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REVIEW

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Current therapeutic targets and multifaceted physiological impacts of caffeine

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Abstract

Caffeine, which shares consubstantial structural similarity with purine adenosine, has been demonstrated as a nonselective adenosine receptor antagonist for eliciting most of the biological functions at physiologically relevant dosages. Accumulating evidence supports caffeine's beneficial effects against different disorders, such as total cardiovascular diseases and type 2 diabetes. Conversely, paradoxical effects are also linked to caffeine ingestion in humans including hypertension–hypotension and tachycardia–bradycardia. These observations suggest the association of caffeine action with its ingested concentration and/or concurrent interaction with preferential molecular targets to direct explicit events in the human body. Thus, a coherent analysis of the functional targets of caffeine, relevant to normal physiology, and disease pathophysiology, is required to understand the pharmacology of caffeine. This review provides a broad overview of the experimentally validated targets of caffeine, particularly those of therapeutic interest, and the impacts of caffeine on organ-specific physiology and pathophysiology. Overall, the available empirical and epidemiological evidence supports the dose-dependent functional activities of caffeine and advocates for further studies to get insights into the caffeine-induced changes under specific conditions, such as asthma, DNA repair, and cancer, in view of its therapeutic applications.

KEYWORDS
caffeine, caffeinism, health, molecular receptors, pharmacology

1 | INTRODUCTION

Caffeine (1,3,7-trimethylxanthine), classified as a natural alkaloid, has been isolated from the different parts of nearly 63 plant species, including tea leaves, coffee beans, kola nuts, cacao beans, bissy nuts, guarana, and mate, which are regularly consumed as ingredients in foods, beverages, herbal supplements, and medications (Bresciani et al., 2014; Mumin et al., 2006). Caffeine shares consubstantial structural similarities with adenosine, a purine nucleoside comprising adenine and ribose, as shown in Figure 1, and hence acts as a competitive antagonist of adenosine. It exhibits a psychostimulant effect on the central nervous system (CNS; Herden & Weissert, 2018) and is globally slurped as a beverage with an average of 70–76 mg per person per day (Oberleitner et al., 2014). Based on the available literature, caffeine consumption at lower doses (<100 mg/day) is stated as harmless in adults, but serious complications are demonstrated in young children and pregnant women (Ghosh et al., 2013). Moreover, higher doses (400–600 mg/day) of caffeine are reported to induce caffeinism, which is characterized by the onset of anxiety, psychomotor agitation, dysphoria, and insomnia (Lopes et al., 2019). Repeated exposure to caffeine is also associated with rapid tolerance and withdrawal-like symptoms, such as headache, irritability, nervousness, and a reduction in energy, following a decrease or abrupt cessation of caffeine after prolonged regular consumption (Addicott, 2014). Regardless of its linked consequences, caffeine has low reinforcing efficacy in comparison to other known classical psychostimulants, implying that it lacks the ability to sustain self-administration or choice behavior (Ferre, 2008).

Interestingly, recent clinical studies linked caffeine consumption with a reduction in risk factors for cardiovascular disorders, type 2 diabetes, hypertension, and the shielding effect in neural cells against neurodegenerative diseases (Lin et al., 2023; O'Keefe et al., 2013; Othman et al., 2023; van Dam & Hu, 2022; Yang et al., 2022). Besides, an epidemiological analysis on the daily consumption of caffeine established a correlation with a reduction in skin cancers, such as non-melanoma, and wrinkle formation, as well as a protective agent against photoaging (Chiang et al., 2015; Cui et al., 2020; Gajewska et al., 2015). In other studies, caffeine has been demonstrated to elicit concentration-dependent anticancer activity via direct or indirect interactions with multiple receptors, as reviewed elsewhere (Cui et al., 2020; Stouth et al., 2023; Tej & Nayak, 2018). Despite the beneficial effects of caffeine at therapeutic concentrations, some paradoxical effects have been reported in humans, including hypertension–hypotension and tachycardia–bradycardia, which may be associated with caffeine targeting divergent molecular targets based on the ingested concentration. For instance, caffeine-induced antagonism of presynaptic adenosine receptors (ARs) may result in enhanced concentrations of catecholamine, or blocking the vasodilatory effects of adenosine via ARs antagonism collectively may result in hypertension (Goldfrank & Hoffman, 2006; Lymperopoulos et al., 2016; Ralevic & Dunn, 2015). Conversely, hypotension may occur in some cases due to phosphodiesterases (PDEs) inhibition when exposed to an overdose of caffeine (Goldfrank & Hoffman, 2006; Holstege et al., 2003). It is, therefore, likely that caffeine can interact with multiple targets or even synergize with endogenous molecules on some of its molecular targets to elicit biological effects on different organs and systems in humans. However, caffeine has escaped a consolidated review highlighting its molecular targets aptly associated with the physiological effects on targeted organs or biological systems. Therefore, the aim of this comprehensive review paper is to collect in-depth literature on caffeine-targeted receptors or biomolecules and caffeine-induced organ-specific physiological impacts on the human body, particularly those of medical interest linked to the development of diseases or disorders. To collect the relevant literature, different databases, including PubMed, Scopus, Web of Science, and Google Scholar, were manually searched without year limit using keywords, including "caffeine and metabolism in humans," "caffeine and pharmacokinetics," "caffeine and molecular receptors," "caffeine and signaling pathways," "caffeine and human physiology," "caffeine and human diseases," "caffeine and health benefits," and "caffeine and pharmacological effects in humans."

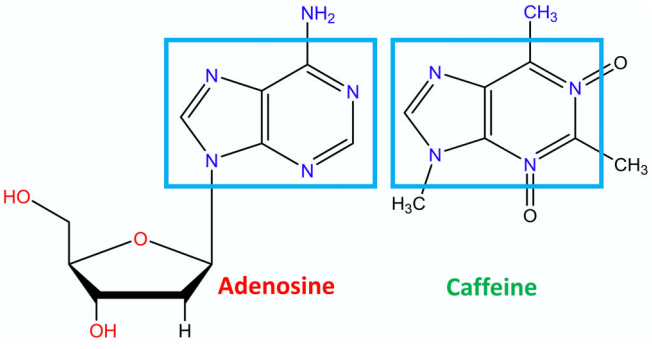

FIGURE 1 Chemical structures of adenosine and caffeine, where box covering on caffeine structure exhibits the structural similarity with purine adenosine at the nitrogenous aromatic region.

2 | CAFFEINE'S JOURNEY THROUGH THE BODY: PHARMACOKINETICS

According to the available literature, several exogenous factors, such as age, diseases, environmental aspects, food, genetic predispositions, medicines, pregnancy, sex, and smoking, can manipulate the caffeine pharmacokinetics in humans, as reviewed elsewhere (Arnaud, 2011; Grzegorzewski et al., 2022; Nehlig, 2018). Thus, a substantial deviation in the half-life, metabolism, and distribution of caffeine has been reported among different individuals (Table 1).

Initially, caffeine was described as a moderately lipophilic molecule (Blanchard & Sawers, 1983), but later studies established its typical features as an amphiphilic molecule (i.e., logP = −0.07) with an ability to split the lipid bilayer and diffuse across the cell membranes (Arnaud, 2011; Carrillo & Benitez, 2000; Sawynok & Yaksh, 1993) or biological barriers such as the blood–brain barrier (BBB; Arnaud, 2011; Sawynok & Yaksh, 1993). Accordingly, caffeine was reported to have rapid and effective absorption to 100%

TABLE 1 Pharmacokinetic properties of caffeine in adults.

Absorption	Parameters
Oral bioavailability	Up to 100%
t_{max}	0.5–2 h
c_{max}	Up to 8–10 mg/L
Distribution	
Volume of distribution	0.6 L/kg; brain penetrant
Plasma protein binding	10%–36% (in vitro)
Half-life	~5 h (varying)
Metabolism	
Metabolizing enzymes	CYP1A2, xanthine oxidase, *N*-acetyltransferase 2 (NAT2)
Main metabolites	Paraxanthine, theobromine, theophylline, 1-methylxanthine, 3,7-dimethyluric acid
Elimination	
Excretion	Renal (metabolites), caffeine is reabsorbed in the tubulus
Clearance	~0.078 L/kg/h (varying)

Abbreviations: t_{max}, time of peak plasma concentration; C_{max}, maximum plasma concentrations.

bioavailability from the gastrointestinal tract (in particular from the small intestine) soon after its oral consumption (Blanchard & Sawyers, 1983). Also, caffeine has been measured to normally achieve a peak plasma concentration within 30–120 min after administration in healthy individuals. According to a report by Blanchard and Sawers (1983), when a healthy adult man absorbs 5 mg/kg of caffeine, the highest concentration of caffeine in the blood (10 μg/mL) is attained within 30 min. However, some individuals may exhibit a varied time interval, which is typically influenced by the mode of administration or other dietary considerations (Arnaud, 2011; May et al., 1982; White Jr et al., 2016). In humans, for example, caffeine absorption from cola and chocolate is delayed (90–120 min) compared with a caffeine capsule (30 min) or with coffee and tea as drinks, and the maximum concentration was decreased by around 25% for both drinks in comparison with 2.05 μg/mL for a caffeine capsule, resulting most likely due to their acidic pH (Marks & Kelly, 1973; Mumford et al., 1996). In another study, rapid absorption of caffeine was noted for caffeine-containing chewing gum, with maximum concentrations obtained between 45 and 80 min postadministration, whereas caffeine-containing capsules showed absorption rate between 85 and 120 min (Kamimori et al., 2002). Similarly, caffeine is reported to have an interindividual variation in half-life range from 2.5 h to a maximum of 12 h (with an average half-life of 5 h) in the blood plasma of healthy individuals (Arnaud, 1993; Benowitz, 1990; El-Din, 2011; Khondker et al., 2017). The observed large variations in the half-life of caffeine are suggested due to the distinct genetic variants related to caffeine metabolism, such as single nucleotide polymorphisms (SNPs) near *ABCG2*, *AHR*, *CD83*, *CYP1A2*, *CYP2A6*, *GCKR*, and *POR* genes (Cornelis et al., 2011, 2015, 2016; Sulem et al., 2011); gastric factors, including caffeine time present in the stomach and gastric pH (Chvasta & Cooke, 1971); and the consumption of additional dietary constituents, involving fiber (Arnaud, 1987; Brachtel & Richter, 1988) by healthy individuals. Changes in fluid intake may also alter the pharmacokinetics of caffeine, which may potentially affect its total body clearance and renal clearance (Trang et al., 1985). Additionally, previous studies have reported an average distribution volume of 0.7 L/kg (Arnaud, 2011; Carrillo & Benitez, 2000) and a low protein binding (10%–35%; Blanchard, 1982; Sawynok & Yaksh, 1993) for caffeine in healthy humans. Nonetheless, it is important to mention that there is no clear evidence supporting the aggregation of caffeine within the tissues of adult humans (Arnaud, 2011; Carrillo & Benitez, 2000), and thus, further studies to decipher the deposition of caffeine or its metabolites in different tissues require a comprehensive investigation of the human population.

Caffeine displays a complex metabolism in the liver by hepatic microsomal enzymes (Da Silva, 2011), as supported by the detection of more than 25 caffeine's metabolites in the human body (Figure 2; Carrillo & Benitez, 2000; Godos et al., 2014; Nehlig, 2018; Thorn et al., 2012). Available evidence supports that caffeine (about 80%–90%) is exclusively metabolized via the N3-demethylation reaction catalyzed by the cytochrome P450 isoform 1A2 (CYP1A2) into its main product, that is, paraxanthine (1,7-dimethylxanthine; Grzegorzewski et al., 2021; Hakooz, 2009). The remaining 11% and 4% concentrations of the consumed caffeine are metabolized into the 1-demethylated product, that is, theobromine, and the 7-demethylated product, that is, theophylline, respectively (Amchin et al., 1999; Kalow & Tang, 1993; Lelo et al., 1986; Miners & Birkett, 1996). Additionally, *N*-acetyltransferase 2 (NAT2) and xanthine oxidase (XO) have been significantly demonstrated to mediate the metabolism of caffeine (Werner Kalow & Tang, 1991). Other cytochrome P450 isozymes, such as CYP3A4/3A5 and CYP2D6, are also reported to be involved in the caffeine metabolism at exorbitant concentrations (millimolar; Arnaud, 2011). All the possible enzymatic reactions and pathways adopted for the caffeine metabolism in the human body are illustrated in Figure 2.

Recent reports have established a significant variance for the caffeine metabolism amongst individuals and suggested to be due to variability in the CYP1A2 enzyme activity (DePaula & Farah, 2019; Gu et al., 1992; Tian et al., 2019). It was found that an A–C substitution in the *CYP1A2* gene at −163 (rs762551) position lessens enzyme inducibility as assessed by plasma or urinary caffeine-to-metabolite ratios after caffeine ingestion (Sachse et al., 1999). Moreover, carriers of the −163C allele were noted for slow metabolism of caffeine, whereas individuals identified as homozygous for the −163A allele showed a rapid metabolism of caffeine (Sachse et al., 1999). In support, research conducted on populations from China, Italy, and the United States revealed that CYP1A2 exhibits varied activity and distribution associated with the observed slow (12%–13%), intermediate (51%–67%), and rapid (20%–37%) phenotypes (Butler et al., 1992). Importantly, such phenotypes can also be considered as key factor for the varied peak plasma concentration and half-life of caffeine in humans. Other studies have also narrated slow caffeine's metabolism

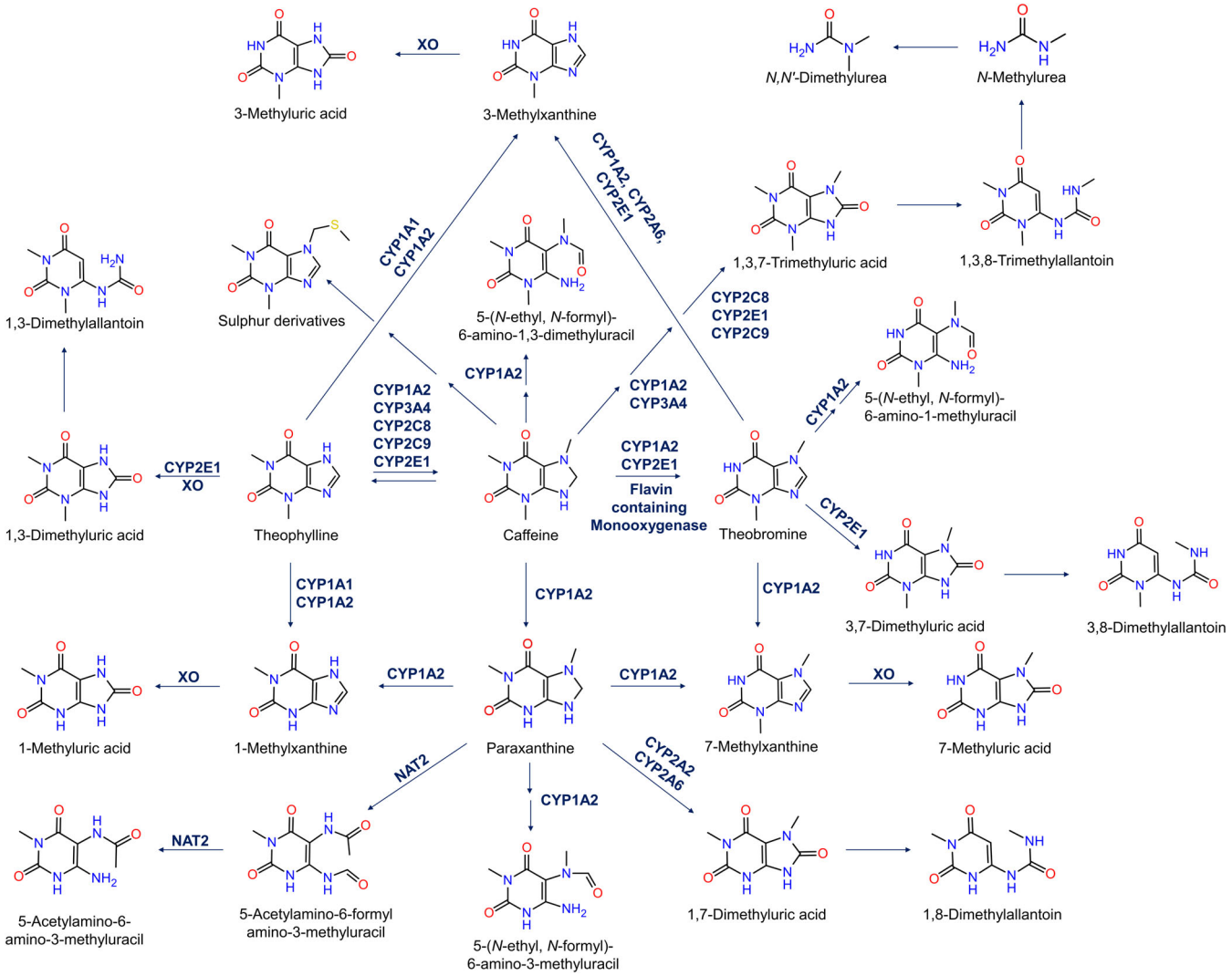

FIGURE 2 Main enzymatic pathways for the caffeine metabolism in the human body. The major enzymes and reactions involved in caffeine metabolism are adopted from previously published reports (Godos et al., 2014; Nehlig, 2018; Thorn et al., 2012).

during pregnancy, conceivably due to reduced activities of CYP1A2, XO, and NAT2 enzymes, which results in an extended caffeine half-life of 12–18 h (Bologa et al., 1991; Grosso & Bracken, 2005). Another study suggested that a daily intake of caffeine by pregnant women may lead to its flow into the fetal circulation, and neither the blood–placental barrier nor the fetus has enzymes to metabolize it, causing aggregation of caffeine in the fetus (Fenster et al., 1991). Accordingly, delayed caffeine metabolism during pregnancy is documented to affect the fetus (Fredholm et al., 1999; Qian et al., 2020). In support, recent studies concluded that pregnant women who consume 300 mg of caffeine per day may endure an elevated risk of fetal intrauterine growth restriction complications (Chen et al., 2014; CARE Study Group, 2008; Qian et al., 2020). Additionally, a recent retrospective cohort analysis of caffeine consumption during pregnancy and longitudinal child growth established that even in amounts below the currently advised guidelines of less than 200 mg per day during pregnancy, maternal caffeine consumption was linked to shorter child height starting at age 4 and persisting to age 8 years. Nonetheless, the clinical implications of this height difference are unclear and warrant future investigation (Gleason et al., 2022).

Mechanistically, caffeine is eliminated from the human body by first-order kinetics, which is efficiently described by a one-compartment open model system, as reviewed elsewhere (Alsabri et al., 2021). Thereof, caffeine and its metabolites are mainly eliminated from the human body through renal excretion in urine (~85%–88%), and partially discharged through fecal excretion (~2%–5%; Arnaud, 2011; Bonati et al., 1982; Callahan et al., 1982). However, a substantial interindividual variance in the half-lives of caffeine clearance and elimination is also reported. For example, an average clearance value ranges from 1 to 3 mL/kg/min, but a coefficient of variation of ~36%, was reported for caffeine in humans (Arnaud, 2011; Dorne et al., 2001). Also, unlike the produced caffeine metabolites that are excreted by the kidney, about 3%–5% of consumed caffeine is excreted unaltered through urine (Arnaud, 2011; Carrillo & Benitez, 2000; Kot & Daniel, 2008; Sawynok & Yaksh, 1993) and can be substantially reabsorbed in the renal tubulus

(White Jr et al., 2016). Additionally, the amount of caffeine excreted from the body can be substantially reduced with an increase in caffeine consumption (Arnaud, 2011; Dorne et al., 2001; Magkos & Kavouras, 2005). In support, statistical analysis showed that this phenomenon can happen at concentrations below 8.7 mg/L, even though it is generally considered to happen at concentrations of about 19.4 mg/L (Magkos & Kavouras, 2005). Another study reported the same phenomenon for caffeine at dosages of 1–4 mg/kg (Arnaud, 2011). Consequently, the large discrepancy in the excretion of caffeine was suggested due to saturation in the CYP1A2 isozyme activity caused by paraxanthine, which is defined as the primary metabolite of caffeine and also an ideal substrate of CYP1A2 isozyme (Mandel, 2002).

Collectively, advanced epidemiological studies should be considered to decipher the relationship between the amount of caffeine intake and genetic polymorphisms or supplementary factors that are most likely to alter the pharmacokinetics of caffeine, leading to beneficial, or detrimental effects in humans.

3 | PHARMACOLOGICAL DIVERSITY AND MULTIFACETED EFFECTS OF CAFFEINE

Caffeine is well reported to exhibit diverse pharmacological and physiological effects in the human body via interaction with several molecular targets involved in different biochemical or signaling pathways (Fredholm et al., 1999; Lopez et al., 1989; McPhersonx et al., 1991; Page et al., 1996; Yu et al., 2009). In this context, the effects of caffeine are elucidated due to direct or indirect interactions with biomolecules or receptors such as PDEs, γ-aminobutyric acid ($GABA_A$) receptors, and ryanodine receptors (RyRs; Fredholm et al., 1999; Lopez et al., 1989; McPhersonx et al., 1991; Page et al., 1996). Conversely, experimental studies discovered a low binding affinity (nontoxic dosages) of caffeine with such molecular targets, suggesting an acute caffeine concentration (and therefore toxic) is required to obtain the desired effects in humans (Yu et al., 2009). For instance, 20 times higher caffeine concentrations are needed to block cyclic nucleotide breakdown operated by PDEs inhibition, 40 times higher concentrations are needed for $GABA_A$ inhibition, and 100 times higher concentrations are required to mobilize intracellular calcium (Ca^{2+}) depots by comparison to the caffeine concentration in the blood after drinking a cup of coffee (Fredholm et al., 1999). Based on these observations, the interaction of caffeine with ARs to exhibit pharmacological actions is more widely accepted for caffeine-induced pharmacological benefits than the interactions with other molecular targets that are most likely activated at acute concentrations (Fredholm et al., 1999). Despite caffeine pharmacokinetics being highly studied in the literature, there has not yet been a direct experimental verification of this theoretical prediction (Lopes et al., 2019).

Therefore, the objective of this section is to integrate the data on therapeutically relevant and experimentally validated molecular targets of caffeine reported in the literature. This section also summarizes the caffeine-induced physiological and pharmaceutical effects in multiple presentations via direct or indirect interaction with the caffeine-targeted biomolecules or pathways.

3.1 | Functional receptors targeted by caffeine

3.1.1 | Adenosine receptors)

ARs (i.e., A_1AR, $A_{2A}AR$, $A_{2B}AR$, and A_3AR) are characterized as a group of glycoproteins with seven transmembrane domains that belong to Class A G-protein-coupled receptors (Fredholm et al., 1997; Jacobson & Gao, 2006). These receptors are activated by the binding of endogenous adenosine as an agonist at a distinct concentration with a specific binding affinity (Figure 3; Conde et al., 2009; Effendi et al., 2020). In humans, A_1AR (inhibitory constant (K_i) = 10 nM) exhibits the highest affinity for adenosine, followed by $A_{2A}AR$ (K_i = 200 nM), $A_{2B}AR$ (K_i = 2000 nM), and A_3AR (K_i = 10,000 nM) measured in cell-based systems (Fredholm, 2010; Fredholm et al., 2000, 2001). Notably, the expression of ARs is regulated by DNA methylation (Micioni Di Bonaventura et al., 2019), which is well-defined as an important epigenetic process for modulating gene expression in different types of cells (Mazziotta et al., 2022).

Under normal physiological conditions, several cellular activities are affected by a group of ARs or by actions that are specific to a single AR. For example, A_1AR and A_3AR, which are generally coupled to Gi/Go proteins, exhibit a variety of effects on signaling molecules such as arachidonate, cyclic adenosine monophosphate (cAMP), choline, inositol 1,4,5-trisphosphate ($InsP_3$), and $InsP_3$/DAG (inositol 1,4,5-trisphosphate/diacylglycerol; Fredholm et al., 2000). Similarly, $A_{2A}AR$ and $A_{2B}AR$ coupled with Gs/Gq proteins are reported to enhance the production of cAMP/calcium (Ca^{2+}) concentrations in cell (Antonioli et al., 2015). Interestingly, caffeine is well-studied as a nonspecific antagonist of all ARs, but it exhibits substantial affinity for A_1AR (regularly expressed in the adrenal gland, brain, eye, spinal cord, heart, skeletal muscle, and adipose tissues; Jacobson & Muller, 2016; Magkos & Kavouras, 2005) and $A_{2A}AR$ (mainly found in the blood vessels, thymus, striatopallidal GABAergic neurons, spleen, lung, and heart; Fredholm et al., 2001; Jacobson & Muller, 2016; Magkos & Kavouras, 2005) under normal physiological conditions (Abo-Salem et al., 2004; Fredholm et al., 2011). In this respect, caffeine is reported with K_i values of about 8.5 and 7.8 mg/L for the A_1AR and $A_{2A}AR$, respectively, whereas other studies have even reported even lower concentrations (Carrillo & Benitez, 2000; Magkos & Kavouras, 2005; Yu et al., 2009). Also, caffeine shows antagonistic activity against the $A_{2B}AR$ subtype (mostly expressed in the bladder, bronchial smooth muscle cecum, and colon) with a dissociation constant (K_d) of 13 μmol/L (Fredholm et al., 1999). However, contrary to the other AR subtypes, tissue expression of the $A_{2B}AR$ does not appear to be as toxicologically significant and shows a poor affinity for the endogenous agonist adenosine (Fredholm et al., 2000, 2001; Jacobson & Muller, 2016; Magkos & Kavouras, 2005). Further, caffeine does not

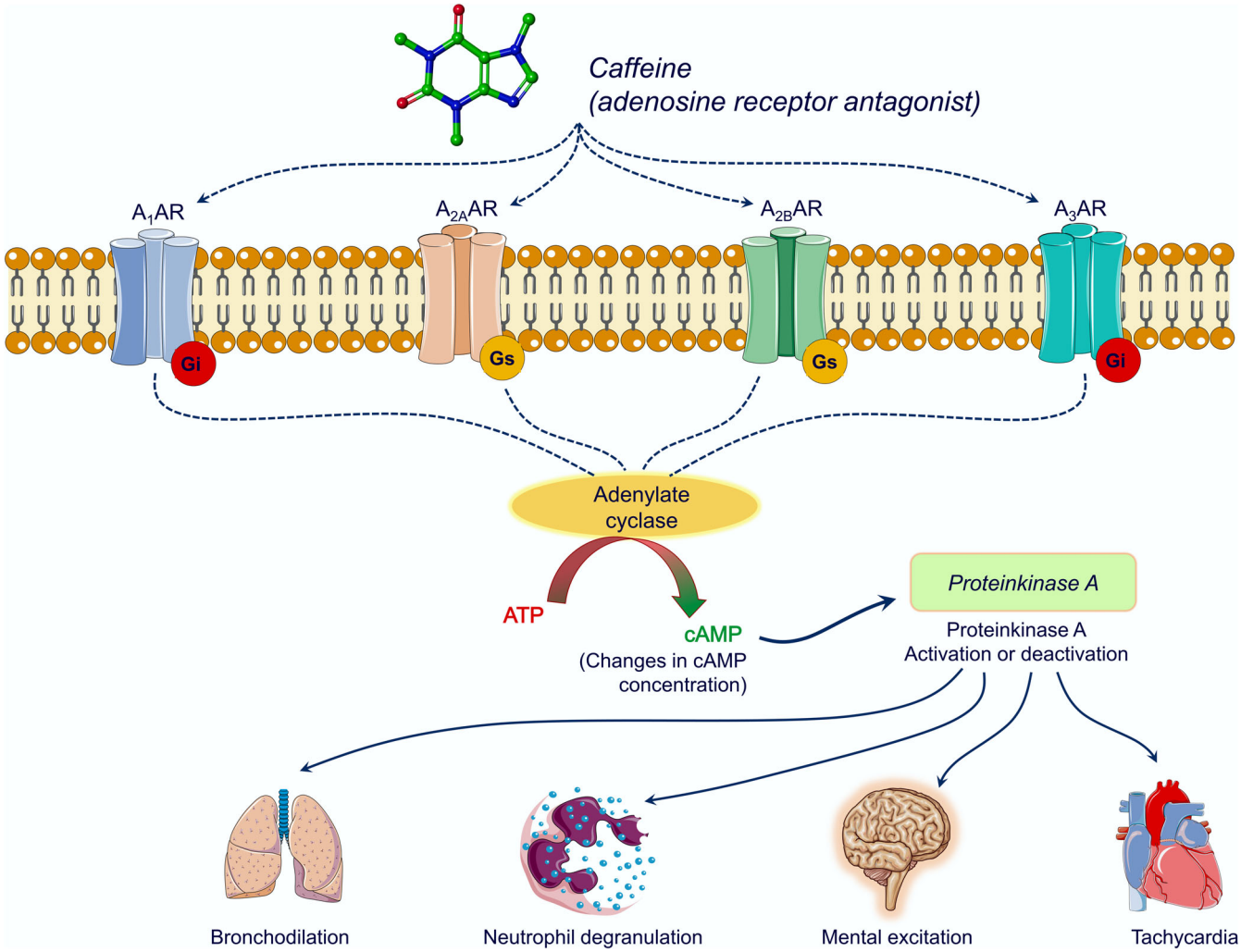

FIGURE 3 Scheme on the modulatory effects of caffeine imposed by binding with different ARs in different organs (A_1AR, A_{2A}AR, A_{2B}AR, and A_3AR; Gi, Gs—inhibitory or stimulatory G-protein).

display a strong affinity ($K_d = 80$ μmol/L) for the A_3AR subtype (Fredholm et al., 1999; Magkos & Kavouras, 2005); hence, this is not frequently reported or discussed in the available literature.

Experimental studies have been conducted to decipher the molecular effect of regular caffeine consumption on the A_1AR, but the obtained results show inconsistency. For instance, some studies reported an upregulation (Daval et al., 1989; Ramkumar et al., 1988), whereas other reports discovered a constant density of A_1AR expression following chronic caffeine treatment up to 42 days (Espinosa et al., 2013; Georgiev & Fredholm, 1993). Meanwhile, it was previously established by Marangos et al. (1984) and Boulenger et al. (1983) that the consequences of caffeine consumption on A_1AR expression mainly depend on the dosage and duration of caffeine intake, respectively. Another study demonstrated that caffeine could promote cell survival under hypoxic conditions by A_1AR inhibition, which further results in the denaturation of hypoxia-inducible factor 1-alpha (Wendler et al., 2007).

Furthermore, the activation of ARs, that is, A_{2A}AR and A_{2B}AR, is associated with a variety of anti-inflammatory effects, including a reduction in neutrophil recruitment and effector activities (Barletta et al., 2012). Particularly, caffeine is established to block the A_{2A}AR with a K_d value of 2.4 μM, and hence, its consequences have been associated with CNS-stimulating effects in humans (Fredholm et al., 1999). For instance, caffeine was reported to induce a decrease in astrocyte proliferation and immunoreactivity by selectively antagonizing A_{2A}AR (Desfrere et al., 2007), implying a direct modulatory mechanism in the prevention of glial scar formation among the caffeine-treated group (Di Martino et al., 2020). Additionally, caffeine-induced A_{2A}AR antagonism has been demonstrated as the prime phenomenon to describe caffeine's dopaminergic and psychostimulant effects (Ferre, 2016). Caffeine is also studied to exhibit significant inhibition of the lipopolysaccharides (LPS)/adenosine 5′-triphosphate (ATP)-induced A_{2A}AR gene transcription and protein expression in THP-1 macrophages, supporting its essential role as a mediator to suppress the Nod-like receptor (NLR) family pyrin domain containing 3 (NLRP3) activation by A_{2A}AR inhibition (Zhao et al., 2019). In previous studies, the alerting and anxiogenic effects of caffeine were linked to SNPs in A_{2A}AR (rs5751876) with the amount of coffee ingestion

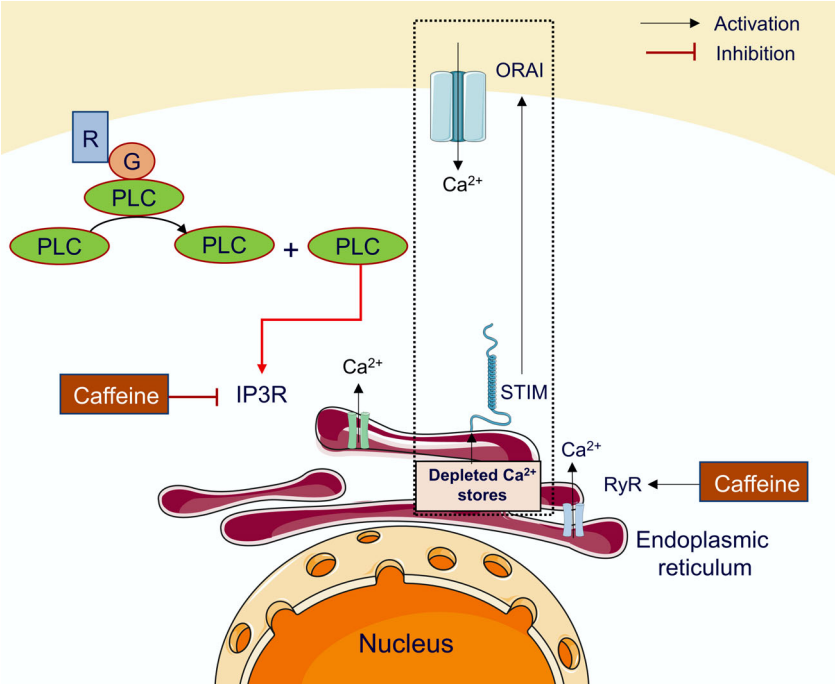

FIGURE 4 Scheme for the effect of caffeine on the intracellular Ca^{2+} homeostasis in excitable cells in two ways: (i) caffeine can block the $InsP_3R$, which reduces Ca^{2+} released from the ER and so decreases intracellular Ca^{2+} levels; and (ii) caffeine can enhance the intracellular Ca^{2+} levels by RyRs activation, resulting in enhance Ca^{2+} released from the ER. In this condition, the store-operated Ca^{2+} entry initiated by Ca^{2+} depletion from the ER might be triggered, which further causes an increase in extracellular Ca^{2+} entering the intracellular compartment (Cui et al., 2020; Prinz & Diener, 2008).

(Childs et al., 2008; Cornelis et al., 2007). A recent study also endorsed caffeine ingestion with an increase in CD4 T-cell counts and a decrease in HIV (human immunodeficiency virus) load among acquired immunodeficiency syndrome (AIDS) patients, possibly due to the immunomodulatory effect of caffeine via $A_{2A}AR$ antagonism (Ramamoorthy et al., 2017). Also, caffeine displays a slight preference for $A_{2B}AR$, which produces a robust dose-dependent analgesic effect. In support, caffeine synergism with drugs, such as paracetamol and nonsteroidal anti-inflammatory drugs, has been demonstrated via $A_{2B}AR$ antagonism (Abo-Salem et al., 2004). In another study, caffeine was studied to reduce the expression of 11-hydroxysteroid dehydrogenase type 2 in human trophoblast cells via $A_{2B}AR$ inhibition (Sharman et al., 2012). Furthermore, the inhibitory (A_1AR and A_3AR) and excitatory ($A_{2A}AR$ and $A_{2B}AR$) effects of ARs, which are mediated in part by changes in cAMP, have been suggested to provide the protective effects induced by caffeine on experimental acute pancreatitis (AP; Burnstock & Novak, 2012). Other studies have linked caffeine-induced antagonism on A_1AR with tachycardia, mental excitation with $A_{2A}AR$ antagonism, bronchodilatation with $A_{2B}AR$ antagonism, and neutrophil degranulation protection via A_3AR antagonism (Figure 3) (Chan et al., 2007; Fukunaga et al., 2003; Joulia et al., 2013; Sullivan et al., 1995; Walaschewski et al., 2013).

Taken together, the diverse expression of ARs in different tissues and organs, possible ARs polymorphisms, and several other factors, such as plasma protein in the cellular microenvironment, may influence the effective concentration and binding affinity of caffeine to exhibit ARs antagonism. Thus, the existence of such factors during interactions analysis of caffeine with ARs under in vitro or in vivo studies may result in inconclusive data interpretation and require well-designed studies with adequate controls to draw a clear conclusion on the warranted binding affinity of caffeine towards ARs.

3.1.2 | Inositol trisphosphate receptor

Several cellular activities are regulated by Ca^{2+} signals emitted from different signaling pathways. In this context, the inositol 1,4,5-trisphosphate/calcium ($InsP_3/Ca^{2+}$) pathway is one of those that functions by either primary or modulatory mechanisms. Herein, a membrane glycoprotein named inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$, further classified into three types, that is, $InsP_3R1$, $InsP_3R2$, and $InsP_3R3$), located on the endoplasmic reticulum (ER) of virtually every cell and functioning as a Ca^{2+} channel, is stimulated by the binding of inositol 1,4,5-trisphosphate ($InsP_3$) as a signaling molecule (Figure 4). Remarkably, the structural complexity of $InsP_3Rs$ varies among different organisms and is essentially required to control physiological and cellular processes such as apoptosis, cell division and proliferation, fertilization, development, behavior, learning, and memory (Bosanac et al., 2002). However, alternation in $InsP_3Rs$ is well characterized to induce disorders in humans, including neurological, immunological, cardiovascular, and neoplastic human disease, as reviewed elsewhere (Gambardella et al., 2020).

Recent studies established that caffeine can act as an inhibitor for the common isotypes of $InsP_3R$ release channels, that is, type 1 ($InsP_3R1$; Saleem et al., 2014) and type 3 ($InsP_3R3$ Kang et al., 2010). For example, caffeine (10 mmol/L) was suggested to inhibit Ca^{2+} release in acutely prepared human glioblastoma cells (which showed two-fold higher expression of $InsP_3R3$ mRNA in comparison to normal cells; $InsP_3R2$ mRNA was unchanged and $InsP_3R1$ mRNA was significantly decreased) and prolong their life span (Kang et al., 2010). In another study, caffeine (70 mM) was suggested to act as an inhibitor of $InsP_3Rs1$ in DT40 cells expressing rat $InsP_3R1$ (GenBank accession number GQ233032.1) isotype without disturbing the binding of $InsP_3$ at millimolar concentrations, while no inhibition

was noted on mouse $InsP_3R2$ (GenBank accession number GU980658.1) isotype or rat $InsP_3R3$ (GenBank accession number GQ233031.1) isotype (Saleem et al., 2014). Also, caffeine is supported to reduce concentration-dependent toxicity of Ca^{2+} signals in pancreatic acinar cells–expressing all three types of $InsP_3Rs$, but only $InsP_3R2$ and $InsP_3R3$ were characterized for predominant physiological Ca^{2+} signaling (Futatsugi et al., 2005), via inhibition of $InsP_3Rs$-mediated signaling, and ameliorate experimental AP; Huang et al., 2017). Thereof, from a mechanistic inhibitory point of view, caffeine can reduce the Ca^{2+} release from $InsP_3Rs$ by preventing $InsP_3$ from being produced by phospholipase C (Toescu et al., 1992), by serving as a strong competitor of ATP at the respective binding site of $InsP_3Rs$ (Maes et al., 2000), or by antagonizing effects through direct binding and a decrease in the open-state probability of IP_3Rs (Bezprozvanny et al., 1994; Saleem et al., 2014). Of note, such functional activities of caffeine were established at acute amounts (mM) and had a range of other consequences, such as RyR stimulation, cyclic nucleotide PDEs inhibition, and even interference with many Ca^{2+} indicators (Michelangeli et al., 1995; Taylor & Tovey, 2010). However, there is no experimental study available, to the best of our knowledge, estimating the direct role of caffeine in altering the gating of $InsP_3Rs$ or its isotypes in humans, which requires further investigation.

Thus, based on the available literature, high concentrations of caffeine may be considered to induce a decrease in Ca^{2+} release from intracellular stores via $InsP_3R2$ or $InsP_3R3$ inhibition in humans. Overall, further insights are also require at the molecular level to detail the action of caffeine with $InsP_3Rs$ isotypes in the treatment of diseases, such as AP, involving high expression of $InsP_3Rs$.

3.1.3 | Ryanodine receptors

The RyRs, classified into RyR1, RyR2, and RyR3 isotypes, are huge homotetrameric Ca^{2+} channels and typically located on the sarcoplasmic reticulum (SR) of skeletal muscle, smooth muscle cells, and cardiac muscle, as well as the ER of cerebellar Purkinje cells and B lymphocytes. The RyRs channels mediate the Ca^{2+}-induced Ca^{2+} release (CICR) phenomenon and are the central site for high susceptibility to a pharmacogenetic condition, that is, malignant hyperthermia.

Notably, caffeine can act as a potent and common agonist of all known RyR isoforms (with an exception for the RyR3 isotype, which has not yet been studied) and substantially increase the Ca^{2+} sensitivity of these channels (Meissner, 1994; Ogawa, 1994). For instance, caffeine is known to activate RyR1 by dropping the inhibitory action of magnesium (Mg^{2+}) and augmenting the stimulating effects of Ca^{2+}, resulting in an increased RyR1 sensitivity to its physiological activators (Figure 4; Herrmann-Frank et al., 1999). Also, caffeine has been stated to activate Ca^{2+} release by decreasing the threshold for luminal, but not cytosolic, Ca^{2+} activation by RyR2 isotype (Kong et al., 2008). In a recent report, caffeine was suggested to induce global changes in RyR1 and RyR2 that result in their extension out of the SR membrane (Bai et al., 2016; des Georges et al., 2016). Another study identified Cys4888 and Cys4891 mutations that can abolish the caffeine-induced activation of RyR2 isotype (Peng et al., 2016). In a prior study, caffeine was also reported to cause an enhancement of Ca^{2+} release via RyRs activation in the skeletal muscles, which subsequently resulted in an elevated concentration of intracellular Ca^{2+} and an excitation–contraction coupling process in mouse muscle (Rossi et al., 2001). Additionally, caffeine was demonstrated to activate the Ca^{2+} release from RyRs by developing a sensitivity of RyRs for Ca^{2+} itself, as noticed in multiple cells (Ozawa, 2010). Remarkably, millimolar doses of caffeine are needed to open RyRs channels (Shi et al., 2003) and such acute concentrations of caffeine can impose supplementary impacts on Ca^{2+} homeostasis, including inhibition of $InsP_3R$-sensitized channels (Daly, 2007). Also, the required high doses of caffeine are unlikely to be attained with regular coffee ingestion. It was estimated that, for instance, ~48.5 mg/L of caffeine is essential to elicit any increment in Ca^{2+} release, while 971–3884 mg/L of caffeine is needed to enhance Ca^{2+} release (Porta et al., 2011; Zulli et al., 2016). Since radical amounts higher than the therapeutic concentrations (100–1000 μmol/L) of caffeine are needed to exhibit such effects, these concentrations do not appear to occur in vivo under normal circumstances. However, these effects may become quite significant in an intoxicated state of caffeine (Carrillo & Benitez, 2000).

Together, structural data on the RyRs have facilitated the process of understanding the caffeine-induced activation of RyRs; however, mutations in RyRs that can cause elimination or enhanced caffeine-induced RyR activation require further investigations. For instance, knowledge of such mutations can be helpful to get mechanistic insights into the regulation of the RyR mutants by caffeine and their multiple effects in skeletal and cardiac muscle-related diseases.

3.1.4 | GABA-benzodiazepine system

GABA, a ligand-gated chloride-selective ion channel, is a well-defined inhibitory neurotransmitter of the CNS and exhibits functional activity using $GABA_A$ (GABA receptor type A), $GABA_B$ (GABA receptor type B), and $GABA_c$ (γ-GABA receptor type C; Zhu et al., 2018). Benzodiazepine (BZD) receptors, as a subset of the $GABA_A$ receptor complex, are expressed throughout the CNS as well as in the kidneys, lungs, liver, and heart (Gross & Booth, 2001). In the CNS, for example, BZDs interact with the BZD receptors to modulate the inhibitory neurotransmitter $GABA_A$ (Griffin et al., 2013). Moreover, several types of BZD receptors are classified based on the α-subunit isoforms and have been associated with distinct clinical consequences. Among the known BZD receptors, the BZ1 receptor is characterized by high expression in the cortex, thalamus, and cerebellum (Rudolph et al., 1999; Sieghart, 1994), while the dorsal horn of the spinal cord, the limbic system, motor neurons, and other regions are highly populated with the BZ2 receptor (Crestani et al., 2001).

Of note, analysis of behavioral and neurochemical evidence in both animals and humans indicated that caffeine modifies or antagonizes the GABA-BZD system (de Angelis et al., 1982; Lopez et al., 1989; Mattila et al., 1982). Initially, caffeine antagonism on ARs

was established to serve as a mediator for the interaction between BZDs and caffeine (Lopez et al., 1989; Nehlig et al., 1987). However, central ARs were affected by caffeine withdrawal, but not the BZD receptor (Boulenger & Marangos, 1989). Thus, the mechanism for this antagonism has been suggested due to the blockage of the BZD receptors by caffeine at high concentrations (Nehlig et al., 1987; Weir & Hruska, 1983). In another study, caffeine exhibited a direct contact with the $GABA_A$ (Daly, 2007) but this interaction had a K_i value of about 280 μmol/L (about 54.3 mg/L; Daly et al., 1994; Yu et al., 2009). Also, caffeine was reported as a weak inhibitor of the $GABA_A$ receptor expressed in *Xenopus oocytes* in a competitive manner ($K_i = 15$ mM) against GABA (1 μM) (Hossain et al., 2002). Hence, caffeine is elucidated to act as a reverse agonist or antagonist in BZDs' action sites (Shi et al., 2003), that is, by blocking the $GABA_A$ receptor (Sawynok, 2011). Based on the available evidence, further investigation is required to decipher the caffeine mode of action on the GABA-BZD system.

3.2 | Caffeine-mediated activities with other biomolecules

3.2.1 | Acetylcholinesterase inhibitor

Acetylcholine (ACh), a low-molecular weight neurotransmitter expressed in both the peripheral nervous system (PNS) and CNS, is accountable for the transmission of neural signals from nerves to terminal glands and muscles (Miroslav Pohanka & Dobes, 2013). However, during aging, excessive activity of acetylcholinesterase (AChE), an enzyme producing choline and acetate from ACh, leads to instant and progressive depletion of ACh. This resulted in impaired functioning of nerve impulses coupled with inadequate neurotransmission (Miroslav Pohanka, 2011, 2012). Interestingly, AChE activity has been correlated with the Alzheimer's disease (AD) pathogenesis by promotion of beta(β)-amyloid fibril development (Silman & Sussman, 2005). Thus, in the past several years, AChE has been focused as a therapeutic target for the identification of pharmacological agents to enhance ACh availability in the brain (Aluko, 2021).

Recent clinical studies suggested that caffeine can inhibit AChE in a dose-dependent manner with an IC_{50} value of 87 μM (Fabiani et al., 2018). Previously, an K_i of about 34 mg/L (Pohanka & Dobes, 2013) was noted for caffeine against AChE, a level that is most probable to be achieved only under intoxicated conditions. Although the exact mechanism by which caffeine exhibits inhibition of the AChE is yet to be solved, the *N*-methyl determinant of the pyrrolidine ring was suggested as an important descriptor in the inhibitory activity of caffeine against the AChE (Karadsheh et al., 1991).

3.2.2 | Cyclic nucleotide PDE inhibitor

Cyclic nucleotide PDEs perform an essential function in intracellular signaling pathways by selectively hydrolyzing the second messenger's cAMP and cyclic guanosine monophosphate (cGMP) that check cAMP- and cGMP-regulated transcription factors and proteins (Cornelis et al., 2007; Keravis & Lugnier, 2012). Of note, PDEs are expressed by 21 genes in humans and further grouped into 11 distinct families (PDE1–PDE11), where several of them even further have isoform subfamilies (Mehta & Patel, 2019). Thereby, PDEs are broadly studied as enzymes with the capability to mediate or maintain the intracellular homeostasis of both cAMP and cGMP (Delhaye & Bardoni, 2021; Levy et al., 2011).

Recent studies have established caffeine as a nonselective competitive inhibitor of PDEs (Evripioti et al., 2019; Huang & Sperlagh, 2021). In this context, caffeine is reported with a K_i value of about 93.2 mg/L and an IC_{50} value varying between 97 and 194 mg/L, respectively, for the different PDEs (Carrillo & Benitez, 2000; Magkos & Kavouras, 2005; Sawynok & Yaksh, 1993). Therefore, in humans, caffeine has been demonstrated to raise the intracellular level of cAMP by inhibiting the PDEs activity in the adipose tissue and skeletal muscles. With the production of free fatty acids and glycerol, these events further encouraged lipolysis by activating hormone-sensitive lipases (Acheson et al., 2004). The enhanced accessibility of these fuels in the skeletal muscle helps to restrict the consumption of muscle glycogen. However, in vivo, or in vitro studies showed that the caffeine or coffee doses required to exhibit the behavioral effects were likely too low to be associated with significant inhibition of PDEs (Burg, 1975; Carrillo & Benitez, 2000; Daly, 1993; Evripioti et al., 2019; Magkos & Kavouras, 2005; Rohrig et al., 2017; Sawynok & Yaksh, 1993).

Based on these observations, it is unlikely for caffeine to exhibit intracellular PDE inhibition, except for situations in which very high, extremely toxic, and perhaps fatal dosages have been consumed. It is important to mention that PDEs show different expression levels under certain pathological conditions. For example, high PDE5 and PDE10 expression levels were reported in adenocarcinomas and colon adenomas by comparison to normal colonic mucosa (Lee et al., 2016; Mehta & Patel, 2019). Meanwhile, caffeine is also advocated for the inhibition of colorectal cancer proliferation by increasing the intracellular concentrations of cAMP and cGMP via PDEs inhibition (Orban et al., 2018); the putative mechanism is depicted in Figure 5. Hence, further studies may be required to decipher the physiological consequences of acute doses of caffeine consumption on different types of PDE activities.

3.2.3 | Phosphatidylinositol 3-kinase inhibitor

The phosphatidylinositol 3-kinase or phosphoinositide 3-kinases (PI3Ks), belongs to a unique family of lipid kinases that catalyze the phosphorylation of the inositol ring at the 3′-hydroxyl group to produce phosphatidylinositol 3-phosphate (PIP), phosphatidylinositol (3,4)-bisphosphate (PIP2), and phosphatidylinositol (3,4,5)-trisphosphate (PIP3; Andrs et al., 2015; Vanhaesebroeck et al., 2001). The PI3Ks comprise three classes, that is, I, II, and III, and essentially participate in various cellular processes, as reviewed elsewhere (Andrs

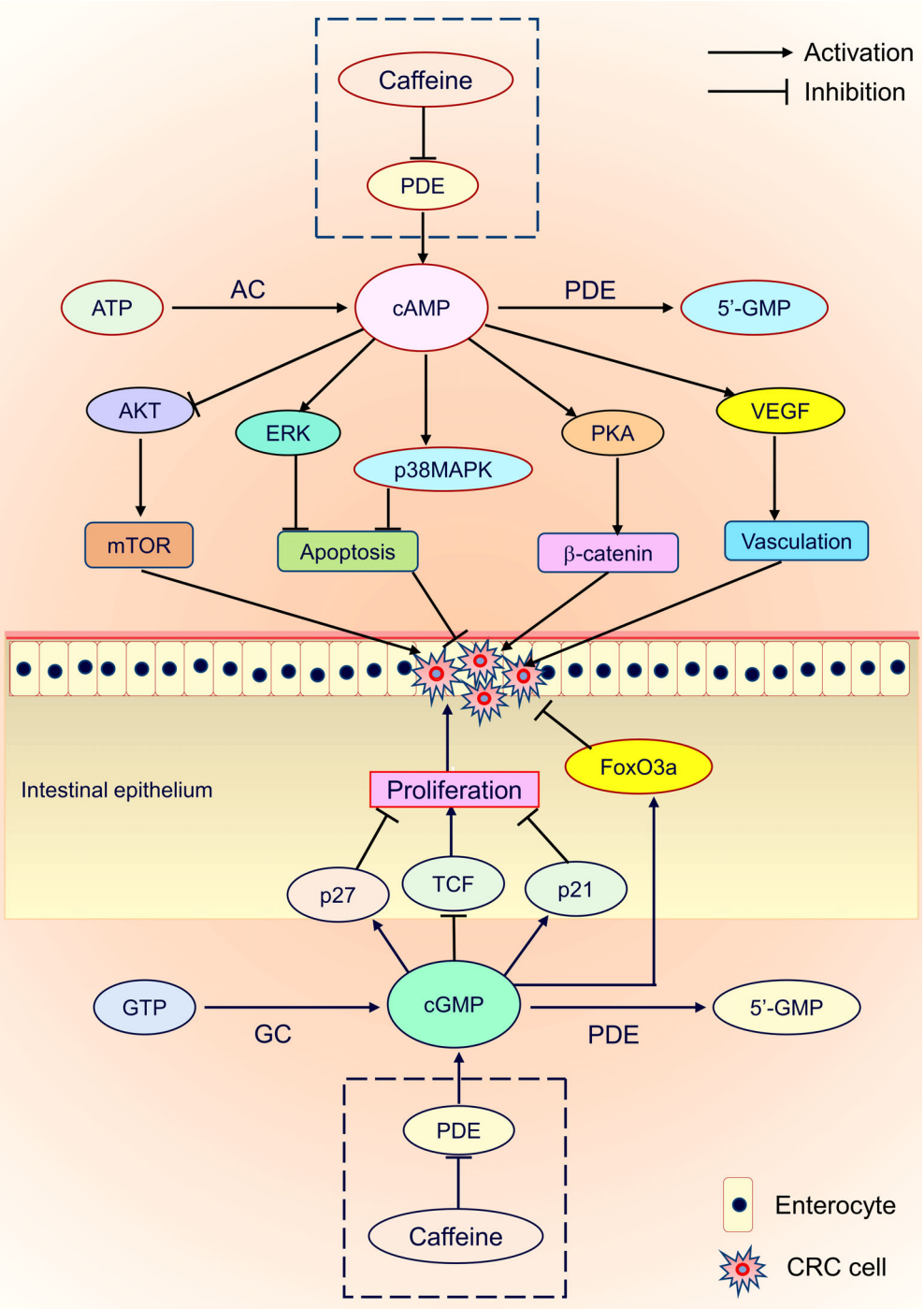

FIGURE 5 Scheme for the inhibitory activity of phosphodiesterases (PDEs) by caffeine, resulting in the accumulation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels. Typically, the intracellular concentration of cAMP and cGMP is modulated by the action of two types of enzymes, that is, adenylate cyclase/guanylyl cyclase as generating enzymes and PDEs as degrading enzymes. Caffeine can cause significant inhibition of PDEs, resulting in the accumulation of cAMP and cGMP, which further interact with several factors and may cause a chain of events in colorectal cancer cells.

et al., 2015; Liu et al., 2009; Yang et al., 2019). Among all the known classes, the Class 1 PI3Ks can be further characterized into Class I_A and Class 1_B subclasses based on the form of the adaptor subunits (Vanhaesebroeck & Waterfield, 1999). For instance, Class I_A, comprising catalytic subunits p110α, p110β, and p110δ along with bind adaptor subunits p85α and p85β, has been related to the growth factor tyrosine kinase receptors (Andrs et al., 2015). Besides, the expression and activity of PI3Ks are scrutinized and modulated by internal signals, such as PTEN (phosphatase and tensin homolog deleted from chromosome 10), under normal conditions, but deregulation of these proteins has been recognized in one third of human cancer development (Arteaga, 2010; Shaw & Cantley, 2006). Of note, the activation of PI3Ks results in the production of PIP3 in the membrane, which further serves as a second messenger and triggers the activation of other targets via phosphorylation, such as protein kinase B (Akt; Nicholson & Anderson, 2002). Consequently, the interaction of Akt with other downstream target molecules results in the initiation of cancer-relevant events, including cell proliferation, growth, and immortalization (Coffer et al., 1998; Downward, 1998). Hence, aberrant activation of the PI3Ks pathway has been associated with the

onset of carcinogenesis and tumor angiogenesis (Osaki et al., 2004; Slomovitz & Coleman, 2012).

Interestingly, caffeine can inhibit Classes I and II PI3Ks. Accordingly, caffeine has been demonstrated to inhibit Class I_A PI3K different domains, that is, PI3K p110α (IC_{50}, 0.4 mM), PI3K p110β (IC_{50}, 0.4 mM), PI3K p110γ (IC_{50}, 1.0 mM), and PI3K p110δ (IC_{50}, 0.075 mM), and Class II PI3K α isoform, that is, PI3K-C2α with IC_{50}, ≈0.4 mM (Foukas et al., 2002). Furthermore, these inhibitory actions of caffeine were shown to provide cytoprotective effects by PI3K/Akt pathway activation in a Parkinson's disease (PD) model of SH-SY5Y cells (Nakaso et al., 2008). Likewise, as PI3K/Akt/mTOR signaling is regulated by PTEN in cancer, caffeine was reported to activate tumor suppressor PTEN by accumulating intracellular cAMP concentration, which results in inhibition of PI3Ks stimulatory effects and induces apoptosis in sarcoma cells (Miwa et al., 2011). In another study, the inhibition of PI3Ks, particularly that of the p110α isoform, by therapeutic doses of caffeine was associated with prothrombotic activity (Gebhard et al., 2012).

In conclusion, PI3Ks are attractive therapeutic targets for the management of cancer, while caffeine can be used to study the inhibitory effect on Class III and other isotypes of PI3Ks. Also, in the last few years, other small molecules have been reported as PI3Ks inhibitors and studied in clinical trials, as reviewed elsewhere (Akinleye et al., 2013; Curigliano & Shah, 2019; Lo et al., 2023; Roskoski, 2021). Thus, future preclinical and clinical studies combining novel small molecule inhibitors of PI3Ks with caffeine may improve the synergistic effect or therapeutic efficacy of cancer treatment or other PI3Ks-linked diseases in humans.

3.2.4 | Phosphatidylinositol 3-kinase-related kinases inhibitor

Phosphatidylinositol 3-kinase-related kinases (PIKKs) are a group of six atypical serine/threonine protein kinases, including ataxia telangiectasia mutated (ATM), ataxia telangiectasia and RAD3 related (ATR), DNA-dependent protein kinase (DNA-PK), human suppressor of morphogenesis in genitalia 1 (hSMG-1), transformation/transcription-associated protein (TRRAP), and mammalian target of rapamycin (mTOR), as reviewed elsewhere (Hill & Lee, 2010; Shiloh & Ziv, 2013; Smith & Jackson, 2003).

ATM and ATR protein kinases are typically engaged and triggered by the double-strand breaks (DSB) in DNA to perform the phosphorylation of several key substrates or proteins participating in DNA damage responses, including instigate the DNA damage checkpoint activation, leading to cell cycle arrest, DNA repair, or apoptosis (Matsuoka et al., 2007; Paull, 2015; Tichý et al., 2010). However, mutations in ATM can cause an inherited cancer-predisposition syndrome named Ataxia-telangiectasia (Savitsky et al., 1995) and a hypomorphic mutation in the ATR gene was proven to cause Seckel syndrome (O'Driscoll et al., 2003). Based on the available evidence, caffeine has been extensively used to study ATM and ATR signaling due to its inhibitory action on these kinases under in vitro conditions and saturation of cell cycle checkpoint responses under in vivo studies with an IC_{50} value of 0.2 and 1.1 mM, respectively (Sarkaria et al., 1999). In the same study, 50% of either ATM- or ATR-dependent substrate phosphorylation inhibition was recorded for caffeine at 1 or 3 mM concentrations, respectively (Sarkaria et al., 1999). Also, caffeine was shown to silence several ATM and/or ATR-dependent cell cycle checkpoints stimulated by infrared (IR) and ultraviolet (UV) rays (Kaufmann et al., 2003). In contrast, another study demonstrated the inhibition of cell cycle checkpoints by caffeine without blocking the ATM and/or ATR signaling pathways (Cortez, 2003). In fact, caffeine was marked for enhanced ATM autophosphorylation in cells when combined with replication inhibitors, suggesting no inhibitory effect of caffeine on the activation of ATM in the in vivo study (Cortez, 2003). In another report, caffeine was advocated to inhibit several ATM-ATR-dependent cell cycle checkpoint responses, such as the G2/M- and S-phase checkpoints (Cortez, 2003; Lau & Pardee, 1982; Rowley, 1992; Schlegel & Pardee, 1986). Collectively, the functional activity of caffeine to overcome the checkpoints was suggested due to its ability to counteract the phosphorylation of substrates used in ATM and ATR protein kinases (Figure 6).

DNA-PK is a holoenzyme consisting of the catalytic subunit of DNA-dependent protein kinases (DNA-PKcs), and this complex has been characterized for its substantial role in the nonhomologous end joining (NHEJ) phenomenon, the principal process utilized to repair DSB in mammals (Gottlieb & Jackson, 1993; Ma et al., 2002). For example, DNA-PKcs are involved in detecting and transmitting signals of DNA damage to proteins, such as p53, which sets off processes that cause cell cycle arrest (Anderson, 1993; Hoekstra, 1997), and phosphorylates a variety of substrates, including Ku70/Ku80, which translocate along the DNA (Yoo & Dynan, 1999). Notably, caffeine was proven to be as an efficient inhibitor of DNA-PK and only moderately inhibits DNA-PK autophosphorylation under in vitro conditions (Block et al., 2004). Furthermore, caffeine has been elucidated to block DNA-PK through a mixed noncompetitive mechanism with respect to ATP, suggesting caffeine can bind, but with varied affinity, to both DNA-PK and DNA-PK–ATP complexes (Block et al., 2004). Accordingly, caffeine has been established to inhibit the purified DNA-PK and DNA-PK-ATP with an IC_{50} value of 0.2–0.6 mM (Block et al., 2004).

Furthermore, hSMG-1 is characterized for its functional role in the regulation of cell cycle checkpoints in response to IR and UV irradiation (Brumbaugh et al., 2004). Also, hSMG-1 expression was associated with optimal p53 activation in human cells after exposure to genotoxic stress, while hSMG-1 mutant cells were observed to have spontaneous DNA damage and intensified sensitivity to IR (Brumbaugh et al., 2004). Previously, hSMG-1 activity was associated with components of the mRNA surveillance complex and found to modulate nonsense-mediated mRNA decay (Yamashita et al., 2001). Interestingly, caffeine was noted to inhibit the kinase activity of hSMG-1 in vitro with an IC_{50} value of ∼0.3 mM (Yamashita et al., 2001). However, the physiological or adverse effects of caffeine antagonism with hSMG-1 under in vitro or in vivo conditions are not yet elucidated.

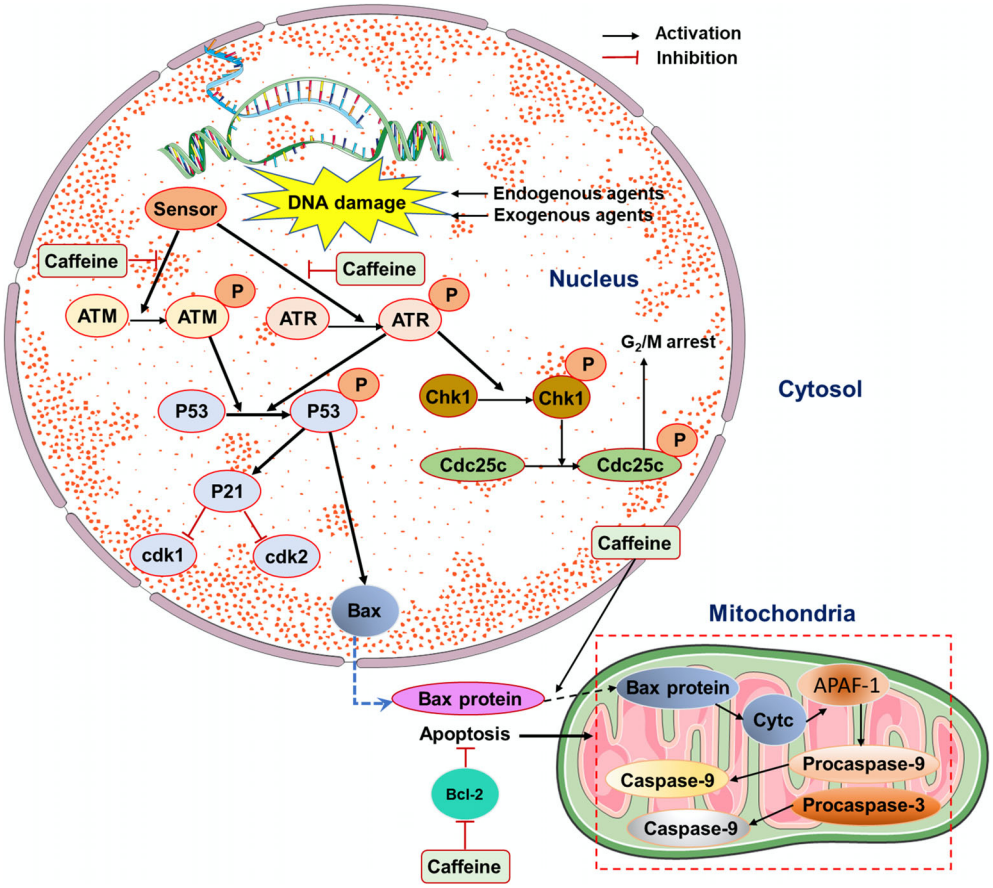

FIGURE 6 Scheme for the molecular impact of caffeine on the DNA repair process. This mechanism involved the phosphorylation of Rad3-related and ATM proteins when a sensor recognized the DNA damage. AT and Rad3-related as well as ATM activation can both be inhibited by caffeine. AT, Rad3-related ataxia telangiectasia, and ATM phosphorylation activated CDK1 culminates in G2/M arrest and p53, further contributed to modification of p21, a downstream target, which influence the cell cycle by blocking CDK1 and CDK2. Bax potentially started the apoptotic process when it entered the cytosol because it is downstream of p53. Caffeine promotes apoptosis by blocking the Bax transportation to the mitochondria from the nucleus and inhibiting the apoptosis inhibitor Bcl-2 (Cui et al., 2020; Zhao, Wu, Zhang, & Zhu, 2013).

Moreover, TRRAP, which possesses no kinase activity, is deciphered as an essential component of several histone acetyltransferase complexes and functionally contributes to the epigenetic regulation of transcription (Lempiainen & Halazonetis, 2009). Even so, the interaction or binding of caffeine with TRRAP has not yet been reported. Besides, mTOR, which forms structurally and functionally two distinct complexes, named mTORC1 and mTORC2, has been reported as a key factor in the regulation of cell proliferation, autophagy, apoptosis, cancer, arthritis, insulin resistance, osteoporosis, and other diseases, as discussed elsewhere (Foster & Fingar, 2010; Laplante & Sabatini, 2009; Liu & Sabatini, 2020; Zou et al., 2020). Of note, caffeine was found to inhibit mTOR with an IC_{50} value of 0.4 mM (Foukas et al., 2002). Moreover, high concentrations of caffeine, that is, 5 and 10 mM, were established to inhibit the mTOR pathway in various cell lines, including HOS osteosarcoma cells, SH-SY5Y neuroblastoma cells, and HeLa cells (Miwa et al., 2012; Xie et al., 2011). Therefore, both direct and indirect inhibition of mTOR by caffeine can be concluded from the available literature.

Taken together, caffeine exhibits diverse inhibitory potential against different members of the PIKK family, while some studies even contradict their inhibition under in vivo conditions. Thus, new strategies can be adopted to decipher the caffeine inhibitory potential against different members of PIKK; for instance, a proteomic analysis may be able to provide an understanding of caffeine antagonism among PIKK's members. Also, as several substrates of ATM, ATR, and DNA-PK are known, the inhibitory potential or autophosphorylation action of caffeine on respective substrates can be studied to validate its functional activity against PIKK's members.

3.2.5 | Glycogen phosphorylase inhibitor

The glycogen phosphorylase (GP) enzyme is characterized for its ability to mediate the digestion of glucose-1-phosphate from glycogen and regulate the release of glucose from the liver (Thomson et al., 2009). Thus, it is studied as a potential therapeutic target for the management of type 2 diabetes and related disorders (Hayes et al., 2014; Oikonomakos, 2002). Interestingly, the human liver phosphorylated glycogen phosphorylase (HLGPb), a prime receptor for the identification of GP inhibitors, is allosterically controlled by the binding of effector molecules and through phosphorylation of the Ser14 residue, both of which stimulate conformational switching in the protein (Madsen et al., 1986; Newgard et al., 1989). Though HLGPb has a minimal functional role, it can be mildly stimulated by AMP. Additionally, the human liver unphosphorylated glycogen phosphorylase (HLGPa) can assume either an active or inactive conformation. Notably, AMP binding and Ser14 phosphorylation stabilized the active conformation, while dephosphorylation, glucose, and the binding of heterocyclic substances stabilized the inactive conformation of HLGPa (Madsen et al., 1986; Newgard et al., 1989).

Caffeine has been characterized as an allosteric modulator of both HLGPa and HLGPb enzymes in humans. For instance, Martin et al. (1998), who evaluated caffeine against HLGPa, obtained an IC_{50} value of 240 μM. In accordance with the IC_{50}, caffeine was also noted with a K_d value of 108 ± 10 μM with HLGPa using surface plasmon resonance (SPR) spectroscopy (Ekstrom et al., 2002). Likewise, caffeine was elucidated to bind at the purine nucleoside-inhibitor site of the HLGPb and marked as the first inhibitor with a K_i value of ~0.1 mM (Madsen et al., 1983; Oikonomakos et al., 2000; Sprang et al., 1982). Correspondingly, caffeine is demonstrated to interact with the inhibitor site of the HLGPb and promote a reduction in the catalytic activity, which synergistically depends on the physiological glucose concentration (Henke & Sparks, 2006; Jakobs et al., 2006; Kasvinsky et al., 1981; Rath et al., 2000; Rocha et al., 2021).

Taking into consideration that caffeine can inhibit both the HLGPa and HLGPb, as well as that the inhibitory potential is affected by the glucose concentration, the therapeutic potency of caffeine as an active pharmacological agent could be structured to comprehend its physiological effect on hepatic glycogenolysis and lower or higher plasma glucose concentrations in type 2 diabetic patients.

3.2.6 | Notum inhibitor

The Wnt signaling pathway is one of the essential biochemical reactions that contribute to the regulation of cellular functions during embryonic development and tissue homoeostasis in adults (Clevers & Nusse, 2012). Notum, an extracellular carboxylesterase enzyme, was recently identified as an important feedback suppressor of Wnt signaling in humans (Kakugawa et al., 2015). Of note, Notum can block Wnt signaling by removing the palmitoleate moiety from Wnt proteins, which is essential in producing the Wnt-Frizzled complex and subsequent signal transduction cassettes (Janda et al., 2012; Kakugawa et al., 2015). A recent study suggested that enhanced Notum expression can stimulate biological aging while its inhibition prompts stem cell rejuvenation (Pentinmikko et al., 2019). In addition, Notum is also reported to substantially influence adult ventricular–subventricular zone neurogenesis (Mizrak et al., 2020).

Experimental studies have supported caffeine as an inhibitor of the Notum enzyme, with a K_d value of 85 μM predicted using SPR measurements (Zhao et al., 2020). In the same study, caffeine exhibited substantial inhibitory potential against purified Notum with an IC_{50} value of 19 μM and restored the Wnt signaling pathway in cellular luciferase assays at an effective concentration (EC_{50}) of 46 μM (Zhao, Ren, et al., 2020). Collectively, based on the available experimental data, therapeutic doses of caffeine may be used to inhibit Notum activity under physiological conditions. In this context, available high-resolution (1.53 Å) crystallized structures of Notum–caffeine complexes have been suggested to collect structural information for the design of highly selective Notum inhibitors for medical applications (Zhao, Ren, et al., 2020). In summary, as therapeutic doses of caffeine can be used to inhibit Notum activity, the available high-resolution Notum–caffeine complexes could be applied in the design and development of caffeine derivatives as potent Notum inhibitors.

4 | ORGAN-SPECIFIC PHYSIOLOGICAL CONSEQUENCES OF CAFFEINE

Caffeine, which belongs to the methylxanthines family, exhibits dose-dependent desirable effects at lower doses (≤400 mg), but shows adverse effects and health issues across multiple organ systems at concentrations higher than this dose of ingestion (Lopes et al., 2019; Shan et al., 2022). Thus, several mechanisms have been suggested for the caffeine pharmacological impact on various organs and systems, including antioxidant and anti-inflammatory activities; some of the elucidated mechanisms or pathways adopted by caffeine to exhibit therapeutic potency in different diseases of the same organ via different receptors or pathways are also briefed in Table 2.

Based on the available literature, caffeine has been concluded to exhibit varied physiological effects among individuals (Smith, 2002; Turnbull et al., 2016). In this context, lower concentrations of caffeine are reported to have desirable effects such as anti-inflammation functions, antiapoptosis activities, free radical-scavenging capabilities, and antioxidant functions (Kumar & Lipshultz, 2019; Shrestha & Jawa, 2017). Meanwhile, 250 mg of caffeine consumption has been stated to increase alertness, arousal, and well-being (e.g., enhanced ecstasy, pleasantness, and peacefulness) in humans (Kaplan et al., 1997; Smith, 2002). Similarly, more than 500 mg of caffeine ingestion are demonstrated to raise anxiety, excitement, nervousness, tension, irritability, tremor, nausea, restlessness, paresthesia, palpitations, perspiration, and possibly dizziness in humans (Kaplan et al., 1997). In other studies, sublethal doses (~7–10 mg/kg) of caffeine are predicted to induce varied symptoms in adults, where an individual may show symptoms such as chills, tremor, headache, palpitations, flushing, and nausea (Bonati et al., 1982; Kaplan et al., 1997; Nardi et al., 2009; Turnbull et al., 2016). Likewise, lethal doses of caffeine are described to stimulate apoptosis by several pathways, such as cell cycle modulation via p53 and caspase pathways (Bode & Dong, 2007; He et al., 2003), apoptosis via caspase-dependent apoptosis (Kuwayama, 2012), or induction of autophagy via the PI3K/Akt/mTOR pathway (Saiki et al., 2011). However, despite adverse effects, habitual caffeine consumption has shown no association with health risks, such as high blood pressure, and has been linked with the development of tolerance to the cardiovascular effects of caffeine over time (Guessous et al., 2014; Zhang et al., 2011). Additionally, some studies have associated caffeine ingestion or coffee as a source of caffeine with the promotion or suppression of tumors, depending on the phase of administration, reviewed elsewhere (Ismail et al., 2021; Nkondjock, 2009; Pauwels & Volterrani, 2021; World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), 2007; Zhao et al., 2020); the activity of coffee as a source of caffeine or caffeine tested on different types of cancers is summarized in Table 3.

TABLE 2 List of organ-/system-specific diseases or disorders studied in relevance to the different concentrations of caffeine and its consequences via direct or indirect interactions with respective biomolecules or pathways.

Organ/system	Disease/disorder	Model organism	Mechanism	Consequences	Reference
Nervous system	Alzheimer's disease (AD)	Human	Decreases Aβ generation, ARs activation, antioxidant activity	Deceases risk of AD	(Gramling et al., 2018; Konishi et al., 2018; Richards & Smith, 2015)
	Parkinson's disease (PD)	Animal (rats), NES cell line AF22, C57BL/6 mice	ARs activation, Cytoprotective effect via PI3K/Akt pathway activation, restores endogenous antioxidant levels and suppresses neuroinflammation	Decease risk of PD	(Holtzman et al., 1991; Karuppagounder et al., 2021; Lashley et al., 2018; Yu et al., 2017)
	Multiple sclerosis (MS)	Animal (C57BL/6 mice)	Reduces the NLRP3 inflammasome activation via the induction of autophagy in microglia	Attenuate autoimmune encephalomyelitis in MS	(Wang et al., 2022)
	Huntington's disease	Human	Unknown	Increase risk of disease	(Ritchie et al., 2007; Simonin et al., 2013)
	Depression	Human	ARs antagonism	Reduced risk of disease	(Hedstrom et al., 2016; Lucas et al., 2011; Richards & Smith, 2015)
	Mood	Animal (rat), human	Antagonism of ARs, AChE inhibition, RyRs alternation	Stimulation at low doses elevate restlessness, excitement, tremor, tinnitus, headache, and insomnia at high doses as well as enhance anxiety	(The International Agency for Research on Cancer (Author), 1991; Bertasi et al., 2021; Hedstrom et al., 2016; Kong et al., 2008; Nawrot et al., 2003; Zampelas et al., 2004)
Eye	Glaucoma	Animal (albino rats)	Blockade of A_{2A}AR causes decrease in retinal neuroinflammation and microglial reactivity	Deceases risk of glaucoma	(Madeira et al., 2016)
Circulatory system	Arrhythmia	Human	Blocking of ARs (mainly subtypes A_1AR and A_2AR) results in enhanced dopamine and noradrenalin, decrease PDEs activity, and increase the cAMP levels	Increase the risk of tachycardia and arrhythmia	(Rodak et al., 2021)
	Bradycardia	Human	Increase intracellular calcium concentrations, release norepinephrine and sensitization of dopamine receptors	Increase arterial pressure and decrease heart rate	(Rodak et al., 2021)

(Continues)

TABLE 2 (Continued)

Organ/system	Disease/disorder	Model organism	Mechanism	Consequences	Reference
	Coronary heart disease (CHD)/acute myocardial infarction (AMI)	Human	Unknown	Protective effect against CHD or AMI	(Gans et al., 2010; Kokubo et al., 2013; Leurs et al., 2010; Miller et al., 2017; Sessoet al., 1999)
Liver	High-fat diet (HFD)-induced hepatic steatosis	Animal (rats)	Decreased the elevated serum ALT, AST, and bilirubin. Decreased the hepatic mRNA expression of fatty acid synthase and acetyl CoA carboxylase Increased the reduced albumin level. Increased the hepatic carnitine palmitoyltransferase 1 and proliferation-activated receptor α expression Regulated hepatic de novo lipogenesis and β-oxidation	Improve HFD-induced hepatic injury	(Helal et al., 2018)
	Nonalcoholic steatohepatitis (NASH)	Animal (rats)	Increased Nrf2 level, attenuated oxidative stress markers, including malondialdehyde and 4-hydroxynonenal, restored normal, reduced glutathione levels, reduced NF-κB activation Reduced inflammatory cytokine level, modulation of the MAPK and TGF-β signaling pathways and reduced HSC activation. Reduced the NLRP3 protein level, NLRP3 inflammasome activation, and TLR4/MAPK/NF-κB signaling pathways	Decrease liver damage in NASH	(Vargas-Pozada et al., 2023)
	Alcohol-induced liver disease (ALD)	Animal (rat alcoholic liver fibrosis)	Blocked the cAMP/PKA/CREB signal pathway through adenosine A_{2A}A receptors in HSC	Protective effects against ALD	(Eltzschig et al., 2012; Wang et al., 2015)
	Cirrhosis	Animal (Wistar rats)	Elicit antioxidant properties and inhibits the elevation of the profibrogenic	Attenuation of the inflammatory and cirrhosis	(Arauz et al., 2014)

TABLE 2 (Continued)

Organ/system	Disease/disorder	Model organism	Mechanism	Consequences	Reference
			cytokine transforming growth factor-β		
	Fibrosis	Human hepatic stellate cell line, animal (Wistar rats)	Directly inhibits hepatic stellate cells (HSC) adhesion and activation mediated through inhibition of focal adhesion kinase and Actin synthesis, stimulation of HSC apoptosis, induction of intracellular F-actin and cAMP expression, and inhibition of procollagen type 1C and alpha-smooth muscle actin expression Inhibits the transcriptional factor Snail-1, downregulating profibrogenic genes, and activates Nrf2 inducing antioxidant enzymes system	Attenuates inflammation and fibrosis	(Gordillo-Bastidas et al., 2013; Shim et al., 2013)
	Acute liver injury	Animal (acute liver injury model: mice)	Induced the expression of NEDD4L and deceased the GRP78 level via ubiquitination	Mitigates the acute liver injury	(Hu et al., 2022)
Lung	Bronchopulmonary dysplasia	Animal (C57Bl/6 mice), preterm infants	Modulate TGF-β signaling, hypoxia-inducible factors regulation	Protecting the lung from hyperoxia-induced lung injury	(Abramson et al., 2017; Dumpa et al., 2019)
Pancreas	Acute pancreatitis	Pancreatic acinar cells Rat/mice model	Induced A_1AR and A_3AR inhibition while A_{2A}AR and A_{2B}AR excitatory function, which are mediated in part by changes in cAMP Reduced pathological IP_3R-mediated pancreatic acinar Ca^{2+} signals in isolated pancreatic acinar cells	Provides protective effects or while ameliorated experimental AP	(Burnstock & Novak, 2012; Huang et al., 2017)
Urinary System	Chronic kidney disease	Cell lines (Baby hamster kidney [HK-21] fibroblast cell line [ATCC, Manassas, VA])	Inhibits hypoxia-induced renal fibroblast activation by its antioxidant property to eliminate intracellular ROS, at least in part, via	Prevent renal fibrosis	(Nilnumkhum et al., 2019)

(Continues)

TABLE 2 (Continued)

Organ/system	Disease/disorder	Model organism	Mechanism	Consequences	Reference
			downstream catalase and Nrf2 mechanisms		
	Kidney stones	Cell lines (Baby hamster kidney [BHK-21] fibroblast cell line [ATCC, Manassas, VA])	Decreases the formation of calcium oxalate monohydrate, decreases the annexin A_1AR	Decreases the risk for stone formation	36
	Urinary tract	Human	Increases rate of glomerular filtration, vasoconstriction of renal afferent arteriole mediated by adenosine via A_1AR during tubuloglomerular feedback	Increase urine production; at high dose Increase risk for urgency incontinence	(Rodak et al., 2021; Wu & Chen, 2020)
Skin	Oxidative stress-induced senescence	Animal (C57BL/6 mice)	A_{2A}R/SIRT3/AMPK-mediated autophagy activation	Protective effects against skin diseases	(Li et al., 2018)
Musculoskeletal system	Function and strength	Human, animal (rat L6 cell line)	ARs antagonism, opening RyRs channel in muscles and myocytes; Ca^{2+} and cAMP/PKA pathway activation, increase in glucose uptake, increase in fat oxidation, and increase mitochondrial biogenesis in skeletal muscle cells	Decrease pain perception, increase sports performance, increase mechanical activity of skeletal muscle	(Domaszewski et al., 2021; Yokokawa et al., 2021)
Immune system	Various cells of the immune system	Human, animal (mice)	Antagonist of the AR receptor and an agonist of TAS2R receptors	Immunomodulatory and bronchodilatory effects, decrease proinflammatory activity	(Romero-Martínez et al., 2021)

Abbreviations: AChE, acetylcholinesterase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cAMP, cyclic adenosine monophosphate; NF-κB, nuclear factor kappa B; PDEs, phosphodiesterases; ROS, reactive oxygen species; RyRs, ryanodine receptors; TGF-β, transforming growth factor-β.

Notably, the use of caffeine as a pharmacologic A_{2A}AR antagonist to promote an antitumor immune response during tumor initiation has been suggested to prevent cancer development (Eini et al., 2015), while A_{2B}AR inhibition by caffeine has been verified to have anticancer effects in animal research (Merighi et al., 2007). Additionally, it is important to mention that questionable hepatic injuries are reported in humans, ranging from secondary to rhabdomyolysis and renal failure after acute doses of caffeine consumption (Campana et al., 2014; Chiang et al., 2014). Caffeine has been also deciphered to elicit thermogenic lipolytic effects, that is, causing an oxidation of fat in adipocytes as well as the delivery of glycerol and fatty acids to the bloodstream (Carrageta et al., 2018; Dulloo, 2011). Another study marked caffeine for the modulation of lipogenic gene expression to suppress lipid accumulation and body weight gain (Zapata et al., 2020). The functional activity of caffeine is associated with an increase in energy expenditure and is noted to promote weight loss when combined with calorie-restricting diets and physical exercise (Davoodi et al., 2014; Schubert et al., 2014). For instance, intraperitoneal administration of caffeine was reported to enhance the production of uncoupling protein-1 (UCP-1) in brown adipose tissue, which further elicits enhanced energy expenditure (Kogure et al., 2002). Apart from the mentioned mechanisms, caffeine can cause an increase in catecholamine concentration, which may be used to explain at least some of the caffeine-induced physiological effects (Carrillo & Benitez, 2000; Mandel, 2002; Shi et al., 1993). Collectively, the typical physiological effects linked with caffeine ingestion may vary amongst individuals, but a large number of side effects are commonly observed upon caffeine intoxication, including cardiovascular symptoms,

TABLE 3 Effect of caffeine on various organ-specific cancer/tumor has been reported using both in vitro and animal model.

Cancer/tumor	Mechanism	Model organism	Consequences	Reference
Glioblastoma multiforme (GBM)	Reduces the expression of MMP-2 and MMP-9 proteins	Human (U-87MG and LN229 glioblastoma cell lines)	Decrease the risk of GBM	(Cheng et al., 2016)
Glioblastoma	Inhibition of calcium release channel inositol 1,4,5-trisphosphate receptor (IP3R) subtype	Human	Inhibit the glioblastoma invasion	(Kang et al., 2010)
Breast cancer	Inhibition of malignant transformation of mammary epithelial cells, inhibition of conversion of dormant tumor cells to micrometastases, micrometastases to macrometastases, or inhibition of tumor cell adhesion and motility. And upregulation the mRNA expression of multiple extracellular matrix genes Reduced ER and cyclin D1 abundance in ER+ cells while reduced the insulin-like growth factor-I receptor (IGFIR) and pAkt levels in both ER^+ and ER^- cells	Animal (mouse), human	Suppress tumor cell invasiveness and metastasis Impaired cell-cycle progression and enhanced cell death	(Rosendahl et al., 2015; Yang et al., 2004)
Lung cancer	Induces G0/G1 cell cycle arrest and downregulation of integrin αv, β3, and FAK/Akt/c-Myc signaling pathway	Human (lung cancer cell lines [NCI-H23], Human primary lung cancer cells [MLC15])	Inhibit cell proliferation, suppresses lung cancer stem cell (CSC)-like properties, reduce filopodia formation, inhibit migration and invasion capability, and reduce the ability of cancer cells to survive and grow in an anchorage-independent manner	(Meisaprow et al., 2021)
Gastric cancer	Activation the caspase-9/-3 pathway	Human (gastric cancer cell lines MGC-803, SGC-7901 [well-differentiated gastric cancer cell line] and GES-1 [human gastric mucosa epithelial cells])	Suppressed GC cell growth and viability and induced apoptosis	(Liu et al., 2017)
Hepatocellular carcinoma (HCC)	Inhibits Akt (also known as protein kinase B) signaling pathway	Human (HCC cell lines HepG2 and Huh7)	Suppress the proliferation, migration, and invasion of HCC	(Dong et al., 2015)
Pancreatic adenocarcinoma	Decreased inflammation marker, such as the level of IL-18, c-reactive protein, and E- selectin; inhibit the activation of nuclear factor kappa B (NF-κB); induce apoptosis	Human	High doses lower the risk of Pancreatic cancer	(Ran et al., 2016)
Colorectal cancer	Activates the DNA repair process, promote apoptosis by inhibiting the translocation of Bax from the nucleus to the mitochondria, promoting the apoptosis inhibitor Bcl-2	Human	Reduce the risk of colorectal cancer	(Cui et al., 2020; Um et al., 2020)

(Continues)

TABLE 3 (Continued)

Cancer/tumor	Mechanism	Model organism	Consequences	Reference
Colon cancer	Inhibits the A_3AR-stimulated cancer cell migration, inhibits the extracellular signal-regulated kinase 1/2 (ERK1/2), p38, and Akt, resulting in reduced adenosine-induced HIF-1α accumulation, VEGF transcriptional activation, and VEGF and IL-8 protein accumulation.	Human (cell line HT29)	Inhibit colon cancer cell growth	(Merighi et al., 2007b)
Bladder cancer	Inhibit G6PDH activity and reduced redox homeostasis	Human and human prostate cancer cell lines	Contradictory results as reported to Inhibit or increase risk of renal cell carcinoma tumor growth/ bladder cancer.	(Wu et al., 2015; Xu et al., 2020)
Prostate cancer	A_{2B}AR antagonism	PC-3 and DU145 cell lines	Antiproliferative and antimetastatic activity	(Pounis et al., 2017)
Osteosarcoma	Inhibition of AKT/mTOR/S6K, NF-κB and MAPK pathways	Human (HOS human osteosarcoma cell line)	Induces apoptosis of osteosarcoma cell	(Miwa et al., 2012)

gastrointestinal symptoms, psychological/neurological symptoms, metabolic symptoms, musculoskeletal symptoms, pulmonary symptoms, tinnitus, dizziness, diuresis, and even death, as detailed and reviewed elsewhere (Banerjee et al., 2014; Bioh et al., 2013; Bonsignore et al., 2014; Davies et al., 2012; Forman et al., 1997; Jabbar & Hanly, 2013; Kerrigan & Lindsey, 2005; Rudolph & Knudsen, 2010; Willson, 2018).

Based on the above-discussed literature for the molecular receptors or biomolecules targeted by caffeine, it can be concluded that caffeine exhibits a multidirectional influence on various organs of the human body. Also, immense literature has been reviewed on the behavioral effects of caffeine (Frigerio et al., 2021; Gardiner et al., 2023; James, 2014; Reichert et al., 2022), pharmaceutical applications of caffeine in neurodegenerative diseases (Kolahdouzan & Hamadeh, 2017; Lu'o'ng & Nguyen, 2015; Pohanka, 2022; Rivera-Oliver & Diaz-Rios, 2014) and toxicity at higher concentrations (Beauchamp et al., 2017; Musgrave et al., 2016; Turnbull et al., 2016; Willson, 2018), thus, we have restricted our following section in the review to key aspects of the manifested physiological effects of caffeine on human organs widely studied in the literature. Additionally, we have also summarized the physiological effects or changes induced by caffeine as an antagonist or agonist of the above-mentioned molecular targets in different organs and systems as well as in related disorders in the human body.

4.1 | Caffeine's effects on brain function and performance

The BBB is a selective barrier, founded by endothelial tight junctions, astrocytes, and pericytes, that mediates the exchange of substances between the blood–brain and retains a constant microenvironment (Abbott et al., 2010). As BBB has proven to significantly participate in cerebrovascular and cell signaling systems, recent animal experimental studies have linked the beneficial effects of caffeine on BBB in neurodegenerative diseases. For example, chronic exposure to caffeine is noted to upregulate the activation of ARs on endothelial cells, which further causes an increment in the cAMP level and provides protection to the BBB (Chen et al., 2008; Chen et al., 2010; Chen et al., 2008; Folcik et al., 1999). Another study suggested that caffeine can modulate BBB permeability via blockage of ARs, inhibition of cAMP-PDEs activity, and regulation of Ca^{2+} release from intracellular spaces (Chen et al., 2010). In contrast, acute caffeine consumption causes an increase in ARs expression on endothelial cells, which further promotes enhanced cAMP production and shields the BBB against damage (Chen et al., 2010; Lin et al., 2022).

As caffeine shares structural similarity with adenosine (Figure 1), it is established that it passes through the BBB to elicit an effect on both the CNS and PNS. Accordingly, caffeine has been suggested to cause an alteration in the brain's metabolic rate by blocking both excitatory and inhibitory neurons (Merola et al., 2017). However, several studies have documented contradictory results on the functional role of caffeine, including suppression (Merola et al., 2017; Park et al., 2014), enhancement (Griffeth et al., 2011), or even no alteration (Xu et al., 2015) on the metabolism of the brain. Besides, evidence collected using physiological parameters, such as oxygen extraction fraction and cerebral blood flow, suggests that caffeine has a localized effect on the striatum (Merola et al., 2017; Vidyasagar et al., 2013). Other studies suggest that caffeine can improve focused attention and elevate activities in the brain via an indirect effect on dopamine (Deslandes et al., 2005; Jones, 2008; Smith et al., 2003). Meanwhile, caffeine is characterized by its ability to elicit protection against

oxidative stress, inhibit excitotoxicity, downregulate neuroinflammatory cytokine release, reduce hippocampal injury, and encourage brain-derived neurotrophic factor (BDNF) levels (Costa et al., 2008; Laurent et al., 2016; Wentz & Magavi, 2009). For instance, caffeine-induced enhancement of activity-dependent BDNF expression in cortical neurons has been associated with neurological benefits (Connolly & Kingsbury, 2010).

Furthermore, regular consumption of caffeine (in moderate doses) is suggested to provide a prophylactic benefit to diminish memory deterioration with aging or AD, as detailed elsewhere (Chen, 2014; Cunha & Agostinho, 2010). In this context, caffeine is well studied for its anti-inflammatory properties in the CNS and for exhibiting neuroprotection function by antagonizing the excitatory A_{2A}AR receptor (Aden et al., 2003; Stockwell et al., 2017). Accordingly, caffeine is noted to reduce memory deterioration in the aging brain, while A_{2A}AR antagonism by caffeine has been associated with a positive effect on hippocampal long-term potentiation associated with memory (Temido-Ferreira et al., 2020). Previously, caffeine ingestion was described to stimulate a state of cortical hyperexcitability via ARs antagonism, which results in improved alertness and enhanced cognitive functions (Janicak, 2002). However, in a recent study, chronic ingestion of caffeine showed no long-lasting alterations in the functionality of cerebral A_1ARs, which were earlier associated with caffeine-induced neuroprotection (Nabbi-Schroeter et al., 2018). Other studies advocated that caffeine could interact with the dopaminergic system, suppress inhibitory (GABAergic) activity, and modulate the GABA receptor. Together, these events result in the regulation of neurotransmitters and, hence, lead to improvements in neurobehavioral measures and neuroprotective effects in animal models, as detailed elsewhere (Alasmari, 2020). In contrast, some studies also suggested that caffeine can cause vasoconstriction, which negatively affects blood circulation and oxygen supply in the brain (Addicott et al., 2009; Buch et al., 2017; Xu et al., 2015; Zhang et al., 2015). These events lead to alternations in the temporal dynamics of the blood oxygenation level dependent (BOLD) response and further trigger an extensive reduction in the functional connectivity of the brain (Griffeth et al., 2011; Liu et al., 2004; Wong et al., 2012). Additionally, substantial negative effects of caffeine have been shown on white matter injury and synaptic plasticity during the developmental stages of the fetus (Cabral-Miranda et al., 2011; Rivkees & Wendler, 2011). Furthermore, A_1ARs antagonism by caffeine in the CNS is marked for causing alternation in hippocampal synaptic transmission, resulting in noticeable effects such as diuresis and tachycardia (Chen, 2019).

Moreover, caffeine is established as a stimulant of alertness and general cognitive performance (Cappelletti et al., 2015; Nehlig, 2010). Despite these beneficial effects of caffeine, excessive consumption of coffee and/or caffeine has been documented to cause dose-related sleep disturbances (Clark & Landolt, 2017). In this context, a positive correlation of caffeine ingestion was established with onset of insomnia, which is characterized as one of the most common sleep-related complications and known to affects the quality of life, including interference in a person's ability to function, exhaustion, overeating, impaired memory, and depression in a high percentage of people globally (Chaudhary et al., 2016; Coleman et al., 1982; Cunnington et al., 2013; Katagiri et al., 2014; Leger et al., 2008; Skarupke et al., 2017). Although the neurobiological mechanisms of sleep are not yet fully understood, the adenosine pathway through A_1ARs and A_{2A}ARs, which are located in widespread areas of the brain, is well-established in the regulation of sleep, arousal, and cognitive functions such as working memory and sustained attention (Rétey et al., 2005, 2006; Snel & Lorist, 2011). Evidence suggests that caffeine act as a competitive inhibitor of adenosine at the ARs to countermeasures the detrimental effect of prolonged wakefulness through potentiating dopaminergic neurotransmission, which leads to motor activation and subsequent alertness (Cappelletti et al., 2015; Fredholm et al., 1999; Landolt, 2008; Lazarus et al., 2019; Urry & Landolt, 2015). However, genetic studies investigating the effects of caffeine on specific cognitive functions are limited and characterized by methodological heterogeneity (Kapellou et al., 2023). In adult twin pairs, for example, a genome-wide search for chromosomal areas linked to caffeine-induced sleeplessness resistance revealed a substantial linkage to a region on the long arm of chromosome 2 (Luciano et al., 2007). Also, in previous studies, caffeine-related sleep loss has been characterized as heritable, and genetic effects were noted independent of those on general insomnia (Luciano et al., 2007). Importantly, a polymorphism in the *ADORA2A* gene (encoding A_{2A}AR) has been identified as a significant factor contributing to the variation in sleep loss and insomnia after caffeine consumption, as extensively studied and reviewed elsewhere (Byrne et al., 2012; Cornelis et al., 2007; Erblang et al., 2019; Holst et al., 2014; Kapellou et al., 2023; Mazzotti et al., 2011; Nunes et al., 2017; Retey et al., 2007). This finding is supported by compelling evidence from mouse models, in which caffeine (at a dose of 15 mg/kg) failed to induced wakefulness in animals with genetically abolished A_{2A}AR function (Huang et al., 2005). Subsequent experiments revealed that specifically genetic deletion of A_{2A}AR receptors in the shell of the nucleus accumbens blocked caffeine-induced wakefulness (Lazarus et al., 2011). In addition to ARs, caffeine has many other biological targets, including $GABA_A$ receptors, RyRs, and PDEs (Mabunga et al., 2015; Mustard, 2014), some of which could be relevant for its effects on sleep physiology. Additionally, a western blot study demonstrated that caffeine administration downregulated the expression of $GABA_A$ receptor subunits (Ko et al., 2018), suggesting an interaction of caffeine with the GABAergic system. Additionally, it was shown that mice treated with caffeine and empty bottle stimulation dramatically reduced brain GABA levels, which is strongly associated with the sleep disruption behaviors in the pentobarbital-induced sleep test (Xu et al., 2023). Based on these findings, it is suggested that individuals with primary insomnia may exhibit differences from good sleepers in terms of their sensitivity to ARs, caffeine metabolization ability, and/or perceived sensitivity to caffeine (Youngberg et al., 2011).

In conclusion, moderate levels (not more than 200 mg caffeine in one setting or 400 mg over the day) of caffeine consumption may result in beneficial effects on human health, such as against neurodegenerative diseases, as given in Table 2. However, chronic doses of caffeine may disturb the quality of sleep and BOLD response,

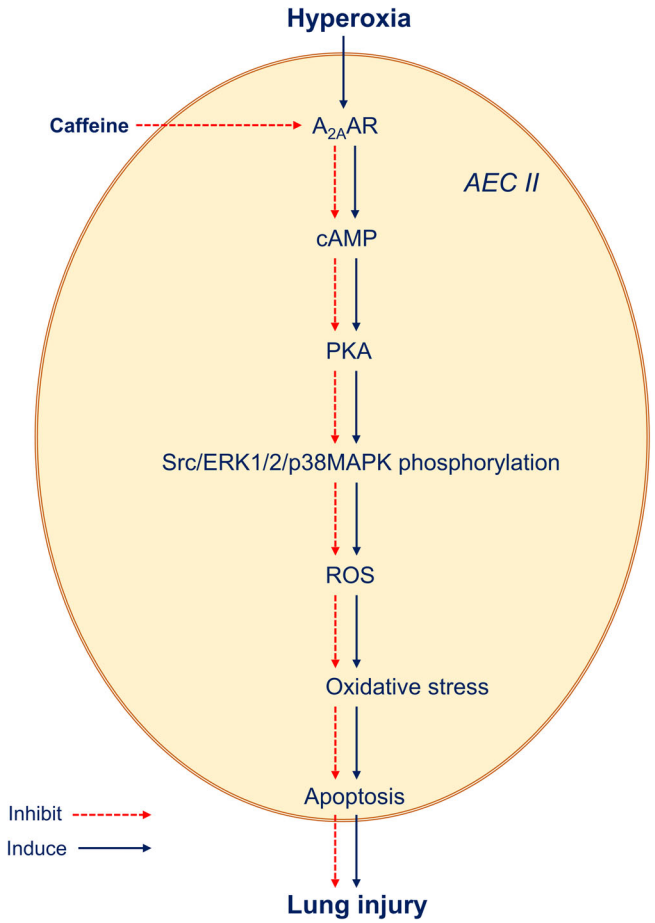

FIGURE 7 Scheme for the molecular pathway of caffeine exhibiting protective effects against hyperoxia-induced type II alveolar epithelial cells (AECs II) injury in vitro. ROS, reactive oxygen species.

resulting in reduced functional connectivity in the brain. Thus, detailed research is warranted to determine the detailed molecular mechanism(s) by which caffeine exhibits protective effects against BBB disruption and brain disorders, and controlled studies should be designed to assess the impact of caffeine in clinically relevant populations.

4.2 | Caffeine's effect on lung function

Caffeine is known to exhibit antiasthmatic effects, which can be explained based on its physiological impact on the lungs, that is, causing bronchial dilation and relaxation of smooth muscles. However, the qualified roles of molecular receptors, such as ARs and PDEs, as modes of caffeine's antiasthmatic actions are still unknown (Brackett & Daly, 1991; Ghai et al., 1987; Persson et al., 1982). Recent experimental studies encouraged the idea that caffeine could excite the respiratory center in the medulla, enhance minute ventilation, boost peripheral chemoreceptors, amplify sensitivity to carbon dioxide, and raise diaphragmatic contractility. These caffeine-induced events have been projected to explain its favorable effect on reducing apnea (Abdel-Hady et al., 2015; Moschino et al., 2020). Previously, caffeine was demonstrated to control the in vitro activation of transforming growth factor-β (TGF-β)-induced epithelial cells and fibroblasts as well as reduce collagen formation in established fibrosis of lung tissue ex vivo (Tatler et al., 2016). Additionally, caffeine consumption in coffee is reported to provide lung-protective benefits via suppressing the NLRP3 inflammasome in THP-1 macrophages and, in part, by decreasing the fabrication of reactive oxygen species (ROS) activated by A_{2A}ARs (Zhao et al., 2019). Also, the inhibitory action of caffeine on A_{2A}ARs has been shown to decease pulmonary inflammatory infiltration and apoptosis, and promote the growth of type II alveolar (ATII) epithelial cells in neonatal mice (Chen et al., 2020). Likewise, another study suggested similar protective effects for caffeine via blockage of the A_{2A}AR/cAMP/PKA/Src/ERK1/2/p38MAPK signaling pathway to reduce the incidence of bronchopulmonary dysplasia (BPD; Wang et al., 2022), as depicted in Figure 7.

In summary, caffeine may exhibit direct or indirect complex interactions with multiple receptors or important cell signaling pathways to maintain normal lung function or improve disorders such as asthma and BPD. However, there are limited studies that have attempted to decipher the molecular targets, or receptors and pathways targeted by caffeine in the lung. Also, most of the investigations on caffeine-induced effects on lungs used in vitro and rodent animal models, while a few studies were able to translate into clinical practice; for instance, caffeine is approved and used in the BPD treatment of preterm infants (Moschino et al., 2020). Hence, extensive research and comprehension of the important molecular targets or cell signaling pathways targeted by caffeine are required to further explore the development of caffeine-based therapeutics for lung diseases or disorders.

4.3 | Effect of caffeine consumption on cardiovascular system

Several studies have assessed the physiological effects of caffeine consumption on cardiovascular outcomes such as cardiac rhythm, heart rate, and stroke volume, thereby lowering the requirement for vasopressors, as well as on the different markers of cardiac disease in humans. The major consequences of caffeine ingestion on cardiovascular health are detailed and reviewed elsewhere (Turnbull et al., 2017; van Dam & Hu, 2022). Typically, caffeine is considered to induce various reversible and short-term cardiovascular physiological effects, including minor elevations in blood pressure (Milanez, 2011; Nawrot et al., 2003; Pelchovitz & Goldberger, 2011). These effects of caffeine on cardiovascular physiology were associated with caffeine-induced ARs antagonism (Mustafa et al., 2009; Sansone et al., 2017). In contrast, Hatano et al. (1995) documented that caffeine enhances

the production of nitric oxide in the endothelium by Ca^{2+} release from the ER via RyR-sensitive Ca^{2+} channel activation and the inhibition of cGMP degradation in the isolated rat aorta, resulting in the caffeine-induced augmentation of endothelium-dependent vasodilatation. Similar endothelium-dependent vasodilation observations were observed and validated for caffeine action in healthy humans (Umemura et al., 2006).

Previously, the prostaglandin antagonistic effects of caffeine were observed and associated with acceleration of the patent ductus arteriosus closure in premature infants (Abdel-Hady et al., 2015; Moschino et al., 2020). For example, after half an hour, a 20 mg/kg intravenous dose of caffeine was reported to substantially enhance the heart rate, mean arterial blood pressure, and capillary oxygen saturation in infants (Hassanein et al., 2015). More recently, caffeine has been demonstrated to enhance hepatic ER-linked Ca^{2+} levels and inhibit the transcriptional activation of the sterol regulatory element-binding protein 2 (SREBP2), which further contributes to the regulation of proprotein convertase subtilisin/kexin type 9 (PCSK9). These events collectively lead to an increase in low-density lipoprotein receptor (LDLR) expression and clearance of circulating low-density lipoprotein cholesterol (LDLc) levels, resulting in reduced cardiovascular disease (CVD) risk (Lebeau et al., 2022). In contrast, a prospective population-based study associated habitual consumption of caffeine (100 mg/day) with a 14% increased risk of CVD (Gaeini et al., 2019). In support, the available literature suggests that caffeine consumption (maximum of 600 mg/day) induces mild, momentary, and rescindable symptoms with no lasting adverse cardiovascular effects, indicating that moderate concentrations of caffeine are not linked with high risks of total CVD, as systematically reviewed elsewhere (Turnbull et al., 2017; van Dam & Hu, 2022). Besides, caffeine is reported to stimulate the sympathetic nervous system to cause enhanced production of norepinephrine via activation of the renin–angiotensin system and a direct effect on the adrenal medulla. These events are also connected with an increase in blood pressure (Geleijnse, 2008). In another study, it was demonstrated that caffeine did not appear to significantly affect cardiac conduction or refractoriness, while moderate doses of caffeine ingestion were linked to significant elevations in systolic and diastolic blood pressure. Together, caffeine in coffee was suggested to have no effect on the induction of supraventricular tachycardia or the faster rates of induced tachycardias (Lemery et al., 2015).

Collectively, the available evidence showed conflicting results for the effects of caffeine consumption on the cardiovascular system in humans. This could be due to the variability in population, dose, and techniques used in the assessment of caffeine-induced physiological effects. However, the studies conducted on animal models have not yet reported significant side effects of caffeine on the cardiovascular system. Overall, the available results support that moderate ingestion of caffeine is not associated with increased risks of total CVD in baseline healthy individuals, but it may reduce CVD risk or provide protection against CVD by removing circulating LDLc levels. It is, therefore, recommended to undertake a controlled clinical study to determine the effect of caffeine ingestion on beneficial effects among healthy and patients diagnosed with CVD populations.

4.4 | Effects of caffeine on liver function

Epidemiologic studies have advocated the beneficial effects of regular caffeine to avoid liver-associated diseases such as alcoholic cirrhosis, hepatic cancers, hepatitis C virus (HCV)-induced liver fibrosis, and nonalcoholic fatty liver disease (NAFLD; Furtado et al., 2014; Jaruvongvanich et al., 2017; Khalaf et al., 2015; Modi et al., 2010; Wang et al., 2015). For example, a cross-sectional study performed on about 6000 adults at high risk of liver damage from various etiologies revealed that caffeine ingestion can substantially reduce the risk of enhanced serum aspartate aminotransferase and alanine aminotransferase activity (Honjo et al., 2001; Ruhl & Everhart, 2005). In another cross-sectional study, an association was established between caffeine consumption and lower liver fibrosis in patients infected by HCV (Oliveira Kda et al., 2015).

Experimental studies have associated caffeine consumption with a significant decrease in the mRNA and protein expression of some proinflammatory cytokines and chemokines, along with blocking neutrophils invasion in the liver, which consequently reduces liver inflammation (Lv et al., 2010). Besides, caffeine consumption in coffee is correlated with inhibition of leptin expression in adipose tissue, hepatic gene expression related to fatty acid synthesis, and inflammatory cytokine gene expression in white adipose tissue (Yamauchi et al., 2010). An investigation using 0.1% caffeine ingestion in male Wistar rats suggested that caffeine can exhibit a pronounced beneficial effect or improvement against carbon tetrachloride (CCl_4)- and diethylnitrosamine-induced liver fibrosis/carcinogenesis, hypothesized due to high expression of the proapoptotic bax protein in the liver, causing mitochondria-dependent programmed cell death of the damaged cells or tissues (Furtado et al., 2014). Previously, caffeine was discovered to prevent hepatocarcinogenesis by enhancing epidermal growth factor receptor (EGFR) expression and activation of the mitogen-activated ERK-regulating kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway (Okano et al., 2008). Gressner et al. (2008) verified that caffeine could provide protective effects against liver fibrosis by significantly downregulating TGF-β-induced connective tissue growth factor expression in hepatocytes by promoting the degradation of TGF-β effector SMAD2, by inhibition of SMAD3 phosphorylation, and by enhancing peroxisome proliferator-activated receptor gamma expression. Arauz et al. (2013) suggested the direct inhibitory effect of caffeine on hepatic stellate cells via downregulation of focal adhesion kinase and alpha-smooth muscle actin synthesis as well as triggering hepatic stellate cell apoptosis; these events collectively lead to a decrease in the progression of liver fibrosis.

A recent systematic review and meta-analysis support the idea that regular consumption of caffeine can decrease the prevalence of hepatic fibrosis in patients with NAFLD (Shen et al., 2016). Meanwhile, in vitro and in vivo analysis demonstrated that caffeine could alleviate NAFLD by augmenting the expression of LDLR protein levels via direct interaction with the EGFR that results in the activation of the EGFR-ERK1/2 signaling pathway (Huang et al., 2023). Furthermore, caffeine consumption has been correlated with reduced adiposity and steatosis in high-fat diet-feeding mice (Yun et al., 2008),

suggesting the beneficial effect of caffeine in the treatment of alcohol-induced fatty liver. In support, caffeine was studied for protective function in alcoholic liver injury and showed a low degree of steatosis and apoptosis, suggesting the inhibition of lipogenic gene activation induced by alcohol in the liver (Lv et al., 2010). Also, caffeine consumption is associated with restoration of lipid peroxidation and glutathione peroxidase levels as well as reduced expression of TGF-β to prevent experimental cirrhosis (Arauz et al., 2014). Another study suggested that caffeine may trigger the hepatic autophagy–lysosomal pathway to prompt fatty acid oxidation in mice (Sinha et al., 2014), but the exact mechanism adopted by caffeine to activate autophagic influx is not yet clear.

It is important to mention that ARs, namely A_{2A}ARs and A_{2B}ARs, have been deciphered as the key mediators of inflammation and fibrosis in the liver, while caffeine can be quickly taken into the liver parenchyma due to first-pass metabolism (Wang et al., 2020). Hence, the protective effects of caffeine against inflammation and fibrosis can be associated with caffeine-induced AR antagonism in the liver (Peng et al., 2008). Additionally, the protective effects of caffeine on hepatocytes were previously suggested due to its ability to inhibit ROS generation (Back et al., 2006). Recently, low doses of caffeine were demonstrated to alleviate acute liver injury by promoting the expression of the neural precursor cell-expressed developmentally downregulated gene 4-like (NEDD4L), which blocks the production of glucose-regulated protein 78 (GRP78) via ubiquitination at its K324 site (Hu et al., 2022).

Overall, the available literature supports the positive physiological effects of caffeine on liver function or associated disorders; however, it is difficult to provide an exact concentration of caffeine to obtain favorable consequences. Moreover, a couple of molecular mechanisms have been suggested for caffeine-induced protective effects in the liver, but again, no mechanism has consistently been demonstrated in human populations. Thus, prospective clinical studies are required to elucidate the "caffeine dose" and potential molecular mechanism adopted by caffeine to exhibit protective function in the human liver.

4.5 | Consequences of caffeine intake on kidney function

The antagonistic action of caffeine on ARs is linked to its physiological effects on the kidneys, including increased blood flow, diuresis, and rennin production (Spielman & Arend, 1991). In this context, caffeine-induced ARs inhibition at juxtaglomerular cells was documented to cause enhanced production of renin, possibly by activation of the renin–angiotensinogen–aldosterone system, but these events were not noticed under physiologically effective doses of caffeine (Tofovic et al., 1991). Also, caffeine was demonstrated to reduce the activation of renal fibroblasts by eliminating intracellular ROS generation due to its antioxidant property and, at least in part, by activating downstream catalase and Nrf2 signaling pathways under hypoxic conditions (Nilnumkhum et al., 2019). Other studies showed caffeine action in the alternation of several processes, such as modification of the baseline renal plasma flow, alteration of kidney hemodynamics, and natriuresis (Brown et al., 1993; Passmore et al., 1987). Notably, these potential factors are known to promote the development of acute kidney injury, especially in high-risk patients with concurrent health problems or comorbidities (Tommerdahl et al., 2022). In contrast, a recent meta-analysis of clinical studies suggested dose-dependently linked caffeine consumption with a decreased incidence of end-stage renal disease, chronic kidney disease (CKD), and albuminuria (Kanbay et al., 2021). In other studies, caffeine consumption has been characterized as an independent factor in lowering the risk of kidney stones, which in turn further decreases the incidence of CKD development (Curhan et al., 1996; Ferraro et al., 2014; Peerapen & Thongboonkerd, 2018). Also, the functional activity of caffeine was linked to reducing the effects of desmopressin, isoproterenol, and prostaglandin E2 in some patients (Belibi et al., 2002; Tseng et al., 1993). In contrast, chronic consumption of caffeine was demonstrated as a potential risk factor for the generation and enlargement of cysts in specific individuals with autosomal dominant polycystic kidney disease (Belibi et al., 2002).

Moreover, caffeine is studied in the kidney to reduce isoform 3 of the sodium/proton exchanger and sodium/potassium adenosine triphosphatase expression, thereby halting renal tubular sodium reabsorption in the kidney. This process further leads to an enhanced withdrawal of free water and solute (Shirley et al., 2002) and has been suggested to completely block the local tubule-glomerular feedback mechanism, which further elevates the delivery of distal sodium (Marx et al., 2016). Interestingly, in the prior study, the effect of caffeine was associated with a reduction in renal oxygen expenditure without altering renal plasma flow or glomerular filtration rate (GFR; Lee et al., 2002). In this respect, analysis of the urinary proteome from 30 healthy individuals reported a reduction in urinary kininogen-1 protein after consumption of caffeine (Peerapen et al., 2017). Altogether, these results are used to postulate that caffeine can potentially enhance renal blood flow and GFR by vasodilatation due to the agglomeration of nonexcreted kinins in the kidney (Peerapen et al., 2017). Another study hypothesized that caffeine consumption could cause the transformation of tubular cell annexin A1 toward the cytoplasm from the apical surface. This results in the shrinkage of the crystal-binding capability of tubular surfaces, thereby providing a protective function against kidney stones (Peerapen & Thongboonkerd, 2016).

In summary, several contradictory effects of caffeine intake on kidney function have been reported among different populations. Thus, further advanced, and controlled studies are required to clarify the beneficial effects of caffeine on kidneys in healthy individuals or patients; if proven, caffeine can be considered as a supplementary therapeutic or nutritional strategy to prevent kidney diseases, particularly in individuals at high risk.

4.6 | Impact of caffeine consumption on immune function

As the immune system is responsible for monitoring and regulating different diseases and disorders, caffeine-induced immunomodulation

has been widely studied and reviewed elsewhere (Al Reef & Ghanem, 2018; Horrigan et al., 2006). Based on the available evidence that immune cells carry ARs, concentrations relevant to regular consumption of caffeine are generally considered to elicit immune function by AR antagonism (Abdel-Hady et al., 2015; Koroglu et al., 2014; Kumar & Lipshultz, 2019). Additionally, the inhibitory action of caffeine (high concentration) on cAMP-PDEs and the subsequent rise in intracellular cAMP concentrations are also deciphered to be part responsible for the caffeine-induced immunomodulatory effects (Horrigan et al., 2006). In a recent study, caffeine was interpreted to promote host defense mechanisms and produce an anti-inflammatory effect via stimulation of the bitter taste receptors (TAS2Rs), which can further modulate the natural killer cell-mediated cytotoxicity, tumor necrosis factor alpha (TNF-α) signaling pathways, T-cell receptor signaling pathways, and chemokine signaling pathways (Sharma & Bansal, 2020).

Experimental studies have demonstrated that caffeine can block the chemotaxis of monocytes and neutrophils (Elferink & Dekoster, 1995; Horrigan et al., 2003) and the production of cytokines that participate in inflammation, like TNF-α (Horrigan et al., 2004; van Furth et al., 1995), which essentially contributes to facilitating inflammation in the body. In this context, a complete inhibition of 2 expression was assessed by increasing the caffeine concentration from 0.73 to 1.9 mg/mL (Ritter et al., 2005). However, a recent study showed that caffeine (0.2 mg/mL) can induce the survival rate of neutrophils isolated from the heart blood of mice (Abbasi et al., 2018). Also, caffeine is reported to diminish the upregulation of proinflammatory cytokines and chemokines, the incursion of macrophages and neutrophils, and tissue damage in animal models exposed to hyperoxic conditions (Weichelt et al., 2013). For example, macrophages from mice treated with caffeine (0.1–1.2 mM) for 24 h showed a substantial reduction in the generation of interleukins, namely, IL-3, IL-6, IL-13, and ROS levels (Samieirad et al., 2017). Another study monitored the effect of caffeine (20 mg/kg for 1 week) on human plasma and tracheal aspirate cells at the end of the first 24 h and the first week revealed no substantial variations in the INF-α, IL-1β, IL-2, or IL-7 levels. However, an increase in expression level was noted for all the measured cytokines in tracheal aspirates (Valdez et al., 2011).

Moreover, caffeine has been reported to promote the number of $CD8^+$ T cells and the overall lymphocyte count in healthy volunteers (Bishop et al., 2005). In contrast, later studies established the inhibitory potential of caffeine on lymphocyte function by lowering the generation of IL-2 and IL-4 via RyRs (Horrigan et al., 2006). On the same note, caffeine was noted to inhibit lymphocyte proliferation by suppressing Th1 and Th2 cell division in humans (Sharif et al., 2017). However, in a prior study, treatment of 2–6 mg/kg caffeine for 1–3.5 h on lymphocytes isolated from human venous blood exhibited no considerable alternation in the number of $CD4^+$ and $CD8^+$ cells (Fletcher & Bishop, 2012), whereas an increase in the number of antigen-stimulated $CD3^+CD56^+$ cells was noted upon caffeine intake (>6 mg/mL) after 1 h (Dulson & Bishop, 2016). Also, caffeine (0.01, 0.02, and 0.04 mg/mL) treatment on cord blood monocytes acquired from infants and triggered by LPS presented a substantial reduction in IL-10 and TNF-α levels, while only IL-10 generation was reduced at caffeine doses higher than 0.02 mg/mL (Chavez-Valdez et al., 2016). On the other hand, a recent study showed that treatment with caffeine on LPS-primed mesenchymal stem cells could promote anti-inflammatory phenotypes (Abbasi et al., 2018).

Additionally, caffeine has been studied to encourage antitumor immune response or cancer immunosurveillance, as evident from the prospective cohort studies (Holick et al., 2010; Nkondjock, 2009; Song et al., 2012); the potential role and adopted mechanism of caffeine against different cancers/tumors are also summarized in Table 3. For instance, caffeine treatment results in an enhanced immune response against tumors by reducing the expression of the programmed cell death protein 1 (PD-1) receptor on infiltrated cytotoxic T lymphocytes, which is suggested due to caffeine-induced antagonism of A_{2A}AR (Tej et al., 2019). In support, a study on an animal model showed that caffeine (0.1% in water) treatment can promote an effective antitumor immune response during tumor initiation, partly through the A_{2A}AR antagonism (Ohta et al., 2006). Previously, caffeine has been suggested to enhance antitumor activity by tumor antigen-specific $CD8^+$ T cells and promote the efficacy of adoptive T cell therapy via A_{2A}AR antagonism (Jin et al., 2010; Ohta et al., 2006). Moreover, antagonizing effects of caffeine on A_{2A}AR and A_3AR are suggested in the inhibition of tumor angiogenesis and IL-8-mediated tumor migration, respectively (Jin et al., 2010).

Collectively, the available literature suggests that caffeine can augment the antitumor immune response through A_{2A}AR and A_3AR inhibition, but substantial clinical studies are missing to unravel the anticancer efficacy of caffeine alone or in combination with available chemotherapeutic agents or immune checkpoint inhibitors. Also, based on the pharmacokinetics of caffeine, the adopted immunomodulatory pathways by caffeine are eligible at concentrations that are appropriate for normal human consumption. Despite the lack of systematic studies examining the effect of caffeine on the immune system, available in vitro and in vivo experimental evidence indicates that caffeine can impact both innate and adaptive immune responses, as depicted in Figure 8.

5 | CONCLUSION

Caffeine is well studied as a mild stimulant with diverse biological effects in humans. Experimental studies have established ARs and PDEs as the main molecular targets of caffeine, which have been associated with several caffeine-induced physiological or pharmacological effects. However, caffeine may elicit biological activity through direct or indirect interactions with additional molecular receptors or biomolecules at both safe and acute concentrations. For instance, caffeine exhibits direct interaction with the EGFR, which results in the activation of the EGFR-ERK1/2 signaling pathway followed by the promotion of enhanced LDLR protein expression to alleviate NAFLD. Importantly, several studies have reported caffeine action on

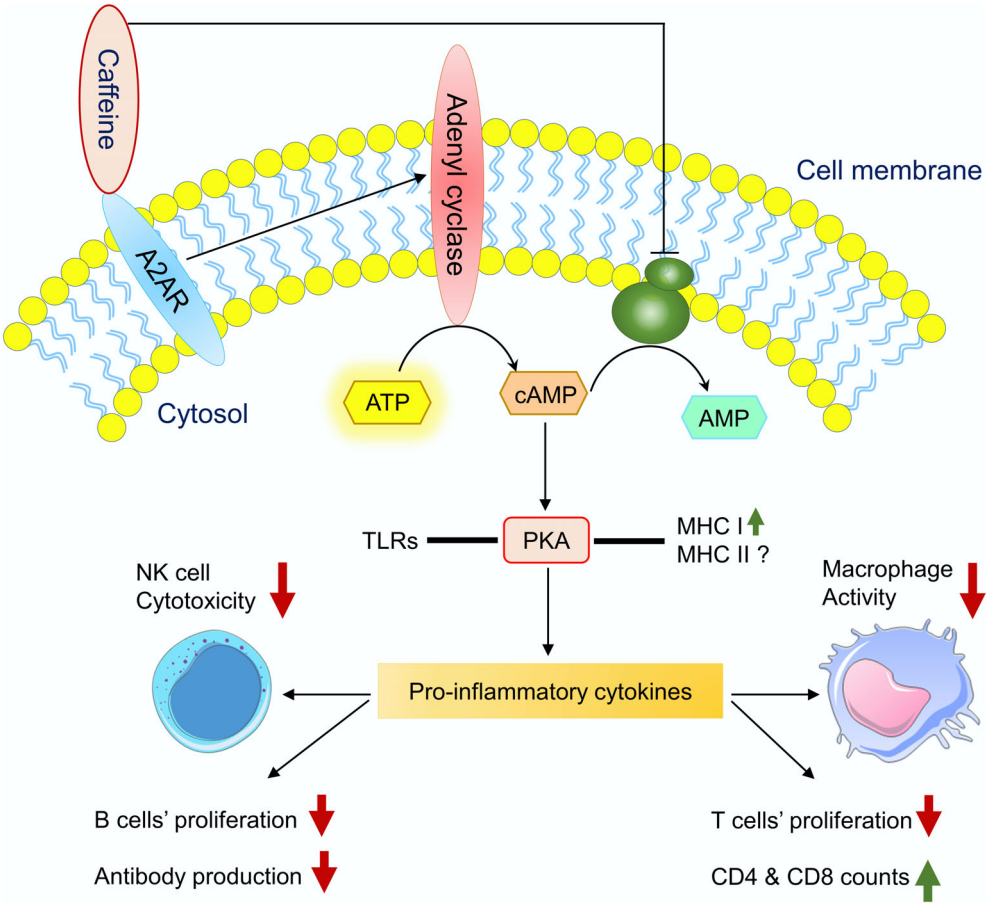

FIGURE 8 A graphical representation of caffeine's primary modulatory effects on various immunological markers. Caffeine activates adenylyl cyclase, which converts adenosine 5′-triphosphate (ATP) to cyclic cyclic adenosine monophosphate (cAMP) after binding to its $A_{2A}AR$. This process initiates an intracellular signaling cascade that is mediated by the upregulation of cAMP by inhibition of phosphodiesterase (PDE). As a result, the extracellular binding of caffeine is increased intracellularly by the second messenger, cAMP. As the cAMP concentrations became high the protein kinase A (PKA) activated, which prevents the release of proinflammatory cytokines. The activity of various immunological components, including macrophages, natural killer (NK) cell cytotoxicity, T cell and B cell proliferations, and antibody production, is lowered when inflammation is controlled. Moreover, it modifies the expression of major histocompatibility Class I molecules (MHC I) and toll-like receptors (Al Reef & Ghanem, 2018).

different organs and biological systems, but observed effects showed inconstancy in the results and have been associated with variation in the used caffeine concentration, the type of product containing caffeine, and individual characteristics (genetics, sex, age, diet, etc.). Therefore, comprehensive efforts need to be directed towards understanding the potential beneficial or adverse effects of caffeine in specific patients and/or healthy populations under well-designed and controlled clinical trials to overcome the common methodological challenges of caffeine research. Conclusively, as caffeine can elicit a multidirectional effect on organ-specific disorders, it can be formulated and developed as an effective therapy against respective organ- or system-associated disorders in humans.

AUTHOR CONTRIBUTIONS

Xinjie Song: Data curation; formal analysis; resources; writing – original draft. **Nikhil Kirtipal:** Data curation; formal analysis; investigation; supervision; writing – original draft. **Sunjae Lee:** Resources; supervision; validation; writing – review and editing. **Petr Malý:** Formal analysis; investigation; supervision; validation; writing – review and editing. **Shiv Bharadwaj:** Conceptualization; formal analysis; investigation; methodology; resources; supervision; validation; visualization; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

DATA AVAILABILITY STATEMENT

No data were used for the research described in the article.

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