Biochemistry and Biophysics Reports 40 (2024) 101837

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

A comprehensive review of arginine kinase proteins: What we need to know?

Brenda Martins Vasconcellos [a], Victor Guimarães Ribeiro [a], Naysha do Nascimento Campos [a], Luis Guilherme da Silva Romão Mota [a], Mônica Ferreira Moreira [a,b,*]

[a] Universidade Federal do Rio de Janeiro, Instituto de Química, 21941-909, Rio de Janeiro, RJ, Brazil
[b] Instituto Nacional em Ciência e Tecnologia em Entomologia Molecular, Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Arginine kinase enzyme
Insect
Phosphoarginine

ABSTRACT

The enzyme arginine kinase (AK), EC 2.7.3.3, catalyzes the reversible phosphorylation of arginine with adenosine triphosphate, forming phosphoarginine, which acts as an energy reservoir due to its high-energy phosphate content that can be rapidly transferred to ADP for ATP renewal. It has been proposed that AK should be associated with some ATP biosynthesis mechanisms, such as glycolysis and oxidative phosphorylation. Arginine kinase is an analogue of creatine kinase found in vertebrates. A literature survey has recovered the physicochemical and structural characteristics of AK. This enzyme is widely distributed in invertebrates such as protozoa, bacteria, porifera, cnidaria, mollusca, and arthropods. Arginine kinase may be involved in the response to abiotic and biotic stresses, being up regulated in several organisms and controlling energy homeostasis during environmental changes. Additionally, phosphoarginine plays a role in providing energy for the transport of protozoa, the beating of cilia, and flagellar movement, processes that demand continuous energy. Arginine kinase is also associated with allergies to shellfish and arthropods, such as shrimp, oysters, and cockroaches. Phenolic compounds such as resveratrol, which decrease AK activity by 50 % in *Trypanosoma cruzi,* inhibit the growth of the epimastigote and trypomastigote forms, making them a significant target for the development of medications for Chagas Disease treatment.

1. Background

Phosphagens are guanidino compounds that become *N*-phosphorylated upon binding to ATP through the actions of phosphagen (guanidine) kinase enzymes [1,2]. In vertebrate organisms, only a single phosphagen, phosphocreatine (CP), is known and is produced by the enzyme creatine kinase (CK), also known as creatine phosphokinase (CPK) (EC 2.7.3.2) [3,4]. Alternatively, in invertebrate organisms, in addition to phosphocreatine, seven other phosphagens can be found: phosphoarginine, phosphoglycocyamine, phosphotaurocyamine, phospholombricine, phosphohypotaurocyamine, phospho-opheline, and phosphoethanolamine, as well as their corresponding phosphokinases [2].

The enzyme arginine kinase (EC 2.7.3.3) (AK) was isolated for the first time from crab muscle [5]. It catalyzes the reversible phosphorylation of arginine, accelerating the transfer of a high-energy γ-phosphoryl (PO−4) group from ATP to arginine [6], forming phosphoarginine and ADP (adenosine diphosphate); said reaction is represented by ATP + arginine ⇌ ADP + phosphoarginine. Phosphoarginine acts as an energy reservoir, not only in the ATP stage but also in the inorganic phosphate (Pi) form, which is returned to the environment through the metabolic consumption of ATP, which can be renewed by phosphagen transfer [7]. Phosphagens can be considered reservoirs of "high-energy phosphates," since the reaction catalyzed by AK remains close to equilibrium, so that ATP is easily formed in the reverse path of the reaction during high energy turnover. Thus, phosphagens are capable of buffering ATP in cells that are subjected to large energy flows [8]. Because the reaction catalyzed by this enzyme is energetically ascending, it was proposed that it should be associated with ATP biosynthesis mechanisms such as glycolysis and oxidative phosphorylation [7].

* Corresponding author. Universidade Federal do Rio de Janeiro, Instituto de Química, 21941-909, Rio de Janeiro, RJ, Brazil.
E-mail address: monica@iq.ufrj.br (M.F. Moreira).

https://doi.org/10.1016/j.bbrep.2024.101837
Received 6 May 2024; Accepted 30 September 2024

2. Physicochemical and structural characteristics

Both Mg^{2+} and Mn^{2+} can activate AK [9]. Although the enzyme also has affinity for the Ca^{2+} ion, the extent of activation by Ca^{2+} is only 40 % compared with activation by Mg^{2+} [10]. The absence of a metal ion results in negligible enzyme activity [11].

The substrate specificity of AK has been studied extensively. The enzyme was initially described as being able to phosphorylate L-arginine and, to a lesser extent, arginine methyl ester, L-homoarginine, and L-canavanine, being considered inactive against D-arginine and other guanidino compounds such as creatine, glycocyamine, and taurocyamine [12]. However, in the annelid *Sabellastarte indica*, the arginine kinase 2 enzyme (AK2) showed strong activity towards D-arginine, while arginine kinase 1 (AK1) showed considerable activity towards lombricine and taurocyamine [13]. In a previous study, it was reported that an AK of *Spirographis spallanzanii* and *Sabella pavonina* showed activity of the same nature for L-arginine and D-arginine [14].

It was proposed that a region of amino acid deletions, called guanidino specificity (GS), is a potential candidate for the guanidino substrate recognition site, since there is a correlation between the size of the amino acid deletion in this region and the mass of the guanidino substrate [15]. It was observed that the Asp^{7} amino acid residue is conserved in every AK sequence, but not in other phosphagen kinase enzymes; therefore, it is possible that this negatively charged amino acid is related to recognition of the positive charge on the AK substrate, arginine [16]. The GS region overlaps with the flexible loops of mitochondrial creatine kinase structures of chicken (60–66 and 316–326), which has the role of removing water during catalysis, moving close to the active site [17] and the *Limulus polyphemus* AK [18]. After the substrate binds to the enzyme and the form changes from open to closed, the loops undergo changes, such as considerable disorder and conformational transitions. The loop in which the most impactful change occurs (residues 309–319) is a highly relevant region during catalysis [19]. The Glu^{314} amino acid residue binds to the arginine guanidino substrate in AK, playing a key role in positioning the substrate in the correct space to optimize the catalysis process [18]. The Arg^{309} residue binds to the negatively charged phosphates of ATP, and as mentioned before, Glu^{314} interacts with the arginine substrate, so that loop 309–319 acts on both substrates and may be necessary for correct positioning of these substrates [19]. In *L. polyphemus*, there are reported interactions from the amino groups and the carboxylate group of the substrate with the loop (residues 63, 64, 65, and 68) of the enzyme. Furthermore, the carboxylate group binds itself to the main chain of the amino group of residues 63, 64, and 65 of AK by hydrogen bonds [18].

In *Nautilus pompilius,* it was demonstrated that the Ser^{63}→Gly amino acid substitution considerably reduces the affinity of the enzyme for the substrate, compared to the wild-type organism, while the Ser^{63}→Thr mutation results in almost complete loss of AK activity, possibly due to steric disruption. The Tyr^{68}→Ser mutant showed complete loss of enzyme activity [20]. X-ray crystallographic analyses of *L. polyphemus* AK showed that after binding to the substrate, the side chain of the Asp^{62} residue in the N-terminal domain binds to the Arg^{193} residue in the C-terminal domain through a hydrogen bond [20]. *N. pompilius* mutants for Asp^{62}→Gly and Arg^{193}→Gly have weak enzyme activity, due to the breaking of hydrogen bonds. The hypothesis is that the hydrogen bond stabilizes the closed state of substrate binding and/or maintains a unique topology, in which the two types of AK substrate (ATP, ADP or arginine, phosphoarginine) are accessible enough for the catalytic reaction [20]. The interaction between the Asp^{62} and Arg^{193} residues is conserved in the ordinary AKs and in the considered atypical AK from the sea cucumber Stichopus, which is related to the CK gene [21]. In Stichopus, Phe^{63} and Leu^{65} residues are involved with the affinity of binding to the arginine substrate [21].

It was demonstrated that changes in the Glu^{59} or Lys^{16} residues reduce enzyme activity by a factor of ten, possibly due to the disruption of salt bridges. However, these residues seem to be more important in maintaining enzyme activity levels than in substrate binding itself [22]. It is evident that binding, activity, and conformational changes are interconnected, and mutations in this region result in damage to activity; nevertheless, this damage may not be related to substrate specificity [22].

ATP-guanidine phosphotransferases have a standard signature sequence, CP(S/T)N(I/L)GT [23,24], which is highly conserved. The conserved Asp^{61} and Arg^{192} residues are involved in the formation of ion pairs, which function in stabilization of the closed state of the protein, i.e., when it is bound to the substrate. The five arginine residues, Arg^{123}, Arg^{125}, Arg^{228}, Arg^{279}, and Arg^{308}, are related to ADP binding [25,26]. Fig. 1 shows a multiple alignment performed using the ClustalW tool (https://www.genome.jp/tools-bin/clustalw) [27] of AK amino acid sequences from the species *L. polyphemus, Bombyx mori, Apis mellifera, Musca domestica, Ctenocephalides felis* (AK1 and AK2), and *Caenorhabditis briggsae* (AK1 and AK2), highlighting the conserved amino acids that are typical of AK, as well as the signature sequence.

The molecular mass of AK may vary considerably according to the taxonomic group and the tissue in which they are found. The first studies that carried out purification and characterization assays on these proteins were performed in crustaceans, since the AK of these organisms comprises 10%–20 % of the extractable protein content of the muscle [6]. In these studies, the molecular mass was determined to be approximately 40 kDa [6,28]. Therefore, it was thought for a period that AK existed only in the ~40 kDa monomeric form [29]. By contrast, these gel filtration experiments showed that there are dimeric AKs of approximately 80 kDa in echinoderms [30,31], as well as in annelids [32] and cnidarians [33]. AKs of both sizes were found in mollusks, but their concentration differed among tissues. In siphon muscles, an AK with a 40 kDa molecular mass is predominant in the adductor muscle; both masses (40 and 80 kDa) can be found in the same proportion, while in the mollusk's foot, only the 80 kDa enzyme is found [34]. Previous studies have identified AKs with a molecular mass of 150 kDa in annelids [35], and this newly discovered enzyme is biochemically and immunologically different from the 80 kDa enzyme [14].

Studies using X-ray crystallography tools were conducted to understand the structure of AK proteins and the conformational changes that occur in these proteins in both their free state and bound to substrates. The three-dimensional AK structures deposited in the RCSB PDB database are listed in Table 1 (https://www.rcsb.org/).

3. Distribution

3.1. Unicellular organisms

Arginine kinase is widely distributed among invertebrates, being described in ciliates *Tetrahymena pyriformis* [54,55], *Paramecium caudatum* [56], and *Paramecium tetraurelia* [57]. There is a large formation of phosphoarginine in the cilia of these organisms [58], which have the role of providing energy for ciliary beating and, therefore, function not only as an energy reservoir but also as an energy donor for the transport of protozoa used in processes that demand continuous energy [56,57]. AK is also described in other unicellular organisms such as flagellated protozoa of the genus Trypanosoma, in which several analyzed species, namely *Trypanosoma cruzi*, *Trypanosoma brucei*, *Trypanosoma vivax*, and *Trypanosoma congolense*, present hypothetical genes of AK [59]. In *T. cruzi*, the etiological agent of Chagas Disease, a hypothetical actin-binding domain, "DAKTFLVWVNE," was identified in the amino acid sequence of AK, suggesting a possible interaction between the enzyme and the cytoskeleton structure, possibly related to cellular movement, in this case, flagellar movement [60]. Moreover, the exponential growth phase in *T. cruzi* in the epimastigote form is positively correlated with AK activity [61]. In the non-replicative trypomastigote form, there is no capture of L-arginine, and enzyme activity is higher than that in the replicative epimastigote form [62]. These data suggest a direct correlation between energy metabolism, mediated by

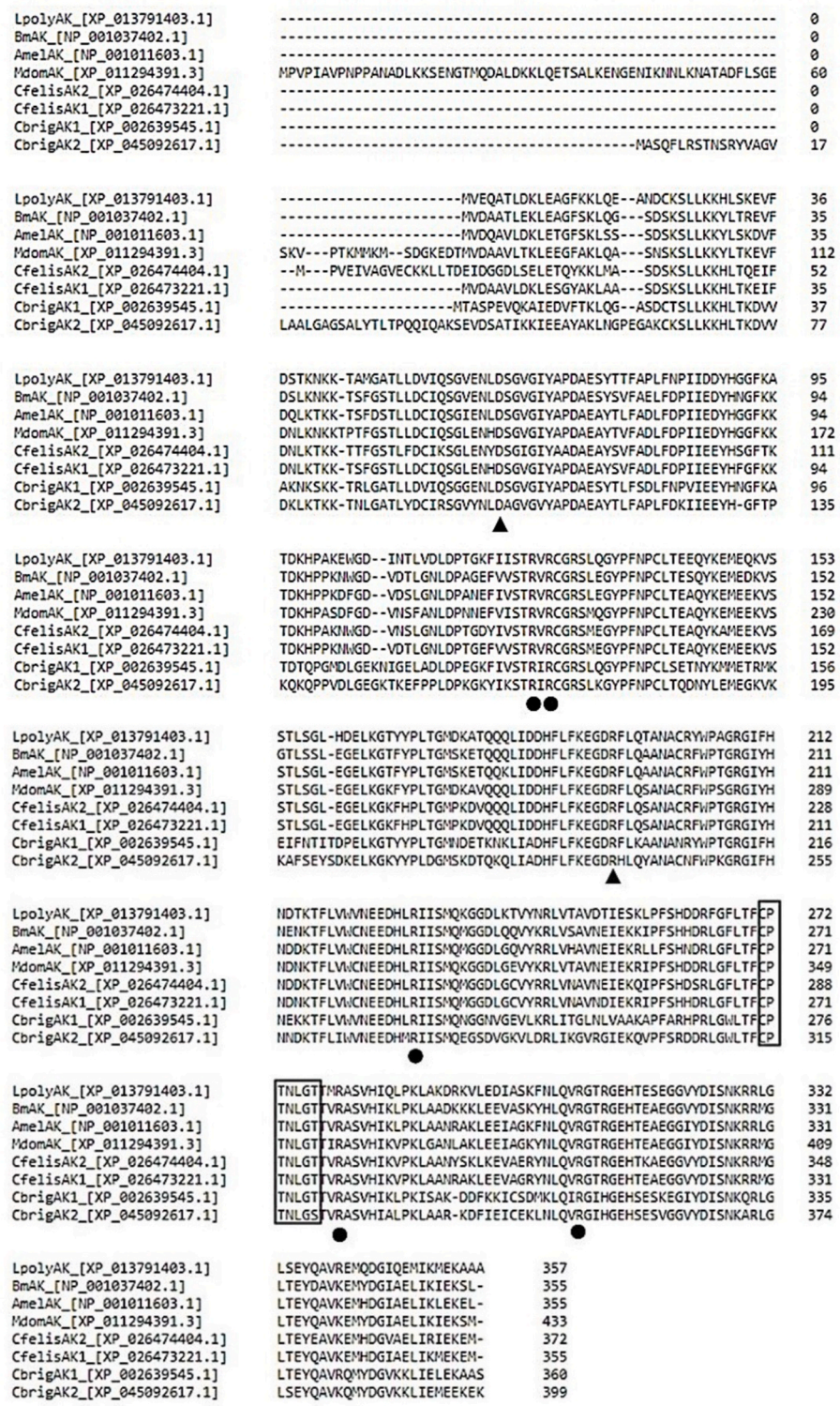

Fig. 1. Multiple alignment of arginine kinase amino acid sequences of arthropods *Limulus polyphemus* (XP_013791403.1), *Bombyx mori* (NP_001037402.1), *Apis mellifera* (NP_001011603.1), *Musca domestica* (XP_011294391.3), *Ctenocephalides felis* (XP_026474404.1 and XP_026473221.1), and the roundworm *Caenorhabditis briggsae* (XP_002639545.1 and XP_045092617.1). The signature sequence is marked by the black rectangle. The amino acids involved in ion-pair formation (Asp^{61} and Arg^{192}) are indicated by black triangles. The conserved arginine residues (Arg^{123}, Arg^{125}, Arg^{228}, Arg^{279}, and Arg^{308}) that bind to ADP are highlighted by black circles.

phosphoarginine, and the capacity for cellular replication in *T. cruzi* [62]. Additionally, a positive correlation was shown between AK overexpression and an increased capacity to survive under conditions of nutritional and pH stress [63], as well as oxidative stress [64].

In *T. brucei*, the protozoan responsible for causing sleeping sickness, the three isoforms identified in this species are in different cellular compartments. AK1 is exclusively located in the flagellum, AK2 in the glycosome and AK3 in the cytosol [65]. In extracts of Phytomonas, a group of flagellates that infect plants, an AK very similar to the one in *T. cruzi* was found, suggesting a close relationship between these two

Table 1
List of three-dimensional structures of arginine kinase proteins published in the RCSB PDB database and their binding agents.

RCSB PDB code	Description of structure	Species	Method	Compound complex	Reference
1BG0	Transition state structure of AK	*Limulus polyphemus*	X-ray diffraction (1.86 Å)	ADP, D-Arg, Mg^{2+}, NO_3	[18].
1M15	Transition state structure of AK	*Limulus polyphemus*	X-ray diffraction (1.2 Å)	ADP, Arg, Mg^{2+}, NO_3	[36].
1P50	Transition state structure of an AK mutant	*Limulus polyphemus*	X-ray diffraction (2.8 Å)	ADP, Arg, Mg^{2+}, NO_3	[37].
1P52	Structure of AK E314D mutant	*Limulus polyphemus*	X-ray diffraction (1.9 Å)	ADP, D-Arg, Mg^{2+}, NO_3	[37].
1SD0	Structure of AK C271A mutant	*Limulus polyphemus*	X-ray diffraction (2.3 Å)	ADP, Arg, Mg^{2+}, Cl, NO_3	[38].
1RL9	Crystal structure of Creatine-ADP AK ternary complex	*Limulus polyphemus*	X-ray diffraction (1.45 Å)	ADP, $C_4H_{11}N_3O_2$, Mg^{2+}	[22].
2J1Q	Crystal structure of AK	*Trypanosoma cruzi*	X-ray diffraction (1.9 Å)	(C3 H8 O3) Glycerol	[39].
3JU6	Crystal structure of dimeric AK in complex with AMPPNP and arginine	*Apostichopus japonicus*	X-ray diffraction (2.45 Å)	$C_{10}H_{17}N_6O_{12}$ P_3, Arg	[40].
3JU5	Crystal structure of dimeric AK	*Apostichopus japonicus*	X-ray diffraction (1.75 Å)	Mg^{2+}	[40].
3M10	Substrate-free form of AK	*Limulus polyphemus*	X-ray diffraction (1.73 Å)	SO^4	[41].
4GVY	Crystal structure of AK in complex with l-citrulline and MgADP	*Limulus polyphemus*	X-ray diffraction (2.091 Å)	ADP, citrulline and Mg^{2+}	[42].
4GVZ	Crystal structure of arginine kinase in complex with D-arg, MgADP, and nitrate	*Limulus polyphemus*	X-ray diffraction (2.96 Å)	D-Arg, Mg^{2+}, ADP, NO_3	[42].
4GW0	Crystal structure of AK in complex with imino-l-ornithine, MgADP, and nitrate	*Limulus polyphemus*	X-ray diffraction (2.448 Å)	ADP, imino-l-ornithine, Mg^{2+}, NO_3	[42].
4GW2	Crystal structure of AK in complex with l-ornithine, MgADP, and nitrate	*Limulus polyphemus*	X-ray diffraction (2.157 Å)	ADP, l-ornithine, Mg^{2+}, NO_3	[42].
4AM1	Crystal structure of AK in the absence of substrate or ligands	*Penaeus vannamei*	X-ray diffraction (1.25 Å)	absent	[43].
4BG4	Crystal structure of AK in a ternary analog complex with arginine, ADP-Mg and NO_3	*Penaeus vannamei*	X-ray diffraction (1.601 Å)	ADP, Arg, β-mercapto-ethanol, Mg^{2+}, NO_3	[44].
4BHL	Crystal structure of AK in binary complex with arginine	*Penaeus vannamei*	X-ray diffraction (1.9 Å)	Arg, β-mercapto-ethanol	[44].
4RF7	Crystal structure of double-domain AK in complex with substrate l-arginine	*Anthopleura japonica*	X-ray diffraction (2.1 Å)	Acetate ion, Arg	[45].
4RF9	Crystal structure of double-domain AK in complex with l-arginine and ATPgS	*Anthopleura japonica*	X-ray diffraction (2.35 Å)	Phospho-thiophospho-ric acid-adenylate ester	[45].
4RF8	Crystal structure of double-domain AK in complex with ADP	*Anthopleura japonica*	X-ray diffraction (2.17 Å)	ADP,4-(2-hydroxyethyl)-1-piperazine-ethanesulfo-nic acid	[45].
4RF6	Crystal structure of double-domain AK	*Anthopleura japônica*	X-ray diffraction (1.95 Å)	absent	[45].
5J99	Ambient temperature transition state structure of AK - crystal 8/Form I	*Limulus polyphemus*	X-ray diffraction (1.7 Å)	ADP, Mg_{2+}, Arg, NO_3	[46].
5J9A	Ambient temperature transition state structure of AK - crystal 11/Form II	*Limulus polyphemus*	X-ray diffraction (1.997 Å)	ADP, Mg_{2+}, Arg, NO_3	[46].
5U92	Crystal structure of AK in complex with arginine	*Polybetes pythagoricus*	X-ray diffraction (2.0 Å)	Arg, Na^+	[47].
5U8E	Crystal structure of substrate-free AK	*Polybetes pythagoricus*	X-ray diffraction (2.18 Å)	Na^+	[47].
6FH3	Protein AKMcsB in the pArg-bound state	*Geobacillusstearothermophilus*	X-ray diffraction (1.85 Å)	Ethylene glycol, phospho-arginine	[48].
6FH2	Protein AKMcsB in the AMP-PN-bound state	*Geobacillusstearothermophilus*	X-ray diffraction (2.7 Å)	AMP phosphor-amidate	[48].
6FH1	Protein arginine kinase McsB in the apo state	*Geobacillus stearothermophilus*	X-ray diffraction (1.7 Å)	Ethylene glycol, formic acid, imidazole	[48].
5ZHQ	Crystal structure of AK	*Scylla paramamosain*	X-ray diffraction (3.002 Å)	SO_4	[49].
6KY3	Structure of AK H284A mutant	*Daphnia magna*	X-ray diffraction (1.34 Å)	Arg, K^+, PO_4	[50].
6KY2	Crystaline structure of AK- WT	*Daphnia magna*	X-ray diffraction (1.87 Å)	PO_4	[50].
6TV6	Octameric McsB	*Bacillus subtilis* subsp. *Subtilis* str. 168	X-ray diffraction (2.5 Å)	Mg^{2+}	[51].
7RE6	Crystal Structure of the brown dog tick AK in absence of substrate or ligands	*Rhipicephalus sanguineus*	X-ray diffraction (1.53 Å)	absent	[52].
7VCJ	AK H227A	*Daphnia magna*	X-ray diffraction (1.75 Å)	NO_3, PO_4	[53].
7EWS	Crystal structure of AK3	*Paramecium tetraurelia*	X-ray diffraction (2.0 Å)	absent	To be published.

species of trypanosomatids, which have a single AK isoform, highlighting the fact that *T. brucei* has the canonical form (cytosolic) and two other isoforms [66].

Genes that encode proteins with unknown functions were deposited in the bacteria database; however, there were blocks of similarity to the C-terminal domain of AK in their sequences, while the N-terminal was absent [67]. Subsequently, genes like AK were deposited in the database, containing C-terminal and N-terminal domains, the same way it occurs in eukaryotic organisms [68]. A few bacterial species contain a complete gene homologous to AK, i.e., with the C-terminal and N-terminal domains present, the largest of the bacterial species carry a sequence homologous to the one in the C-terminal domain [69]. This homologous sequence was named MscB [70]. McsB has a phosphagen kinase-like domain, containing an adaptation in its structure that allows it to target protein substrates. In addition, it also has a phosphoarginine binding domain, providing an allosteric increase in the kinase activity of proteins that carry phosphoarginine [48].

After the complete sequencing of some proteobacteria, such as *Desulfotalea psychrophila* LSv54 [71], *Sulfurovum* sp. NBC37-1 [72], *Myxococcus xanthus*, and *Moritella* sp. [73], sequences like that of AK were found in these species, containing all the amino acid residues necessary for enzyme activity [74]. Phylogenetic analysis showed that the cluster containing the four bacterial species mentioned above are closer to eukaryotic AKs than to bacterial AKs related to McsB [74]. Andrews *et al.* [74] was the first to describe and characterize a bacterial AK in the species *D. psychrophila*. In the bacterium *M. xanthus*, AK plays a vital role in the formation of fruiting bodies and viable spores [75]. Suzuki *et al.* [69] discussed the evolution of AKs in bacteria, according to phylogenetic analyses, the AK sequences of bacteria are grouped into two different clusters, named cluster A, in which are grouped the species *Oceanithermus profundus*, *Nitratifractor salsuginis*, *Moritella* sp., *Sulfuruvum* sp., *Sulfurovum lithotrophicum*, 14 species of ciliates, and one porifera, and cluster B, which includes most invertebrate species and the bacterial species *Desulfobacterium autotrophicum*, *D. psychrophila*, *M. xanthus*, and *Ahrensia* sp. Cluster A possibly diverged at an early stage in the evolution of AKs, and there is the hypothesis that these genes were inserted by horizontal transfer [69]. In a more recent study, it was verified that cluster B, described by Suzuki *et al.* [69], is subdivided into two clusters: B and B′, in which cluster B′ comprises species *D. autotrophicum* and *D. psychrophila*, and cluster B mainly encompasses species of the genus Myxococcus [76].

3.2. Multicellular organisms

In the phylum Porifera, the amino acid sequence of AK was deduced in the species *Suberites domuncula*. It has been observed that AK overexpression in this species occurs as a response to exposure to exogenous silicic acid. Silicic acid is a spicule component in Demospongiae, whose synthesis and formation demand a considerable energy reserve [77]. According to Conejo *et al.* [78] AK could participate in energy transport within flagellated choanocytes in sponges. In the phylum Cnidaria, AK was isolated and characterized in the sea anemone *Anthopleura japonicus* [33]. Subsequently, the physicochemical characteristics of this enzyme were determined; nevertheless, the physiological role of AK in this phylum has not been explained.

The role of AK in arthropods has been extensively investigated, being found mostly in muscles [79–82], indicating a role in cellular energy metabolism [81]. In addition, AK is found in other organs, such as the middle intestine, hepatopancreas, salivary gland, hemolymph, head, ovaries, Malpighian tubule, and compound eyes [82–88]. The tissue distribution of AK and their respective genes may indicate a high energy demand in these compartments through the maintenance of constant ATP levels in the cells [89].

More recently, the role of AK in response to viral infection has been investigated. The cDNA derived from the shrimp *Penaeus stylirostris* showed upregulation of AK in the hepatopancreas 30–40 h after infection with the White Spot Virus (WSV) when compared to non-infected shrimp [86]. Similarly, a proteomic analysis of hemolymph of the crab *Scylla serrata* after WSV infection showed upregulation of the AK [85]. This response might indicate metabolic stress caused by the viral infection [85]. In the shrimp *Litopenaeus vannamei*, WSV infection induced high expression of AK in the muscles and hemocytes, suggesting an association with the immune response [81]. Further, preincubation of AK with WSV increases viral infection in shrimp, resulting in the promotion of pathogenicity [81]. Alternatively, Wang *et al.* [90] showed that after 6 h of WSV infection in the shrimp *Fenneropenaeus chinensis*, AK and other proteins related to the cellular structure of energy metabolism were downregulated. Differences in upregulation and downregulation of AK in the systems studied might be related to the timing of the viral infection and the shrimp species studied. Studies in mosquitoes that are disease vectors, such as *Anopheles gambiae*, the vector of malaria disease, show that silencing the *ak* gene promotes reduction of infection by the protozoa *Plasmodium falciparium* and *Plasmodium berghei* in the host's middle intestine [91]. In *Aedes aegypti*, the main vector of dengue, zika, and chikungunya fevers, after infection with the dengue virus serotype 2, there was an upregulation of proteins related to metabolism, such as pyruvate carboxylase, saposin, aspartate aminotransferase, and AK [92].

Insecticide metabolism is a process that requires a great energy demand [93]. In this context, some studies have shown a correlation between the AK and insecticides. In the Chinese bee *Apis cerana cerana*, the insecticides pyriproxifen and phoxim, as well as the herbicide paraquat, induced overexpression of the AK mRNA, indicating that the AK is induced and activated after exposure to chemical stress [94]. Overexpression of AK protein was reported in field populations of the cotton bollworm *Helicoverpa armigera* resistant to pyrethroid insecticides (Adana and Mardin provinces, Turkey) when compared to susceptible populations [95]. Dawkar *et al.* [96] showed that artificial feeding of *H. armigera* containing chlorpyrifos induces up to threefold upregulation of AK protein in the intestine, as well as cytochrome P450 (CYP) and carboxyl/choline esterase, i.e., important proteins in the detoxification of insecticides [97,98], accompanied by an increase in enzyme activity and transcriptional levels of AK, which were superior to those in the control groups. In the beetle *Tribolium castaneum*, exposure to deltamethrin insecticide resulted in an increase in the transcriptional levels of AK1 and AK2 from 2 to 4 h after treatment. Additionally, silencing of genes *ak1* and *ak2* of *T. castaneum* triggered a decrease in the survival of beetles treated with deltamethrin [93]. These results indicate that AK may be involved in the response to chemical stress, being capable of aiding the metabolism of insecticide molecules [96]. On the other hand, in the mosquito *Culex quinquefasciatus*, vector of lymphatic filariasis, the treatment with temephos insecticide reduced AK expression in the midgut, suggesting a possible decrease in energy metabolism as a result of cellular stress caused by exposure to the insecticide [99].

Some studies have shown that AK responds to different types of stress in arthropods. In the shrimp *Marsupenaeus japonicus*, the AK enzyme was upregulated under hypoxic conditions [100]. In *A. cerana cerana*, exposure to several abiotic stresses, such as cadmium chloride, hydrogen peroxide, vitamin C, and extreme temperatures (4 °C and 42 °C), as well as biotic stresses induced by the ecdysone hormone and fungus *Ascosphaera apis*, resulted in upregulation of AK [94]. In *T. castaneum*, stresses caused by low and high temperatures (4 °C and 45 °C, respectively) and by the herbicide paraquat also increased gene expression levels of AK1 and AK2. Moreover, silencing genes *ak1* and *ak2* drastically reduces the tolerance of these individuals to such stress conditions [87]. In a more recent study, it was observed that exposure of the mosquito *A. aegypti* to gamma radiation promotes upregulation of the AK protein [101].

To investigate the biological function of AK, some authors used the molecular tool RNA interference (RNAi). Phenotypes such as the decrease in the survival rate [26,82,88,102–104]; morphological changes such as darkening of the integument [26] and malformation of the wings and cuticle [87]; and deleterious effects on development such

as reduced pupation rates [82,87,105], oviposition [87,102], and hatching rates were observed [87,88,102]. This set of results suggests that the *ak* gene is essential for survival, development, and fecundity in insects.

Due to the success of *ak* gene silencing, this gene is considered a high-potential molecular target for effective insect control based on RNAi technology [106]. Supporting this hypothesis, transgenic *Arabidopsis* plants expressing dsRNA directed at the *ak* gene were tested against the *H. armigera* species. As a result, it was observed that caterpillars eat less transgenic plants. Alternatively, caterpillars that atethe transgenic plants showed high mortality rates and delayed development compared to the caterpillars who were only fed wild plants [103]. Ai *et al.* [107] conducted similar tests using two types of transgenic tobacco plants expressing dsRNA-*ak* on the aforementioned species. The silencing molecules were able to reduce the size and body mass of the caterpillars, in addition to promoting repellent behavior. Camargo *et al.* [108] used two different dsRNA-*ak* delivery approaches to the tomato pest *Tuta absoluta* through *in vitro* uptake of dsRNA by the petiole and by *Agrobacterium*-mediated transformation. In both approaches, mortality, developmental delays, smaller body size and reduced herbivory were observed, the latter being more intense in transgenic plants.

In the phylum Nematoda, AK has been characterized in some species. In the model organism *Caenorhabditis elegans*, five AK isoforms were found, one of which (ARGK-2) was possibly located in the mitochondria. All these identified AKs have kinetic constants typical of AKs observed in other species [8]. In the species *Toxocara canis*, *Toxocara vitulorum*, and *Ascaris lubricoides*, immunofluorescence tests detected the presence of AK in the muscles, epidermis, intestine, oviduct, and uterus, i.e., metabolically active compartments [109]. Experiments with cultures of goat peripheral blood mononuclear cells (PBMC) treated with different concentrations of recombinant AK from *Haemonchus contortus* induced an increase in the cytokines IL-4, IL-10, IL-17, and IFN-γ; suppressed cell proliferation; reduced cell migration; and increased nitric oxide production and apoptosis [110]. These results show the participation of AK in the parasite-host interaction, regulating the host's immune functions [111]. Alternately, Xu *et al.* [111] showed a different result, in which rabbit PBMC stimulated by two recombinant AKs from the parasitic arthropod *Sarcoptes scabiei* resulted in a significant increase in cell proliferation, decreased apoptosis, upregulation of the genes Bcl-2, Bcl-xl, and NF-kB (p65), downregulation of Bax genes; an increased rate of cell migration, and promotion of interleukin (IL-4 and IL-17) secretion; and inhibition of IL-2, IFN-g, and IL-10 secretion. A possible application of AK in the immunodetection of *T. canis* infection in humans was tested, however, the antigen shows cross-reactivity with *Toxoplasma gondii*, *Plasmodium vivax*, and *Entamoeba histolytica* [112].

In the phylum Mollusca, specifically in the species *Patinopecten yessoensis*, four AK protein-coding genes were identified. In acidic pH conditions, the genes *ak2*, *ak3*, and *ak4* were upregulated in the mantle, gills, and striated muscle [113]. In the species *Sepia pharaonis*, the transcriptional levels of AK in the muscles and liver were increased under low-salinity conditions [114]. The AK response to stress confirms the results obtained by other authors in other models, suggesting a relationship between these proteins and their respective genes and energy homeostasis control during environmental changes.

4. Allergens

Allergic diseases represent an important cause of morbidity in the world, strongly impacting health systems and the economy [115]. It is estimated that 30%–40 % of the population worldwide is affected by some type of allergy [116], and the prevalence of these diseases, as well as their complexity and severity, tend to increase, especially in young adult patients and children [117]. Allergies include rhinitis, dermatitis, asthma, drug allergy, hives (urticaria), insect allergy, anaphylaxis, angioedema, and food allergy [118].

Food allergy corresponds to a pathological reaction of the immune system, which occurs after ingestion of a food protein antigen [119]. Shellfish allergy (mollusks and crustaceans) is one of the most common food allergies in the world [120]. In the last 20 years, several allergens have been sequenced and identified in molluscan and crustacean species. In general, these allergens are proteins of low molecular weight, with acidic isoelectric points, that are soluble in water, and have high thermal stability [121]. Tropomyosin was the first allergen found in shellfish. Subsequently, other proteins were reported, such as myosin light chain (MLC), sarcoplasmic calcium-binding protein (SCP), and AK [122]. The latter was reported in crab [123,124], shrimp [125,126], moth, cockroach, lobster, and mussel [127].

Binder *et al.* [127] were the first to describe AK as an allergen, showing IgE reactivity in serum samples from patients with a history of type 1 allergy to recombinant AK from *Plodia interpunctella*. Furthermore, experiments with basophils from two patients sensitive to recombinant AK from *P. interpunctella* resulted in the release of histamine [127], a molecule with a relevant function in allergic responses [128]. Later, a ~40 kDa protein was found that binds to IgE, very common in sera from shrimp-allergic patients, and it was designated as Pen m 2, with the amino acid sequence of this protein being very similar (90 %) to the AK sequences of the crustaceans *M. japonicus*, *Homarus gammarus*, and *Procambarus clarkii* [125]. An antibody to this protein (Pen m 2) was synthesized for immunoblotting assay. The results showed reactivity to purified AKs of other crustacean species, as well as sera from shrimp-allergic patients, confirming the identity of AK protein as a common crustacean allergen [125]. A monoclonal antibody (MAb38G6) specific for the *Periplaneta americana* allergen, secreted by hybridoma clone 38G6 [129] and a heptapeptide phage to recognize it was tested [130]. The two-dimensional electrophoresis analysis showed eight reactive spots for MAb38G6, and all of the proteins were found to be homologous to AK. All the serum samples from cockroach-allergic patients contained IgE bound to a protein purified by affinity to MAb38G6, i.e., AK, unlike non-allergic patients, whose sera were not reactive [130].

Due to the antigenicity of AK observed in mammals, this protein has been considered as a candidate for vaccines [131]. AK vaccines were analyzed in mice that were previously sensitized to crude cockroach extract (*P. americana*) containing AK. There was an increase in the amount of IgG1 specific to the crude cockroach extract in the group that received the AK vaccine [132]. Additionally, inflammatory cells such as neutrophils, eosinophils, and lymphocytes were reduced in bronchoalveolar lavage fluid, with a decrease in the degrees of histopathological damage and lower expression of the cytokines IL-4, IL-5, IL-13, and TNF-α in the lungs, compared to the results before vaccination [132]. A more recent study obtained similar results, in which the AK vaccine in allergic mice resulted in a decrease in the degree of histopathological damage, as well as the degree of goblet cells, reduced collagen and fibrosis deposition in lung tissue, and lower gene expression of cytokines, compared to the group that received the placebo vaccine [133].

5. Inhibitory molecules

In the past few years, some AK protein inhibitor molecules have been found, most of them being phenolic compounds [134]. It was reported that two *Camellia sinensis* catechins inhibit the enzyme activity of recombinant AK from *T. cruzi* by 50 % nanomolar concentrations [135]. It was observed that rutin inhibits around 80 % of AK activity (at concentrations of 20–60 μM), being a non-competitive inhibitor. Moreover, the thermodynamic properties found indicate that rutin spontaneously binds to AK, and hydrophobic interactions are involved in this binding [136]. The inhibitory effects of quercetin and luteolin were tested against the enzyme activity of AK from *Locusta migratoria manilensis*. These compounds were able to inhibit 50 % of AK activity at concentrations of 12 and 24 μM, respectively [137]. Predictions of molecular interaction by the docking technique demonstrated that the compounds

rutin, quercetin, and luteolin are located within the hydrophobic pocket of the enzyme, forming hydrogen bonds with amino acids present in the active site region, possibly constituting the principal mechanism of inhibition [136,137]. Resveratrol is located within the hydrophobic pocket of the enzyme, along with the other compounds mentioned above, however, there are no hydrogen bonds with the protein. To inhibit 50 % of the AK activity of *T. cruzi*, a concentration of 325 μM was needed. Furthermore, the compound was able to inhibit the growth of the epimastigote and trypomastigote forms of *T. cruzi* (IC50 of 98 and 77 μM, respectively) [138]. More recently, it was reported that the polyphenolic pigment delphinidin also has trypanocidal activity against the trypomastigote form of *T. cruzi*, in addition to interacting with the AK protein, showing inhibitory effects [139]. Molecular docking simulations demonstrated that delphinidin docks onto the ATP/ADP-binding site, specifically where ribose-phosphate binding occurs [139].

It is important to highlight that phenolic compounds are safe for human health, as they are currently used in the treatment of diseases such as hypertension, metabolic disorders, and neurodegenerative diseases [140]. The trypanocidal activity of resveratrol documented by Valera-Vera *et al.* [138,139] encourages novel research on the development of medications for Chagas Disease treatment.

Funding information

This research was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil, Instituto Nacional de Ciência e Tecnologia em Entomologia Molecular, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, and Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Brazil -Edital: E-26/201.331/2016 and E-26/211.534/2021.

CRediT authorship contribution statement

Brenda Martins Vasconcellos: Conceptualization, Writing – original draft. **Victor Guimarães Ribeiro:** Conceptualization, Formal analysis. **Naysha do Nascimento Campos:** Investigation, Writing – review & editing. **Luis Guilherme da Silva Romão Mota:** Investigation, Writing – review & editing. **Mônica Ferreira Moreira:** Funding acquisition, Writing – review & editing.

Declaration of competing interest

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 paper.

Data availability

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

Acknowledgments

The authors Vasconcellos, B.M and Guimarães-Ribeiro, V. are recipients of a graduate fellowship from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). MOTA, L. G. S. R is an undergraduate fellowship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

[1] J.F. Morrison, D.E. Griffiths, A.H. Ennor, The purification and properties of arginine phosphokinase, Biochem. J. 65 (1) (1957) 143.
[2] W.R. Ellington, Evolution and physiological roles of phosphagen systems, Annu. Rev. Physiol. 63 (1) (2001) 289–325.
[3] T. Suzuki, T. Furukohri, Evolution of phosphagen kinase: primary structure of glycocyamine kinase and arginine kinase from invertebrates, J. Mol. Biol. 237 (3) (1994) 353–357.
[4] K. Uda, W.R. Ellington, T. Suzuki, A diverse array of creatine kinase and arginine kinase isoform genes is present in the starlet sea anemone Nematostella vectensis, a cnidarian model system for studying developmental evolution, Gene 497 (2) (2012) 214–227.
[5] K. Lohmann, Hydrolysis of adenylphosphoric and arginine phosphoric acids in the crab muscle, Biochem. Z. 282 (1935) 109–119.
[6] S.L. Blethen, N.O. Kaplan, Purification of arginine kinase from lobster and a study of some factors affecting its reactivation, Biochemistry 6 (5) (1967) 1413–1421.
[7] F.J. Hird, The importance of arginine in evolution, Comp. Biochem. Physiol. B Comp. Biochem. 85 (2) (1986) 285–288.
[8] D. Fraga, M. Aryal, J.E. Hall, E. Rae, M. Snider, Characterization of the arginine kinase isoforms in Caenorhabditis elegans, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 187 (2015) 85–101.
[9] D.E. Griffiths, J.F. Morrison, A.H. Ennor, A study of the kinetics of the reactions catalysed by arginine phosphokinase, Biochem. J. 65 (1) (1957) 153.
[10] S.L. Blethen, Kinetic properties of the arginine kinase isoenzyme of Limulus polyphemus, Arch. Biochem. Biophys. 149 (1) (1972) 244–251.
[11] R. Virden, D.C. Watts, E. Baldwin, Adenosine 5′-triphosphate–arginine phosphotransferase from lobster muscle: purification and properties, Biochem. J. 94 (3) (1965) 536.
[12] R. Virden, D.C. Watts, The distribution of guanidine-adenosine triphosphate phosphotransferases and adenosine triphosphatase in animals from several phyla, Comp. Biochem. Physiol. 13 (2) (1964) 161–177.
[13] K. Uda, T. Suzuki, A novel arginine kinase with substrate specificity towards D-arginine, Protein J. 26 (2007) 281–291.
[14] Y. Robin, C. Klotz, Y. Guillou, Y. Benyamin, A spermatozoa-specific isoenzyme of arginine kinase in sabellid worms. Biochemical and immunological comparison with muscle enzyme, Comp. Biochem. Physiol. Part B: Comparative Biochemistry 52 (3) (1975) 387–392.
[15] T. Suzuki, Y. Kawasaki, T. Furukohri, W.R. Ellington, Evolution of phosphagen kinase. VI. Isolation, characterization and cDNA-derived amino acid sequence of lombricine kinase from the earthworm Eisenia foetida, and identification of a possible candidate for the guanidine substrate recognition site, Biochim. Biophys. Acta Protein Struct. Mol. Enzymol. 1343 (2) (1997) 152–159.
[16] T. Suzuki, Y. Kawasaki, Y. Unemi, Y. Nishimura, T. Soga, et al., Gene duplication and fusion have occurred frequently in the evolution of phosphagen kinases–a two-domain arginine kinase from the clam Pseudocardium sachalinensis, Biochim. Biophys. Acta Protein Struct. Mol. Enzymol. 1388 (1) (1998) 253–259.
[17] K. Fritz-Wolf, T. Schnyder, T. Wallimann, W. Kabsch, Structure of mitochondrial creatine kinase, Nature 381 (6580) (1996) 341–345.
[18] G. Zhou, T. Somasundaram, E. Blanc, G. Parthasarathy, W.R. Ellington, et al., Transition state structure of arginine kinase: implications for catalysis of bimolecular reactions, Proc. Natl. Acad. Sci. USA 95 (15) (1998) 8449–8454.
[19] G. Zhou, W.R. Ellington, M.S. Chapman, Induced fit in arginine kinase, Biophys. J. 78 (3) (2000) 1541–1550.
[20] T. Suzuki, H. Fukuta, H. Nagato, M. Umekawa, Arginine kinase from Nautilus pompilius, a living fossil: site-directed mutagenesis studies on the role of amino acid residues in the guanidino specificity region, J. Biol. Chem. 275 (31) (2000) 23884–23890.
[21] K. Uda, T. Suzuki, Role of amino acid residues on the GS region of Stichopus arginine kinase and Danio creatine kinase, Protein J. 23 (2004) 53–64.
[22] A. Azzi, S.A. Clark, W.R. Ellington, M.S. Chapman, The role of phosphagen specificity loops in arginine kinase, Protein Sci. 13 (3) (2004) 575–585.
[23] A. Bairoch, PROSITE: a dictionary of sites and patterns in proteins, Nucleic Acids Res. 19 (Suppl) (1991) 2241.
[24] C. Dumas, J. Camonis, Cloning and sequence analysis of the cDNA for arginine kinase of lobster muscle, J. Biol. Chem. 268 (29) (1993) 21599–21605.
[25] F. Dong, N. Zhang, Z. Xie, X. Meng, Qian, et al., Characterization and in vitro expression of arginine kinase gene in the invasive western flower thrips, Frankliniella occidentalis, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 229 (2019) 51–57.
[26] Y.M. Ma, N. Chen, J.Y. Tan, M.Y. Li, S. Liu, Molecular characterization of an arginine kinase from Lasioderma serricorne and the effect of gene silencing on larval survival, J. Stored Prod. Res. 99 (2022) 102032.
[27] J.D. Thompson, D.G. Higgins, T.J. Gibson, Clustal W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice, Nucleic Acids Res. 22 (22) (1994) 4673–4680.
[28] R. Virden, D.C. Watts, R.L. Watts, D.B. Gammack, J.H. Raper, Adenosine 5′-triphosphate–arginine phosphotransferase from lobster muscle. Molecular weight, Biochem. J. 99 (1) (1966) 155.
[29] S.L. Blethen, N.O. Kaplan, Characteristics of arthropod arginine kinases, Biochemistry 7 (6) (1968) 2123–2135.
[30] B. Moreland, D.C. Watts, R. Virden, Phosphagen kinases and evolution in the Echinodermata, Nature 214 (5087) (1967) 458–462.
[31] A. Ratto, B.M. Shapiro, R. Christen, Phosphagen kinase evolution: expression in echinoderms, Eur. J. Biochem. 186 (1-2) (1989) 195–203.
[32] N.V. Thoai, N.V. Thiem, G. Lacombe, J. Roche, Hétéroenzymes d'acide adénosine 5′-triphosphorique: L-arginine phosphotransférase, Biochim. Biophys. Acta (BBA) - Enzym. Biol. Oxid. 122 (3) (1966) 547–550.
[33] T. Suzuki, Y. Kawasaki, T. Furukohri, Evolution of phosphagen kinase: isolation, characterization and cDNA-derived amino acid sequence of two-domain arginine kinase from the sea anemone Anthopleura japonicus, Biochem. J. 328 (1) (1997) 301–306.

[34] B. Moreland, D.C. Watts, Molecular weight isoenzymes of arginine kinase in the mollusca and their association with muscle function, Nature 215 (5105) (1967) 1092–1094.
[35] Y. Robin, C. Klotz, N. van Thoai, Unspecific arginine kinase of molecular weight 150 000: purification and properties, Eur. J. Biochem. 21 (2) (1971) 170–178.
[36] M.S. Yousef, F. Fabiola, J.L. Gattis, T. Somasundaram, M.S. Chapman, Refinement of the arginine kinase transition-state analogue complex at 1.2 Å resolution: mechanistic insights, Acta Crystallogr. Sect. D Biol. Crystallogr. 58 (12) (2002) 2009–2017.
[37] P.S. Pruett, A. Azzi, S.A. Clark, M.S. Yousef, J.L. Gattis, et al., The putative catalytic bases have, at most, an accessory role in the mechanism of arginine kinase, J. Biol. Chem. 278 (29) (2003) 26952–26957.
[38] J.L. Gattis, E. Ruben, M.O. Fenley, W.R. Ellington, M.S. Chapman, The active site cysteine of arginine kinase: structural and functional analysis of partially active mutants, Biochemistry 43 (27) (2004) 8680–8689.
[39] P. Fernandez, A. Haouz, C.A. Pereira, C. Aguilar, P.M. Alzari, The crystal structure of Trypanosoma cruzi arginine kinase, Proteins: Struct., Funct., Bioinf. 69 (1) (2007) 209–212.
[40] X. Wu, S. Ye, S. Guo, W. Yan, M. Bartlam, Z. Rao, Structural basis for a reciprocating mechanism of negative cooperativity in dimeric phosphagen kinase activity, Faseb. J. 24 (1) (2010) 242–252.
[41] X. Niu, L. Bruschweiler-Li, O. Davulcu, J.J. Skalicky, R. Brüschweiler, M. S. Chapman, Arginine kinase: joint crystallographic and NMR RDC analyses link substrate-associated motions to intrinsic flexibility, J. Mol. Biol. 405 (2) (2011) 479–496.
[42] S.A. Clark, O. Davulcu, M.S. Chapman, Crystal structures of arginine kinase in complex with ADP, nitrate, and various phosphagen analogs, Biochem. Biophys. Res. Commun. 427 (1) (2012) 212–217.
[43] A.A. Lopez-Zavala, R.R. Sotelo-Mundo, K.D. Garcia-Orozco, F. Isac-Martinez, L. G. Brieba, E. Rudiño-Piñera, Crystallization and X-ray diffraction studies of arginine kinase from the white Pacific shrimp Litopenaeusvannamei, Acta Crystallogr., Sect. F: Struct. Biol. Cryst. Commun. 68 (7) (2012) 783–785.
[44] A.A. López-Zavala, K.D. García-Orozco, J.S. Carrasco-Miranda, R. Sugich-Miranda, E.F. Velázquez-Contreras, et al., Crystal structure of shrimp arginine kinase in binary complex with arginine—a molecular view of the phosphagen precursor binding to the enzyme, J. Bioenerg. Biomembr. 45 (2013) 511–518.
[45] Z. Wang, Z. Qiao, S. Ye, R. Zhang, Structure of a double-domain phosphagen kinase reveals an asymmetric arrangement of the tandem domains, Acta Crystallogr. Sect. D Biol. Crystallogr. 71 (4) (2015) 779–789.
[46] M.H. Godsey, O. Davulcu, J.C. Nix, J.J. Skalicky, R.P. Brüschweiler, M. S. Chapman, The sampling of conformational dynamics in ambient-temperature crystal structures of arginine kinase, Structure 24 (10) (2016) 1658–1667.
[47] A. Laino, A.A. Lopez-Zavala, K.D. Garcia-Orozco, J.S. Carrasco-Miranda, M. Santana, V. Stojanoff, C.F. Garcia, Biochemical and structural characterization of a novel arginine kinase from the spider Polybetespythagoricus, PeerJ 5 (2017) e3787.
[48] M.J. Suskiewicz, B. Hajdusits, R. Beveridge, A. Heuck, L.D. Vu, et al., Structure of McsB, a protein kinase for regulated arginine phosphorylation, Nat. Chem. Biol. 15 (5) (2019) 510–518.
[49] Y. Yang, G.Y. Liu, H. Yang, M.J. Hu, M.J. Cao, et al., Crystal structure determination of Scylla paramamosain arginine kinase, an allergen that may cause cross-reactivity among invertebrates, Food Chem. 271 (2019) 597–605.
[50] Z. Rao, S.Y. Kim, X. Li, Y.J. Kim, J.H. Park, Insight into structural aspects of histidine 284 of Daphnia magna arginine kinase, Mol. Cell. 43 (9) (2020) 784.
[51] B. Hajdusits, M.J. Suskiewicz, N. Hundt, A. Meinhart, R. Kurzbauer, et al., McsB forms a gated kinase chamber to mark aberrant bacterial proteins for degradation, Elife 10 (2021) e63505.
[52] A.C. Gomez-Yanes, E.N. Moreno-Cordova, K.D. Garcia-Orozco, A. Laino, M. A. Islas-Osuna, A.A. Lopez-Zavala, R.R. Sotelo-Mundo, The arginine kinase from the tick rhipicephalus sanguineus is an efficient biocatalyst, Catalysts 12 (10) (2022) 1178.
[53] D.S. Kim, K. Jang, W.S. Kim, M. Ryu, J.H. Park, Y.J. Kim, Crystal structure of H227A mutant of arginine kinase in Daphnia magna suggests the importance of its stability, Molecules 27 (3) (2022) 884.
[54] D.C. Watts, L.H. Bannister, Location of arginine kinase in the cilia of Tetrahymena pyriformis, Nature 226 (5244) (1970) 450–451.
[55] J. Michibata, N. Okazaki, S. Motomura, K. Uda, Fujiwara, et al., Two arginine kinases of Tetrahymena pyriformis: characterization and localization, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 171 (2014) 34–41.
[56] M. Noguchi, T. Sawadah, T. Akazawa, ATP-regenerating system in the cilia of Paramecium caudatum, J. Exp. Biol. 204 (6) (2001) 1063–1071.
[57] D. Yano, T. Suzuki, S. Hirokawa, K. Fuke, T. Suzuki, Characterization of four arginine kinases in the ciliate Paramecium tetraurelia: Investigation on the substrate inhibition mechanism, Int. J. Biol. Macromol. 101 (2017) 653–659.
[58] D.C. Watts, L.H. Bannister, Location of arginine kinase in the cilia of Tetrahymena pyriformis, Nature 226 (5244) (1970) 450–451.
[59] M.R. Miranda, L.A. Bouvier, G.E. Canepa, C.A. Pereira, Subcellular localization of Trypanosoma cruzi arginine kinase, Parasitology 136 (10) (2009) 1201–1207.
[60] C.A. Pereira, G.D. Alonso, M.C. Paveto, A. Iribarren, M.L. Cabanas, H.N. Torres, M.M. Flawiá, Trypanosoma cruzi arginine kinase characterization and cloning: a novel energetic pathway in protozoan parasites, J. Biol. Chem. 275 (2) (2000) 1495–1501.
[61] G.D. Alonso, C.A. Pereira, M.S. Remedi, M.C. Paveto, L. Cochella, et al., Arginine kinase of the flagellate protozoa Trypanosoma cruzi: regulation of its expression and catalytic activity, FEBS Lett. 498 (1) (2001) 22–25.
[62] C.A. Pereira, G.D. Alonso, S. Ivaldi, A. Silber, M.J.M. Alves, et al., Arginine metabolism in Trypanosoma cruzi is coupled to parasite stage and replication, FEBS Lett. 526 (1–3) (2002) 111–114.
[63] C.A. Pereira, G.D. Alonso, S. Ivaldi, A.M. Silber, M.J.M. Alves, H.N. Torres, M. M. Flawiá, Arginine kinase overexpression improves Trypanosoma cruzi survival capability, FEBS Lett. 554 (1–2) (2003) 201–205.
[64] M.R. Miranda, G.E. Canepa, L.A. Bouvier, C.A. Pereira, Trypanosoma cruzi: oxidative stress induces arginine kinase expression, Exp. Parasitol. 114 (4) (2006) 341–344.
[65] F. Voncken, F. Gao, C. Wadforth, M. Harley, C. Colasante, The phosphoarginine energy-buffering system of Trypanosoma brucei involves multiple arginine kinase isoforms with different subcellular locations, PLoS One 8 (6) (2013) e65908.
[66] G.E. Canepa, C. Carrillo, M.R. Miranda, M. Sayé, C.A. Pereira, Arginine kinase in Phytomonas, a trypanosomatid parasite of plants, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 160 (1) (2011) 40–43.
[67] W.R. Ellington, T. Suzuki, Evolution and divergence of creatine kinases, in: Creatine Kinase, Nova Science Publishers, Inc., New York, 2006, pp. 1–26.
[68] K. Tanaka, K. Uda, M. Shimada, K.I. Takahashi, S. Gamou, et al., Evolution of the cytoplasmic and mitochondrial phosphagen kinases unique to annelid groups, J. Mol. Evol. 65 (2007) 616–625.
[69] T. Suzuki, S. Soga, M. Inoue, K. Uda, Characterization and origin of bacterial arginine kinases, Int. J. Biol. Macromol. 57 (2013) 273–277.
[70] J. Fuhrmann, A. Schmidt, S. Spiess, A. Lehner, K. Turgay, et al., McsB is a protein arginine kinase that phosphorylates and inhibits the heat-shock regulator CtsR, Science 324 (5932) (2009) 1323–1327.
[71] R. Rabus, A. Ruepp, T. Frickey, T. Rattei, B. Fartmann, et al., The genome of Desulfotalea psychrophila, a sulfate-reducing bacterium from permanently cold Arctic sediments, Environ. Microbiol. 6 (9) (2004) 887–902.
[72] S. Nakagawa, Y. Takaki, S. Shimamura, A.L. Reysenbach, K. Takai, K. Horikoshi, Deep-sea vent ε-proteobacterial genomes provide insights into emergence of pathogens, Proc. Natl. Acad. Sci. USA 104 (29) (2007) 12146–12150.
[73] B.S. Goldman, W.C. Nierman, D. Kaiser, S.C. Slater, A.S. Durkin, et al., Evolution of sensory complexity recorded in a myxobacterial genome, Proc. Natl. Acad. Sci. USA 103 (41) (2006) 15200–15205.
[74] L.D. Andrews, J. Graham, M.J. Snider, D. Fraga, Characterization of a novel bacterial arginine kinase from Desulfotaleapsychrophila, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 150 (3) (2008) 312–319.
[75] J. Bragg, A. Rajkovic, C. Anderson, R. Curtis, J. Van Houten, et al., Identification and characterization of a putative arginine kinase homolog from Myxococcus xanthus required for fruiting body formation and cell differentiation, J. Bacteriol. 194 (10) (2012) 2668–2676.
[76] D. Fraga, K. Stock, M. Aryal, C. Demoll, L. Fannin, M.J. Snider, Bacterial arginine kinases have a highly skewed distribution within the proteobacteria, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 233 (2019) 60–71.
[77] S. Perovic-Ottstadt, M. Wiens, H.C. Schröder, R. Batel, M. Giovine, et al., Arginine kinase in the demosponge Suberites domuncula: regulation of its expression and catalytic activity by silicic acid, J. Exp. Biol. 208 (4) (2005) 637–646.
[78] M. Conejo, M. Bertin, S.A. Pomponi, W.R. Ellington, The early evolution of phosphagen kinases—insights from choanoflagellate and poriferan arginine kinases, J. Mol. Evol. 66 (2008) 11–20.
[79] T. Wallimann, H.M. Eppenberger, Properties of arginine kinase from Drosophila melanogaster, Eur. J. Biochem. 38 (1) (1973) 180–184.
[80] A.B. Lang, C. Wyss, H.M. Eppenberger, Localization of arginine kinase in muscle fibres of Drosophila melanogaster, J. Muscle Res. Cell Motil. 1 (1980) 147–161.
[81] F.F. Ma, Q.H. Liu, G.K. Guan, C. Li, J. Huang, Arginine kinase of Litopenaeus vannamei involved in white spot syndrome virus infection, Gene 539 (1) (2014) 99–106.
[82] X.L. Qi, X.F. Su, G.Q. Lu, C.X. Liu, G.M. Liang, et al., The effect of silencing arginine kinase by RNAi on the larval development of Helicoverpa armigera, Bull. Entomol. Res. 105 (5) (2015) 555–565.
[83] M.E. Chamberlin, Mitochondrial arginine kinase in the midgut of the tobacco hornworm (Manduca sexta), J. Exp. Biol. 200 (21) (1997) 2789–2796.
[84] R. Kucharski, R. Maleszka, Arginine kinase is highly expressed in the compound eye of the honey-bee, Apis mellifera, Gene 211 (2) (1998) 343–349.
[85] W. Liu, D. Qian, X. Yan, Proteomic analysis of differentially expressed proteins in hemolymph of Scylla serrata response to white spot syndrome virus infection, Aquaculture 314 (1–4) (2011) 53–57.
[86] K.M. Astrofsky, M.M. Roux, K.R. Klimpel, J.G. Fox, A.K. Dhar, Isolation of differentially expressed genes from white spot virus (WSV) infected Pacific blue shrimp (Penaeus stylirostris), Arch. Virol. 147 (2002) 1799–1812.
[87] N. Zhang, H. Jiang, X. Meng, K. Qian, Y. Liu, et al., Broad-complex transcription factor mediates opposing hormonal regulation of two phylogenetically distant arginine kinase genes in Tribolium castaneum, Commun. Biol. 3 (1) (2020) 631.
[88] K. Qian, Q. Guan, H. Zhang, N. Zhang, X. Meng, H. Liu, J. Wang, RNAi-mediated knockdown of arginine kinase genes leads to high mortality and negatively affect reproduction and blood-feeding behavior of Culex pipiens pallens, PLoS Neglected Trop. Dis. 16 (11) (2022) e0010954.
[89] H. Wang, L. Zhang, L. Zhang, Q. Lin, N. Liu, Arginine kinase: differentiation of gene expression and protein activity in the red imported fire ant, Solenopsisinvicta, Gene 430 (1–2) (2009) 38–43.
[90] B. Wang, F. Li, B. Dong, X. Zhang, C. Zhang, J. Xiang, Discovery of the genes in response to white spot syndrome virus (WSSV) infection in Fenneropenaeus chinensis through cDNA microarray, Mar. Biotechnol. 8 (2006) 491–500.
[91] G. Jaramillo-Gutierrez, J. Rodrigues, G. Ndikuyeze, M. Povelones, A. Molina-Cruz, et al., Mosquito immune responses and compatibility between Plasmodium parasites and anopheline mosquitoes, BMC Microbiol. 9 (2009) 1–11.

[92] A. Chowdhury, C.M. Modahl, D. Missé, R.M. Kini, J. Pompon, High resolution proteomics of Aedes aegypti salivary glands infected with either dengue, Zika or chikungunya viruses identify new virus specific and broad antiviral factors, Sci. Rep. 11 (1) (2021) 23696.
[93] N. Zhang, J. Wei, H. Jiang, H. Ge, Y. Zheng, Meng, et al., Knockdown or inhibition of arginine kinases enhances susceptibility of Tribolium castaneum to deltamethrin, Pestic. Biochem. Physiol. 183 (2022) 105080.
[94] X. Chen, P. Yao, X. Chu, L. Hao, X. Guo, et al., Isolation of arginine kinase from Apis cerana cerana and its possible involvement in response to adverse stress, Cell Stress & Chaperones 20 (2015) 169–183.
[95] M. Konus, C. Koy, S. Mikkat, M. Kreutzer, R. Zimmermann, M. Iscan, M. O. Glocker, Molecular adaptations of Helicoverpa armigera midgut tissue under pyrethroid insecticide stress characterized by differential proteome analysis and enzyme activity assays, Comp. Biochem. Physiol. Genom. Proteonomics 8 (2) (2013) 152–162.
[96] V.V. Dawkar, Y.R. Chikate, T.H. More, V.S. Gupta, A.P. Giri, The expression of proteins involved in digestion and detoxification are regulated in Helicoverpa armigera to cope up with chlorpyrifos insecticide, Insect Sci. 23 (1) (2016) 68–77.
[97] K. Lu, Y. Song, R. Zeng, The role of cytochrome P450-mediated detoxification in insect adaptation to xenobiotics, Current Opinion in Insect Science 43 (2021) 103–107.
[98] C. Cruse, T.W. Moural, F. Zhu, Dynamic roles of insect carboxyl/cholinesterases in chemical adaptation, Insects 14 (2) (2023) 194.
[99] P.D. Games, S.N. Alves, B.B. Katz, J.M. Tomich, J.E. Serrão, Differential protein expression in the midgut of Culex quinquefasciatus mosquitoes induced by the insecticide temephos, Med. Vet. Entomol. 30 (3) (2016) 253–263.
[100] H. Abe, S. Hirai, S. Okada, Metabolic responses and arginine kinase expression under hypoxic stress of the kuruma prawn Marsupenaeus japonicus, Comp. Biochem. Physiol. Mol. Integr. Physiol. 146 (1) (2007) 40–46.
[101] V. Shetty, N.J. Shetty, S.K. Jha, R.C. Chaubey, Gamma radiation induced changes in expression of heat shock proteins (Hsc70 and Hsp83) in the dengue vector Aedes aegypti (L.), J. Vector Borne Dis. 59 (2) (2022) 145–153.
[102] Y. Zhao, G. Yang, G. Wang-Pruski, M. You, Phyllotretastriolata (Coleoptera: Chrysomelidae): arginine kinase cloning and RNAi-based pest control, Eur. J. Entomol. 105 (5) (2008) 815.
[103] F. Liu, X.D. Wang, Y.Y. Zhao, Y.J. Li, Y.C. Liu, J. Sun, Silencing the HaAK gene by transgenic plant-mediated RNAi impairs larval growth of Helicoverpa armigera, Int. J. Biol. Sci. 11 (1) (2015) 67.
[104] E.C. Andrade, W.B. Hunter, RNAi feeding bioassay: development of a non-transgenic approach to control Asian citrus psyllid and other hemipterans, Entomol. Exp. Appl. 162 (3) (2017) 389–396.
[105] S. Fu, Z. Liu, J. Chen, G. Sun, Y. Jiang, et al., Silencing arginine kinase/integrin β1 subunit by transgenic plant expressing dsRNA inhibits the development and survival of Plutella xylostella, Pest Manag. Sci. 76 (5) (2020) 1761–1771.
[106] V.S.R. Kola, P. Renuka, M.S. Madhav, S.K. Mangrauthia, Key enzymes and proteins of crop insects as candidate for RNAi based gene silencing, Front. Physiol. 6 (2015) 119.
[107] X.Y. Ai, S. Ren, L. Huang, X.N. Liu, N. Liu, Transgenic tobacco expressing dsRNA of the arginine kinase gene exhibits enhanced resistance against Helicoverpa armigera, Bull. Insectol. 72 (1) (2019).
[108] R.A. Camargo, G.O. Barbosa, I.P. Possignolo, L.E. Peres, E. Lam, et al., RNA interference as a gene silencing tool tocontrol Tuta absoluta in tomato (Solanumlycopersicum), PeerJ 4 (2016) e2673.
[109] D.G.R.S. Kulathunga, S. Wickramasinghe, R.P.V.J. Rajapakse, L. Yatawara, W. R. Jayaweera, et al., Immunolocalization of arginine kinase (AK) in Toxocaracanis, toxocaravitulorum, and Ascaris lumbricoides, Parasitol. Res. 111 (2012) 663–671.
[110] M. Ehsan, W. Gao, J.A. Gadahi, M. Lu, X. Liu, et al., Arginine kinase from Haemonchus contortus decreased the proliferation and increased the apoptosis of goat PBMCs in vitro, Parasites Vectors 10 (2017) 1–14.
[111] Y. Xu, Z. Xu, X. Gu, Y. Xie, R. He, et al., Immunomodulatory effects of two recombinant arginine kinases in Sarcoptes Scabiei on host peripheral blood mononuclear cells, Front. Immunol. 13 (2022) 1035729.
[112] A. Varghese, O.K. Raina, D. Chandra, B.R. Mirdha, N.H. Kelawala, et al., Sero-detection of Toxocaracanis infection in human with T. canis recombinant arginine kinase, cathepsin L-1 and TES-26 antigens, Acta Parasitol. 62 (4) (2017) 775–778.
[113] Z. Yang, X. Huang, H. Liao, Z. Zhang, F. Sun, et al., Structure and functional analysis reveal an important regulated role of arginine kinase in Patinopecten yessoensis under low pH stress, Aquat. Toxicol. 222 (2020) 105452.
[114] S.J. Yin, L. Zhang, L. Zhang, J. Wan, W. Song, et al., Metabolic responses and arginine kinase expression of juvenile cuttlefish (Sepia pharaonis) under salinity stress, Int. J. Biol. Macromol. 113 (2018) 881–888.
[115] M. Sánchez-Borges, B.L. Martin, A.M. Muraro, R.A. Wood, I.O. Agache, et al., The importance of allergic disease in public health: an iCAALL statement, World Allergy Organization Journal 11 (2018) 1–3.
[116] R. Pawankar, The unmet global health need of severe and complex allergies: meeting the challenge, World Allergy Organization Journal 5 (2) (2012) 20–21.
[117] R. Pawankar, G.W. Canonica, S.T. Holgate, R.F. Lockey, M.S. Blaiss, WAO white book on allergy, Milwaukee, WI: World Allergy Organization 3 (2011) 156–157.
[118] E.G. Weinberg, The WAO white book on allergy 2011-2012, Current Allergy & Clinical Immunology 24 (3) (2011) 156–157.
[119] W. Yu, D.M.H. Freeland, K.C. Nadeau, Food allergy: immune mechanisms, diagnosis and immunotherapy, Nat. Rev. Immunol. 16 (12) (2016) 751–765.
[120] J.H. Dunlop, C.A. Keet, Epidemiology of food allergy, Immunology and Allergy Clinics 38 (1) (2018) 13–25.
[121] A.L. Lopata, J. Kleine-Tebbe, S.D. Kamath, Allergens and molecular diagnostics of shellfish allergy, Molecular Allergy Diagnostics: Innovation for a Better Patient Management (2017) 399–414.
[122] M. Pedrosa, T. Boyano-Martínez, C. García-Ara, S. Quirce, Shellfish allergy: a comprehensive review, Clin. Rev. Allergy Immunol. 49 (2015) 203–216.
[123] A.M.A. Rahman, S.D. Kamath, A.L. Lopata, J.J. Robinson, R.J. Helleur, Biomolecular characterization of allergenic proteins in snow crab (Chionoecetes opilio) and de novo sequencing of the second allergen arginine kinase using tandem mass spectrometry, J. Proteonomics 74 (2) (2011) 231–241.
[124] M. Rosmilah, M. Shahnaz, H.M. Zailatul, A. Noormalin, I. Normilah, Identification of tropomyosin and arginine kinase as major allergens of Portunuspelagicus (blue swimming crab), Trop. Biomed. 29 (3) (2012) 467–478.
[125] C.J. Yu, Y.F. Lin, B.L. Chiang, L.P. Chow, Proteomics and immunological analysis of a novel shrimp allergen, Pen m 2, J. Immunol. 170 (1) (2003) 445–453.
[126] A.M. Abdel Rahman, S.D. Kamath, S. Gagne, A.L. Lopata, R. Helleur, Comprehensive proteomics approach in characterizing and quantifying allergenic proteins from northern shrimp: toward better occupational asthma prevention, J. Proteome Res. 12 (2) (2013) 647–656.
[127] M. Binder, V. Mahler, B. Hayek, W.R. Sperr, M. Schöller, et al., Molecular and immunological characterization of arginine kinase from the Indianmealmoth, Plodia interpunctella, a novel cross-reactive invertebrate pan-allergen, J. Immunol. 167 (9) (2001) 5470–5477.
[128] E. Scholar, Histamine. xPharm: the Comprehensive Pharmacology Reference, 2009, pp. 1–6.
[129] N. Sookrung, P. Diraphat, W. Chaicumpa, P. Tongtawe, Y. Sakolvaree, et al., Cockroach allergen detection and cockroach allergens of allergic Thai patients, Asian Pac. J. Allergy Immunol. 21 (1) (2003) 1.
[130] N. Sookrung, W. Chaicumpa, A. Tungtrongchitr, P. Vichyanond, C. Bunnag, et al., Periplaneta americana arginine kinase as a major cockroach allergen among Thai patients with major cockroach allergies, Environ. Health Perspect. 114 (6) (2006) 875–880.
[131] S. Umair, J.S. Knight, R.J. Bland, H.V. Simpson, Molecular and biochemical characterisation of arginine kinases in Haemonchus contortus and Teladorsagiacircumcincta, Exp. Parasitol. 134 (3) (2013) 362–367.
[132] P. Meechan, A. Tungtrongchitr, U. Chaisri, K. Maklon, N. Indrawattana, et al., Intranasal, liposome-adjuvanted cockroach allergy vaccines made of refined major allergen and whole-body extract of Periplaneta americana, Int. Arch. Allergy Immunol. 161 (4) (2013) 351–362.
[133] P. Prangtaworn, K. Mahasongkram, A. Saeung, U. Chaisri, W. Seesuay, et al., A component-resolved therapeutic vaccine for cockroach allergy made of Per a 9 and transforming growth factor-β homologue, an immunosuppressive protein of Brugiamalayi, Front. Immunol. 12 (2021) 676558.
[134] C. A Pereira, Arginine kinase: a potential pharmacological target in trypanosomiasis, Infect. Disord. - Drug Targets 14 (1) (2014) 30–36.
[135] C. Paveto, M.C. Güida, M.I. Esteva, V. Martino, J. Coussio, et al., Anti-Trypanosoma cruzi activity of green tea (Camellia sinensis) catechins, Antimicrob. Agents Chemother. 48 (1) (2004) 69–74.
[136] X.Q. Wu, W.J. Zhu, Z.R. Lü, Y. Xia, J.M. Yang, et al., The effect of rutin on arginine kinase: inhibition kinetics and thermodynamics merging with docking simulation, Int. J. Biol. Macromol. 44 (2) (2009) 149–155.
[137] H.R. Wang, W.J. Zhu, X.Y. Wang, Mechanism of inhibition of arginine kinase by flavonoids consistent with thermodynamics of docking simulation, Int. J. Biol. Macromol. 49 (5) (2011) 985–991.
[138] E.A. Valera-Vera, M. Sayé, C. Reigada, F.S. Damasceno, A.M. Silber, et al., Resveratrol inhibits Trypanosoma cruzi arginine kinase and exerts a trypanocidal activity, Int. J. Biol. Macromol. 87 (2016) 498–503.
[139] E. Valera-Vera, C. Reigada, M. Sayé, F.A. Digirolamo, F. Galceran, et al., Trypanocidal activity of the anthocyanidin delphinidin, a non-competitive inhibitor of arginine kinase, Nat. Prod. Res. 36 (12) (2022) 3153–3157.
[140] M.M. Rahman, M.S. Rahaman, M.R. Islam, F. Rahman, F.M. Mithi, et al., Role of phenolic compounds in human disease: current knowledge and future prospects, Molecules 27 (1) (2021) 233.