EXPLORING LACTIC ACID BACTERIA AND METABOLITE-TARGET INTERACTIONS IN UNDERNUTRITION PREVENTION: A NETWORK PHARMACOLOGY AND MOLECULAR DOCKING APPROACH

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ABSTRACT

Undernutrition is a major global issue, particularly in children, leading to stunting, wasting, and compromised immune function. Disruption of gut microbiota is a key factor in undernutrition, making probiotics, especially Lactic Acid Bacteria (LAB), a potential solution for improving nutritional status. This study explores the role of LAB and their metabolites in preventing undernutrition using network pharmacology and molecular docking approaches to identify potential molecular targets and related pathways. Network pharmacology tools like TargetNet, SEA, and SwissTargetPrediction were used to predict gene targets influenced by LAB metabolites. Cytoscape was used to build protein-protein interaction (PPI) networks, and molecular docking simulations evaluated the binding of LAB metabolites to key proteins associated with undernutrition. A total of 603 potential genes were identified, including human serum albumin (ALB), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). Pathway analysis linked these proteins to immune response, nutrient absorption, and metabolic regulation. Molecular docking confirmed stable interactions with LAB metabolites. LAB and their metabolites show promise in managing undernutrition by modulating gut health and supporting nutrient absorption, providing a basis for future clinical applications.

Keywords: Undernutrition, Lactic Acid Bacteria (LAB), Probiotics, Network Pharmacology, Molecular Docking.

INTRODUCTION

Undernutrition is a condition of nutritional imbalance that affects individual health, particularly in children, with long-term impacts on physical growth and cognitive development (World Health Organization, 2024). According to World Health Organization (WHO) data in 2022, around 149 million children under the age of five experienced stunting caused by chronic undernutrition, while 45 million children suffered from wasting due to acute undernutrition, and 37 million children were affected by obesity, which increases the risk of non-communicable diseases. The Indonesian Health Survey (SKI) 2023 reported that 21.5% of children under five experienced stunting and 8.5% experienced wasting (Kementerian Kesehatan Republik Indonesia, 2023). Stunting and wasting

demonstrate that undernutrition remains a significant public health problem both in Indonesia and globally.

Stunting hinders children's physical development and increases the risk of future diseases, while wasting makes children more vulnerable to infections. A child suffering from undernutrition is more susceptible to infections. In addition, undernutrition also leads to reduced muscle mass, weaker muscle strength, and lower physical performance compared to children who are not undernourished. This condition increases the likelihood of experiencing sarcopenia in old age, a condition characterized by loss of muscle mass, decreased muscle strength, and reduced physical performance, with up to three times greater risk compared to individuals who did not experience undernutrition during childhood (Lengelé et al., 2021).

Children suffering from undernutrition are more frequently affected by diarrhea compared to well-nourished children. Research by The et al. (2018) has shown that undernourished children with diarrhea tend to experience gut dysbiosis, a condition in which the balance of intestinal microbiota is disrupted. Another study conducted in Indonesia also demonstrated a significant difference between children with normal nutritional status and those with undernutrition, further supporting the evidence that undernourished children are more likely to develop gut dysbiosis (Gatya et al., 2022).

Probiotics are defined by the Food and Agriculture Organization (FAO) as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014). These beneficial microbes are widely recognized for their ability to restore and maintain the balance of gut microbiota, a condition often disrupted in cases of dysbiosis. Probiotics have been extensively used to address intestinal imbalances as well as a variety of health problems ranging from gastrointestinal disorders to immune-related conditions (Kim et al., 2019). Given this potential, probiotics may also play a crucial role in managing gut dysbiosis observed in undernourished children. By improving the composition of intestinal microbiota, probiotics could support better nutrient absorption, enhance immune response, and reduce the frequency of infections, thereby helping to break the cycle between undernutrition and poor health outcomes. This highlights the importance of considering probiotic interventions as part of comprehensive strategies to improve child nutrition and overall health.

REVIEW OF LITERATURE

Undernutrition is a form of nutritional imbalance characterized by insufficient intake of macronutrients (energy, protein) and/or micronutrients, manifesting as wasting, stunting, or micronutrient deficiencies, and it exerts deleterious effects on child growth, cognition, immunity, and metabolic homeostasis. In parallel, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host," a definition upheld by the International Scientific Association for Probiotics and Prebiotics (ISAPP) and widely adopted in recent literature (Hill et al., 2014; Ji et al., 2023). These definitions provide the foundational conceptual framework for evaluating how probiotics might intervene in the pathophysiology of

undernutrition and its related gut disturbances.

Children suffering from undernutrition are more vulnerable to infectious diseases, particularly enteric infections such as diarrhea, due to compromised mucosal immunity, impaired barrier function, and disrupted gut homeostasis (Carvalho et al., 2025). The bidirectional interplay between intestinal infections and undernutrition exacerbates a vicious cycle: repeated diarrheal episodes hinder nutrient absorption, reduce intake, and intensify undernutrition, which in turn further impairs gut integrity and immune defense (Arredondo-Hernandez et al., 2022). Environmental enteric dysfunction (EED), a subclinical disorder marked by chronic inflammation and increased intestinal permeability, is thought to mediate this vicious cycle, limiting nutrient uptake and fueling low-grade systemic inflammation that aggravates growth impairment (Arredondo-Hernandez et al., 2022; Carvalho et al., 2025)

Recent meta-analyses have highlighted the potential of probiotics to help manage malnutrition-related outcomes in undernourished children, including reductions in diarrheal episodes, lower incidence of respiratory tract infections, and modest improvements in anthropometric measures such as weight-for-age and height-for-age (Paiandeh et al., 2024). These findings suggest that probiotics may act through multiple pathways, ranging from modulation of the gut microbiota and enhancement of mucosal immunity to improved nutrient absorption and barrier integrity. Complementing these human studies, experimental work in animal models has provided further mechanistic support. For example, Park et al., (2025) demonstrated in a mouse model of induced malnutrition that probiotic supplementation improved growth parameters, restored microbial balance, and reduced systemic inflammation. Together, these strands of evidence reinforce the concept that probiotics could serve as a valuable adjunct to nutritional interventions, not only by addressing acute infections but also by promoting more resilient long-term growth and health outcomes in the context of undernutrition. Nevertheless, despite these encouraging outcomes, there has been no study that specifically investigates the molecular mechanisms underlying probiotic action in the context of undernutrition. This gap in knowledge underscores the need for research that explores how probiotic strains—particularly lactic acid bacteria—interact with molecular targets and metabolites relevant to nutritional recovery.

This study aims to explore the role of Lactic Acid Bacteria (LAB) and their metabolites in preventing undernutrition using network pharmacology and molecular docking. The primary objective is to identify potential molecular targets and their associated biological pathways. Therefore, this research seeks to answer the question: "What are the potential molecular targets and related pathways influenced by LAB and their metabolites in the prevention of undernutrition?".

METHODOLOGY

Preparation of ligands: This study used the sequence metabolites and Short Chains Fatty Acids (SCFAs) from profiling of the Lactic Acid Bacteria (LAB) that has been reported previously (Markowiak-Kopeć & Śliżewska, 2020; Spaggiari et al., 2024). Three top metabolites

and three top SCFAs chosen, such as Inosine, Acetic Acid, Acetycoline, Butyrate Acid, Indole-3 Lactic Acid, and Propionic Acid.

Prediction of Active Compound Targets: In this study, several integrative tools such as TargetNet (Yao et al., 2016), SEA (Gfeller et al., 2013), and SwissTargetPrediction (Daina et al., 2019) were utilized to predict potential gene targets of the active compounds of Lactic Acid Bacteria (LAB) in relation to undernutrition. Different prediction methods were applied by these tools to gather target gene information. The identified genes were then input into the String database to obtain the gene symbols for each predicted target. To ensure consistency across various platforms, all genes were standardized according to the HUGO Gene Nomenclature Committee (HGNC) gene symbols. Only entries with a "Homo sapiens" origin were included in the subsequent analysis. The genes were then aggregated, and a Venn diagram was created to visualize the overlaps between the predicted targets (Szklarczyk et al., 2019). The compound targets from the databases were further examined using the ClueGo plugin in Cytoscape (Bindea et al., 2009) for pathway enrichment analysis. Acetic acid is too short to be searched in SwissTargetPrediction.

Relation of Known Protein Targets: Protein targets associated with undernutrition were identified by searching the GeneCard database (https://www.genecards.org/) using the keyword "undernutrition in humans." After obtaining the relevant targets, they were entered into the String database to retrieve the corresponding gene symbols for each target. Redundant targets were excluded. A Venn (https://bioinfogp.cnb.csic.es/tools/venny/) diagram was then used to illustrate the overlap and uniqueness of the identified targets (Oliveros, J.C, 2024).

Network Formation and Validation: The interconnection between compounds of Lactic Acid Bacteria (LAB) and their potential targets for undernutrition prevention was explored by constructing a protein-protein interaction (PPI) network using the STRING database integrated with Cytoscape. The protein targets were derived from the predicted genes of three databases, alongside undernutrition-related targets from the GeneCard database. A Venn diagram was used to visualize the overlap between these targets. The topological properties of each node in the interaction network were computed, including network centrality (NC), degree, degree centrality (DC), eigenvector centrality (EC), betweenness centrality (BC), closeness centrality (CC), and local average connectivity (LAC). Nodes associated with higher-ranking targets were considered to play a significant role within the PPI network. Additionally, several databases such as MetaScape (Zhou et al., 2019) ShinyGO (Ge et al., 2020), WebGestalt (Liao et al., 2019) were employed to analyze the biological functions within the network, including GO/KEGG analysis for the target network, compound-target network, and target-pathway network.

Molecular Docking Study : The docking simulation in this study was performed using Molegro Virtual Docker (MVD) software version 2013.6.0, developed by CLC-bio (Thomsen & Christensen, 2006). Prior to beginning the docking process, the protein structure and optimized ligands were properly prepared. All structural issues in the amino acid residues of the protein were identified and corrected.

Bonds, bond orders, hybridization, and charges (calculated by MVD) were then assigned to both the protein and ligand models. Additionally, explicit hydrogens were added, and flexible torsions in the ligands were identified. Therefore, the docking radius was set to 10 Å to encompass the entire surface of the identified cavities in the binding sites. The MolDock scoring function was applied with a grid resolution of 0.30 Å for the docking process. The choice of MolDock was based on its efficiency and accuracy as a scoring function. In the MVD software, the MolDock operation used the piecewise linear potential (PLP) scoring function, which considers hydrogen bond directionality and charges. The MolDock Simplex Evolution (MolDock SE) docking algorithm was also utilized, running 10 times for each ligand, with 1500 iterations and a population size of 50. The docking process converged after 1500 iterations, resulting in the lowest energy poses. The most stable complexes obtained from the docking were exported to Discovery Studio 2025 for visualizing the major residual interactions between the ligands and the protein's active sites.

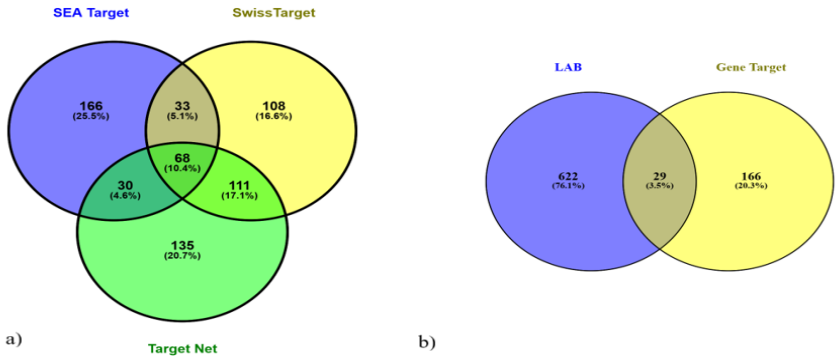

Figure 1. a) Venn diagram illustrating the overlapping and particular genes predicted from those three databases. b) Venn diagram showing the number of overlapped and particular genes from both LAB substances and Undernutrition

RESEARCH RESULT

Prediction of Specific Targets for Active Compounds in LAB. For the purpose of predicting the relationship between the active compounds of LAB (Lactic Acid Bacteria) and the prevention of undernutrition, the SMILE representations of each active molecule were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) for further investigation. As shown in Figure 1(a), multiple targets were identified across the platforms: 135 targets from TargetNet, 166 from SEA, and 108 from SwissTarget. After eliminating duplicate targets, overlapping genes were identified, as illustrated in Figure 5. Of these, 68 genes were common to both SEA and TargetNet, 111 genes were common to both SwissTarget and TargetNet, and 30 genes were common to both SEA and SwissTarget. A total of 70 genes were found across all three platforms. After eliminating the overlaps, 208 unique genes were identified. In total, 603 genes were selected as potential targets for the active compounds to aid in undernutrition.

Identification of Therapeutic Targets for Undernutrition: The GeneCard database was used to identify approved targets related to stunted growth and to compare the gene similarities between the known therapeutic targets and predicted targets. As shown in Figure 1(b), 622 gene targets were obtained from the LAB (represented in blue), while 166 approved therapeutic targets related to undernutrition were identified from GeneCard (shown in yellow). As a result, 29 genes were found to connect LAB with undernutrition, as illustrated in the Venn diagram Figure 1(b).

Network Construction and Topological Analysis: To create a protein-protein interaction (PPI) network for the 29 genes and evaluate their networks, the STRING online tool and Cytoscape software were used with a confidence parameter of 0.40 (Figure 2). To ensure clarity between the databases and platforms, the HUGO Gene Nomenclature Committee (HGNC) gene symbols were applied for all genes. The topological analysis of the PPI network was conducted using the CytoNCA program. Table 1 presents the results of the topological analysis. Notably, the proteins human serum albumin (ALB), interleukin 6 (IL6), and tumor necrosis factor alpha (TNF-Alpha) were ranked highest based on the network analysis, suggesting their potential strong association with undernutrition. Additional parameters are provided in columns 3–9 of Table 1, indicating no significant differences in gene ranking across various criteria.

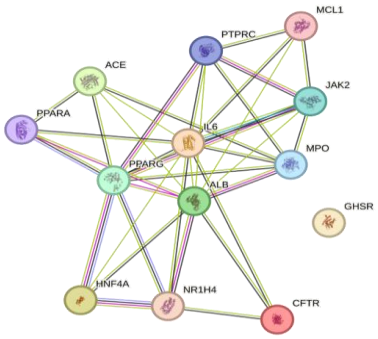

Figure 2. Protein–protein interaction (PPI) network of the 29 target genes is visualized in the 3D form.

Integrated Pathway and GO Analysis: The MetaScape server was used to analyze 29 shared targets and verify several pathways within the LAB and undernutrition network. The integrated pathways and GO analysis results are displayed in figure 3, with a specific focus on the "regulation of hormone levels" and “response to nutrient levels”, which was linked to undernutrition This finding suggests a strong correlation between the 29 shared proteins and nutritional status in humans. Additionally, these 29 genes were further analyzed using the webGestalt database for GO enrichment, as shown in Figure 4, which categorizes the genes in cellular components (CC), biological processes (BP), and molecular functions (MF). In the biological process (Figure 4(a)), “metabolic process”, “response to stimulus”, and “biological regulation” were found to be linked to nutritional

status in humans. The cellular components and molecular functions also indicated connections to *cell growth*, as illustrated in Figures 4(b) and 4(c), respectively.

Integrative Network Analysis and Target Selection: To explore the pathways associated with the 29 obtained protein targets, these genes were submitted to the SkinyGO, identifying ten relevant pathways. *Pathways such as* "Response to nutrient levels," "response to stress," "regulation of hormone levels," and "response to extracellular stimulus" *were* identified as closely related to human nutrition. These findings highlight the importance of investigating these pathways to understand human health mechanisms.

Cytoscape **Software for Network Analysis**: Cytoscape software was used to integrate the data from 6 active compounds of LAB, the 29 shared genes, and the 10 pathways (Figure 5). This complex network demonstrates the correlation between the compounds and their respective targets, which play a role in correct undernutrition.

Molecular Docking: From the previous network pharmacology study, 29 protein targets were identified in relation to undernutrition. To minimize computational complexity, three primary targets with the highest network topology scores and strongest biological relevance were selected for molecular docking: human serum albumin (ALB, PDB ID: 1AO6), interleukin-6 receptor (IL-6R, PDB ID: 1N26), and peroxisome proliferator-activated receptor gamma (PPARG, PDB ID: (PPARG, PDB ID: 6O67). The selection of these three proteins was also based on their rank in the network pharmacology study, which demonstrated their strong association with nutritional status. ALB was chosen as a biomarker and carrier protein, IL-6R as a mediator of inflammation often elevated in malnutrition, and PPARG as a nuclear receptor regulating energy metabolism and adipogenesis. The results are presented in Table 2.

Table 1. Topological Network Evaluation of the PPI Network Based on the 29 Target Genes Shared by LAB Active Substances and Undernutrition

Rank	Gene	Subgraph	Degree	EC	IC	LAC	BC	CC	NC
1	ALB	22346,9	24	0,36	5,9	8,4	118,8	0,9	22,9
2	IL6	20001,4	23	0,34	5,9	7,6	133,2	0,8	20,2
3	TNF	18364,0	21	0,32	5,7	7,7	75,9	0,8	18,1
4	PPARG	15473,3	19	0,30	5,6	7,5	72,6	0,7	15,6
5	ACE	9623,8	13	0,23	5,0	7,1	21,1	0,7	9,9
6	F2	6970,6	12	0,20	4,9	5,5	64,7	0,6	7,5
7	MPO	6767,9	10	0,20	4,6	6,6	6,6	0,6	8,2
8	PPARA	6577,0	10	0,19	4,6	6,2	6,7	0,6	7,3
9	MGAM	5675,6	10	0,18	4,6	6,0	31,5	0,6	8,1

10	JAK2	5639,3	10	0,18	4,6	5,8	15,4	0,6	8,6
11	HNF4A	5189,2	9	0,17	4,4	5,3	4,5	0,6	6,5
12	G6PD	5131,2	9	0,17	4,4	5,3	9,9	0,6	6,4
13	TTR	5080,5	9	0,17	4,4	5,6	5,0	0,6	6,6
14	PTPRC	4535,3	8	0,16	4,3	6,0	1,7	0,6	7,6
15	NR1H4	4499,4	8	0,16	4,3	4,8	5,3	0,6	6,0
16	CYP2C9	3872,4	9	0,15	4,4	3,8	9,0	0,6	4,5
17	GSR	3744,1	7	0,15	4,0	4,6	5,4	0,6	5,4
18	SERPINA6	3725,2	8	0,15	4,3	4,3	5,1	0,6	5,0
19	SI	3540,5	8	0,14	4,3	4,8	22,3	0,6	6,3
20	PDGFRA	3300,3	6	0,14	3,8	5,0	0,0	0,5	6,0
21	PLAT	3272,8	6	0,14	3,8	5,0	0,0	0,5	6,0
22	CYP27B1	3224,0	6	0,14	3,8	4,0	0,9	0,5	4,8
23	SHBG	3205,7	6	0,14	3,8	4,0	1,1	0,5	4,8
24	MCL1	2223,3	5	0,11	3,5	4,0	0,0	0,5	5,0
25	CFTR	1673,8	4	0,10	3,1	3,0	0,0	0,5	4,0
26	HK2	1139,9	6	0,08	3,8	3,0	7,4	0,5	4,2
27	DNMT3A	323,6	2	0,04	2,3	1,0	0,0	0,5	2,0
28	GAA	200,4	3	0,03	2,7	2,0	0,0	0,4	3,0
29	GHSR	49,5	1	0,02	1,7	0,0	0,0	0,4	0,0

The ligand-target protein interactions visualized in this study were selected based on the results with the highest rerank scores. Analysis of these interactions indicates that hydrogen bonds and various hydrophobic interactions significantly contribute to the binding stability of the ligand to the target protein. The ligand Inosine formed hydrogen bonds with residues Ser183, Asp108, and Tyr141 of the ALB protein, as well as with residues Arg288, Leu226, and Glu295 of PPARG. For the Indole-3 Lactic Acid ligand, hydrogen bonding was observed with residue Leu182 in ALB and with Ser119 and Thr125 in IL6-R. Meanwhile, Acetylcholine formed hydrogen bonds with Glu96 (IL6-R) and Cys285 (PPARG). These residues play a crucial role in stabilizing the ligand-protein complex through these bonds.

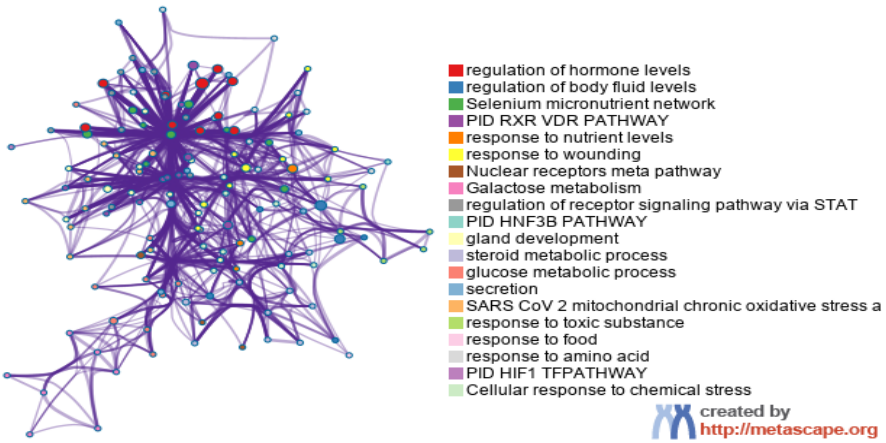

Figure 3. Integrated pathways of 29 protein targets utilizing the Metascape tool

Additionally, various hydrophobic interactions were identified, where Inosine interacted with residues such as Val162 and Ala194 (van der Waals and Pi-Alkyl interactions) in ALB, and with Leu333 and Met329 in PPARG. Indole-3 Lactic Acid exhibited hydrophobic interactions with residues like Phe157 and Ile142 in ALB, and with Trp115 and Val93 in IL6-R. These interactions help to enhance the binding affinity and stability of the ligand to the target protein. This docking analysis indicates that key residues such as Tyr141 (ALB), Arg288 (PPARG), and Thr125 (IL6-R) are involved in crucial binding interactions. Ligands that bind to these residues are predicted to enhance protein stability, which could be valuable for therapeutic applications

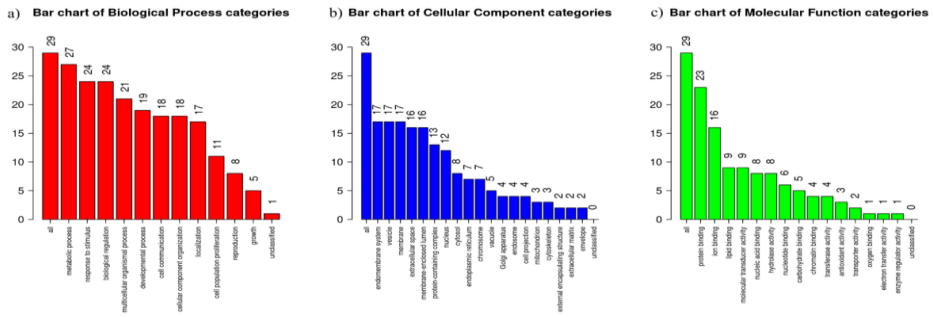

Figure 4. GO analysis of LAB chemical target–gene interactions to identify the correlation

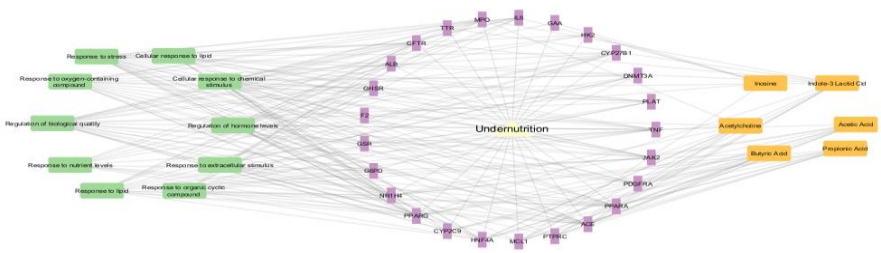

Figure 5. Comprehensive representation of the generated network

Our docking results further confirm that these interactions contribute significantly to the stability and function of the complexes, suggesting that these ligands could serve as potential candidates for therapeutic interventions, such as supplements to address nutritional deficiencies.

DISCUSSION

Network pharmacology is an integrative approach that combines systems biology and pharmacology to understand how bioactive compounds interact with multiple targets within the body (Li et al., 2023). This methodology is particularly useful in studying of action. complex diseases like undernutrition, where multiple pathways are involved. By constructing interaction networks between drugs, targets, and diseases, researchers can identify potential therapeutic targets and mechanisms .

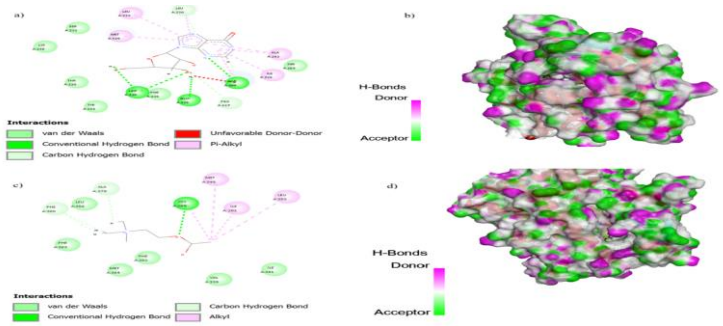

Figure 6. a) 2D Interactions PPARG and Inosine, b) 3D Interactions PPARG and Inosine,

c) 2D Interactions PPARG and Acetylcholine, d) 3D Interactions PPARG and Acetylcholine

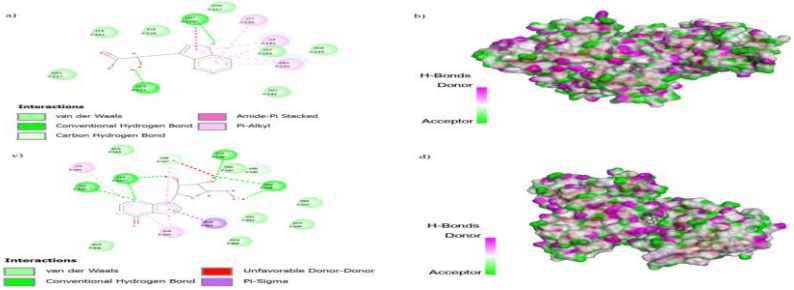

Figure 7. a) 2D Interactions ALB and Indole-3 Lactic Acid, b) 3D Interactions ALB and Indole-3 Lactic Acid, c) 2D Interactions ALB and Inosine, d) 3D Interactions ALB and Inosine

In the context of probiotics, network pharmacology has been employed to elucidate how microbial metabolites influence host health. For instance, a study by Karim et al., (2023) utilized network

pharmacology and molecular docking to identify key targets of short-chain fatty acid-producing microbial metabolites against kidney cancer and inflammation. In undernutrition study, Arwansyah et al., (2023) utilized network pharmacology and molecular docking to identify key targets of Moringa oleifera against stunting. This approach highlighted the potential of microbial metabolites in modulating disease pathways through multi-target interaction.

Recent studies have provided insights into the mechanisms by which probiotics may aid in the prevention and treatment of undernutrition. A systematic review by Paiandeh et al. (2024) examined the effects of probiotic, prebiotic, and synbiotic supplements on anthropometric measures and respiratory infections in malnourished children. The review found that these supplements could improve weight and height in undernourished children, suggesting a potential role in combating undernutrition Additionally, a study by Ahmadi-Khorram et al., (2025) conducted a double-blind, randomized, placebo-controlled trial involving underweight participants. The trial assessed the effects of probiotic supplementation on stress and inflammation markers. The results indicated that probiotics could mitigate stress and inflammation, which are often elevated in undernutrition and can impair nutrient absorption and utilization.

Randomized studies have demonstrated the beneficial effects of probiotics in models of undernutrition. For example, a study by Kambale et al., (2023) investigated the role of probiotics in children with uncomplicated severe acute malnutrition. The study found that probiotic supplementation could improve clinical outcomes, including reducing diarrhea, which is a common complication in undernutrition.

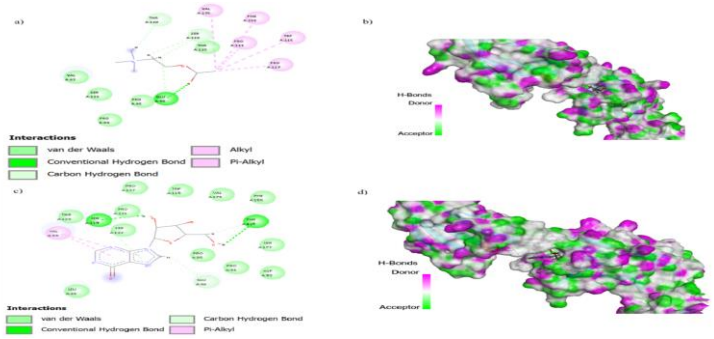

Figure 8. a) 2D Interactions IL6-R and Acetylcholine, b) 3D Interactions IL6-R and Acetylcholine, c) 2D Interactions IL6-Rand Indole-3 Lactic Acid, d) 3D Interactions IL6-Rand Indole-3 Lactic Acid

In vivo study, probiotics demonstrated the beneficial effects of probiotics in mice and rats models. For example Park et al., (2025), Lactobacillus plantarum supplementation in malnourished mice demonstrated significant improvements in both muscle mass and muscle length. The supplementation restored the balance of gut microbiota, which plays a critical role in nutrient absorption, inflammation control, and muscle protein synthesis. Besides, Da Fonseca et al.,(2025) has shown that increased levels of

BDNF can have a profound impact on brain function, particularly in neuroplasticity (the ability of the brain to reorganize itself) and neurogenesis (the process of generating new neurons), which are essential for cognitive abilities.

The findings from these studies underscore the multifaceted role of probiotics in addressing undernutrition. Probiotics may enhance gut health, modulate immune responses, and improve nutrient absorption, all of which are crucial in managing undernutrition.

The integration of network pharmacology approaches allows for a deeper understanding of the complex interactions between probiotics and host pathways, facilitating the development of targeted interventions. Moreover, the clinical evidence supports the incorporation of probiotics into nutritional strategies for undernourished populations.

Table 2. Molecular Docking

Target Protein	Ligand	Rerank Score	Interactions and involved residues
ALB (PDB ID:1AO6)	Inosine	-938.764	**Conventional Hbond:** Ser183, Asp108, Tyr141 **vdW:** Gln196, Arg145, Pro110, Val162, Asn109, Asn458, Asn429 **Carbon Hbond:** His146, Arg197, Pro147 **Unfavorable:** Arg197 **Pi-Sigma:** Gln259 **Pi-Alkyl:** Lys190, Ala194, Arg197
	Indole-3 Lactic Acid	-668.766	**Conventional Hbond:** Leu182 **vdW:** Arg117, Tyr161, Tyr138, Phe157, Phe149, His146 **Carbon Hbond:** Leu185 **Amide-Pi Stacked:** Arg186 **Pi-Alkyl:** Leu185, Lys190, Ile142, Gly189
IL6-R (PDB ID:1N26)	Indole-3 Lactic Acid	-835.907	**Conventional Hbond:** Ser119, Thr125 **vdW:** Pro117, Trp115, Val175,

			Phe155, Ser177, Asp92, Pro94, Glu96, Pro95, Leu69, Ser122, Thr120 **Carbon Hbond:** Pro121 **Pi-Alkyl:** Val93
	Acetylcholine	-594.502	**Conventional Hbond:** Glu96 **vdW:** Val93, Ser122, Pro95, Pro94 **Carbon Hbond:** Thr120, Ser119, Thr125 **Alkyl:** Val175, Pro121, Pro117 **Pi-Alkyl:** Phe155, Trp115

Target Protein	Ligand	Rerank Score	Interactions and involved residues
PPARG (PDB ID:6O67)	Inosine	-812.024	**Conventional Hbond:** Arg288, Leu226, Glu295 **vdW:** Ser332, Leu333, Lys230, Thr229, Tyr222, Phe226, Pro227, Ser289 **Pi-Alkyl:** Leu330, Met329, Ala292, Ile326 **Carbon Hbond:** Arg288 **Unfavorable:** Arg288
	Acetylcholine	-558.396	**Conventional Hbond:** Cys285 **vdW:** Phe360, Phe363, Phe282, Met364, Val339, Ile341 **Carbon Hbond:** Ala278, Leu356 **Alkyl:** Met348, Ile281, Leu353

However, further research is needed to determine optimal probiotic strains, dosages, and treatment durations to maximize therapeutic benefits.

Based on the presented methodology and analysis, this research is predicated on several key assumptions. The study fundamentally presumes the validity of its *in silico* models, asserting that network pharmacology and molecular docking can accurately predict tangible biological interactions within the human body. Consequently, it is assumed that the high binding affinities and identified protein targets in the simulations

correlate with real-world molecular mechanisms. The researchers also assume that the selected metabolites—Inosine, Acetylcholine, and Indole-3 Lactic Acid—are significant representatives and the primary drivers of the beneficial effects of Lactic Acid Bacteria on nutritional status, despite the diverse range of metabolites produced. Furthermore, the identified target proteins, such as ALB, IL-6R, and PPARG, are assumed to play a central and crucial role in the pathophysiology of undernutrition, implying that their modulation will lead to clinically relevant improvements. Underpinning the entire research framework is the core assumption of a direct causal relationship between gut dysbiosis and undernutrition, suggesting that modulating the gut microbiota with probiotics can directly and significantly improve nutrient absorption and host health.

CONCLUSIONS

This study confirms that Lactic Acid Bacteria (LAB) and their metabolites play a vital role in addressing undernutrition by modulating several biological pathways. Through network pharmacology and molecular docking, key proteins and pathways involved in undernutrition recovery, such as immune modulation and nutrient absorption enhancement, have been identified. Probiotics, especially LAB, offer a promising intervention for children and individuals suffering from undernutrition by improving gut health, reducing inflammation, and enhancing muscle growth. While this research lays the foundation for future studies, specific directions are recommended for future researchers to translate these computational findings into clinical applications. Investigators are encouraged to validate these in silico results through in vitro and in vivo studies to confirm the predicted interactions between LAB metabolites and key protein targets. Ultimately, well-designed randomized controlled trials are necessary to determine the most effective strains, optimal dosages, and treatment regimens to maximize the therapeutic benefits of probiotics in clinical settings for undernourished populations.

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