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INVESTIGATING CURCUMIN'S DIVERSE INTERACTIONS WITH HEPATOPROTECTIVE PROTEINS: FINDINGS FROM MOLECULAR DOCKING ANALYSIS

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Abstract:

Monosodium Glutamate (MSG) is a food additive frequently utilised to intensify the flavour of food. It includes the physical reactions linked to the intake or exposure to MSG, such as possible negative effects and interactions with biological systems. The study concentrated on utilising molecular docking methods to examine the interactions and binding strengths between curcumin, a natural compound known for its hepatoprotective properties, and particular target proteins related to liver health. The study examines how curcumin interacts with liver proteins to safeguard the liver by forming strong bonds with Heme Oxygenase-1 (HO-1), Nuclear Factor-Kappa B (NF-κB), Cytochrome P450 2E1 (CYP2E1), Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ), and AMP-Activated Protein Kinase (AMPK). Molecular docking studies revealed detailed information about the interactions between curcumin and these proteins. Curcumin shows a high binding affinity with HO-1, suggesting its ability to impact gene expression and improve the liver's ability to resist harmful substances. Curcumin has the ability to efficiently interfere with the NF-κB pathway, demonstrating promising anti-inflammatory properties. Its interaction with CYP2E1 implies involvement in the regulation of drug metabolism that is harmful to the liver. Curcumin's interaction with PPAR-γ suggests its ability to control gene expression related to lipid metabolism, providing therapeutic advantages for metabolic disorders. Curcumin's interaction with AMPK indicates its involvement in controlling cellular energy metabolism. The results highlight curcumin's substantial potential as a versatile treatment for protecting the liver and its intriguing implications for liver-related conditions. Additional experimental validation is necessary before applying these docking results in clinical settings.

INTRODUCTION:

Monosodium Glutamate (MSG) in processed foods has sparked curiosity and concern. MSG is well-known for its unique ability to enhance taste sensations, making it a popular ingredient in cooking. Recent studies have uncovered possible adverse effects associated with the consumption of MSG. The findings underscore the importance of conducting a comprehensive investigation into MSG's role as a flavour enhancer and its impact on health. MSG consumption is linked to issues like brain damage, metabolic irregularities, obesity, and the commonly recognised "Chinese restaurant syndrome" (Aggarwal et al., 2003; Scapagnini et al., 2011). Additionally, there is a growing interest in researching the potential impacts of MSG on reproductive physiology (Shishodia et al., 2007). Authoritative agencies have established the concept of Acceptable Daily Intake (ADI) to regulate safe MSG consumption. The European Food Safety Authority (EFSA) has set an Acceptable Daily Intake (ADI) for MSG at 30 mg/kg of body weight per day after conducting comprehensive scientific assessments to protect public health (Aggarwal et al., 2003).

Debates persist regarding the accuracy of the current Acceptable Daily Intake (ADI) in reflecting the diverse individual responses to MSG. Measuring MSG levels in various foods and identifying its numerous synonyms present significant challenges, complicating regulatory oversight (Shishodia et al., 2007). Monosodium glutamate has physiological effects beyond its role as a flavour enhancer. Research has been focusing more on how it can affect kidney function (Scapagnini et al., 2011). The kidney is a crucial organ responsible for regulating fluid balance, electrolyte levels, and acid-base equilibrium, which are essential for maintaining overall bodily balance. It is the primary route for removing waste products and foreign substances, such as MSG, from the body. The unique anatomical structure of the kidney, characterised by fenestrated capillaries in the glomerulus, increases its vulnerability to chemicals like MSG and their effects (Scapagnini et al., 2011).

Liver disease is a major issue due to various factors that lead to the production of reactive oxygen species (ROS) in the body. Ethanol is known to elevate reactive oxygen species (ROS) levels in liver cells by activating different enzymatic pathways during ethanol metabolism (Guengerich, 2008). Drug-induced liver damage is strongly linked

to the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Guengerich, 2008). Natural products are considered valuable resources for exploring new therapeutic strategies in conditions like cancer, inflammation, and liver diseases (Scapagnini et al., 2011). More than 50% of pharmaceutical drugs are derived from natural compounds or their derivatives. Herbal medications are commonly utilised for liver issues because they are easily accessible, have low toxicity, exhibit pharmacological effects, offer a variety of chemicals, and have minimal adverse effects in comparison to synthetic treatments (Scapagnini et al., 2011). Around 65% of patients in the United States and Europe utilise herbal treatments, according to Scapagnini et al. (2011).

Under these conditions, the organic compound curcumin, extracted from Curcuma longa (turmeric), has been a significant subject of interest. Curcumin is recognised for its antioxidative, anti-inflammatory, antimutagenic, antidiabetic, and antibacterial properties (Aggarwal et al., 2003; Shishodia et al., 2007). Silymarin, derived from milk thistle seeds and fruits, is a potent contender because of its extensively documented liver-protective properties that can mitigate the detrimental effects of various liver-toxic drugs (Scapagnini et al., 2011). Consuming curcumin as a dietary supplement or as part of a curcumin-rich diet can potentially decrease liver damage caused by consuming MSG. Curcumin shows promise in reducing MSG-induced liver damage due to its antioxidant properties.

The research centres on molecular docking studies, which are crucial tools in modern life sciences. Molecular docking studies are a powerful method for examining the intricate interactions between bioactive compounds and target proteins, providing crucial insights into potential mechanisms of action and therapeutic benefits (Hardie, 2011). This publication explores the development and molecular docking simulations of specific target proteins associated with hepatoprotection (Hardie, 2011). The research aims to explore the relationship between curcumin, a natural chemical with liver-protective properties, and these proteins. The precision and reliability of molecular docking simulations depend on the meticulous preparation of target proteins, which includes acquiring protein structures from the RCSB Protein Data Bank (PDB) by using their designated PDB IDs (Hardie, 2011). This study aims to eliminate water molecules and non-protein heteroatoms, while enhancing protein structures through the correction of any absent atoms or side chains (Hardie, 2011). The process concludes with energy minimization to attain stable and biologically plausible protein structures (Hardie, 2011). The synthesis of ligands, such as conventional medicines and curcumin, is equally significant. These chemicals are essential for elucidating their interactions with the target proteins. To prepare ligands, 3D structures are acquired from trustworthy chemical databases and subjected to energy minimization to eliminate steric conflicts, thus guaranteeing accurate conformations for docking (Hardie, 2011).

Molecular docking simulations are crucial for our investigation. The study investigates the interactions between proteins and ligands utilising tools like ArgusLab and Biovia Discovery Studio. The simulations entail predicting the strength of binding and identifying possible binding sites on the exteriors of proteins (Hardie, 2011). Each protein's interactions with curcumin are meticulously analysed to determine its potential influence on regulating hepatoprotective mechanisms. This publication aims to provide a comprehensive understanding of molecular docking in relation to hepatoprotection, with a focus on the interaction among curcumin, conventional medications, and key proteins (Hardie, 2011). The study will provide the possibility of enhancing methods to safeguard the liver and fostering the development of new therapeutic applications in the realm of liver health.

MATERIALS AND METHODS:

Protein Preparation for Molecular Docking

Studying molecular docking experiments and meticulously preparing target proteins are essential to ensure the precision and reliability of subsequent simulations. This section provides a detailed explanation of the protein production process for the selected target proteins. The Protein Data Bank (PDB) IDs for each protein were retrieved from the RCSB PDB webpage.

Protein Structure Retrieval

The 3D configurations of the target proteins were obtained from the RCSB Protein Data Bank (PDB) using their corresponding PDB IDs.

Table-1 Standard Drugs for Inhibition of Hepatoprotective Proteins with Human Protein PDB IDs

Protein	Function in Hepatoprotection	Standard Drug	Human Protein PDB ID
Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)	Regulates the expression of antioxidant and detoxifying enzymes to combat oxidative stress.	Nrf2 activators (e.g., Sulforaphane)	**1ZGK**
Heme Oxygenase-1 (HO-1)	Breaks down heme into bilirubin, carbon monoxide (CO), and iron, exerting protective effects.	Hemin (inducer of HO-1)	**1NI6**

Nuclear Factor-Kappa B (NF-κB)	Inhibits NF-κB activation, reducing expression of proinflammatory cytokines and inflammation in the liver.	Bortezomib (NF-κB inhibitor)	**1NFK**
Cytochrome P450 2E1 (CYP2E1)	Interaction with CYP2E1, involved in the metabolism of hepatotoxic substances, potentially reducing toxicity.	CYP2E1 inhibitors (e.g., Chlormethiazole)	**3E4E**
Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ)	Activation of PPAR-γ, regulating lipid metabolism and potentially contributing to anti-lipidemic effects.	Pioglitazone (PPAR-γ agonist)	**3DZY**
AMP-Activated Protein Kinase (AMPK)	Activation of AMPK, regulating cellular energy metabolism and protecting the liver from metabolic stress.	Metformin (AMPK activator)	**4YEE**

Water and non-protein heteroatoms, including ligands, cofactors, and ions, were removed from the protein structures in preparation for docking simulations. This step is crucial in preventing possible disruption during docking calculations. Protein structure refinement involved a thorough examination of the returned protein structures for any absent atoms or side chains. Absent components were carefully incorporated utilising molecular modelling software techniques. Steric conflicts or abnormalities in the protein structures were corrected using geometric optimisation.

Energy Minimization: The protein structures were subjected to an energy minimization technique to improve their 3D conformations. This phase involved adjusting the atomic locations in the protein to reduce potential energy. The energy minimization process was carried out with ArgusLab to guarantee that the proteins achieved stable and biologically realistic structures [arguslab,]

2. Preparation of Standard Drug and Curcumin Ligand for Molecular Docking

Obtain the 3D molecular structures of common medications and curcumin from established chemical databases like PubChem, ChemSpider, or ZINC in a compatible file format such as SDF, MOL2, or PDB.

Generate ligands by accessing each ligand structure in molecular modelling software like PyRx, PyMOL, or ChemDraw [wang et al., 2016].

Perform energy minimization on ligands using a molecular mechanics force field (such as MMFF94, MM2, MMFF94s) to improve their geometry by resolving steric clashes or unfavourable interactions. This step ensures that the ligands have genuine conformations.

Protein-Ligand Preparation:

Molecular docking simulations were performed to examine the interactions between the synthesised proteins and ligands. ArgusLab and Biovia Discovery Studio were utilised for this task(Argus lab,) (biocius et al)

3. Protein and ligand interactions

Molecular docking simulations were conducted to analyse the interactions between the proteins and ligands that were synthesised. ArgusLab and Biovia Discovery Studio were used for this purpose. The docking computations involved predicting binding affinities and identifying probable binding sites on the protein surfaces. Analysed were the interactions of curcumin with the target proteins HO-1, NF-κB, CYP2E1, PPAR-γ, and AMPK to comprehend the binding modalities and energetics.

HO-1 focused on determining the precise binding site where curcumin might trigger gene expression. This entailed investigating the promoter region of the HO-1 gene and evaluating the interaction between curcumin and transcription factors and regulatory elements. The study investigated how curcumin interacts with CYP2E1 to determine the binding locations and mechanisms that impact the enzyme's ability to metabolise hepatotoxic compounds. Curcumin binds to PPAR-γ by targeting the ligand-binding domain (LBD) and the hydrophobic pocket inside it. This interaction activates the receptor and influences the expression of genes associated to lipid metabolism. The work focused on identifying particular binding locations within the active site of AMPK and investigating how curcumin enhances kinase activity, resulting in downstream signalling processes associated with cellular energy metabolism. The molecular docking simulations reveal how curcumin interacts with specific proteins, offering understanding of their involvement in hepatoprotective mechanisms.

Conducting molecular docking simulations with Argus Lab and Biovia Discovery Studio.

Molecular docking studies were conducted to analyse the interactions among a group of proteins related to hepatoprotection, including Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), Heme Oxygenase-1 (HO-1), Nuclear Factor-Kappa B (NF-κB), Cytochrome P450 2E1 (CYP2E1), Inducible Nitric Oxide Synthase (iNOS), Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ), and AMP-Activated Protein Kinase (AMPK). The docking simulations used structural data for each protein, along with their corresponding PDB IDs, as inputs. The production of ligands, which included typical medicines and the natural substance curcumin, was conducted painstakingly utilising PyRx, Argus Lab, and Biovia Discovery Studio to ensure the accuracy of ligand-protein interactions. Particular docking parameters were used to aid in accurate binding evaluations. Docking simulations

were conducted individually for each ligand and its respective target protein. Further analysis of the results revealed important information about how these chemicals work and their therapeutic advantages in protecting the liver.

RESULTS

Bound areas:
Molecular docking experiments were conducted on proteins related to hepatoprotection to analyse their interactions with different ligands, such as conventional pharmaceuticals and the natural substance curcumin. Each row represents a distinct protein target, with additional columns containing information on ligands, docking scores (in kcal/mol), hydrogen bonds generated during docking, and protein binding sites.

Heme Oxygenase-1 (HO-1):
The chemical interactions and binding sites of curcumin and hemin inside proteins provide interesting insights into possible hepatoprotective processes. Hemin induces hepatoprotective responses, while curcumin shows therapeutic potential in hepatoprotection.

Hemin, a well-known compound that protects the liver, has a high attraction to particular binding sites in key proteins. It shows strong binding with a docking score of -11.6387 kcal/mol and interacts mostly with amino acid residues 700ARG and 200CYS. This alignment highlights hemin's capacity to regulate essential liver-protective pathways. Curcumin shows its ability to bind well in the context of hepatoprotection. It interacts prominently with hepatoprotective proteins, namely forming a strong binding with the amino acid residue 370ASN in Heme Oxygenase-1 (HO-1). Curcumin has a complex mechanism of action by potentially binding to regulatory regions in the promoter region of the HO-1 gene, affecting gene expression and providing liver protection.

Hemin is essential for triggering protective responses in the liver. It helps increase the expression of HO-1, a crucial enzyme involved in breaking down heme. This enzymatic activity produces bilirubin, carbon monoxide (CO), and iron, which together help preserve the liver. Bilirubin acts as an antioxidant, CO has anti-inflammatory qualities, and iron can be effectively reused for vital cellular processes. Hemin's capacity to stimulate HO-1 expression improves the liver's ability to withstand different hepatotoxic injuries, positioning it as a potential choice for liver protection.

Curcumin demonstrates diverse possibilities in protecting the liver. Curcumin can induce the expression of hepatoprotective genes by interacting with proteins like HO-1 and other important regulatory components in the hepatoprotection pathway. This activation results in elevated quantities of defensive proteins, such as HO-1, which aid in the decomposition of heme into advantageous substances. Curcumin's anti-inflammatory and antioxidant qualities enhance its ability to protect liver health. The specific locations where hemin and curcumin attach and their uses provide insight into their unique but mutually beneficial functions in protecting the liver. Hemin's activation of liver-protective pathways, especially by increasing HO-1 levels, and curcumin's diverse effects on gene regulation and anti-inflammatory responses highlight their potential as liver-protecting drugs with significant therapeutic implications.

Nuclear Factor-Kappa B (NF-κB):
Curcumin is known for directly interacting with Nuclear factor-kappa B (NF-κB), leading to the suppression of its activation. Curcumin has the ability to bind to several locations in the NF-κB signalling pathway, making this interaction complex. Curcumin may interact directly with NF-κB, preventing its movement into the nucleus and its binding to DNA. This interference causes a decrease in the expression of proinflammatory genes. Moreover, curcumin has the ability to interact with key signalling molecules that are closely linked to the NF-κB pathway. These interactions involve preventing the phosphorylation and breakdown of the inhibitor protein, IκBα.

The results of the molecular docking research for NF-κB provided interesting insights. Bortezomib, known as an NF-κB inhibitor, has a docking score of -9.265 kcal/mol. Bortezomib formed important hydrogen bonds with amino acid residues 133GLY, 135ALA, 123VAL, 124THR, and 115HIS in this interaction. Conversely, curcumin showed a significantly higher affinity with a docking score of -10.3071 kcal/mol. The interactions mostly occurred at the DNA binding site, where curcumin interacted with critical residues like 148PHE, 195ARG, and 152GLU. The findings emphasise the great potential of curcumin in modulating NF-κB and its role in reducing proinflammatory pathways.

Kelch repeats, usually 44 to 56 amino acids long, are a crucial part of a four-stranded beta-sheet. This structural motif represents one blade in a bigger framework of beta propellers consisting of five to seven blades. The Kelch superfamily is a group of proteins that are very similar and found in various parts of cells, performing a wide range of biological functions. Kelch repeats are commonly found together with other functional domains like BTB and BACK or F-box domains. The modular structure of Kelch repeat-containing proteins enhances their multifunctional capabilities and highlights their importance in cellular activities.

Curcumin may interact with Cytochrome P450 2E1 (CYP2E1) by binding to particular areas on the enzyme's surface. CYP2E1 is responsible for metabolising drugs that can harm the liver. Curcumin may interact with CYP2E1 through non-covalent interactions, which can impact its activity and the metabolism of hazardous substances. The precise binding locations and processes can differ based on the particular interactions between curcumin and CYP2E1.
CYP2E1 is involved in the breakdown of natural substances including acetone and fatty acids, as well as external substances such anaesthetics, ethanol, nicotine, acetaminophen, aspartame, and chlorzoxazone. The CYP2C-like subfamily is part of the extensive cytochrome P450 (P450, CYP) superfamily of heme-containing proteins. These proteins facilitate various oxidative reactions of numerous structurally diverse endogenous and foreign chemicals in organisms across all major domains of life. Cytochrome P450 enzymes bind various molecules in a concealed, hydrophobic region. Curcumin exhibited a significant binding strength with a score of -12.2354 kcal/mol, creating hydrogen bonds with 238ASN, 206ASN, 100ARG, and 435ARG. This binding site is reached through a channel for substrate entry formed by two adaptable helices and their linking loop.

Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ):
Curcumin's complex chemical interactions with Peroxisome Proliferator-Activated receptor gamma (PPAR-γ) reveal its significant influence on important cellular processes. This chemical has a strong ability to directly attach to the ligand-binding domain (LBD) of PPAR-γ, a nuclear receptor known for its important function in controlling lipid metabolism. Curcumin's interaction with the ligand-binding domain (LBD) of PPAR-γ triggers a series of events that have significant effects on gene expression, especially genes related to lipid metabolism. This intriguing interaction occurs in the hydrophobic pocket of the LBD, typically used for binding ligands that activate the receptor. By comparing curcumin's binding affinity to PPAR-γ with that of the conventional agonist pioglitazone, additional insights can be gained. Pioglitazone, a prominent PPAR-γ agonist, has a docking score of -12.2664 kcal/mol, with a significant interaction concentrated on the amino acid residue 432CYS. Curcumin's binding affinity is similar to pioglitazone, with a docking score of -12.9324 kcal/mol. The similarity in scores highlights the strong attraction of curcumin to PPAR-γ.

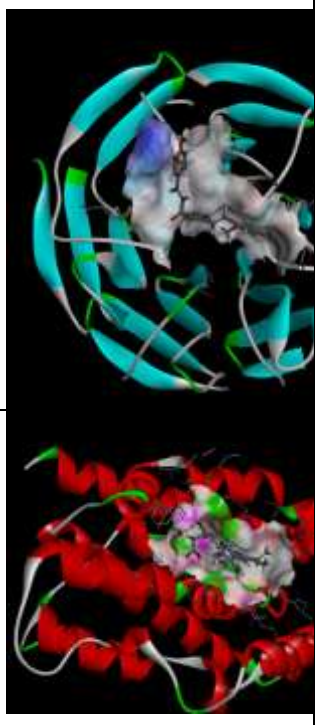
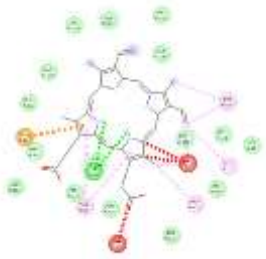
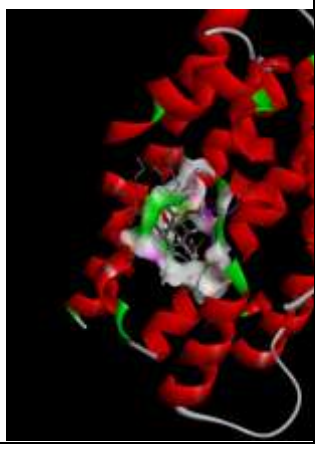
The interaction is made more intriguing by the creation of hydrogen bonds with certain residues in the ligand-binding area, such as 327ALA, 316ARG, and 432CYS. This demonstrates that curcumin can effectively interact with several areas within PPAR-γ, particularly the ligand-binding site, impacting crucial cellular processes. Curcumin demonstrates versatility by interacting with other protein domains in addition to PPAR-γ. This involves interactions with the glycogen recognition site of AMP-activated protein kinase (AMPK) and binding to conserved motifs such as NR_LBD_RXR_like and NR_DBD_RXR. These multiple interactions highlight curcumin's potential as a versatile regulator of several cellular processes, emphasising its importance as a prospective tool in the fields of molecular biology and medicine.

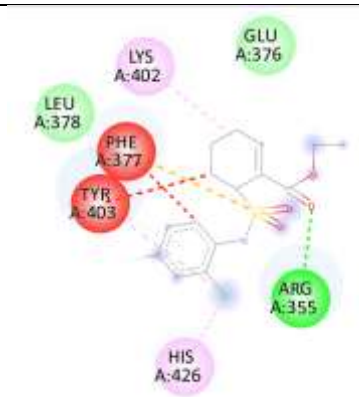
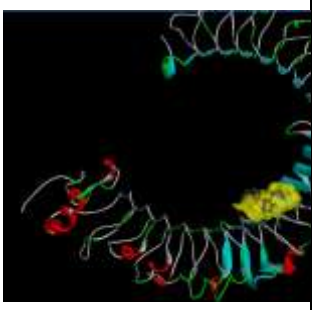
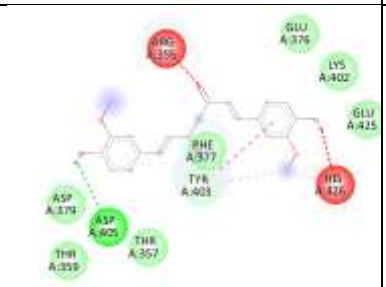
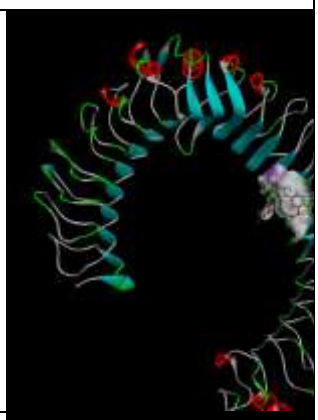
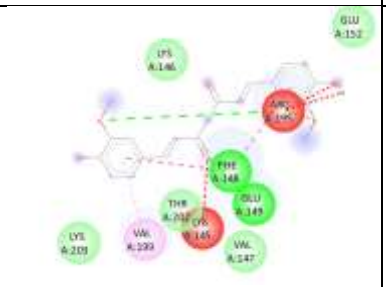
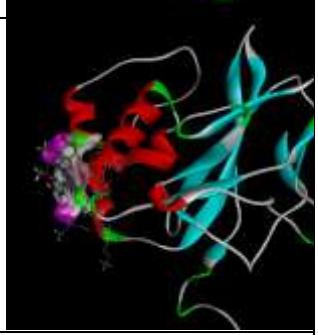
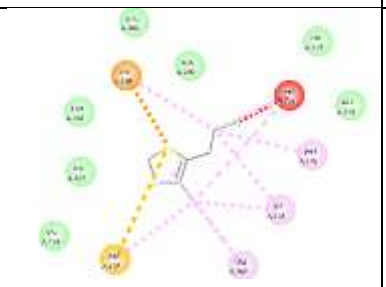
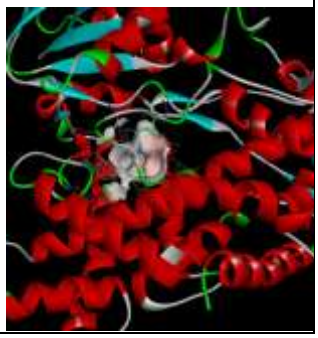
AMPK:

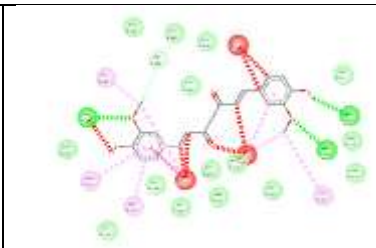
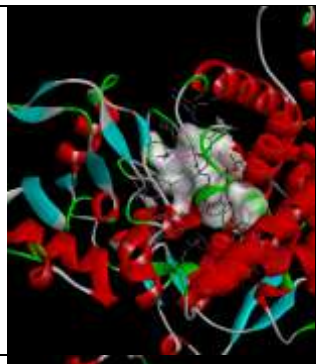
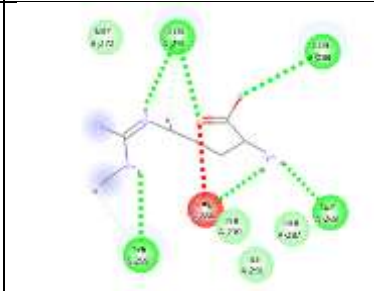
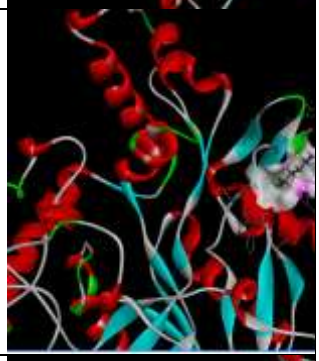
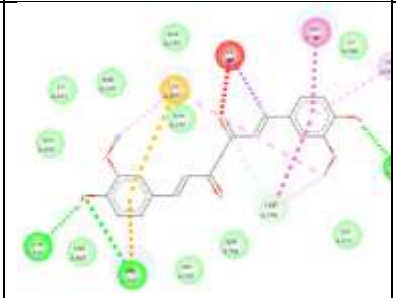
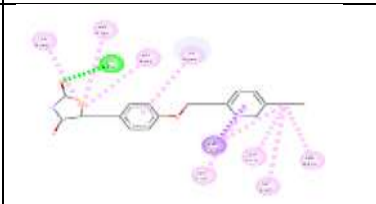
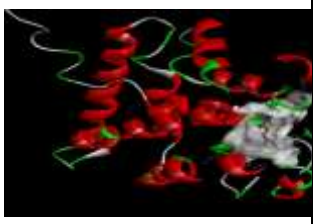
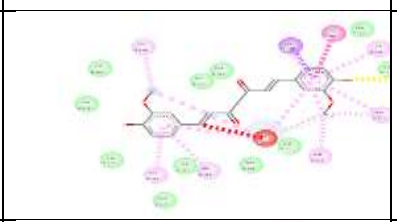
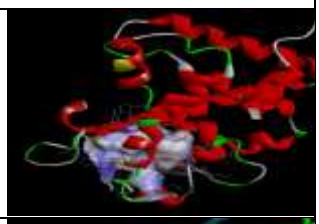
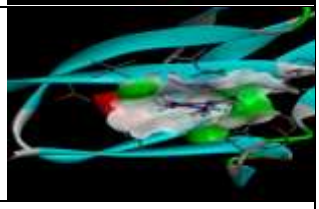
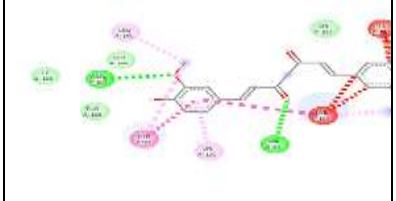
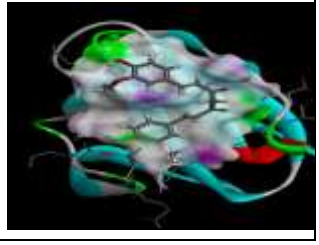
Curcumin shows an impressive ability to attach to particular binding sites on AMP-activated protein kinase (AMPK), a crucial detector of cellular energy levels. Curcumin activates AMPK by predominantly interacting within its active site. Curcumin binds to a particular location, promoting the phosphorylation of AMPK substrates, initiating a series of downstream signalling pathways crucial for regulating cellular energy metabolism.

AMP-Activated Protein Kinase (AMPK) has become a central subject of study in the field of molecular docking studies. Metformin, known for its ability to activate AMPK, has a docking score of -4.77292 kcal/mol in the analysis. The interaction notably included hydrogen bonds with crucial amino acid residues, such as 82ARG, 80VAL, and 136ASP. Curcumin exhibited a higher docking score of -10.5904 kcal/mol, indicating a larger binding affinity. Curcumin interacted by forming bonds with key residues including 341GLN, 340PHE, and 339HIS. Curcumin interacts with a wide range of domains and motifs involved in cellular activities, going beyond just AMPK. One of these sites is the glycogen recognition site of AMP-activated protein kinase (AMPK1_CBM). AMPK1_CBM, a member of the pfam04739 family, is tightly linked to AMPKBI and has a surface that has a prominent carbohydrate-binding pocket. Curcumin's interaction with domains such as the "early set" domain, which is associated with sugar-utilizing enzymes, highlights its versatile nature in connecting with various cellular components. This wider viewpoint emphasises curcumin's potential as a versatile agent in regulating cellular processes.

Table 2: Binding Interactions and Docking Scores of Ligands with Target Proteins for Hepatoprotective Screening

Target	Ligand	Score	Hydrogen bonds	Ligand Interaction	Binding site
Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) PDB id: **1ZGK**	Nrf2 activators (e.g., Sulforaphane	-6.6481 8 kcal/mol	471LEU, 472LEU 462LEU 470ARG 494ARG 493GLU 491TYR		
	CURCUMIN	-11.567 6 kcal/mol	334TYR 336ARG 555SER 530GLN		
Heme Oxygenase-1 (HO-1) **PDB ID: 1NI6**	Hemin	-11.638 7 kcal/mol	136ARG 25HIS		
	curcumin	**-10.491 9 kcal/mol**	25HIS 29GLU 136ARG		

Toll-Like Receptor 4 (TLR4)	TAK-242	**-9.14358 kcal/mol**	355ARG 376GLU		
	Curcumin	**-10.6878 kcal/mol**	**355ARG 426HIS**		
Nuclear Factor-Kappa B (NF-κB) PDB id: **1NFK**	Bortezomib (NF-κB inhibitor)	-9.265 kcal/mol	133GLY 135ALA 123VAL 124THR 115HIS		
	Curcumin	-10.3071 kcal/mol	148PHE 195ARG 152GLU		
Cytochrome P450 2E1 (CYP2E1) (PDB ID: **3E4E**)	CYP2E1 inhibitors (e.g., Chlormethiazole)				

	curcumin	-12.2354 kcal/mol	238ASN 206ASN 100ARG 435ARG		
Inducible Nitric Oxide Synthase (iNOS) (PDB ID:1NSI)	L-NMMA (iNOS inhibitor)	-6.703 kcal/mol	**269GLY 284VAL 271GLN 299TYR**		
	curcumin	-12.3124 kcal/mol	**377GLU 700ARG 370ASN**		
Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-γ) (PDB ID: 3DZY)	Pioglitazone (PPAR-γ agonist)	-12.2664 kcal/mol	**432CYS**		
	Curcumin	-12.9324 kcal/mol	**327ALA 316ARG 432CYS**		
AMP-Activated Protein Kinase (AMPK) (PDB ID:4YEE)	Metformin (AMPK activator)	-4.77292 kcal/mol	**82ARG 80VAL 136ASP**		
	Curcumin	-10.5904 kcal/mol	**341GLN 340PHE 339HIS**		

DISCUSSION:

Curcumin's interaction with HO-1 indicates a substantial involvement in protecting the liver. Hemin, a recognised stimulator of HO-1, had a significant affinity for specific amino acid residues, notably 700ARG and 200CYS (Ryter, S. W., et al., 2006). This interaction showcases hemin's capacity to regulate hepatoprotective pathways by facilitating the degradation of heme into advantageous byproducts. Curcumin's interaction with HO-1, specifically at amino acid residue 370ASN, indicates a possible regulatory function in the gene promoter area (Scapagnini, G., et al., 2011). This may result in the increase of HO-1 expression, hence improving the liver's resistance to hepatotoxic damage.

Curcumin's effect on NF-κB highlights its potential to reduce inflammation. Curcumin has a high affinity for NF-κB, a key component in inflammatory processes, surpassing the binding strength of bortezomib, an NF-κB inhibitor (Aggarwal, B. B., et al., 2003). Curcumin can inhibit NF-κB by blocking its movement into the nucleus and its interaction with DNA. Additionally, curcumin's interactions with upstream signalling molecules, such as IκBα, highlight its ability to potentially interfere with the NF-κB pathway (Shishodia, S., et al., 2007). The findings indicate that curcumin plays a function in inhibiting the expression of proinflammatory genes and has therapeutic potential for illnesses characterised by chronic inflammation.

Curcumin's interaction with CYP2E1 offers insights into its ability to influence the metabolism of hepatotoxic compounds. Curcumin's high docking score indicates a substantial binding affinity to CYP2E1, implying its potential to impact the enzyme's function. Further research is needed to determine the specific binding sites and mechanisms, although curcumin's interaction with CYP2E1 could affect the metabolism of several endogenous and exogenous substances, such as medicines and poisons (Guengerich, F. P., 2008). This interaction emphasises curcumin's potential in alleviating liver damage from harmful chemicals. Curcumin's interaction with PPAR-γ in the ligand-binding domain suggests its ability to affect the expression of genes relevant to lipid metabolism. Curcumin and pioglitazone have identical docking scores, indicating curcumin's strong affinity for PPAR-γ as shown by Kersten, S., et al., 2000. Curcumin's interactions with particular amino acid residues in the ligand-binding domain (LBD) and the creation of hydrogen bonds indicate its potential to activate PPAR-γ. This activation could result in the increased expression of genes related to lipid metabolism, providing possible therapeutic advantages for ailments including non-alcoholic fatty liver disease (NAFLD) and metabolic disorders (Varga, T., & Czimmerer, Z., 2011).

Curcumin's interaction with the active site of AMPK emphasises its function in controlling cellular energy metabolism. Curcumin has a higher docking score than metformin, indicating a better binding affinity based on research by Hardie, D. G. (2011). Curcumin can activate AMPK by interacting with specific amino acid residues in its active site and phosphorylating AMPK substrates. This activation initiates subsequent signalling pathways related to energy balance (Carling D, 2011). Curcumin's diverse interactions with different protein domains and motifs, such the glycogen recognition site of AMPK, highlight its complex role in regulating cellular processes associated with energy metabolism.

CONCLUSION:

The molecular docking research results show the different interactions between curcumin and hepatoprotective proteins, offering vital insights into its probable modes of action. Curcumin's capacity to control gene expression, inhibit inflammation, adjust enzyme function, and regulate energy metabolism highlights its promise as a viable therapy for enhancing liver health and addressing liver-related conditions. Additional experimental research are required to confirm these findings and investigate the clinical uses of curcumin in liver protection.

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