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Mineral and Insilico Study of Sapat Siam Fish (*Trichopodus pectoralis*, Regan 1910) on Appetite Regulation

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Abstract

Backgrounds: Sapat siam fish (*Trichopodus pectoralis*, Regan 1910) production in South Kalimantan is in second place after Papuyu. Fish meat contains water, protein, fat and ash. 40-90% of the protein is collagen protein and the rest is mineral residue and inorganic salts such as magnesium carbonate and calcium carbonate. Apart from that, it also contains calcium, phosphorus, Zn, Fe, K and Na which are beneficial for humans. Fish can be used to overcome the occurrence of wasting. In toddlers wasting experienced decreased appetite and lack of minerals Fe, Ca and Zn.

Objectives: This research aims to determine the mineral content of fish meat specifically Fe, Ca and Zn and the influence of that minerals on appetite regulation.

Methods: Analysis of mineral content in Sapat siam fish meat using the AAS method and analysis of the influence of Fe, Ca and Zn minerals using the in silico method.

Results: Sapat siam fish meat contains Fe, Ca and Zn with concentrations of 34.5 ± 0.8485, 1,670 ± 183.8478 and 22.8 ± 0.1414, respectively. Fe, Ca and Zn affect Leptin, NPY, IL-1β

Conclusion: Sapat siam fish affects appetite

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INTRODUCTION

Inland water areas are a source of fish production. Fisheries production in Indonesia in 2021 will be 21 million tons (Indonesian Ministry of Maritime Affairs and Fisheries, 2021a), while fisheries production in South Kalimantan was 218,545 tons with a production value of 6.7 Trillion rupiah (Indonesian Ministry of Maritime Affairs and Fisheries, 2021b). This high production rate is accompanied by an increase in fish consumption rates in Indonesia by 55.37 kg/capita in 2021. The fish consumption rate in South Kalimantan itself in 2021 will be 61.74 kg/capita, greater than the consumption rate in Indonesia. Sapat siam (*Trichopodus pectoralis*, Regan 1910) is one of the fish consumed in South Kalimantan.[3] Sapat siam fish production is ranked second after Papuyu (South Kalimantan Province Fisheries Service, 2018).

Fish meat contains water, protein, fat and ash. Protein is the largest component in fish scales. 40-90% of the protein is collagen protein and the rest is mineral residue and inorganic salts such as magnesium carbonate and calcium carbonate.[5] Fish also contain calcium, phosphorus, Zn, Fe, K, and Na which are beneficial for humans.[6] Fish is used to treat stunting and wasting in children. In wasting toddlers there is a deficiency of Fe, Ca and Zn.[7]

Regulation of appetite influence by Ghrelin, leptin, NPY (Neuropeptide Y), ARC, IL-1β, AgRP. Ghrelin is a hormone produced in the stomach.[8] Appetite regulation also involves several neuropeptides such as Agouti related Peptide (AgRP). AgRP works to stimulate food intake and cause weight gain. Neuropeptide Y (NPY) works to stimulate appetite. NPY is expressed in the same neurons as AgRP, but NPY is expressed in other regions of the hypothalamus and brain.[9–11] This research aims to determine the mineral content of Sapat siam fish specifically Fe, Ca and Zn and the influence of that minerals on appetite regulation by in silico method

METHODS

Materials

Sapat siam fish was obtained from the Martapura market, Banjar District, South Kalimantan

Preparation of Sapat siam Fish

The scales of the fish obtained are cleaned and the meat is removed. The fish meat was washed and dried using an oven at 50^0C for 3 days. The dried fish meat is then ground to obtain meat powder. Then ready for further analysis

Analysis of Mineral Content

Mineral content analysis was carried out using a Shimadzu AA-6300 atomic absorption spectrophotometer (AAS) and following the procedures carried out by [12]

Insilico analysis

The scientific method employed in this research project involved a series of systematic steps. Firstly, ligands and proteins relevant to the research question were identified by conducting thorough searches on databases such as RCSB.org and PubChem. The search criteria included specific

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structural features, functional properties, and biological relevance to the research focus. Next, the ligand structures were modified by inserting metal ions, such as calcium (Ca), iron (Fe), and zinc (Zn), using the BIOVIA Discovery Studio Visualizer. This software tool facilitated precise placement of the metal ions within the ligand molecules, ensuring accurate representation of the desired metal-ligand interactions. Subsequently, water molecules and inherent ligands were removed from the protein structure using PyMOL. This step aims to isolate the protein molecule and eliminate any potential interference or bias caused by solvent molecules or pre-existing ligands. By removing these components, the focus was solely on the interaction between the prepared ligands and the protein receptor. After these preparations, the ion-inserted ligands, non-inserted ligands, and their respective receptor proteins were prepared for docking simulations using PatchDock.

PatchDock operates on the principle of geometric matching, employing a scoring function to predict binding conformations between a ligand and receptor protein through rigid-body docking simulations. This powerful software tool utilizes algorithms and scoring functions to generate potential binding conformations between the ligands and receptors. The simulations take into account the three-dimensional structures and molecular interactions, providing insights into the most favorable binding modes and potential affinity between the ligands and the receptor. By aligning complementary surface patches, the algorithm identifies favorable interactions and assigns scores based on shape complementarity, electrostatics, and desolvation energy. Finally, the docking results were visualized and analyzed using the BIOVIA Discovery Studio Visualizer. This software facilitates the examination and interpretation of the docking processes and interactions. The visual representation of the docked complexes offers valuable insights into the spatial arrangement of the ligands within the receptor's binding site, as well as the nature of the interactions, such as hydrogen bonding, hydrophobic contacts, or metal coordination.

RESULTS

1. Mineral levels in Sapat siam fish

Table 1. Mineral content in Sapat siam fish

No	Mineral	Level (µg/g)
1	Fe	34.5 ± 0.8485
2	Ca	1,670 ± 183.8478
3	Zn	22.8 ± 0.1414

2. Insilico Analysis

a. Ghrelin

Receptors 7NA8, Chain R

The entry with the identifier 7NA8 in the RCSB Protein Data Bank (PDB) represents the structures of human ghrelin receptor-Gi complexes with ghrelin and a synthetic agonist. Ghrelin is a peptide hormone that plays a role in regulating appetite and energy balance. It binds to the ghrelin

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receptor, which is a G protein-coupled receptor (GPCR) located on the cell membrane. The complex formed between the ghrelin receptor and Gi protein is of particular interest because it is involved in signaling pathways that regulate various physiological processes, including hunger, satiety, and metabolism. The complex includes the ghrelin receptor, which is a transmembrane protein, and the Gi protein, which is a guanine nucleotide-binding protein. The structure provides insights into the interaction between the ghrelin receptor and its ligands, ghrelin, and a synthetic agonist. The ligands bind to specific regions on the ghrelin receptor, triggering a cascade of signaling events that regulate cellular responses.[13]

Ligand: Ghrelin 1-4 (C25H38N4O8)

IUPAC: H-Gly-Ser-Ser(octanoyl)-Phe-OH

b. leptin

Receptors 1AX8, Chain A

The entry 1AX8 in the RCSB Protein Data Bank (PDB) corresponds to the crystal structure of the human obesity protein leptin. Leptin is a cytokine that plays a crucial role in regulating body weight and energy balance. Mutations in the gene encoding leptin or its receptor can lead to obesity, infertility, and diabetes in mice. The crystal structure of the mutant form of human leptin (leptin-E100) was determined using X-ray diffraction. The resolution of the structure is 2.40 Å, which provides detailed information about the arrangement of atoms in the protein. The structure of leptin-E100 reveals a four-helix bundle, similar to other members of the long-chain helical cytokine family. This structural motif is important for the biological activity of leptin. Despite being a mutant form [14,15]

Ligand: Leptin (93-105) Human

IUPAC:H-DL-Asn-DL-Val-DL-xiIle-DL-Gln-DL-xiIle-DL-Ser-DL-Asn-DL-Asp-DL-Leu-DL-Glu-DL-Asn-DL-Leu- DL-Arg-OH

c. ARC (Human Arc C-lobe)

Receptors 6TN7, Chain B

The entry 6TN7 in the RCSB Protein Data Bank (PDB) corresponds to the crystal structure of the human Arc C-lobe. The Arc protein, also known as activity-regulated cytoskeleton-associated protein, plays a crucial role in synaptic plasticity and the normal functioning of the brain. It interacts with various neuronal postsynaptic proteins. The crystal structure of 6TN7 provides insights into the structural properties and peptide ligand binding of the C-terminal domain of Arc, which consists of tandem domains known as the N-lobe and C-lobe. The N-lobe contains a peptide binding site capable of binding multiple targets. The researchers measured the affinity of human Arc towards various peptides derived from stargazin and guanylate kinase-associated protein (GKAP), which are known interactors of Arc. They refined the specificity determinants of Arc and identified two binding sites in the GKAP repeat region. These interactions were confirmed through X-ray crystallography. GOL is a small molecule that interacts with the human Arc C-lobe protein.

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Glycerol is commonly used as a cryoprotectant in X-ray crystallography experiments to prevent damage to the protein crystals during freezing. The presence of GOL in the crystal structure suggests that it may play a role in stabilizing the protein or mediating protein-ligand interactions Glycerol is commonly used as a cryoprotectant in X-ray crystallography experiments to prevent damage to the protein crystals during freezing. The presence of GOL in the crystal structure suggests that it may play a role in stabilizing the protein or mediating protein-ligand interactions Glycerol is commonly used as a cryoprotectant in X-ray crystallography experiments to prevent damage to the protein crystals during freezing. The presence of GOL in the crystal structure suggests that it may play a role in stabilizing the protein or mediating protein-ligand interactions.[16]
Ligand: Glycerol (GLYCERIN; PROPANE-1,2,3-TRIOL)

d. Human Neuropeptide Y (5ZBH)

Receptor 5ZBH, Chain A

The entry 5ZBH in the Protein Data Bank (PDB) refers to the crystal structure of the Human Neuropeptide Y Y1 Receptor in complex with the ligand BMS-193885. The structure provides insights into the binding mode of the ligand and the receptor's conformation. The Human Neuropeptide Y Y1 Receptor is a signaling protein that plays an important role in food intake, anxiety, and cancer biology. It belongs to the G-protein-coupled receptor superfamily. The receptor is a membrane protein and is expressed in Homo sapiens (human) and Enterobacteria phage T4. The expression system used for this structure is Spodoptera frugiperda. The ligand in complex with the receptor is BMS-193885, which is a small molecule compound of 9AF, the ligand interacts with the receptor through specific binding sites, and the crystal structure provides information about the interactions between the ligand and the receptor residues. The 5ZBH entry and its associated publication provide valuable information for understanding the binding behavior of the Neuropeptide Y Y1 Receptor and its potential as a target for structure-based drug discovery. The crystal structure and the insights gained from it can contribute to the development of therapeutics targeting the NPY receptor system.[17]

Ligands: 9AF

e. HUMAN INTERLEUKIN-1 BETA (9ILB)

Ligand: Interleukin-1beta (163-171)

The structure with the PDB code 9ILB corresponds to the protein Human Interleukin-1 Beta (IL-1β). Interleukin-1 Beta is a signaling protein involved in the immune response and inflammation processes in the human body. It plays a crucial role in mediating the body's response to infection, injury, and other pathological conditions. The protein's structure was determined using X-ray crystallography, a technique that allows scientists to visualize the arrangement of atoms in a crystal. The resolution of the structure is 2.28 Å, which refers to the level of detail at which the atoms are resolved in the structure. The 9ILB structure consists of a single protein chain, which is the monomeric form of Interleukin-1 Beta. The protein chain is composed of 153 amino acids, and its sequence corresponds to the human IL-1β protein. The protein's amino acid sequence provides important information about its biological function and the interactions it can form with

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other molecules. In addition to the protein structure, you mentioned a ligand associated with 9ILB: Interleukin-1beta (163-171). A ligand is a small molecule or another protein that binds to a specific site on the protein of interest, affecting its function. In this case, Interleukin-1beta (163-171) is a specific region or peptide derived from Interleukin-1 Beta that interacts with the protein A ligand is a small molecule or another protein that binds to a specific site on the protein of interest, affecting its function. In this case, Interleukin-1beta (163-171) is a region specific or peptide derived from Interleukin-1 Beta that interacts with the protein A ligand is a small molecule or another protein that binds to a specific site on the protein of interest, affecting its function. In this case, Interleukin-1beta (163-171) is a specific region or peptide derived from Interleukin-1 Beta that interacts with the protein.[18]

f. AgRP (1HYK)

Ligand: Suleparoid (Heparan sulphate)

Binding between AgRP (AGOUTI-RELATED PROTEIN) (87-132) and heparan sulphate has been shown to have implications in the regulation of appetite. AgRP is known to play a role in modulating feeding behavior and energy homeostasis, while heparan sulphate is a polysaccharide found on cell surfaces involved in various cellular processes. The binding interaction between AgRP and heparan sulphate can be influenced by the presence of metal ions such as Ca, Fe, and Zn. These metal ions have the potential to affect the appetite-regulating properties of AgRP, either by stimulating or inhibiting appetite. The binding site of AgRP (87-132) on heparan sulphate and the key residues responsible for the interaction have been identified through structural analyses. The positively charged regions of AgRP, often due to the presence of lysine or arginine residues, interact with the negatively charged sulfate groups on heparan sulfate. These interactions contribute to the stabilization of the AgrP-heparan sulphate complex and play a crucial role in mediating its biological functions. The binding of AgRP to heparan sulphate may modulate signal transduction pathways, cellular adhesion, or other processes involved in cell communication and tissue development

Table 1. Ca Metal Bonds with ghrelin, leptin, ARC, NPY, IL-1β, AgRP

Ligand	Highest Score	Atomic Contact Energy (ACE) (KJ/mol)	transformation	areas
ghrelin	6740	-354.34	-1.84 -0.75 -1.50; 142.52 141.88 116.69	793.30
Leptin	10446	-508.73	1.04 0.18 0.45; 51.86 -41.28 14.02	515.30
ARC	1538	-23.74	-1.32 0.80 1.09; 18.91 -6.79 136.32	156.90
NPY	6770	-431.59	2.81 -0.31 -1.23; 22.87 16.89 -72.71	911.20
IL-1β	7240	-403.57	0.87 0.20 0.36; -28.81 20.27 -16.12	968.90
AgRP	3668	-84.75	2.53 -0.61 2.87 6.67 -2.23 -1.98	451.80

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Table 2. Fe metal binding with ghrelin, leptin, ARC, NPY, IL-1β, AgRP

	Highest Score	Atomic Contact Energy (ACE) (KJ/mol)	transformation	areas
ghrelin	6248	-319.82	-0.46 1.29 -1.39; 126.34 117.96 101.06	768.60
Leptin	10420	-484.17	1.04 0.18 0.45; 51.86 -41.28 14.02	509.50
ARC	1426	-11.32	-2.30 -0.72 0.88; 10.77 12.20 139.05	148.40
NPY	7108	-398.04	2.78 -0.34 -1.22; 23.26 16.88 -72.83	908.20
IL1B	8428	-374.25	-1.20 -0.44 3.00; -4.06 10.57 pm -8.16	1064.30
AgRP	3782	-29.31	2.62 -0.61 2.75 6.05 -1.96 -3.02	442.00

Table 3. Zn metal binding with ghrelin, leptin, ARC, NPY, IL-1β, AgRP

	Highest Score	Atomic Contact Energy (ACE) (KJ/mol)	transformation	areas
ghrelin	6334	-325.34	-1.63 -0.21 2.23; 148.63 128.39 112.79	712.30
Leptin	10702	-450.83	-2.25 -0.82 0.07; 52.84 -41.13 20.32	440.00
ARC	1414	-32.93	-2.01 -0.65 1.07; 10.94 12.50 138.30	152.50
NPY	6964	-393.93	2.79 -0.32 -1.25; 23.55 16.89 -73.03	883.60
IL1B	8070	-450.82	-0.38 0.85 1.83; -15.48 15.62 -22.79	1137.30
AgRP	3806	-42.96	2.62 -0.61 2.75 6.05 -1.96 -3.02	443.40

Table 4. Ca, Zn and Fe metal binding with ghrelin, leptin, ARC, NPY, IL-1β, AgRP

	Highest Score	Atomic Contact Energy (ACE) (KJ/mol)	transformation	areas
ghrelin	6138	-370.68	-0.60 1.24 -1.27 126.72 118.30 101.34	812.00
Leptin	10112	-527.29	-1.01 0.05 -2.84 69.96 -34.68 14.81	519.70
ARC	1370	-33.71	-2.51 1.18 -2.39 10.64 11.87 139.55	144.30
NPY	6476	-411.65	2.65 -0.27 -1.21 23.03 16.67 -73.07	876.20
IL-1β	7270	-421.00	-0.34 -0.62 -2.47 -10.48 13.12 18.90	987.90
AgRP	3910	-136.28	0.55 0.71 2.68 -0.71 -15.01 -2.49	488.60

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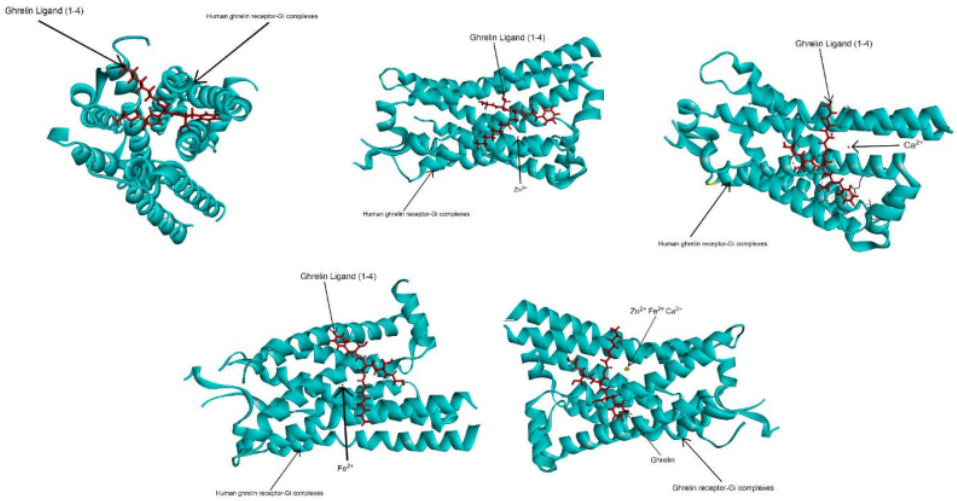

Figure 1. Image of Ghrelin's bond with Fe, Ca and Zn

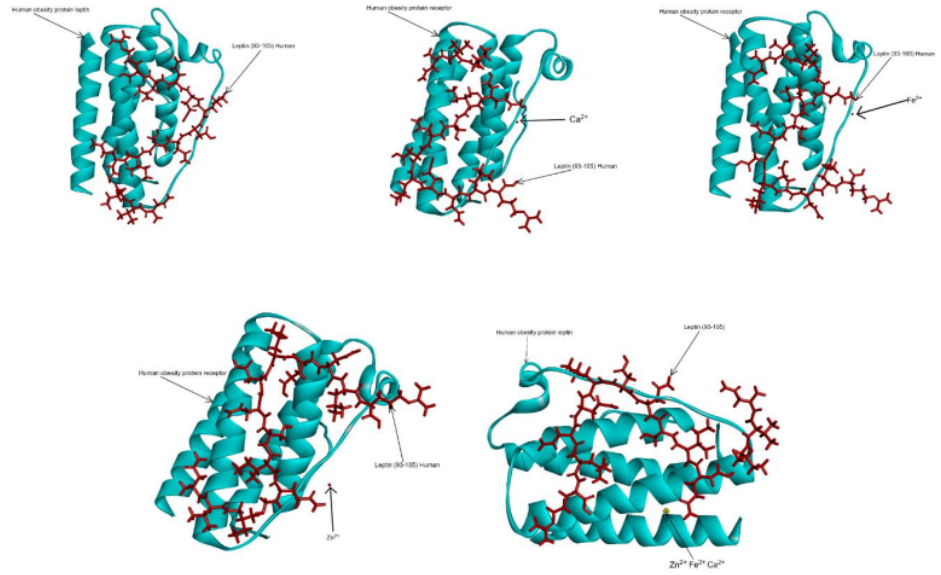

Figure 2. Image of Leptin binding with Fe, Ca and Zn

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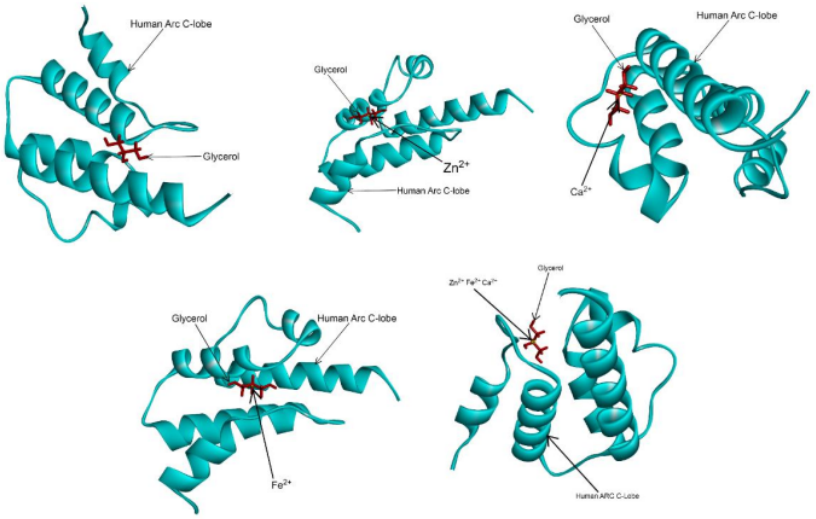

Figure 3. Image of ARC binding with Fe, Ca and Zn

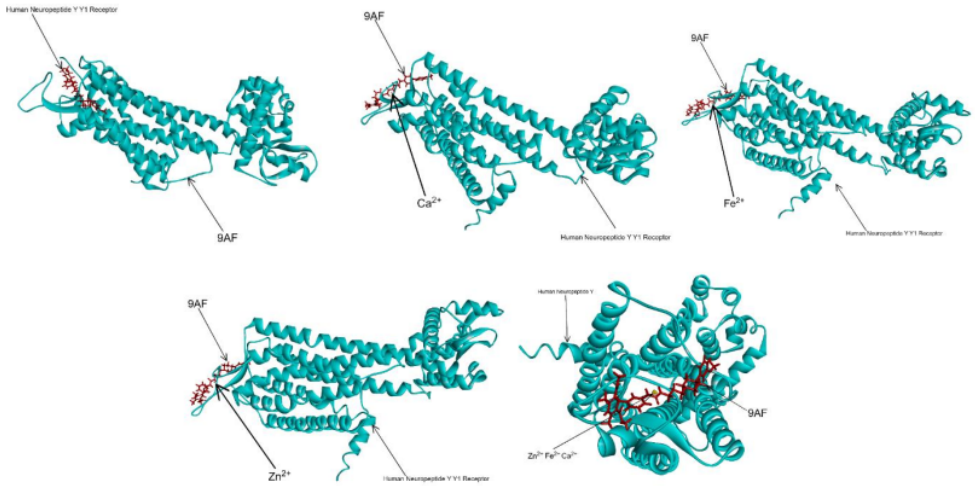

Figure 4. Image of NPY binding with Fe, Ca and Zn

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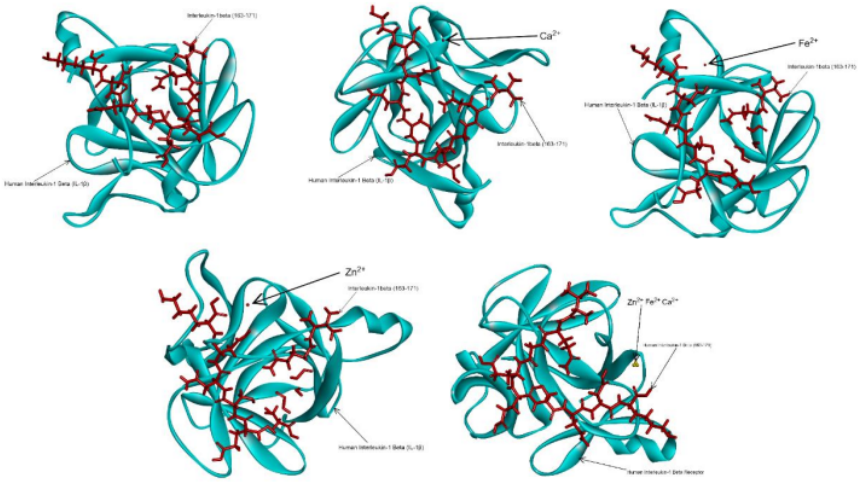

Figure 5. Images of IL-1β binding with Fe, Ca and Zn

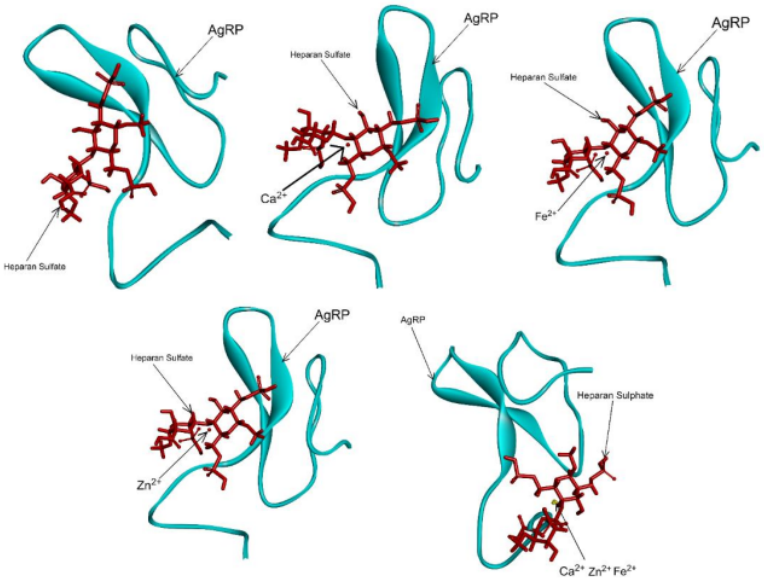

Figure 6. Images of AgRP binding with Fe, Ca and Zn

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DISCUSSION

The research aimed to investigate the docking of Ghrelin, NPY (Neuropeptide Y), Leptin, IL-1 Beta, ARC, and AgRP with their respective receptors or ligands using the PatchDock algorithm. Additionally, the ligands were tested for the presence of metal ions (Ca^{2+}, Fe^{2+}, or Zn^{2+}) and in their non-added forms. The focus was on examining the effect of metal ion addition on the docking results, particularly on the ACE (Atomic Contact Energy) values. The results of the docking simulations revealed that the ACE values for the ligand-receptor complexes were consistently lower when metal ions were added compared to the ligands without metal ions. This implies that the presence of metal ions enhances the binding affinity between the ligands and their respective receptors. specifically, when Ghrelin, NPY, Leptin, IL-1β, ARC, or AgRP were docked with their receptors or ligands in the presence of Ca^{2+}, Fe^{2+}, or Zn^{2+}, the resulting ACE values were consistently smaller compared to the docking simulations without the added metal ions. This indicates that the metal ions facilitated stronger interactions and improved the overall stability of the ligand-receptor complexes. These findings suggest that the addition of Ca^{2+}, Fe^{2+}, or Zn^{2+} ions can enhance the binding affinity between the studied ligands and their receptors or ligands. The presence of these metal ions likely contributed to the formation of additional coordination bonds or electrostatic interactions, leading to a more favorable docking outcome the resulting ACE values were consistently smaller compared to the docking simulations without the added metal ions. This indicates that the metal ions facilitated stronger interactions and improved the overall stability of the ligand-receptor complexes. These findings suggest that the addition of Ca^{2+}, Fe^{2+}, or Zn^{2+} ions can enhance the binding affinity between the studied ligands and their receptors or ligands. The presence of these metal ions likely contributed to the formation of additional coordination bonds or electrostatic interactions, leading to a more favorable docking outcome the resulting ACE values were consistently smaller compared to the docking simulations without the added metal ions. This indicates that the metal ions facilitated stronger interactions and improved the overall stability of the ligand-receptor complexes. These findings suggest that the addition of Ca^{2+}, Fe^{2+}, or Zn^{2+} ions can enhance the binding affinity between the studied ligands and their receptors or ligands. The presence of these metal ions likely contributed to the formation of additional coordination bonds or electrostatic interactions, leading to a more favorable docking outcome or Zn^{2+} ions can enhance the binding affinity between the studied ligands and their receptors or ligands. The presence of these metal ions likely contributed to the formation of additional coordination bonds or electrostatic interactions, leading to a more favorable docking outcome or Zn^{2+} ions can enhance the binding affinity between the studied ligands and their receptors or ligands. The presence of these metal ions likely contributed to the formation of additional coordination bonds or electrostatic interactions, leading to a more favorable docking outcome.[19–21]

Regarding the study's relevance to wasting in underweight children and their deficiency in Fe, Ca, and Zn is crucial for understanding the potential implications of the docking results. Ghrelin, NPY, Leptin, IL-1 Beta, ARC, and AgRP are all bioactive molecules that play important roles in various physiological processes, including appetite regulation, metabolism, and immune response.[22] Wasting in underweight childrenwho are deficient in Fe, Ca, and Zn, it becomes relevant to investigate how the addition of these compounds affects the interaction between these bioactive molecules and their respective receptors or ligands. The docking results suggest that the

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presence of metal ions (Ca2+, Fe2+, or Zn2+) during the binding of these bioactive molecules may influence their affinity for their receptors or ligands. Considering the deficiencies in Fe, Ca, and Zn in underweight children, it is plausible that the addition of these metal ions could potentially modulate the interaction between the studied molecules and their receptors, leading to altered signaling pathways or biological responses.[23]

The role of iron, calcium, and zinc in metabolic processes, their impact on health, and how the presence of these metal ions can affect the binding of bioactive molecules related to appetite regulation, immune response, and other physiological processes such as iron is a crucial component of hemoglobin, the protein in red blood cells that carries oxygen throughout the body. It is also involved in various enzymatic reactions related to energy production, DNA synthesis, and immune function. Iron deficiency can lead to anemia, fatigue, impaired cognitive development, and weakened immune system. In the context of wasting and underweight conditions, iron deficiency may contribute to reduced energy production and impaired immune response, further exacerbating the state of undernutrition.[24] Calcium is essential for bone health, muscle contraction, nerve signaling, and blood clotting. It also plays a role in regulating hormone secretion and cellular processes. Inadequate calcium intake can lead to weakened bones, increased risk of fractures, muscle cramps and impaired nerve function. Calcium deficiency may affect the regulation of appetite-related molecules such as Ghrelin, NPY, and Leptin, potentially influencing hunger and satiety signals and contributing to disrupted appetite regulation in underweight children.[25] Zinc is involved in numerous enzymatic reactions and is essential for immune function, protein synthesis, wound healing, and DNA synthesis. Zinc deficiency can impair immune response, delay growth and development, and increase susceptibility to infections. Wasting and underweight conditions caused by zinc deficiency may compromise immune function, impair appetite regulation, and disrupt the signaling pathways involving bioactive molecules such as IL-1 Beta, ARC, and AgRP.[26]

The presence of iron, calcium, and zinc ions during the binding of bioactive molecules can potentially influence their conformation, stability, and affinity for their receptors or ligands. These metal ions may directly interact with the bioactive molecules or indirectly affect the binding through allosteric modulation or structural changes in the receptor. The altered binding affinity or signaling pathways due to the presence of these metal ions can impact appetite regulation, immune response, and other physiological processes related to wasting and underweight conditions. Understanding the interplay between mineral deficiencies and the binding of bioactive molecules provides valuable insights into the potential mechanisms underlying wasting in underweight children. It highlights the complex relationship between nutrition, metabolic processes, and the regulation of various physiological functions. Further research and experimental studies are needed to elucidate the specific molecular mechanisms and functional consequences of metal ion interactions with these bioactive molecules in the context of wasting and mineral deficiencies.[27]

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CONCLUSION

The presence of Fe, Ca and Zn in Sapat siam fish meat will affect appetite

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