observed associations likely reflect broad patterns rather than precise dose-response relationships.

The relationship between coffee consumption and depression may be nonlinear. Some evidence suggests a J-shaped or U-shaped pattern, where moderate consumption confers protection while very high consumption may increase risk or produce no additional benefit (Grosso et al., 2016; Wang et al., 2016). This nonlinearity is consistent with caffeine's dose-dependent effects on arousal, anxiety, and sleep. Low doses may enhance mood and cognitive performance, whereas high doses may produce anxiety, jitteriness, sleep disruption, and physiological stress activation. The optimal dose likely varies across individuals due to genetic, metabolic, and sensitivity differences.

Population-specific factors influence observed associations. Sex differences have been reported, with some studies suggesting that women may derive greater mood benefits from coffee consumption, potentially related to hormonal interactions with caffeine metabolism (Temple & Ziegler, 2011; Lauri & Bäckström, 2019). Age also modifies effects, with older adults exhibiting slower caffeine metabolism and increased sensitivity to adverse effects such as sleep disruption and anxiety (Swift & Tiplady, 1988). Cultural and geographic factors shape both consumption patterns and depression risk, and studies from diverse populations—including Asian cohorts—have generally supported the protective association, suggesting that the relationship may be broadly consistent across cultures (Pham et al., 2014; Kimura et al., 2020). However, the magnitude of association and optimal consumption levels may differ across populations.

Recent meta-analyses have rated the evidence quality for coffee and depression as low to moderate, primarily due to the observational study designs, heterogeneity in exposure assessment, and potential residual confounding (Grosso et al., 2016; Torabynasab et al., 2023). This evidence quality rating underscores that while the association is consistent, causality remains unproven. Mechanistic studies can provide biological plausibility, but they cannot establish that coffee consumption prevents or treats depression in humans. The translation from molecular mechanisms to clinical recommendations requires additional evidence from randomized controlled trials and studies examining coffee's effects in clinical populations.

Coffee Components and Bioactive Compounds: Beyond Caffeine

Coffee is a complex matrix containing hundreds of bioactive compounds that contribute to its sensory properties and biological activities (Socała et al., 2020). Caffeine is the most recognized component, but coffee also contains chlorogenic acids (CGAs), trigonelline, melanoidins, quinides, diterpenes (cafestol and kahweol), and various polyphenols, each with distinct biological effects (Liang & Kitts, 2015; Tajik et al., 2017). Understanding the contributions of individual compounds, as well as their interactions, is essential for interpreting coffee's effects on mental health.

Caffeine (1,3,7-trimethylxanthine) is the principal psychoactive compound in coffee, acting primarily as a non-selective antagonist at adenosine A1 and A2A receptors (Fredholm, 1995). Caffeine is rapidly absorbed, reaching peak plasma concentrations approximately 30-60 minutes after ingestion, with a half-life of 3-5 hours in healthy adults, though this varies considerably due to genetic and environmental factors (Liguori et al., 1997). Beyond adenosine antagonism, caffeine influences multiple neurotransmitter systems including dopamine, serotonin, norepinephrine, and glutamate, as discussed in subsequent sections. However, caffeine's effects are not limited to mood modulation; it also affects sleep, anxiety, cardiovascular function, and metabolism (Nehlig, 2022).

CGAs are a family of polyphenolic compounds abundant in coffee, constituting approximately 5-12% of green coffee beans by weight and up to 2-4% of roasted coffee (Farah & Donangelo, 2006). The most abundant CGAs are 5-caffeoylquinic acid, 3-caffeoylquinic acid, and 4-caffeoylquinic acid, along with feruloylquinic and dicaffeoylquinic acid derivatives. CGAs exhibit potent antioxidant and anti-inflammatory properties, potentially contributing to coffee's neuroprotective effects (Xu et al., 2012; Hwang et al., 2014). They can scavenge reactive oxygen species, inhibit the production of pro-inflammatory cytokines, and modulate signaling pathways involved in inflammation and oxidative stress (Krakauer, 2002; Liang & Kitts, 2015). CGAs also influence glucose metabolism and insulin sensitivity, with potential implications for metabolic health and mood (Shu-Yuan et al., 2009). The concentration of CGAs in coffee varies with roasting; lighter roasts retain higher CGA content, while darker roasts contain lower levels due to thermal degradation (Castaldo et al., 2021). This variability complicates comparisons across studies and underscores the importance of considering coffee preparation in research.

Trigonelline, an alkaloid derived from nicotinic acid, is another important coffee component, typically present at 0.5-1.5% in green beans and partially degraded during roasting to produce nicotinic acid (niacin) (Yagasaki et al., 2002). Trigonelline has demonstrated neuroprotective effects in experimental models, potentially through antioxidant mechanisms, anti-inflammatory actions, and stimulation of neurotrophic factors such as BDNF (Mirzaie et al., 2016; Chowdhury et al., 2018). Some studies suggest that trigonelline may promote neuronal survival and reduce neuroinflammation, making it relevant to mood regulation and neurodegenerative disease prevention (Chowdhury et al., 2018; Khalili et al., 2018). However, the evidence for trigonelline's effects on mood in humans is limited, and most studies have been conducted *in vitro* or in animal models.

Melanoidins are high molecular weight, brown-colored compounds formed during the Maillard reaction in coffee roasting (Borrelli et al., 2002). These compounds exhibit antioxidant properties and may modulate inflammation, though their bioavailability and biological effects are less well-characterized than those of caffeine and CGAs (Moreira et al., 2012; Gerardi et al., 2025). Quinides, formed during coffee processing, also possess antioxidant and anti-inflammatory activities, potentially contributing to coffee's neuroprotective profile (Mukherjee & Pal, 2013; Krishnaveni et al., 2015). Diterpenes (cafestol and kahweol) are present in unfiltered coffee and have been studied for their effects on cholesterol metabolism, but their relevance to mental health is uncertain (Urgert & Katan, 1997).

The interplay between coffee components is likely synergistic. Caffeine may enhance the absorption or activity of other compounds, while CGAs, polyphenols, and trigonelline may mitigate some of caffeine's adverse effects, such as excessive sympathetic activation or oxidative stress (Lopes et al., 2023). This syner-

gy suggests that coffee's effects cannot be reduced to caffeine alone. Moreover, the method of coffee preparation significantly influences the concentrations of bioactive compounds. Espresso brewing typically yields higher caffeine concentration per volume but lower CGA content compared to filter coffee, while cold brew extraction may preserve higher CGA levels due to lower extraction temperatures (Ludwig et al., 2012). These variations have important implications for interpreting research findings and formulating dietary recommendations.

The bioavailability of coffee compounds varies considerably. Caffeine is highly bioavailable and readily crosses the blood-brain barrier, whereas polyphenols and CGAs are extensively metabolized by gut microbiota and have limited systemic bioavailability (Crozier et al., 2008). The metabolites produced by gut microbial fermentation may contribute to biological effects, including modulation of inflammation and neurotransmitter synthesis (Crozier et al., 2008). This gut-mediated pathway represents an important mechanism through which coffee compounds may influence the brain, connecting coffee consumption to the gut-brain axis.

Adenosine Receptor Antagonism: A Double-Edged Mechanism

Caffeine's primary molecular action is antagonism of adenosine receptors, particularly the A1 and A2A subtypes, which are widely distributed throughout the central nervous system (Fredholm, 1995). Adenosine is a neuromodulator that accumulates during wakefulness, promoting sleep pressure by inhibiting neuronal excitability, reducing neurotransmitter release, and inducing vasodilation (Porkka-Heiskanen & Kalinchuk, 2011). By blocking adenosine receptors, caffeine reduces adenosine-mediated inhibition, leading to increased neuronal firing, enhanced neurotransmitter release, and heightened arousal (Reichert et al., 2022). This mechanism explains caffeine's well-established effects on alertness, cognitive performance, and wakefulness, but it also accounts for potential adverse effects on sleep, anxiety, and stress reactivity (Hughes, 1996; Roehrs & Roth, 2008).

The A1 receptor is ubiquitously expressed in the brain, including regions involved in mood regulation such as the prefrontal cortex, hippocampus, striatum, and amygdala (Schindler et al., 2001). A1 receptor activation generally inhibits neuronal activity by reducing cyclic AMP production, modulating potassium and calcium channels, and suppressing neurotransmitter release. Caffeine's blockade of A1 receptors disinhibits these circuits, promoting glutamate, dopamine, and norepinephrine release, which may enhance mood, motivation, and cognitive function under favorable conditions (Solinas et al., 2002; Ferré, 2010). However, excessive A1 antagonism can also produce overstimulation, contributing to anxiety, restlessness, and sleep disruption (Hughes, 1996; van Calker et al., 2019).

The A2A receptor is highly expressed in the striatum, nucleus accumbens, and other regions involved in reward and motivation (Fredholm, 1995). A2A receptors modulate dopaminergic signaling, and their antagonism by caffeine can enhance dopamine release and receptor sensitivity, contributing to caffeine's reinforcing and mood-enhancing effects (Cauli & Morelli, 2005; Fuxe et al., 2007). A2A receptor blockade has been associated with reduced depressive-like behavior in animal models, and some evidence suggests that A2A receptor polymorphisms may influence susceptibility to depression and anxiety (Yu et al., 2009; Kaster et al., 2015). However, A2A antagonism also contributes to caffeine's arousal-promoting effects, which can interfere with sleep and recovery when consumption is poorly timed (Landolt et al., 1995; Clark & Landolt, 2017).

The effects of adenosine receptor antagonism are dose-dependent and context-dependent. At low to moderate doses (approximately 200-400 mg caffeine daily), the balance may favor beneficial effects on mood, alertness, and cognitive performance in many individuals (Lieberman et al., 1987; Smit & Rogers, 2000). At higher doses, the same mechanism may produce overstimulation, anxiety, jitteriness, and sleep disruption, which can worsen mood (Karacan et al., 1976). Importantly, tolerance develops with regular consumption, reducing both the beneficial and adverse effects over time, and acute effects are more pronounced after periods of abstinence (Yeomans et al., 2002).

Individual variability in adenosine receptor sensitivity, mediated in part by genetic polymorphisms in ADORA2A, significantly influences responses to caffeine. The ADORA2A rs5751876 variant has been associated with caffeine-induced anxiety, with some studies suggesting that carriers of the T allele may be more susceptible to anxiogenic effects (Rogers et al., 2010; Fulton et al., 2018). However, findings have been inconsistent, and the functional significance of this polymorphism remains incompletely characterized (Childs et al., 2008). Other genetic factors, including variants in ADORA1, may also influence sensitivity but have been less extensively studied.

The connection between adenosine receptor antagonism and sleep is particularly important for men-

tal health. Caffeine's blockade of A1 receptors reduces sleep pressure and delays sleep onset, while A2A receptor antagonism may also contribute to arousal (Porkka-Heiskanen et al., 2002; Huang et al., 2024). When consumed in the afternoon or evening, caffeine can significantly reduce total sleep time, slow-wave sleep, and sleep efficiency, effects that persist for several hours due to caffeine's half-life (Drake et al., 2013; Clark & Landolt, 2017). Poor sleep quality is a robust risk factor for depression, anxiety, and emotional dysregulation, suggesting that caffeine's sleep-disrupting effects could offset any direct mood benefits (Riemann et al., 2015; Palagini et al., 2019). This bidirectional relationship highlights the need to consider timing of consumption and individual sensitivity when evaluating coffee's effects on mental health.

Monoamine System Modulation: Neurotransmitter Effects in Context

Caffeine influences monoamine neurotransmitter systems—specifically serotonin (5-HT), dopamine (DA), and norepinephrine (NE)—which play central roles in mood regulation, motivation, and emotional well-being (Hensler, 2010; Belujon & Grace, 2017). The monoamine hypothesis of depression posits that deficiencies in these neurotransmitters contribute to depressive symptoms, and many antidepressant medications target monoamine systems (Delgado, 2000). Caffeine's effects on monoamines are largely indirect, mediated through adenosine receptor antagonism, which disinhibits neurotransmitter release and modulates reuptake mechanisms (Alasmari, 2020).

Serotonergic System

Caffeine increases serotonin release from presynaptic neurons and may inhibit serotonin reuptake *via* the serotonin transporter (SERT), thereby increasing synaptic serotonin availability (Berkowitz & Spector, 1971). Chronic caffeine consumption has been associated with increased sensitivity of 5-HT1A and 5-HT2A receptors, which may amplify serotonergic signaling and promote mood stabilization (Yamato et al., 2002; Nugent et al., 2013). Additionally, caffeine inhibits monoamine oxidase A (MAO-A), an enzyme that degrades serotonin and other monoamines, potentially further increasing neurotransmitter availability (Grzelczyk et al., 2021). These effects are consistent with the observed association between coffee consumption and reduced depressive symptoms in epidemiological studies. However, the magnitude of these effects in humans is modest compared to conventional antidepressants, and caffeine should not be considered a substitute for evidence-based treatments.

The relationship between caffeine and serotonin is context-dependent. Acute caffeine consumption can produce transient mood improvement, particularly in states of fatigue or low arousal, but chronic consumption may lead to neuroadaptive changes that alter baseline serotonergic function (Young & Leyton, 2002). Withdrawal from caffeine, even after moderate consumption, produces symptoms including fatigue, depressed mood, and irritability, which may reflect reduced serotonergic activity (Juliano & Griffiths, 2004). This dependence cycle complicates the interpretation of caffeine's effects on mood, as individuals may consume caffeine to avoid withdrawal rather than to achieve net mood benefits.

Dopaminergic System

Caffeine enhances dopaminergic transmission through several mechanisms. Adenosine A2A receptors are co-localized with dopamine D2 receptors in the striatum, and A2A antagonism disinhibits dopamine release and signaling (Cauli & Morelli, 2005; Fuxe et al., 2007). This effect is particularly prominent in the mesolimbic pathway, which is central to motivation, reward, and pleasure. Caffeine's dopaminergic effects contribute to its reinforcing properties and may explain its association with improved mood and reduced anhedonia (diminished ability to experience pleasure) in some studies (Argyropoulos & Nutt, 2013; Volkow et al., 2015). Chronic caffeine consumption may upregulate D2 receptor expression, potentially enhancing dopaminergic responsiveness (Powell et al., 2001). However, excessive dopaminergic stimulation can also produce anxiety, restlessness, and psychosis in vulnerable individuals (Volkow et al., 2015).

The behavioral context of caffeine consumption modulates dopaminergic effects. When caffeine is consumed to enhance performance in work or academic settings, its dopaminergic effects may reinforce productivity and engagement. Conversely, when caffeine is used to compensate for sleep deprivation or to maintain prolonged studying or work sessions, it may contribute to maladaptive cycles of overwork, fatigue, and stress, as discussed in recent research on problematic overstudying (Kosecka et al., 2025). In such contexts, caffeine's mood-enhancing effects may be transient and followed by withdrawal-related mood deterioration.

Noradrenergic System

Caffeine increases norepinephrine release through adenosine receptor antagonism, particularly *via* A2A receptors, which inhibit noradrenergic neuronal firing (Berkowitz et al., 1970; Donoso et al., 2006). Norepinephrine is central to the brain's stress response, arousal, and attention systems, and its modulation affects mood, alertness, and cognitive function (Morilak et al., 2005). Caffeine's noradrenergic effects contribute to its wake-promoting properties and may improve mood and energy levels, particularly during states of fatigue. However, excessive norepinephrine activation can also produce anxiety, hyperarousal, and sympathetic activation, consistent with caffeine's anxiogenic effects at higher doses (Fitzgerald, 2013).

Implications for Depression and Anxiety

The net effect of caffeine on monoamine systems depends on dose, timing, individual sensitivity, and psychiatric vulnerability. In individuals without anxiety disorders, moderate caffeine consumption may enhance monoaminergic signaling sufficiently to improve mood without producing adverse effects (Jiang et al., 2022). However, in individuals with generalized anxiety disorder, panic disorder, or high anxiety sensitivity, even moderate caffeine doses can trigger or worsen anxiety symptoms (Lee et al., 1985; Bruce & Lader, 1989). Similarly, in individuals with bipolar disorder, caffeine may precipitate hypomania or mania in vulnerable individuals (Rosen et al., 2023). These population-specific effects underscore the need for personalized recommendations and caution in clinical populations. The key neurotransmitter systems modulated by caffeine and coffee components, along with genetic factors influencing individual responses, are summarized in Table 1.

Anti-inflammatory Actions: Neuroimmune Modulation

Chronic low-grade inflammation is increasingly recognized as a contributing factor in depression pathophysiology, with elevated pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) observed in depressed individuals (Miller et al., 2009;

Table 1. Central neurotransmitter modulation by caffeine and coffee components.

Mechanism	Bioactive Compound	Key Molecular Targets	Effect on Mood / Brain Function	Evidence Level	References
Adenosine Receptor Antagonism	Caffeine	A1 & A2A receptors	Disinhibition of CNS; ↑ alertness, arousal, and cognitive performance	Animal / Human	(Ferré, 2010; Fredholm, 1995)
Increased Neuronal Excitability	Caffeine	A1 receptor / Glutamate release	↑ synaptic plasticity, memory, and cognitive performance	Animal	(Daly et al., 2020; Solinas et al., 2002)
Dopaminergic Modulation	Caffeine	A2A receptor / D2 receptors	Boosts motivation, pleasure, and reward sensitivity; ↓ anhedonia	Animal / Human	(Cauli & Morelli, 2005; Volkow et al., 2015)
Serotonergic Enhancement	Caffeine	5-HT release / SERT inhibition / MAO-A inhibition	Mood stabilization; ↑ emotional well-being	Animal	(Berkowitz & Spector, 1971; Yamato et al., 2002)
Noradrenergic Activation	Caffeine	A2A blockade / NE firing rate	↑ Alertness, stress response, and emotional regulation	Animal	(Berkowitz §et al., 1970; Fitzgerald, 2013)
Genetic Modulation of Response	Caffeine (metabolism)	CYP1A2 (rs762551)	Fast *vs.* Slow metabolizers: alters duration of caffeine exposure	Human (Epidemiological)	(Low et al., 2024)
Genetic Modulation of Sensitivity	Caffeine (receptor)	ADORA2A (rs5751876)	Alters sensitivity to caffeine-induced anxiety and arousal	Human (Clinical)	(Fulton et al., 2018)

Roohi et al., 2021). Coffee contains numerous compounds with anti-inflammatory and immunomodulatory properties, including polyphenols, CGAs, caffeic acid, and to a lesser extent, caffeine (Jung et al., 2017; Castaldo et al., 2021). These compounds may exert antidepressant-relevant effects by reducing systemic and neuroinflammation.

Coffee polyphenols, particularly CGAs, inhibit the production of pro-inflammatory cytokines in immune cells and microglia, the brain's resident immune cells (Muqaku et al., 2016; Murata et al., 2023). CGAs can suppress the activation of nuclear factor kappa B (NF-κB), a transcription factor central to inflammatory responses, thereby reducing the expression of inflammatory genes (Santangelo et al., 2007). Additionally, CGAs may inhibit the NLRP3 inflammasome, a multiprotein complex that mediates IL-1β and IL-18 production, further dampening neuroinflammatory responses (Wang et al., 2022). These mechanisms are relevant to depression because neuroinflammation can disrupt monoamine synthesis, impair neuroplasticity, and contribute to neuronal damage (Mechawar & Savitz, 2016).

Caffeine itself has direct effects on microglial activation. By antagonizing adenosine A2A receptors on microglia, caffeine may inhibit microglial overactivation and subsequent release of neurotoxic inflammatory mediators (Madeira et al., 2017; Colella et al., 2018). This effect has been demonstrated in experimental models of neurodegenerative disease, where caffeine administration reduced microglial activation and inflammation (Ullah et al., 2015). However, the relationship between caffeine and microglia is complex, and adenosine signaling plays diverse roles in immune regulation, with both pro-inflammatory and anti-inflammatory effects depending on context (Saura et al., 2005).

The anti-inflammatory effects of coffee are likely modest compared to pharmacological anti-inflammatory agents but may be clinically significant when combined with other lifestyle factors that modulate inflammation (Dludla et al., 2023). Regular coffee consumption has been associated with lower levels of inflammatory markers in epidemiological studies, though findings have been inconsistent and effect sizes are small (Lopez-Garcia et al., 2006; Loftfield et al., 2015). The clinical relevance of these effects for depression remains uncertain, as inflammation is only one contributor to depression pathophysiology, and anti-inflammatory effects may not translate to symptom improvement in all individuals.

The relationship between coffee, inflammation, and mental health is bidirectional. Chronic stress and depression are associated with elevated inflammation, which may increase vulnerability to adverse effects of caffeine, such as sleep disruption and metabolic dysregulation. Conversely, anti-inflammatory effects of coffee may be most relevant in individuals with elevated baseline inflammation, such as those with obesity, metabolic syndrome, or chronic stress. Future research should examine whether coffee's anti-inflammatory effects are most pronounced in specific subpopulations.

BDNF and Neuroplasticity Enhancement: Adaptive or Compensatory?

Brain-derived neurotrophic factor (BDNF) is a key regulator of neuronal survival, synaptic plasticity, and neurogenesis, with reduced BDNF levels consistently observed in depression and stress-related disorders (Yu & Chen, 2011; Yang et al., 2020). Animal studies and some human data suggest that caffeine and coffee components may increase BDNF expression and signaling, potentially promoting neuroplasticity and resilience (Costa et al., 2008; Kakio et al., 2015). Caffeine's effects on BDNF appear to be mediated through multiple pathways, including dopamine and glutamate signaling, activation of the insulin receptor substrate 2 (IRS2) pathway, and modulation of cAMP response element-binding protein (CREB) (Costa et al., 2008; Moosavi et al., 2015; Lao-Peregrín et al., 2017). Polyphenolic compounds such as CGAs may also activate the MAPK pathway, leading to increased BDNF expression (Ontawong et al., 2023; Qin et al., 2023).

The relevance of BDNF for depression is well-established, with numerous studies showing that antidepressant treatments (pharmacological, behavioral, and lifestyle) increase BDNF levels (Duman & Monteggia, 2006). If coffee consumption elevates BDNF, this could provide a mechanistic basis for its observed association with lower depression risk. However, several caveats are warranted. Most evidence for coffee- or caffeine-induced BDNF increases comes from animal studies, and human data are limited (Costa et al., 2008; Kakio et al., 2015). The magnitude of BDNF elevation is modest compared to that produced by exercise or antidepressant medications. Moreover, BDNF effects are context-dependent: acute stress can transiently increase BDNF, whereas chronic stress reduces it, and the net effect on mood depends on the balance of these factors (Licznerski & Jonas, 2018).

Caffeine's effects on BDNF may be influenced by genetic factors. The BDNF Val66Met polymorphism (rs6265) is associated with reduced activity-dependent BDNF secretion and has been linked to depres-

sion vulnerability (Egan et al., 2003). Whether caffeine's effects on BDNF differ by genotype has not been extensively studied, but this represents an important area for future research. Additionally, lifestyle factors such as exercise, diet, and sleep quality interact with BDNF regulation and may modulate caffeine's effects (Hötting & Röder, 2013; Phillips, 2017).

There is also a potential compensatory or maladaptive aspect to caffeine's effects on BDNF. Chronic caffeine consumption leads to neuroadaptive changes, including altered adenosine receptor density and sensitivity, which may normalize BDNF levels over time (Rocha-Mendonça et al., 2015). Withdrawal from caffeine can transiently reduce BDNF expression, potentially contributing to withdrawal-related mood deterioration (Basu Mallik et al., 2022). This pattern suggests that caffeine's effects on BDNF may be most pronounced in individuals who have developed dependence and experience withdrawal when caffeine is absent.

Oxidative Stress Reduction: Antioxidant Defense Mechanisms

Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, contributing to neuronal damage, neuroinflammation, and depression pathophysiology (Bhatt et al., 2020). Coffee is a rich source of dietary antioxidants, including chlorogenic acids, caffeic acid, melanoidins, and other polyphenols, which may protect against oxidative damage by scavenging free radicals, enhancing endogenous antioxidant enzymes, and modulating antioxidant signaling pathways (Prasanthi et al., 2010; Abreu et al., 2011; Liang & Kitts, 2014). These antioxidant properties have been invoked to explain coffee's potential neuroprotective and mood-enhancing effects.

CGAs and caffeic acid are potent ROS scavengers, neutralizing superoxide, hydroxyl radicals, and other reactive species that damage cellular components (Chen & Ho, 1997; Hung et al., 2006). Coffee consumption has been associated with reduced oxidative stress markers in human studies, though effect sizes are modest and findings have been inconsistent (Hoelzl et al., 2010). In addition to direct scavenging, coffee compounds may upregulate endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Magalhães et al., 2016; Badshah et al., 2019). Nrf2 is a transcription factor that regulates the expression of numerous antioxidant genes; its activation by coffee components may enhance the brain's intrinsic antioxidant defenses (Kobayashi & Yamamoto, 2005; Kobayashi et al., 2020).

Mitochondrial function is closely linked to oxidative stress and mood regulation. Mitochondria are primary sources of ROS, and mitochondrial dysfunction contributes to neuronal damage and depression pathophysiology (Giménez-Palomo et al., 2021; Trigo et al., 2022). Caffeine and CGAs have been shown to enhance mitochondrial function, improve bioenergetics, and reduce ROS production in experimental models (Dragicevic et al., 2012; Zhou et al., 2016). These effects may be mediated through activation of AMPK and PGC-1α pathways, which regulate mitochondrial biogenesis and function (Spyridopoulos et al., 2008; Schnuck et al., 2018). Enhanced mitochondrial function could improve neuronal resilience to stress and reduce oxidative damage, potentially contributing to mood benefits.

The clinical significance of coffee's antioxidant effects for depression is uncertain. While oxidative stress is implicated in depression, antioxidant interventions have generally shown limited efficacy as stand-alone treatments (Biesalski & McGregor, 2007). Coffee's antioxidant properties may be relevant as part of a broader dietary pattern that supports brain health, rather than as a targeted antidepressant strategy. Furthermore, excessive antioxidant intake can have adverse effects, and the optimal balance between oxidants and antioxidants is complex (Halliwell, 2013). The main cellular resilience pathways—antiinflammatory, antioxidant, and neuroplasticity—that may mediate coffee's effects on mood are summarized in Table 2.

Hypothalamic-Pituitary-Adrenal Axis Modulation: Stress Response Context

The hypothalamic-pituitary-adrenal (HPA) axis is a key neuroendocrine system mediating the stress response, with dysregulation implicated in depression and anxiety disorders (Lopez-Duran et al., 2009; Guilliams & Edwards, 2010). Chronic coffee consumption may modulate HPA axis activity through effects on corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (Novak et al., 2013; Fischer et al., 2021). Caffeine acutely increases cortisol secretion, consistent with its sympathomimetic effects and role in stress activation (Lovallo et al., 2006). However, chronic consumption may lead to adaptive responses, with some studies suggesting blunted cortisol reactivity in habitual consumers (Yamato et al., 2005; Gür et al., 2024).

Table 2. Cellular resilience: Anti-inflammatory, antioxidant, and neuroplasticity pathways.

Mechanism	Bioactive Compound	Key Molecular Targets	Effect on Mood / Brain Function	Evidence Level	References
Reduction of Pro-inflammatory Cytokines	Polyphenols / CGAs	TNF-α, IL-6 / NF-κB pathway	↓ Systemic and neuroinflammation; protects against inflammation-induced depressive behavior	Animal / *In vitro*	(Miller et al., 2009; Roohi et al., 2021)
Microglial Activation Inhibition	Caffeine	A2A receptors on microglia / NLRP3 inflammasome	Blocks chronic neuroinflammation and release of neurotoxic factors	Animal / *In vitro*	(Madeira et al., 2017; Wang et al., 2022)
Oxidative Stress Scavenging	CGAs / Caffeic acid	ROS neutralization	Protects neurons and hippocampal cells from oxidative damage	Animal / *In vitro*	(Abreu et al., 2011)
Upregulation of Antioxidant Enzymes	Caffeine / Polyphenols	SOD, Catalase, GPx / Nrf2-Keap1 pathway	Boosts enzymatic ROS detoxification and endogenous antioxidant defense	Animal	(Badshah et al., 2019; Kobayashi & Yamamoto, 2005)
BDNF Expression & Signaling	Caffeine / CGAs	TrkB receptor / MAPK / IRS2 pathway	Promotes neurogenesis, synaptic plasticity, and resilience to stress	Animal / *In vitro*	(Costa et al., 2008; Lao-Peregrín et al., 2017)
Mitochondrial Protection & Bioenergetics	Caffeine / Chlorogenic acid	AMPK / PGC-1α / ETC	Improves energy metabolism; ↓ ROS production; supports neuronal health	Animal / *In vitro*	(Dragicevic et al., 2012; Zhou et al., 2016)

The relationship between caffeine and HPA axis function is context-dependent. Acute caffeine administration prior to psychological stress can amplify cortisol and cardiovascular responses, potentially worsening stress reactivity (al'Absi et al., 1995).

Polyphenols in coffee may also influence HPA axis function indirectly by reducing inflammation and oxidative stress, which can dysregulate HPA axis activity (Yahfoufi et al., 2018). Chronic inflammation is associated with HPA axis hyperactivity and glucocorticoid resistance, contributing to stress-related disorders (Silverman & Sternberg, 2012). By attenuating inflammation, coffee polyphenols may help normalize HPA axis function, particularly in individuals with elevated baseline inflammation (Sakakibara & Shimoi, 2020).

The net effect of coffee on HPA axis and stress is uncertain and likely varies across individuals based on genetic factors, habitual intake, stress levels, and timing of consumption. In individuals with anxiety disorders or high stress reactivity, caffeine may exacerbate HPA axis activation and worsen symptoms (Richardson et al., 1995; Cornelis, 2019). In individuals with lower stress reactivity and moderate intake, coffee may have minimal or no adverse effects on HPA axis function. The distinction between adaptive and maladaptive HPA axis modulation is essential but often overlooked in mechanistic reviews.

Gut-Brain Axis Influence: Microbiome-Mediated Effects

The gut-brain axis represents a bidirectional communication system between the gastrointestinal tract and the central nervous system, with the gut microbiome playing a central role in mood regulation, neuroinflammation, and neurotransmitter synthesis (Evrensel & Ceylan, 2015; Mohajeri et al., 2018). Coffee contains compounds that may influence gut microbial composition and function, potentially contributing to its effects on mood through the gut-brain axis (Hegde et al., 2022; Saygili et al., 2024).

Coffee polyphenols, particularly CGAs, have prebiotic properties, promoting the growth of beneficial bacteria such as Bifidobacteria and Lactobacilli while inhibiting pathogenic species (Usta-Gorgun & Yilmaz-Ersan, 2020; Rodríguez-Daza et al., 2021). These bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, which have anti-inflammatory effects, strengthen the gut barrier, and may cross the blood-brain barrier to influence neuroinflammation and neurotrophic signaling (Dalile et al., 2019; Liu et al., 2021). SCFAs have been shown to enhance BDNF expression, providing a potential mechanism linking coffee consumption to neuroplasticity (Varela et al., 2015). However, the effects of coffee on

gut microbiota are modest compared to dietary interventions such as fiber or probiotic supplementation.

The gut microbiome also influences monoamine production, particularly serotonin (5-HT) (Stasi et al., 2019). Approximately 90% of the body's serotonin is produced in the gut, primarily by enterochromaffin cells, and gut microbial composition affects serotonin synthesis and availability (Reigstad et al., 2014). Dysbiosis has been associated with reduced serotonin levels and depression (Xiong et al., 2023). By modulating gut microbial composition, coffee may indirectly influence serotonin production, potentially contributing to mood regulation. However, evidence for this pathway in humans is limited, and the magnitude of effect is uncertain.

Caffeine itself may affect gut motility and permeability. Moderate caffeine consumption can stimulate gastrointestinal motility, while excessive intake may increase intestinal permeability (leaky gut), allowing pro-inflammatory substances to enter the bloodstream and potentially exacerbate neuroinflammation (Silva et al., 2022). The relationship between coffee, gut permeability, and mood is complex and likely depends on individual factors, including genetics, diet, and overall health status.

The gut-brain axis represents an emerging area of research, and causal relationships between coffee, microbiome changes, and mood are difficult to establish. Much of the evidence comes from animal studies or small human trials, and findings are not always consistent (Hegde et al., 2022; Gallego-Barceló & Abalo, 2025). Future research should incorporate metagenomic analyses and examine whether specific microbial profiles predict mood responses to coffee consumption.

Genetic Moderators: CYP1A2 and ADORA2A

Genetic variability significantly influences individual responses to caffeine, with two genes—*CYP1A2* and *ADORA2A*—receiving the most attention as moderators of caffeine metabolism and sensitivity (Fulton et al., 2018; Low et al., 2024). Understanding these genetic factors is essential for interpreting the relationship between coffee consumption and depression, as they may explain why some individuals benefit from coffee while others experience adverse effects.

CYP1A2 and Caffeine Metabolism

CYP1A2 is the primary enzyme responsible for caffeine metabolism, accounting for approximately 95% of caffeine clearance in the liver (Grant et al., 1983). The *CYP1A2* gene exhibits considerable genetic variability, with the -163C>A (rs762551) polymorphism being the most extensively studied (Sachse et al., 1999). Individuals carrying the A allele (CYP1A2*1A) are typically classified as "fast metabolizers," whereas those with the C allele (CYP1A2*1F) are "slow metabolizers", though the functional significance of this polymorphism is debated and may be modified by environmental factors such as smoking (Cornelis et al., 2006; El-Sohemy et al., 2007).

Slow metabolizers have prolonged caffeine exposure, potentially increasing susceptibility to adverse effects including anxiety, sleep disruption, palpitations, and stress activation at lower doses (Rodenburg et al., 2012; Low et al., 2024). In contrast, fast metabolizers clear caffeine more rapidly, which may reduce adverse effects but also diminish beneficial effects and potentially lead to more frequent consumption to maintain stimulation. This pharmacogenetic variation has important implications for coffee's effects on mental health. Slow metabolizers may be more vulnerable to caffeine-induced anxiety and insomnia, which could worsen depression risk, while fast metabolizers may derive greater mood benefits from caffeine's alerting effects.

ADORA2A and Caffeine Sensitivity

ADORA2A encodes the adenosine A2A receptor, a primary target of caffeine in the central nervous system (Fredholm, 1995). The ADORA2A rs5751876 (1976C>T) polymorphism has been associated with caffeine-induced anxiety and sleep disturbances (Rogers et al., 2010; Fulton et al., 2018). Carriers of the T allele may have increased A2A receptor availability or sensitivity, making them more susceptible to caffeine's stimulant and anxiogenic effects. However, findings have been inconsistent, and the functional impact of ADORA2A polymorphisms on caffeine sensitivity is not fully understood (Childs et al., 2008).

Other ADORA2A variants, including rs35320474 and rs3990, have also been studied, but evidence for their functional significance is limited. Gene-gene interactions between *CYP1A2* and *ADORA2A* may further modulate caffeine responses, though few studies have examined these interactions (Cornelis, 2019). Additionally, epistatic interactions with other genes involved in monoamine metabolism, stress response, and neuroplasticity may influence individual responses but have not been systematically investigated.

Implications for Research and Practice

Genetic variability complicates the interpretation of epidemiological studies and the formulation of dietary recommendations. Studies that aggregate all participants, regardless of genotype, may mask significant subgroup differences in coffee's effects on mood and depression risk. Future research should stratify analyses by CYP1A2 and ADORA2A genotype when possible and consider gene-environment interactions, including lifestyle factors such as smoking, sleep, and stress.

From a clinical perspective, genetic testing for CYP1A2 and ADORA2A is not yet indicated for coffee consumption recommendations, as the evidence base is insufficient and the predictive value of these polymorphisms for mood outcomes is uncertain. However, healthcare providers should be aware of individual variability in caffeine sensitivity and consider recommending reduced consumption or avoidance of evening caffeine in individuals who report anxiety, insomnia, or stress exacerbation following coffee intake.

Sleep Disruption: A Primary Pathway

Sleep disruption is one of the most important pathways through which caffeine may negatively affect mental health, yet it is frequently treated as a peripheral caveat in mechanistic reviews (Clark & Landolt, 2017). Caffeine's adenosine receptor antagonism directly interferes with sleep pressure, delaying sleep onset, reducing total sleep time, and altering sleep architecture, particularly slow-wave sleep (Drake et al., 2013; Clark & Landolt, 2017). These effects are dose-dependent and can persist for hours after consumption due to caffeine's half-life (Huang et al., 2024).

Acute sleep deprivation and chronic sleep restriction are robust risk factors for depression, anxiety, emotional dysregulation, and impaired cognitive function (Zhang et al., 2017; Palagini et al., 2019). Sleep disruption affects multiple neurobiological systems implicated in mood disorders, including monoamine function, HPA axis activity, neuroinflammation, oxidative stress, and neuroplasticity (Irwin, 2019). Thus, even if caffeine exerts direct mood-enhancing effects through monoamine modulation or BDNF upregulation, these benefits may be offset or reversed when consumption impairs sleep quality and duration.

The relationship between caffeine and sleep is bidirectional. Poor sleep increases fatigue and may increase caffeine consumption to maintain wakefulness and performance, creating a cycle of caffeine use, sleep disruption, and compensatory consumption (Kim et al., 2025). This pattern is particularly common in academic, occupational, and shift-work contexts, where caffeine is used to override natural sleep-wake rhythms (O'callaghan et al., 2018; Kosecka et al., 2025). In such cases, caffeine functions as a maladaptive coping mechanism, reinforcing the cycle of overwork and fatigue that contributes to stress and mood deterioration.

Individual variability in caffeine's effects on sleep is influenced by genetic factors, including CYP1A2 and ADORA2A polymorphisms, as well as habitual intake, timing of consumption, and age (Clark & Landolt, 2017). Slow metabolizers and individuals with high A2A receptor sensitivity may be particularly vulnerable to caffeine-induced sleep disruption. Moreover, the effects of caffeine on sleep are more pronounced when consumed in the afternoon or evening, and individuals who consume caffeine close to bedtime are at greater risk (O'callaghan et al., 2018).

A balanced review of coffee's effects on mental health must integrate sleep disruption as a primary pathway rather than a minor caveat. Studies that examine coffee's effects on mood without controlling for sleep may overestimate direct beneficial effects while underestimating indirect adverse effects through sleep impairment. Future research should include objective sleep measures, such as actigraphy or polysomnography, to better understand the relationship between coffee consumption, sleep, and mood. Systemic and contextual pathways, including HPA axis modulation, gutbrain communication, metabolic effects, sleep disruption, and maladaptive coping patterns, are summarized in Table 3.

Energy Drinks: A Distinct Exposure Context

The discussion of caffeine's effects on mental health is incomplete without considering the distinct context of energy drink consumption. Energy drinks, which contain caffeine along with other stimulants (taurine, guarana, ginseng), high sugar content, and additives, represent a different exposure profile than coffee (Reissig et al., 2009; Seifert et al., 2011). Their marketing targets adolescents and young adults with messaging around performance, stimulation, and fatigue reduction, which may increase their use as compensatory tools rather than ordinary dietary beverages (Kosecka et al., 2025; Mularczyk-Tomczewska et al., 2025).

Energy drink consumption has been associated with numerous adverse outcomes, including insomnia, anxiety, palpitations, and substance use, particu-

Table 3. Systemic and contextual pathways: HPA axis, gut-brain, metabolism, sleep, and maladaptive use.

Mechanism	Bioactive Compound / Exposure	Key Molecular Targets / Context	Effect on Mood / Brain Function	Evidence Level	References
HPA Axis Modulation (Adaptive)	Caffeine (chronic)	↓ CRH/ACTH; blunted cortisol reactivity	May improve stress resilience in habitual consumers	Human	(Fischer et al., 2021; Lovallo et al., 2006)
HPA Axis Activation (Maladaptive)	Caffeine (acute/high dose)	↑ Cortisol & sympathetic activation	May exacerbate stress and anxiety in vulnerable individuals	Human	(Lovallo et al., 2006)
Gut Microbiome Modulation	Polyphenols / CGAs	Prebiotic effect; ↑ Bifidobacterium & SCFAs	SCFAs cross BBB; ↑ BDNF and ↓ neuroinflammation	Animal / Human	(Saygili et al., 2024)
Gut-Brain Signaling & Barrier Integrity	Coffee compounds	↓ Gut permeability; ↑ neurotransmitter synthesis	Reduces leaky gut and systemic inflammation	Animal / *In vitro*	(Iriondo-DeHond et al., 2021)
Metabolic Pathway Modulation	Caffeine / CGAs	AMPK / PGC-1α / Glucose uptake	Supports neuronal energy homeostasis and neurotransmitter synthesis	Animal / *In vitro*	(Lopes et al., 2023; Spyridopoulos et al., 2008)
Sleep Disruption (Primary Caveat)	Caffeine (afternoon/evening)	A1/A2A antagonism (blocks sleep pressure)	Delays sleep onset, reduces SWS; leads to fatigue and worsening of mood	Human (Clinical)	(Clark & Landolt, 2017; Drake et al., 2013)
Maladaptive Coping / Overstudying	Caffeine (behavioral context)	Compensatory use to override fatigue	Reinforces work/ study addiction; increases stress, anxiety, and burnout	Human (Epidemiological)	(Kosecka et al., 2025)
Energy Drink Context	Caffeine + additives (taurine/sugar)	High-dose stimulant + sugar rush	Distinct risk profile; associated with insomnia, jitteriness, and dependence in youth	Human (Epidemiological)	(Mularczyk-Tomczewska et al., 2025)

larly in adolescents and young adults (Visram et al., 2016; Al-Shaar et al., 2017). A systematic review and meta-analysis found that energy drink consumption significantly increased the odds of insomnia and jitteriness compared with control conditions (Alsunni, 2015). The high sugar content of many energy drinks also contributes to metabolic dysregulation and mood fluctuations, further complicating interpretation (Pereira et al., 2022).

The social and behavioral context of energy drink consumption differs fundamentally from coffee drinking. Energy drinks are often consumed in high-stress, performance-demanding situations—studying, athletic competition, shift work—where caffeine is used to override fatigue and maintain function (Kosecka et al., 2025). This compensatory use pattern may reinforce maladaptive behaviors, such as sleep deprivation, overwork, and neglect of restorative activities, which worsen mental health over time. In contrast, coffee consumption is more often integrated into social routines and may not be associated with the same pattern of maladaptive use.

These distinctions are essential for interpreting the evidence base. Studies that aggregate all caffeine sources may obscure differential effects of coffee *versus* energy drinks on mental health. Coffee's complex matrix of bioactive compounds may mitigate some adverse effects, while energy drinks' high sugar content, additives, and consumption patterns may amplify them (Temple & Ziegler, 2011). The recent ban on energy drink sales to minors in several countries reflects growing recognition of these risks (Ercoşkun, 2025).

A balanced review should acknowledge that coffee and energy drinks are not interchangeable and that caffeine's effects are product-context dependent. Recommendations about caffeine consumption should differentiate between moderate coffee drinking and energy drink use, particularly in vulnerable populations such as adolescents, young adults, and individuals with psychiatric vulnerabilities.

Timing and Dosage Considerations

The dose-response relationship between caffeine and mental health is nonlinear, with moderate consumption associated with benefits in some studies and high consumption associated with adverse effects

(Lieberman et al., 1987; Ruxton, 2008). The optimal dose likely varies across individuals based on genetic factors, habitual intake, and sensitivity. Most studies suggest that 2-4 cups of coffee per day (approximately 200-400 mg caffeine) represent a moderate intake range associated with lower depression risk in epidemiological studies (Grosso et al., 2016). However, these findings are population averages and may not apply to individuals with high sensitivity, slow metabolism, or anxiety disorders.

Timing of consumption is equally important. Morning consumption aligns with natural cortisol rhythms and may enhance alertness and performance without disrupting sleep (Bailey & Heitkemper, 1991). Afternoon or evening consumption, however, can interfere with sleep onset and architecture, potentially offsetting mood benefits and contributing to stress and fatigue (Clark & Landolt, 2017). The half-life of caffeine (approximately 3-5 hours in healthy adults) means that caffeine consumed at 4 PM may still be substantially present in the blood at bedtime, affecting sleep quality (Liguori et al., 1997). For individuals with slow metabolism or high sensitivity, the window for safe consumption may be even narrower.

Individual tolerance develops with regular consumption, reducing both beneficial and adverse effects over time (Chou et al., 1985; Yeomans et al., 2002). This tolerance may lead individuals to increase consumption to achieve desired effects, creating a cycle of escalation that increases risk of adverse outcomes. Conversely, individuals who consume coffee intermittently may experience more pronounced effects but also more withdrawal-related mood deterioration during abstinence.

The context of consumption—including sleep status, stress levels, meal timing, and concurrent medications—modulates caffeine's effects. Consumption during periods of sleep deprivation may be more likely to produce adverse effects due to heightened adenosine levels and increased sensitivity to arousal (Baur, 2024). Consumption with meals may reduce gastric irritation and slow caffeine absorption, potentially moderating peak effects (Zaman et al., 2019). These contextual factors are rarely considered in mechanistic reviews but are essential for understanding real-world effects.

Interaction with Therapeutic Approaches

The interaction between coffee consumption and conventional antidepressant treatments is an important clinical consideration. Caffeine may potentiate the effects of SSRIs, which increase serotonin availability, through its own serotonergic effects (Kale et al., 2010). Some studies have suggested that caffeine may enhance antidepressant efficacy or reduce side effects, though evidence is limited and findings have been inconsistent (Kale & Addepalli, 2014). However, caffeine also increases the risk of serotonin syndrome when combined with serotonergic agents, particularly MAO inhibitors (Gillman, 2005). This potential interaction is clinically relevant for patients taking antidepressants, especially at higher doses.

Caffeine may also interact with other psychiatric medications. Caffeine antagonizes benzodiazepines and other sedative medications, potentially reducing their efficacy or increasing required doses (Mattila et al., 1992). It may also interact with stimulant medications used for ADHD, potentially increasing cardiovascular and anxiety risks (Dodd et al., 2025). These interactions highlight the need for healthcare providers to inquire about caffeine consumption and consider its implications when prescribing psychotropic medications.

The relationship between coffee consumption and behavioral interventions, such as cognitive-behavioral therapy (CBT), is understudied but potentially relevant. Caffeine's effects on arousal, anxiety, and sleep may influence engagement and outcomes in psychotherapy (Sheppard et al., 2012). Patients who consume high doses of caffeine may experience increased anxiety, emotional lability, and sleep disruption, which could interfere with therapeutic progress. Conversely, moderate caffeine consumption may enhance alertness and engagement during therapy sessions.

Lifestyle interventions for depression, including exercise and dietary modification, may interact with coffee consumption. Physical activity and coffee consumption may have additive or synergistic effects on mood, given that both influence monoamine systems, BDNF, and inflammation (Hogervorst et al., 2008). However, caffeine consumed immediately before exercise can increase heart rate and stress responses, potentially reducing exercise enjoyment and adherence (Graham, 2001). The net effect of combining coffee consumption with lifestyle interventions requires further research.

Conclusion: Toward a Conditional Model

This review has critically examined the molecular mechanisms through which chronic coffee consumption may influence mood and depression risk, while emphasizing that these effects are conditional on dose, timing, genetic factors, sleep, stress, behavioral context, and individual vulnerability. The

evidence supports biological plausibility for several pathways—adenosine receptor antagonism, monoamine modulation, anti-inflammatory actions, BDNF upregulation, antioxidant effects, HPA axis modulation, gut-brain axis interactions, and metabolic regulation—that could mediate coffee's association with reduced depression risk in epidemiological studies. However, the same mechanisms can produce adverse effects, including anxiety, sleep disruption, stress activation, and maladaptive coping, depending on context and individual factors.

A revised model should distinguish between coffee as a complex beverage and caffeine as an isolated compound, recognizing that coffee's bioactive matrix includes numerous compounds beyond caffeine that may contribute to its overall biological activity. This distinction is essential because many mechanistic studies are based on caffeine administration, whereas epidemiological evidence examines coffee consumption. The effects of coffee cannot be reduced to caffeine alone, and the complex interactions among coffee compounds, their metabolites, and the gut microbiome likely modulate biological outcomes.

Genetic variability in CYP1A2 and ADORA2A should be recognized as important moderators of caffeine metabolism and sensitivity, though the evidence base is incomplete and clinical applications are premature. Slow metabolizers and individuals with high A2A receptor sensitivity may be more vulnerable to caffeine-induced anxiety, sleep disruption, and stress activation, potentially reducing any mood benefits and increasing adverse effects. Future research should stratify by genotype and examine gene-environment interactions with sleep, stress, and lifestyle factors.

Sleep disruption represents a primary pathway through which caffeine may negatively affect mental health, and it should be integrated into mechanistic models rather than treated as a peripheral caveat. Even if caffeine exerts direct mood benefits, these may be offset by impaired sleep quality and duration, particularly in vulnerable populations and when caffeine is consumed in the afternoon or evening. The bidirectional relationship between caffeine and sleep—where caffeine disrupts sleep and sleep disruption increases caffeine consumption—can create cycles of dependence and worsening mental health.

The review also emphasizes the importance of behavioral context, including use of caffeine to compensate for fatigue, maintain academic or work performance, or regulate negative affect. This compensatory use pattern, particularly common in students and shift workers, may reinforce maladaptive behaviors and worsen mental health over time. Energy drink consumption represents a distinct exposure context, with different user groups, product composition, and social meaning than coffee consumption, and findings from energy drink studies should not be generalized to coffee.

Several methodological limitations constrain the evidence base. Most studies are observational, precluding causal inference; standardized caffeine content measurements are lacking; genetic factors are rarely considered; and clinical populations are underrepresented. The narrative review method itself is subject to selection bias, and future systematic reviews with transparent methodology would strengthen the evidence base.

Clinically, coffee should not be recommended as a universal antidepressant, but healthcare providers may consider discussing individual caffeine sensitivity, timing, and context with patients. For individuals without anxiety, sleep, or stress vulnerabilities, moderate morning coffee consumption may be safe and potentially beneficial. For individuals with anxiety disorders, sleep disorders, or high caffeine sensitivity, avoidance or limitation of caffeine, especially in the afternoon and evening, may be advisable. Personalized recommendations based on genetic testing remain premature, but patients' subjective responses to caffeine should guide recommendations.

Future research should address several priorities: (1) randomized controlled trials examining coffee's effects on depression in clinical populations, with stratification by genetic factors; (2) studies incorporating objective sleep measures to examine the interplay between caffeine, sleep, and mood; (3) investigations of coffee's effects on the gut microbiome and its relevance to mood; (4) research on individual differences in response, including genetic, metabolic, and psychological factors; and (5) longitudinal studies examining the effects of caffeine reduction or cessation on mood and sleep in heavy consumers.

In summary, coffee may confer mood benefits under specific conditions—moderate dose, appropriate timing, individual tolerance, and favorable behavioral context—but these effects are not universal or unconditional. A conditional risk-benefit model, incorporating biological plausibility, individual variability, and contextual factors, provides a more accurate framework for understanding coffee's relationship with mental health than a unidirectional antidepressant model. This nuanced perspective supports informed choices about coffee consumption while avoiding overstatement of its therapeutic potential.

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