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Predictive In Silico Epigenomic Molecular Analysis of the *Aspergillus salvadorensis* Sequence

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Abstract:
The epigenomic analysis of the *Aspergillus salvadorensis* sequence shows a highly complex regulatory architecture, in which epigenetic mechanisms, hydrolytic enzymatic activity and antifungal resistance systems converge. The detection of regions enriched in CpG dinucleotides, together with the presence of repetitive sequences, suggests the existence of regulation mediated by DNA methylation and chromatin remodeling, key processes in transcriptional control in filamentous fungi. These epigenetic characteristics probably modulate the expression of genes involved in the degradation of polysaccharides, including enzymes of the glycosyl hydrolases and glucanase family, as well as genes associated with cellular defense mechanisms, such as transporters of the ABC (ATP-Binding Cassette) and MFS (Major Facilitator Superfamily) families. The coexistence of these elements suggests that *A. salvadorensis* has a dynamic regulatory network that allows it to optimize its adaptive response to fluctuating environmental conditions and chemical stress. The open reading frame (ORF) predicted by ORF 190 is achieved by translating the sequence into protein, this corresponds to a linear polypeptide of approximately 172 amino acids, consistent with the previous gene prediction. The analysis of its sequence reveals a high density of residues susceptible to post-translational modifications, including lysines (K), arginines (R), serines (S), threonine (T) and tyrosines (Y), which constitute potential sites of functional regulation. Acetylation of lysine residues suggests a role in modulating protein activity and mediating protein-protein interactions. Methylation in lysines and arginines indicates possible roles in epigenetic regulation and in the formation of macromolecular complexes. Likewise, phosphorylation in serine, threonine and tyrosine residues points to the participation of this protein in kinase-dependent cell signaling pathways, which supports its probable role in regulatory processes. The sequence presents a high density of widely distributed CpG sites susceptible to methylation, while acetylation and phosphorylation are inferred indirectly as a function of the structural and functional context of the chromatin, without corresponding to defined positions within the linear DNA sequence. These results reinforce the close relationship between epigenetic mechanisms and metabolic functionality in filamentous fungi, highlighting the biotechnological potential of *A. salvadorensis* in processes that require both degradative capacity and tolerance to antifungal compounds.
Keywords: Epigenomic, silico, CpG, ORF, proteins*, Aspergillus salvadorensis*.

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INTRODUCTION

The genus *Aspergillus* is one of the most diverse and economically significant groups of filamentous fungi in the world (Echevarría and Iqbal, 2021; Iqbal *et al.*, 2021). Fungi of the genus *Aspergillus* are characterized by their high metabolic versatility and their key role in the mineralization of organic matter in various ecological niches. This capacity is supported by the secretion of a wide repertoire of extracellular hydrolytic enzymes including cellulases, hemicellulases and proteases that allow the depolymerization of complex substrates into easily assimilated low molecular weight compounds (de Vries *et al.*, 2017; de Vries and Visser, 2001; Pouris *et al.*, 2024).

In the last decade, it has been established that the regulation of these metabolic processes is not determined exclusively by encoded genetic information, but also depends on epigenetic mechanisms, such as DNA methylation and post-translational histone modifications. These mechanisms are actively involved in modulating gene expression in response to environmental cues and stress conditions. In parallel, several species of *Aspergillus* have developed resistance systems against antifungal agents, which include overexpression of efflux transporters (mainly of ABC and MFS families) and the activation of detoxifying enzymes; these processes are also, at least in part, under epigenetic control (Gacek and Strauss, 2012; Keller, 2019; Verweij *et al.*, 2009).

In this context, the present study aims to characterize the genomic sequence of *Aspergillus salvadorensis*, in order to elucidate the interaction between epigenetic regulation and its resistance mechanisms, thus providing an integrated view of its functional organization and biological potential.

MATERIALS AND METHODS

In silico epigenomic analysis is defined as a systematic computational workflow aimed at converting primary sequencing data into biologically significant information. This process begins with the quality assessment of the FASTQ files, where low-quality reads are filtered out and technical artifacts, such as adapter sequences, are removed to ensure the integrity and reliability of the dataset. The purified reads are then aligned against a reference genome using specialized algorithms that establish precise genomic coordinates; in the case of methylation studies, this step involves greater complexity due to chemical cytokine conversions, which requires specific tools capable of modeling such transformations (Bolger *et al.*, 2014; Krueger and Andrews, 2011).

Once alignment is complete, the analysis focuses on the detection of enriched regions using peak calling, a statistical approach that identifies significant accumulations of reads associated with epigenetic marks or regulatory protein binding. These regions are then subjected to functional annotation, allowing their classification into genomic elements such as promoters, coding regions or distal regulatory elements, including enhancers. In addition, the integration with transcriptomic data allows correlations to be established between epigenetic modifications and levels of gene expression, facilitating the inference of states of activation or repression. The final interpretation is supported by visualization tools, such as genomic navigators, which allow the regulatory landscape to be reconstructed at the cellular level (Robinson *et al.*, 2011; Zhang *et al.*, 2008).

In silico epigenomic analysis integrates fundamentals of molecular biology and bioinformatics to study gene regulation without altering the primary DNA sequence, by processing large volumes of data generated by next-generation sequencing (NGS) technologies. This approach makes it possible to map epigenetic modifications, such as DNA methylation and histone modifications, providing critical information on transcriptional control mechanisms (Laird, 2010).

In the case of *Aspergillus salvadorensis*, the application of this approach is particularly relevant, as it allows the identification of epigenetic signatures associated with key physiological processes, such as growth, the production of secondary metabolites and adaptation to changing environmental conditions. Likewise, the use of bioinformatics tools makes it possible to predict patterns of gene regulation in response to specific stimuli such as environmental stress or biotic interactions, constituting a solid basis for subsequent functional studies and the use of this organism in biotechnological applications (Galagan *et al.*, 2005; Slotkin and Martienssen, 2007; Xie *et al.*, 2025).

RESULTS

In the epigenomic analysis of *Aspergillus salvadorensis*, the identification of orthologs such as K08139, K08150, K08158 and K08197, all belonging to the superfamily of transporters MFS transporter, suggests a close relationship between chromatin status and the regulation of transport of essential metabolites (Table 1). These transporters include sugar–H^+ cotransport systems, solute-facilitating transporters, multiple-protein proteinresistance (DHA1 family), and iron uptake systemsusing siderophores, reflecting a key functional network for metabolic adaptation and response to the environment.

From an epigenomic perspective, the expression of these genes may be modulated by histone marks such as H3K27me3 and H3K9me3. In regions where sugar or solute transporters predominate, more open or dynamically regulated chromatin domains are likely to be found, where H3K27me3 acts as a reversible silencing mechanism, allowing activation under specific conditions, such as changes in nutrient availability. In contrast, genes associated with drug resistance or more specialized functions, such as H^+-type iron transporters, could be located in more compact regions or close to heterochromatin, where H3K9me3 contributes to a more stable silencing, activating only under stress or iron-limiting conditions.

The variation in the quantitative values observed (e.g., higher relative abundance in K08158 vs. K08197) could reflect differences in chromatic accessibility, where regions with less epigenetic repression have greater basal expression. Thus, the epigenome of *Aspergillus salvadorensis* not only structurally organizes the genome, but also coordinates the differential expression of MFS transporters, integrating environmental signals with regulation mechanisms at the chromatin level to optimize the survival and adaptation of the organism.

Table 1. DNA sequence *Aspergillus salvadorensis*. MACROGEN INC. 2024

COG ID *Aspergillus*	Orthology	/KEGG
K08139	MFS transporter, SP family, sugar:H+ symporter	32.7721
K08150	MFS transporter, SP family, solute carrier family 2 (facilitated	29.4278
K08158	MFS transporter, DHA1 family, multidrug resistance protein	67.4331
K08197	MFS transporter, SIT family, siderophore-iron:H+ symporter	1.3256

The in silico analysis of the 23,263 base pair genomic sequence of *Aspergillus salvadorensis* reveals a complex organization with significant epigenetic regulatory potential. A key feature of the sequence is the widespread and frequent distribution of CpG dinucleotides throughout nearly its entire length, without CpG-free regions (Figure 1). These motifs often appear in repetitive patterns such as CG, CGG, and GCG, indicating a high GC content and suggesting the presence of multiple CpG-rich regions or potential CpG islands. Rather than being confined to a single promoter-like region, these CpG-enriched segments are dispersed across the sequence, particularly in intermediate and terminal regions, pointing to a distributed regulatory architecture.

Fig. 1. *Aspergillus salvadorensis sequence.* 2024

Although the sequence allows the identification of potential methylation sites, it does not provide direct information about their actual epigenetic state. Nevertheless, regions rich in guanine and cytosine are likely associated with euchromatin, which is typically transcriptionally active and accessible, while repetitive or AT-rich regions may correspond to heterochromatin, characterized by compaction and gene silencing. This suggests a dynamic chromatin organization in which active and repressed domains coexist and can shift depending on cellular conditions.

The sequence also indicates the possible presence of regulatory elements such as transcription factor binding sites, whose functionality depends on chromatin accessibility and epigenetic modifications. In addition, repetitive motifs may represent transposable elements, which are commonly silenced through DNA methylation and histone modifications to maintain genomic stability. These features are consistent with what is known about fungi of the genus *Aspergillus*, where epigenetic regulation plays a crucial role in environmental adaptation, stress response, and metabolic flexibility.

From a functional perspective, the sequence suggests the presence of genes encoding hydrolytic enzymes, such as glycosyl hydrolases and endo-β-1,4-glucanases, indicating a metabolic capacity geared toward the degradation of complex polymers like lignocellulose. This has important ecological implications in organic matter recycling and significant biotechnological applications, including biofuel production and waste treatment. Additionally, the sequence may contain genes related to antifungal resistance, such as ABC and MFS transporters, whose expression can be modulated by epigenetic mechanisms, contributing to adaptive responses under environmental stress.

Structurally, the presence of multiple start codons and potential open reading frames suggests that the fragment contains portions of several genes rather than a single coding unit. However, definitive identification of specific proteins requires further computational and experimental validation. The sequence also reflects a dual chromatin organization, with less repetitive, gene-rich regions corresponding to euchromatin and highly repetitive segments associated with heterochromatin and transcriptional repression.

Importantly, this type of in silico analysis is inherently inferential. While it enables the identification of regions with regulatory potential, it cannot determine actual methylation patterns, chromatin states, or histone modifications, which depend on cellular context and require experimental approaches such as bisulfite sequencing, ChIP-seq, or ATAC-seq. Overall, the findings suggest that *Aspergillus salvadorensis* possesses a sophisticated and dynamic epigenetic regulatory system that allows flexible control of gene expression. This adaptability likely supports its ability to respond to environmental changes, optimize metabolic processes, and maintain genomic stability. The sequence also holds considerable value for multiple fields, including biotechnology, microbial ecology, functional genomics, medicine, and synthetic biology, highlighting its potential for both fundamental research and applied sciences.

From the above sequence of *Aspergillus salvadorensis*, the following protein is obtained:

From the above sequence obtained in ORF190 Finder, multiple open reading frames (ORFs) are identified, among which ORF190 stands out, which encode a protein of approximately 172 amino acids (Figure 2). This length is consistent with small to medium-sized proteins with specific regulatory or catalytic functions in fungi such as *Aspergillus salvadorensis*, and is suitable for detailed functional analyses.

The associated protein sequence has a diverse amino acid composition, with an abundance of residues such as lysine (K), arginine (R), serine (S), threonine (T) and tyrosine (Y), which are classic sites of post-translational modifications. In particular, the frequency of lysines suggests a high potential for acetylation and methylation, modifications that can influence structural stability, subcellular localization and the ability to interact protein-protein or protein-DNA. In addition, the presence of arginines reinforces the possibility of protein methylation, a relevant process in the regulation of macromolecular complexes.

Likewise, the abundance of serine and threonine residues, together with the presence of tyrosines, indicates multiple potential phosphorylation sites. These modifications are characteristics of proteins involved in cell signaling pathways, where the action of kinases allows protein activity to be rapidly modulated in response to environmental stimuli or intracellular signals. In filamentous fungi, this type of regulation is critical for processes such as stress adaptation, regulation of secondary metabolism, and response to antifungal compounds.

From a structural perspective, the moderate length of ORF190 suggests the possible presence of compact functional domains or structurally defined regions, capable of mediating specific interactions. This raises the hypothesis that the protein could participate in broader regulatory networks, possibly acting indirectly in epigenetic processes, for example, by modulating transcription factors or chromatin-associated proteins.

The amino acid profile of the protein encoded by ORF190 indicates a high potential for regulation by post-translational modifications, supporting its possible role in dynamic and regulated cellular processes. This type of characteristic is especially relevant in advanced studies, such as functional characterization, immunoinformatics or the identification of biotechnological targets. Further analysis using specific prediction tools would allow the modification sites to be accurately mapped and their impact on the three-dimensional structure and biological function of the protein to be assessed.

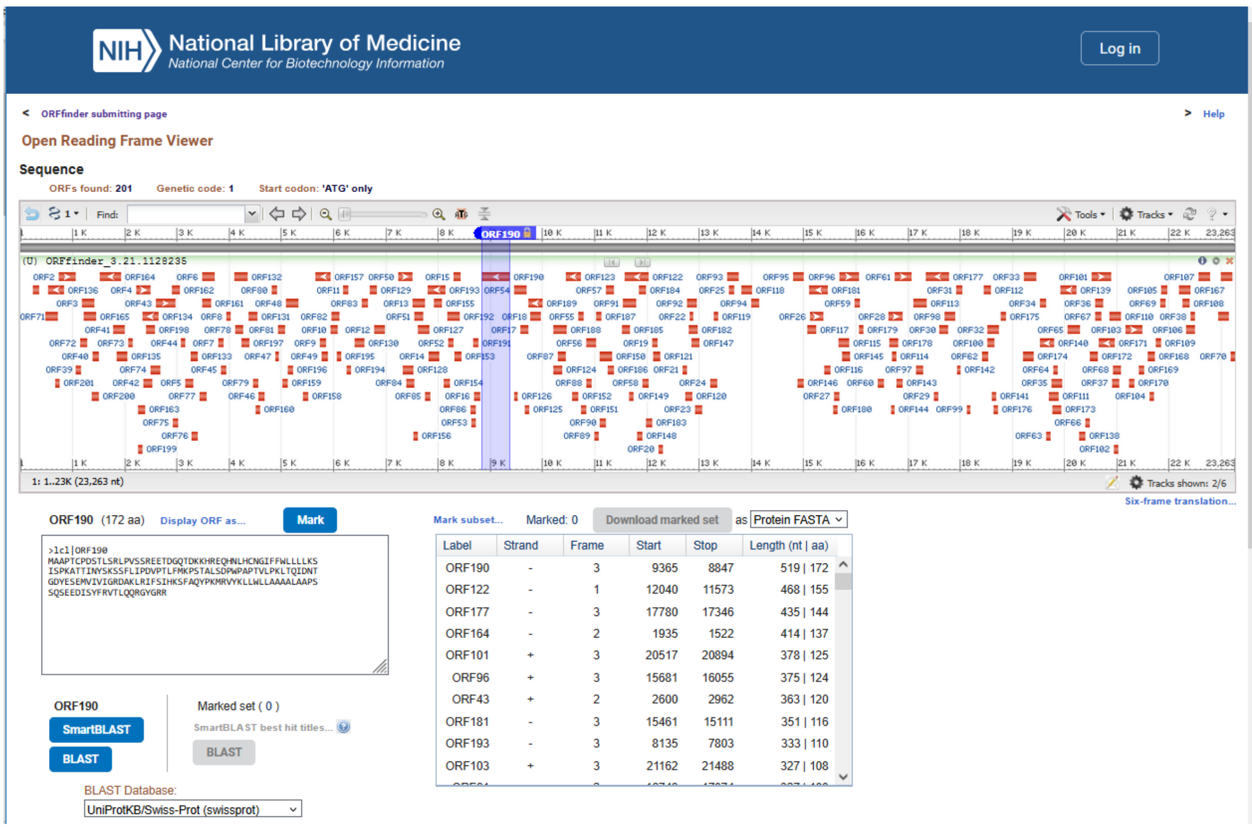

Fig. 2. ORF 190 protein. ORFinder 2025.

In the DNA sequence analyzed, the epigenetic modifications are not organized as discrete linear entities equivalent to sequence motifs, but their location responds to functional relationships with certain nucleotide patterns. DNA methylation is the only modification that can be directly mapped to specific positions, as it occurs predominantly in CpG dinucleotides. Since these CpG sites are widely distributed throughout the sequence, with a higher density in inner regions and towards the 3' end, these segments represent the main potential targets for methylation. In particular, the regions previously identified as CpG islands, characterized by a high GC content and a high frequency of CpG dinucleotides, correspond to genomic domains with regulatory relevance and differential susceptibility to methylation.

In contrast, acetylation does not occur on the DNA molecule, but on lysine residues in the N-terminal tails of histones, so it cannot be mapped directly onto the nucleotide sequence. However, there is a well-established functional association between regions rich in nonmethylated CpG and open chromatin states, which are usually correlated with elevated levels of histone acetylation. In this context, CpG-enriched segments within the sequence can be inferred as regions potentially associated with an acetylated state under transcriptionally active conditions.

Similarly, phosphorylation is a post-translational modification that primarily affects proteins, including histones and regulatory factors, and does not depend on a specific pattern in the DNA sequence. Their distribution is determined by dynamic cellular processes, such as intracellular signaling and response to genomic damage, rather than by the primary organization of nucleotides. Therefore, although it can be functionally associated with active or regulated genomic regions, it is not possible to delimit phosphorylation sites from the sequence itself.

The sequence has a high density of widely distributed methylation-susceptible CpG sites, while acetylation and phosphorylation are inferred indirectly based on the structural and functional context of the chromatin, without corresponding to defined positions within the linear DNA sequence.

DISCUSSION

In silico epigenomic analysis can be understood as a tool to decipher the rules that determine when and how genes are expressed, that is, the control system that regulates genome activity through bioinformatics programs (Allis and Jenuwein, 2016; Bhat *et al.*, 2022; Bird, 2002). Unlike DNA, whose sequence remains relatively constant, the epigenome is dynamic and responds to environmental stimuli, acting through chemical “switches” such as DNA methylation and histone modifications (Dan *et al.*, 2026; Feil and Fraga, 2012). Through bioinformatics tools, it is possible to map these regulatory elements and generate functional hypotheses without relying exclusively on laboratory experimentation (Jones and Takai, 2001).

One of its main applications is the identification of regulatory regions, such as promoters and enhancers, that determine the intensity and context of gene expression (Kouzarides, 2007). By analyzing chromatin accessibility and epigenetic marks, active or repressed regions of the genome can be predicted. This approach is especially relevant in biomedicine, for example, in the study of cancer, where it allows the detection of aberrant methylation patterns associated with the silencing of tumor suppressor genes or the activation of oncogenes, facilitating the identification of biomarkers and potential therapeutic targets (Chen *et al.*, 2024; Esteller, 2008; Stępniak *et al.*, 2021).

Likewise, epigenomic analysis plays a key role in areas such as personalized medicine, pharmacogenomics, and toxicogenomics, by making it possible to evaluate how environmental factors such as diet, stress, or exposure to chemical compounds influence gene regulation (Dan *et al.*, 2026; Feil and Fraga, 2012). In drug development, these approaches contribute to understanding and optimizing therapies aimed at modifying the epigenetic state, such as methylation or histone deacetylase inhibitors (Griazeva *et al.*, 2023; Kouzarides, 2007; Li *et al.*, 2024).

In the case of *Aspergillus salvadorensis*, sequence analysis suggests a genomic organization characterized by the coexistence of potentially active regions and regions subject to epigenetic silencing. The presence of multiple clustered CpG sites indicates the possible existence of regulatory microdomains susceptible to DNA methylation, while the abundance of repetitive sequences suggests the formation of heterochromatic regions associated with gene repression (Bird, 2002; Dai *et al.*, 2024). This pattern is consistent with what has been observed in fungi of the genus *Aspergillus*, where epigenetic regulation is essential for adaptation to variable environmental conditions (Allis and Jenuwein, 2016).

From a functional point of view, the sequence presents regions compatible with genes that encode hydrolytic enzymes such as glycosyl hydrolases, endo-β-1,4-glucanases, proteases, and lipases, suggesting a metabolic capacity oriented toward the degradation of complex polymers. The regulation of these genes can be explained by a dynamic epigenetic model: in the presence of substrates such as cellulose, chromatin remodeling and demethylation processes promote gene activation; in the absence of substrate, methylation and chromatin compaction lead to gene silencing (Kouzarides, 2007). This type of regulation allows high metabolic efficiency, optimizing energy resource use.

The sequence suggests the possible presence of genes associated with antifungal resistance, such as transporters of the ABC and MFS families, as well as detoxifying enzymes. In fungi, these systems are not always constitutively active but can be induced by epigenetic changes. For example, exposure to antifungal agents may trigger chromatin modifications that activate efflux pump expression, facilitating organism survival (Feil and Fraga, 2012; Patra *et al.*, 2022).

The identified repetitive motifs could act as epigenetic regulatory elements, functioning as silencing regions or “switches” that modulate the expression of nearby genes. These elements are especially important in controlling potentially toxic genes or metabolically expensive pathways, contributing to the organism’s functional balance (Bird, 2002).

Taken together, these findings reinforce the idea that *Aspergillus salvadorensis* possesses a sophisticated regulatory system in which DNA methylation and chromatin organization interact to flexibly control gene expression. This type of epigenetic architecture is key to its adaptive capacity, metabolic efficiency, and potential for biotechnological applications (Allis and Jenuwein, 2016).

The predictive epigenomic analysis of the sequence attributed to *Aspergillus salvadorensis* reveals a highly structured and functionally diverse genomic organization, in which multiple levels of regulation converge. The identification of fragments with coding potential, particularly those compatible with hydrolytic enzymes, suggests a metabolic capacity aimed at the degradation of complex polymers, especially lignocellulose. These enzymes play an essential ecological role and have high biotechnological value in industrial processes such as biofuel production and waste treatment (Kouzarides, 2007; Rosas-Vega *et al.*, 2025).

From a structural perspective, the sequence shows marked heterogeneity in nucleotide composition, with alternating GC-rich and AT-rich regions. This pattern suggests genome organization into euchromatin domains associated with transcriptional activity and heterochromatin linked to gene silencing, a characteristic feature of filamentous fungi (Allis and Jenuwein, 2016).

The presence of multiple CpG dinucleotides distributed along the sequence indicates potential DNA methylation sites. Although less prevalent in fungi than in higher eukaryotes, DNA methylation is associated with transposable element silencing and regulation of gene clusters involved in secondary metabolism (Bird, 2002; Zhang *et al.*, 2024).

Additionally, promoter-like regions rich in AT sequences and TATA box motifs were identified, which are essential for transcription complex assembly. These regions are regulated not only by sequence composition but also by histone modifications such as H3K4me3 (activation) and H3K9me3 (repression), enabling fine and reversible gene regulation (Kouzarides, 2007).

Repetitive and low-complexity regions suggest heterochromatic domains that contribute to genomic stability and coordinated regulation of metabolic pathways. Furthermore, potential non-coding RNA-generating regions introduce another regulatory layer, modulating gene expression at the post-transcriptional level (Feil and Fraga, 2012; Lamping and Krebber, 2025).

The analysis indicates the integration of multiple epigenetic mechanisms: chromatin organization, DNA methylation, histone modification, repetitive sequence silencing, and non-coding RNA regulation. This complexity supports a highly coordinated regulatory network essential for environmental adaptation (Allis and Jenuwein, 2016; Bure *et al.*, 2022; Zhang *et al.*, 2026).

CONCLUSION

The analysis of the *Aspergillus salvadorensis* sequence reveals a complex genomic organization, in which epigenetic mechanisms play a central role in the regulation of genes linked to both polymer degradation and antifungal resistance. The presence of CpG-enriched regions, together with repetitive sequences, suggests a dynamic gene expression control system, capable of modulating the activation or repression of genes depending on environmental conditions. This regulatory plasticity is consistent with the adaptive capacity observed in filamentous fungi and reinforces the biotechnological potential of the species, especially in biodegradation processes and in the development of strategies against antifungal resistance. Likewise, the analysis of the protein encoded by ORF190, with an approximate length of 172 amino acids, shows the presence of key residues lysine (K), arginine (R), serine (S), threonine (T) and tyrosine (Y) that constitute potential sites of post-translational modifications. Acetylation and methylation in lysine and arginine residues suggest regulatory functions, possibly related to protein-protein interaction or the formation of macromolecular complexes. On the other hand, phosphorylation in serines, threonine and tyrosine indicate a dynamic control mediated by cell signaling pathways, which points to a predominantly regulatory role of this protein, rather than structurally or exclusively catalytic.

These results integrate genomic and protein evidence that suggests the existence of a sophisticated regulatory system in *A. salvadorensis*, where epigenetics and post-translational modifications act in a coordinated manner to optimize the body's response to its environment. However, it will be necessary to complement these findings with experimental studies to validate the predictions and delve into the molecular mechanisms that support these functions.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

GENERATIVE AI STATEMENT

This study used Generative AI tools in data reorganization. We confirm that all AI-assisted processes were critically reviewed by the author’s to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the author’s.

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