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FROM PHYLOGENY TO PHARMACOLOGY: THERAPEUTIC INSIGHTS INTO THE ANTI-DIABETIC POTENTIAL OF *MOMORDICA CYMBALARIA*

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ABSTRACT: *Momordica cymbalaria*, an underexplored vegetable crop native to India, holds significant therapeutic potential due to its traditional antidiabetic use. This study explores its phylogenetic characterization, protein structure modelling, and phytochemical profiling, emphasizing its role in diabetes management. The 5.8S rRNA internal transcribed spacer sequence was retrieved from NCBI and analysed using BLAST, identifying 17 related species and insights into its evolutionary positioning. Phylogenetic analysis revealed close relationships with *Momordi cafoetida* and distant similarity to *Momordica balsamina*. Protein structure prediction using SWISS-MODEL and PyMOL identified key structural features and active sites. Three open reading frames (ORFs) were identified, potentially encoding proteins involved in diabetes-related pathways. Phytochemical analysis using Dr. Duke's and IMPPAT databases highlighted bioactive compounds such as beta-sitosterol, ergosterol, and alpha-eleostearic acid (ESA), a potent antidiabetic compound. ESA modulates the adipose deposition pathway and improves glucose regulation by interacting with proteins like peroxisome proliferator-activated receptor gamma (PPARG) and ribosomal protein L19. *In-silico* analysis demonstrated ESA's ability to enhance GLUT-4 and beta-glucokinase activity, facilitating glucose uptake and improving metabolic efficiency. These findings underline the molecular basis of antidiabetic properties in *Momordica cymbalaria*, emphasizing its potential as a natural therapeutic. This study provides a strong foundation for pharmacological research, blending traditional knowledge with modern science to advance plant-based diabetes management.

INTRODUCTION: *Momordica cymbalaria*, an underexplored vegetable crop, carries significant importance due to its traditional medicinal applications Renowned for its potential antidiabetic and antioxidant attributes, this plant, indigenous to India, serves as a reservoir of bioactive compounds [1]. The convergence of traditional wisdom and scientific exploration is evident in *Momordica cymbalaria* (MC), shedding light on natural remedies and potential health advantages [2].

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The crop's inherent properties can be harnessed by various pharmaceutical industries for formulating drugs targeting diabetic issues [3]. A noteworthy study demonstrated a substantial decrease in blood glucose, cholesterol, and triglyceride levels in alloxan-induced diabetic rats following a 15-day treatment with dried fruit powder derived from MC, confirming its anti-diabetic potential [4].

It was observed that MC seeds have shown ability to lower blood glucose levels and improved the lipid profile in diabetic rats [5]. Saponins and triterpenoid saponins isolated from this plant have found to possess anti-diabetic activity, potentially increasing insulin secretion and regenerating pancreatic beta cells [6, 7]. Various components of the Momordica plant, including phenolic acids, flavonoids, carotenoids, triterpenoids, and

phytosterols, contribute to its diverse array of bioactive compounds [8-10]. The recent literature emphasizes the considerable health benefits associated with these phytochemicals, particularly their potent antidiabetic, antitumor, and antioxidant properties [10, 11]. Employing prior *in-silico* analysis can aid in targeting their roles in human health and enhancing their anti-diabetic efficacy [12]. In this article, we will deal about the construction of phylogenetic tree of related species, protein structure determination and visualization, identification of phytochemicals and their role in anti-diabetic properties in human body.

MATERIALS AND METHODS:

Identification of Similar Sequences: The nucleotide sequence of *Momordica cymbalaria* ribosomal RNA, available in FASTA format, was retrieved from the NCBI database. Similar sequences from related species were identified through a BLAST (Basic Local Alignment Search Tool) analysis [13]. The taxonomical properties of these similar species were examined to establish their evolutionary and biological relevance.

Construction of Phylogenetic Tree: A Multiple Sequence Alignment (MSA) was performed to study interrelationships among species using the Clustal Omega tool [14]. Based on the aligned sequences, a phylogenetic tree was constructed to identify closely related species and to infer evolutionary connections within the dataset.

Protein Structure Prediction and Visualization: The 3D structure of the protein encoded by the *Momordica cymbalaria* nucleotide sequence was modeled using the SWISS-MODEL workspace, a web-based tool for homology modelling [15]. The generated backbone structure was refined and visualized using PyMOL, an open-source molecular visualization tool, to analyze structural features and functional domains.

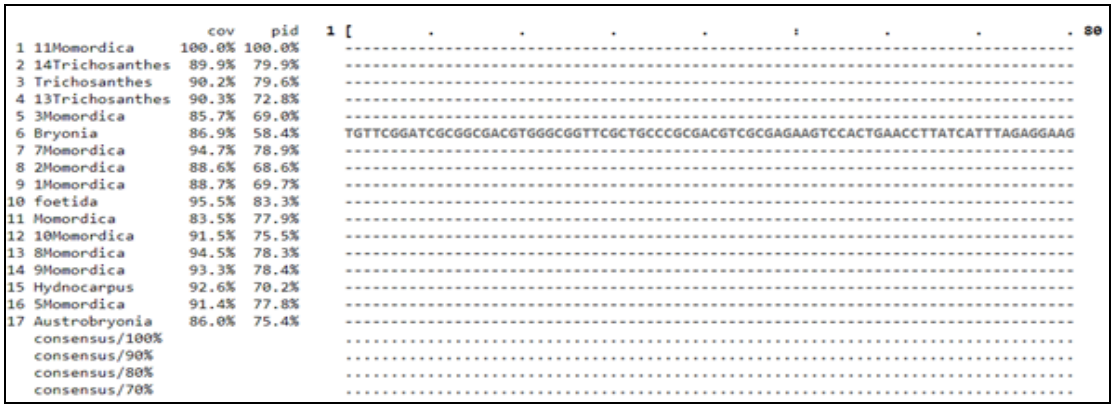
Prediction of Protein-Coding Regions: The TRANSLATE tool from the Expasy bioinformatics suite was employed to predict coding regions within the nucleotide sequence. This tool facilitated the identification of open reading frames (ORFs) and translated regions, providing insights into the protein-coding potential of the sequence.

Identification of Phytochemicals Present: Phytochemical profiling of *Momordica cymbalaria* was conducted using the Dr. Duke's Phytochemical and Ethnobotanical Database. Additional details such as compound name, plant source, and biosynthesis pathways were extracted using the IMPPAT (Indian Medicinal Plants, Phytochemistry and Therapeutics) database [16]. This comprehensive analysis provided insights into the bioactive compounds and their therapeutic potential.

Mechanism of Action of Potential Phytochemicals: The mechanisms of action of identified phytochemicals were investigated using the STITCH database, which integrates data on chemical-protein interactions, metabolic pathways, and drug-target relationships. Structural and functional annotations, along with interaction maps, were utilized to understand binding mechanisms, pathway involvement, and potential drug-like properties of the phytochemicals.

RESULTS AND DISCUSSION:

Identification of Similar Sequences: The nucleotide sequence of the 5.8S rRNA internal transcribed spacer of *Momordica cymbalaria* in FASTA format was obtained from the NCBI database.



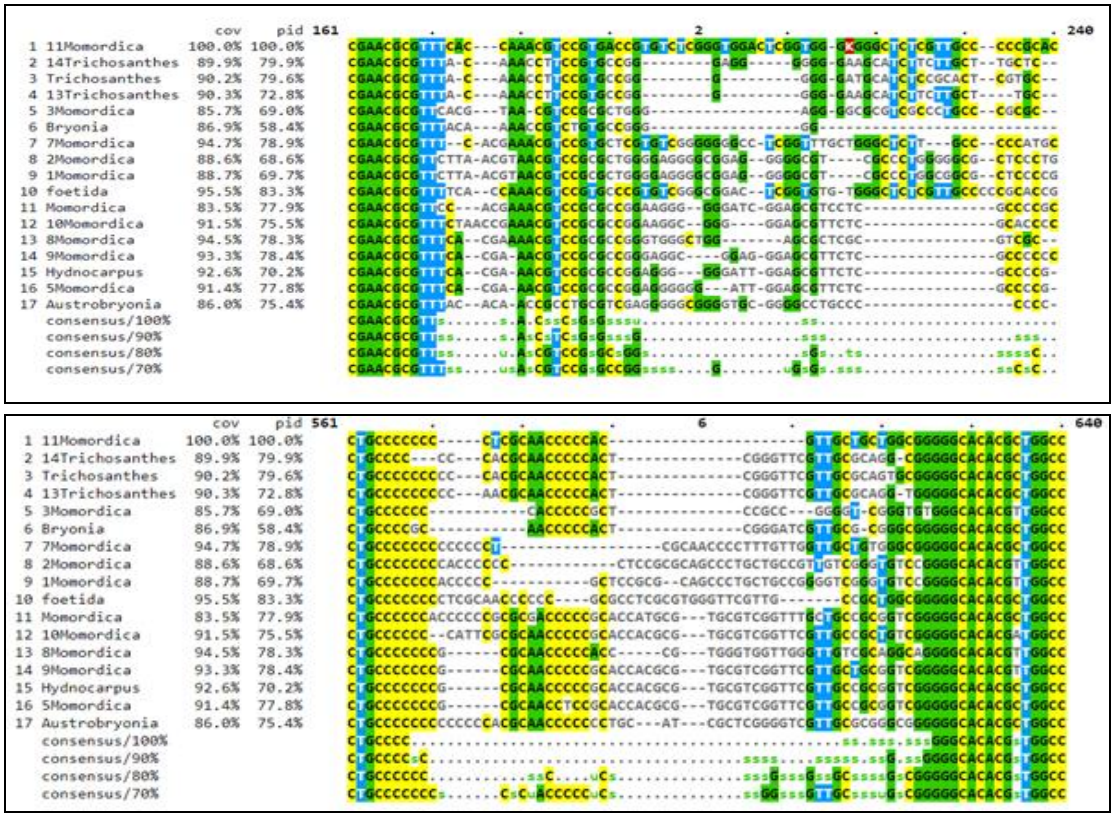


FIG. 1: MULTIPLE SEQUENCE ALIGNMENT IN CLUSTAL OMEGA

Through BLAST analysis, seventeen species related to *Momordica cymbalaria* were identified, providing a foundation for understanding its evolutionary lineage and functional relevance. These results highlighted the phylogenetic positioning and the conservation of ribosomal RNA sequences among related species **Fig. 1.**

Construction of Phylogenetic Tree: The phylogenetic analysis revealed that *Momordica cymbalaria* is most closely related to *Momordica foetida* and more distantly related to *Momordica balsamina*. The alignment of sequences across the seventeen analyzed species indicated varying degrees of genetic similarity. The constructed phylogenetic tree underscored evolutionary relationships, suggesting potential shared functional traits and conserved biological mechanisms among closely related species **Fig. 2.**

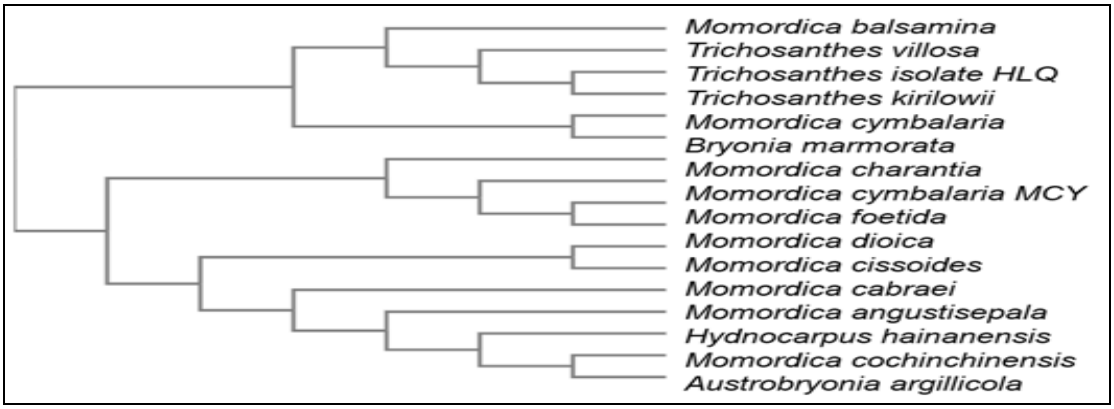


FIG. 2: PHYLOGENETIC TREE OF RELATED SPECIES OF MOMORDICA CYMBALARIA

Protein Structure Prediction and Visualization: The protein encoded by *Momordica cymbalaria* was modeled using SWISS-MODEL with two template structures. The resulting 3D protein model was visualized and analyzed using PyMOL software. This visualization highlighted key structural features, including potential active sites and binding domains. The detailed configuration of

the protein provided insights into its functional roles, especially in therapeutic applications such as anti-diabetic activity **Fig. 3.**

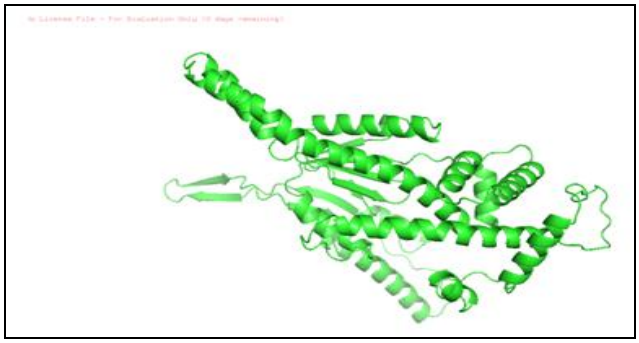


FIG. 3: MCY PROTEIN VIZUALIZED WITH PYMOL SOFTWARE

Prediction of Protein-Coding Regions: Three significant open reading frames (ORFs) were identified from the nucleotide sequence using Expasy's TRANSLATE tool. These ORFs were predicted to encode proteins with crucial roles in modulating diabetes-related pathways. This finding establishes a molecular link between the genetic composition of *Momordica cymbalaria* and its potential therapeutic effects.

Identification of Phytochemicals Present in *Momordica cymbalaria*: Phytochemical analysis using Dr. Duke's database revealed the presence of several bioactive compounds, including beta-sitosterol, ergosterol, stearic acid, and myristic acid. Further investigation using the IMPPAT database identified alpha-eleostearic acid **Fig. 4** as a key compound with anti-diabetic properties. This compound was found to modulate the adipose deposition pathway and play a significant role in controlling blood glucose levels. The presence of such phytochemicals highlights the medicinal potential of *Momordica cymbalaria* in metabolic regulation.

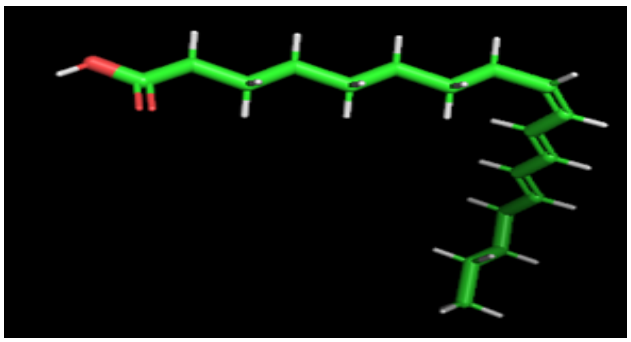


FIG: 4: ESA – ELEAOSTEARIC ACID: CHEMICAL STRUCTURE

Mechanism of Action of Potential Phytochemical in the Human Body: Alpha-eleostearic acid (ESA), a major phytochemical from *Momordica cymbalaria* seeds, was predicted to interact with two critical human proteins: peroxisome proliferator-activated receptor gamma (PPARG) and ribosomal protein L19 **Fig. 5.**

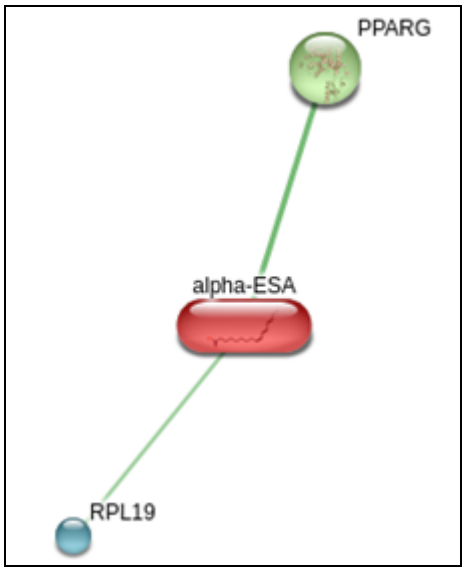


FIG. 5: INTERACTION OF ESA IN THE HUMAN BODY

These interactions facilitate anti-diabetic activity by influencing glucose homeostasis and adipose tissue function.

PPARG Activation: ESA's interaction with PPARG was shown to enhance the activation of GLUT2 and beta-glucokinase pathways, which are pivotal for glucose uptake and metabolism [17]. PPARG is known to regulate adipose tissue dynamics and improve liver and pancreatic beta-cell functionality, directly impacting glucose homeostasis [18].

Sequence Similarity: The interaction was further supported by high sequence similarity between ESA and PPARG-binding domains: 75.6% similarity at positions 101–186, 97.8% at 107–477, and 100% at 102–505 amino acid positions, reinforcing the molecular basis for ESA's efficacy.

Mechanistic Impact: The action of ESA on PPARG underlines its ability to enhance metabolic efficiency and ameliorate diabetic conditions by restoring glucose balance in liver and pancreatic tissues [19].

CONCLUSION: This study underscores the therapeutic potential of *Momordica cymbalaria* through a comprehensive analysis involving phylogenetic characterization, protein structure modeling, and phytochemical profiling. By identifying alpha-eleostearic acid as a potent anti-diabetic agent, the research highlights the medicinal relevance of this plant and provides a strong foundation for further pharmacological exploration.

The investigation unveils closely related species to *M. cymbalaria* and identifies proteins linked to its anti-diabetic properties. *In-silico* analyses, supported by prior research, emphasize the pivotal role of GLUT-4 and PPARγ upregulation induced by fruit extracts of *M. cymbalaria* in improving glucose transport. The findings suggest that the extract enhances glucose uptake by modulating critical targets such as GLUT-4 and PPARγ, thereby contributing to better glucose homeostasis. This study not only provides valuable insights into the molecular mechanisms underlying the plant's anti-diabetic activity but also highlights its potential as a natural therapeutic candidate for diabetes management.

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