In Silico Investigation of Curcumin as a Natural Antimicrobial Alternative for Human Umbilical Cord Mesenchymal Stem Cell Culture

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ABSTRACT:

Due to their capacity to replicate themselves, differentiate into various types of cells, and modulate the immune system, UC-MSCs (Human Umbilical Cord Mesenchymal Stem Cells) are attracting a lot of attention in regenerative medicine. However, the use of "traditional" antibiotics routinely used to isolate and grow UC-MSCs creates serious problems regarding the potential for resistance to those antibiotics, toxicity to the cells themselves, and altered exhibit cell behavior. It is known that curcumin, a yellow pigment extracted from turmeric (Curcuma longa), has significant antimicrobial, antioxidant, anti-inflammatory, and reparative capabilities; therefore, it can be used as a good alternative to traditional antibiotics to treat UC-MSCs during culture. To evaluate the safety, biological compatibility, molecular targets, and antimicrobial effectiveness of curcumin in the UC-MSC culture, an integrated in silico study was used as the basis for conducting this research. SwissADME was used to determine Curcumin's Pharmacokinetic and Drug-Likeness Properties. Toxicity was evaluated using ProTox-3.0, GUSAR, and_ToxTree. Molecular targets were predicted from Curcumin using SwissTargetPrediction and compared with UC-MSC associated gene from GeneCards. Venn analysis identified common molecular targets of curcumin and UC-MSC; the commonality of targets was investigated through the construction of Protein–Protein Interaction Networks (PPI networks) in Cytoscape. Additionally, the frequence of curcumin as an antimicrobial in relation to bacterial and fungal protein that could contaminate stem cells during culture were researched through molecular docking. SwissADME was used to determine Curcumin's Pharmacokinetic and Drug-Likeness Properties. Toxicity was evaluated using ProTox-3.0, GUSAR, and_ToxTree. Molecular targets were predicted from Curcumin using SwissTargetPrediction and compared with UC-MSC associated gene from GeneCards. Venn analysis identified common molecular targets of curcumin and UC-MSC; the commonality of targets was investigated through the construction of Protein–Protein Interaction Networks (PPI networks)

in Cytoscape. Additionally, the frequency of curcumin as an antimicrobial in relation to bacterial and fungal protein that could contaminate stem cells during culture were researched through molecular docking studies.

1. INTRODUCTION

Due to their ability to grow quickly, develop into multiple cell types, have little chance of causing a bad reaction when given to someone else, and be easy to get from umbilical cords, human umbilical cord mesenchymal stem cells (UC-MSCs) are some of the most promising types of cells used in regenerative medicine (Nagamura-Inoue, 2014). They have been found to be effective in many medical applications such as healing tissue and healing wounds and treating autoimmune diseases and degenerative diseases (diseases that cause a decline in physical or mental functioning) — all of which require the UC-MSCs to be sterile when they are taken from the mother(s) and cultured (Shang et al., 2021)

Traditionally, combinations of antibiotics like the penicillin family and the streptomycin family of antibiotics are routinely added to the media used to transport and culture UC-MSCs to protect the UC-MSCs from becoming contaminated with bacteria and fungi (Attari et al., 2015). While these antibiotics work, the long-term use of them can cover up low-level contamination from bacteria or fungus, contribute to bacteria and fungus that become resistant to antibiotics and possibly have an effect on how the UC-MSCs grow/develop and produce their genetics. Therefore, researchers are trying to find a natural antibiotic alternative that will protect the UC-MSCs to be used for transplantation and at the same time not negatively affect the quality of the UC-MSCs used (Yang et al., 2020).

Curcumin, which is the main bioactive component from turmeric (Curcuma longa), has a wide range of pharmacological properties with antimicrobial, antioxidant, anti-inflammatory, anticancer and wound healing properties (Yang et al., 2020). It has been shown by previous researchers to have an effect on inhibiting (blocking) the growth of an extensive range of bacteria and fungi. Curcumin has also been shown to control cellular signaling involved in cell life (proliferation), cell death (apoptosis), and the body's response to reactive oxygen species and tissue repair (El-Saadony et al., 2023) (Ciuca & Racovita, 2023).

Over the last few years, advances in bioinformatics have provided us with new ways to evaluate microbial potential and safety using bioinformatics tools prior to conducting experiments on the safety and efficacy of naturally occurring substances (Lakshminarayanan et al., 2025). Some examples of the bioinformatics tools commonly used in this area include pharmacokinetic prediction, toxicity profiling, network pharmacology, protein interaction analysis, and molecular docking. By employing these different tools, we can evaluate the mechanisms of action of a substance and its therapeutic potential (Ciuca & Racovita, 2023)

In the current study, we sought to evaluate the antimicrobial potential of curcumin in a stem cell culture model utilizing UC-MSCs through an integrated bioinformatic analysis model. More specifically, we evaluated curcumin's pharmacokinetic properties, toxicity profile, and its interaction with UC-MSCs. We also evaluated curcumin's ability to inhibit growth of the microbes commonly found in stem cell cultures.

2. MATERIALS AND METHODS:

2.1 Structural Retrieval of Curcumin

The primary place to conduct this study was to retrieve the chemical structure of curcumin from the PubChem database (Compound CID: 969516) in SDF format, which would use for all future computational analyses related to this study (PubChem, n.d.)

2.2 Pharmacokinetic and Drug-Likeness Analysis

A pharmacokinetic and drug-likeness analysis of curcumin was conducted using the SwissADME database. Physicochemical properties of curcumin were analyzed for lipophilicity, solubility, pharmacokinetic properties, bioavailability, drug-likeness, molecular weight, hydrogen-bond donors and acceptors, topological polar surface area (TPSA), gastrointestinal absorption, blood-brain barrier permeability, Cytochrome P450 inhibition, and Lipinski's rule of five (Daina et al., 2017) (Molecular Modelling Group of the Swiss Institute of Bioinformatics, n.d.)

2.3 Toxicological Prediction

Toxicological prediction of curcumin was conducted using the ProTox-3.0, GUSAR and ProTox-3.0 was used to predict acute toxicity (based on routes of administration), hepatotoxicity, mutagenicity, carcinogenicity, cytotoxicity, immunotoxicity, and pathway-associated toxic endpoints. GUSAR was used to predict acute rodent toxicity and environmental toxicity as well as antitarget interactions. Toxtree version 3.1.0 was utilized to assess biodegradability, structural toxicity alerts, genotoxicity, and Ames mutagenicity (Banerjee et al., 2024) (Van Wyk et al., 2025) (Atioğlu et al., 2021)

2.4 Curcumin Target Identification

To identify the possible molecular targets for curcumin, Swiss Target Prediction (STP) provided predicted target genes with probability scores for further use in the study (Yadav & Eswari, 2022)

2.5 Collection of UC-MSC-related Genes.

The analyses were conducted with UC-MSC associated genes obtained from the Genecards database and using various keywords for mesenchymal stem cells, stemness, proliferation, differentiation and tissue regeneration.

2.6 Venn Analysis.

Using Venny software, the predicted curcumin targets were compared to UC-MSC associated genes to find out common targets, and any overlapping genes were considered potential mediators of curcumin's activity in UC-MSCs (Collazos, n.d.)

2.7 Protein-Protein Interaction Network Analysis.

STRING was used to create a protein-protein interaction network with the overlapping target genes. The PPIs were created and visualized using Cytoscape to find hubs and key clusters of interactions (*Network Analysis With Cytoscape*, n.d.).

2.8 Molecular Docking

Molecular docking studies on curcumin were conducted with AutoDock Vina (PyRx interface) (Trott & Olson, 2009)against selected targets of microbial proteins that have been implicated in survival (via replication or metabolism) of bacteria and fungi, including DNA Gyrase, Topoisomerase IV (ParC; essential for DNA replication) and MurA (acts in peptidoglycan synthesis), as well as FabI (involved in fatty acid biosynthesis), PBP2 (an essential penicillin-binding protein), SorA (a repressor that prevents sorbitol from being utilized), ERG11 (the target for antifungal azoles), and HSP90 (a chaperone protein). Binding affinity scores as obtained from the docking calculations were recorded and the protein-ligand interactions were visualized using ChimeraX

Table 1. Target Proteins

S.NO	Protein Targets	PDB ID
1.	DNA Gyrase	9N39
2.	Topoisomerase IV (ParC)	1ZVT
3.	MurA	2Z2C
4.	FabI	2FHS
5.	PBP2	9I9T
6.	SorA	1T2W
7.	ERG11	5TZ1
8.	HSP90	6CJR

3. RESULTS:

3.1INSILICO CYTOTOXICITY PREDICTION:

3.1.1 TOXICITY ANALYSIS:

Table 2. SWISS ADME Analysis

Parameter	Value	Interpretation
Molecular Formula	$C_{21}H_{20}O_6$	Polyphenolic compound
Molecular Weight	368.38 g/mol	Within Lipinski limit (<500 g/mol)
H-Bond Acceptors	6	Favorable protein interactions
H-Bond Donors	2	Supports molecular binding
Rotatable Bonds	8	Moderate molecular flexibility
Topological Polar Surface Area (TPSA)	93.06 Å²	Suitable membrane permeability
Consensus LogP	2.97	Balanced lipophilicity
Water Solubility (ESOL)	Soluble	Good aqueous compatibility
Water Solubility (Ali Model)	Moderately Soluble	Acceptable solubility
Water Solubility (Silicos-IT)	Moderately Soluble	Supports biological application
Gastrointestinal Absorption	High	Good absorption potential
Blood-Brain Barrier Permeability	No	Limited CNS penetration

P-glycoprotein Substrate	No	Reduced cellular efflux
CYP1A2 Inhibition	No	Low metabolic interaction risk
CYP2C19 Inhibition	No	Low metabolic interaction risk
CYP2C9 Inhibition	No	Low metabolic interaction risk
CYP2D6 Inhibition	No	Low metabolic interaction risk
CYP3A4 Inhibition	No	Low metabolic interaction risk
Lipinski Rule Violations	0	Excellent drug-likeness
Ghose Rule Violations	0	Satisfied
Veber Rule Violations	0	Satisfied
Egan Rule Violations	0	Satisfied
Muegge Rule Violations	0	Satisfied
Bioavailability Score	0.55	Moderate oral bioavailability
PAINS Alerts	0	No false-positive structural alerts
Brenk Alerts	2	Minor structural alerts
Synthetic Accessibility	2.97	Easy to obtain/synthesize

The SwissADME analysis shows that curcumin has good pharmacokinetic, physicochemical (including molecular weight of 368.38 g/mol and consensus LogP score of 2.97) and bioavailability characteristics along with high GI absorption. Curcumin meets all of the major filters for drug-likeness without violation and produced no alerts for PAINS indicating a reliable pharmacokinetic profile. The compound was also predicted to have low potential to cross the blood-brain barrier (BBB) and low potential for cytochrome P450 inhibition. Collectively, these results support further evaluation of curcumin as an appropriate, biocompatible, natural antimicrobial alternative for use in human umbilical cord mesenchymal stem cell culture systems (Rai et al., 2023) (*Table - PMC*, n.d.)

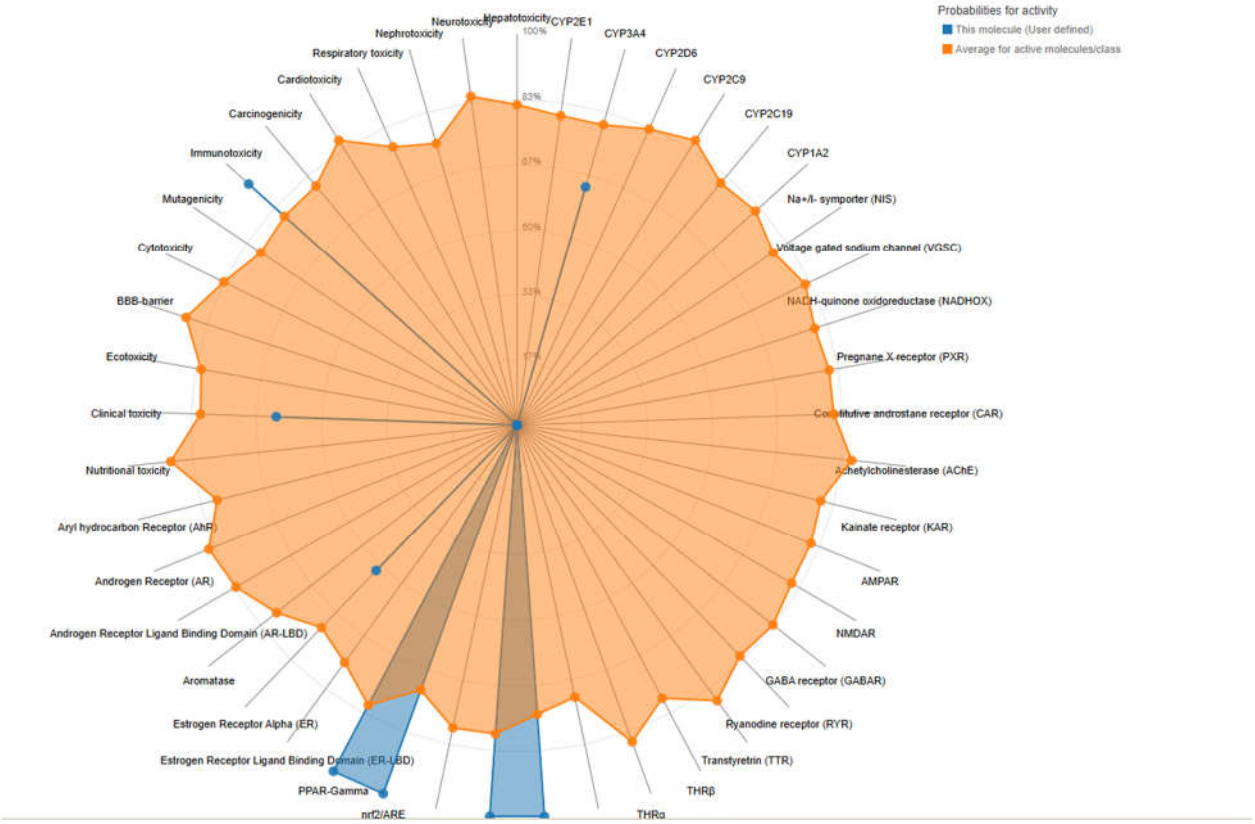

Fig.1 ProTox Toxicity Prediction of Curcumin

ProTox 3.0 suggested that predictive toxicity profiling showed a good safety record for curcumin (low acute toxicity [LD50 = 2000 mg/kg], no hepatotoxicity, mutagenicity, carcinogenicity or cytotoxicity). Furthermore, there was a strong association between curcumin and Nrf2/ARE, PPAR-γ, p53 and mitochondrial membrane potential signalling pathways indicating propitious antioxidant, cytoprotective, and regenerative activity of curcumin. Overall, these data justify ongoing/continued experimental exploration into the utility of curcumin as an ideal candidate for naturally derived antimicrobials for UC-MSC.

Table 3. GUSAR Predictions

	Parameter	**Result**	**Interpretation**
Antitarget Profile	Total Predicted Antitargets	9	Limited off-target interactions identified
	5-HT1B Receptor	Antagonist	Potential serotonergic interaction
	5-HT2A Receptor	Antagonist	Potential serotonergic interaction
	5-HT2C Receptor	Antagonist	Potential serotonergic interaction
	α1-Adrenergic Receptor	Antagonist	Potential adrenergic modulation
	α2A-Adrenergic Receptor	Antagonist	Potential adrenergic modulation

	Amine Oxidase A	Inhibitor	Possible involvement in neurotransmitter metabolism
	Estrogen Receptor	Antagonist	May influence hormone-responsive pathways
	Dopamine D1 Receptor	Antagonist	Potential dopaminergic interaction
	Dopamine D3 Receptor	Antagonist	Potential dopaminergic interaction
Environmental Toxicity	Bioaccumulation Factor (Log10 BCF)	1.272	Low-to-moderate bioaccumulation potential
	Daphnia magna LC50 (-Log10 mol/L)	6.151	Low aquatic toxicity
	Fathead Minnow LC50 (-Log10 mmol/L)	-3.657	Limited toxicity towards fish
	Tetrahymena pyriformis IGC50 (-Log10 mol/L)	2.207	Low-to-moderate protozoan toxicity
Acute Toxicity	Rat Oral LD50	3822 mg/kg	Very low acute toxicity
	Rat Intraperitoneal LD50	528.9 mg/kg	Low toxicity
	Rat Intravenous LD50	149.7 mg/kg	Moderate toxicity
	Rat Subcutaneous LD50	2409 mg/kg	Low toxicity
OECD Toxicity Classification	Oral	Class 5	Practically non-toxic
	Intraperitoneal	Class 5	Practically non-toxic
	Subcutaneous	Class 5	Practically non-toxic
	Intravenous	Class 4	Slightly harmful at high doses

Curcumin has been evaluated using GUSAR based computational toxicological assessment and has a positive safety profile. The antitarget prediction identified 9 potential off-target interactions involving serotonin, dopamine, adrenergic, and estrogen receptors which suggest that curcumin may pharmacologically exhibit pleiotropic effects; however, no significant toxicological concerns were noted. The environmental toxicity evaluation suggests that curcumin has a low potential for bioaccumulation and limited toxicity to aquatic organisms, therefore having an environmentally friendly profile. The acute toxicity predictions for oral, intraperitoneal and subcutaneous administration of curcumin all resulted in high LD50 values, indicating that these modes of administration would primarily fall under OECD Toxicity Class 5, whereas intravenous administration would fall under OECD Toxicity Class 4. Overall, the data support the conclusion that curcumin has low acute toxicity, low environmental risk and potential for safety and therefore warrants additional evaluation as an alternative natural antimicrobial agent in the culture of human umbilical cord mesenchymal stem cells (UC-MSC) (GenExplain, n.d.) (Moetlediwa et al., 2024) (Lopresti et al., 2012)

Table 4. Toxtree Predictions:

Parameter	Outcome
Biodegradability	Positive
Genotoxicity	Negative
Ames Mutagenicity	Negative
Structural Toxicity Alerts	Absent
Toxicophore Presence	Not Significant
Environmental Persistence	Low
Overall Safety Prediction	Favorable

Analyzing the chemical criteria using Toxtree, it was found that curcumin had a good toxicity profile. Curcumin has been estimated as biodegradable and there were no structural alerts to raise concerns about genotoxicity or Ames mutagenicity. In addition, the evaluation of the structure for S/T/P toxicity did show that there are aromatic and polyphenolic functional groups in the structure but there are not enough toxicophoric characteristics identified to concern the potential toxicity risk for curcumin. As a result of this assessment, curcumin was identified as having low toxicity risk and suggests that it can be used in developing natural antimicrobial alternatives for use in human umbilical cord mesenchymal stem cell culture systems (Mulla et al., 2025) (Asif et al., 2024)

3.2 TARGET ANALYSIS:

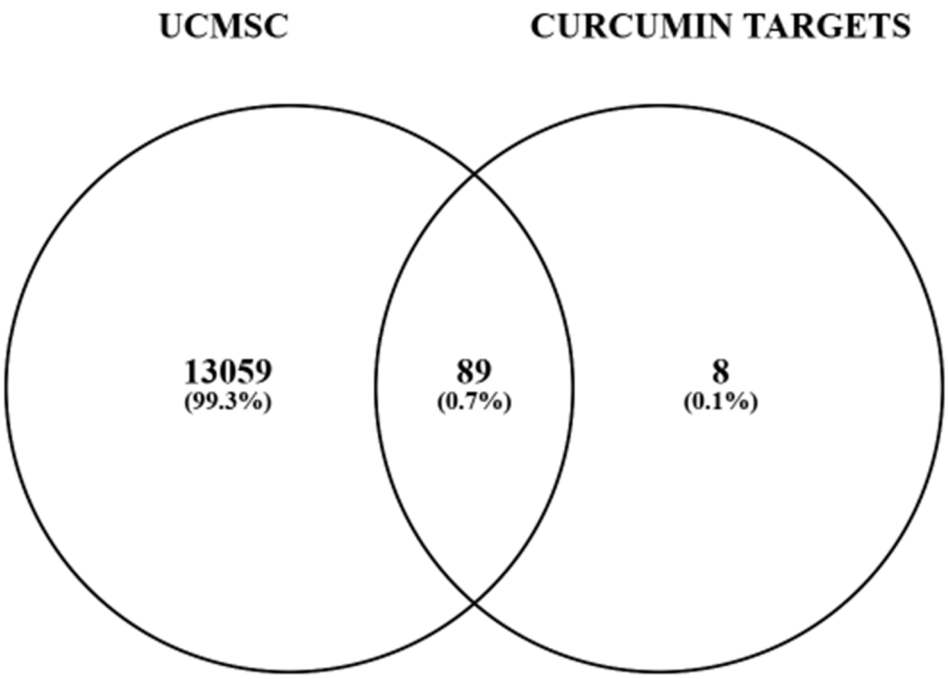

Fig. 2 Common targets between UCMSC and Curcumin

Using Venn Analysis, we compared predicted targets of curcumin with potential target genes associated with UCMSCs to determine the number of overlapping genes between the datasets.

There were 89 overlapping genes in the two datasets, as well as 13,059 unique UCMSC-associated genes not found in curcumin targets; however, there were eight genes unique to curcumin and not included in the analysis. The 89 overlapping genes may serve as potential molecular targets by which curcumin regulates biological processes associated with stem cells. All overlapping targets were subsequently assessed by network/pathway enrichment analyses to gain insight into how curcumin exhibits its effects on UCMSCs (Wanjiang et al., 2020)

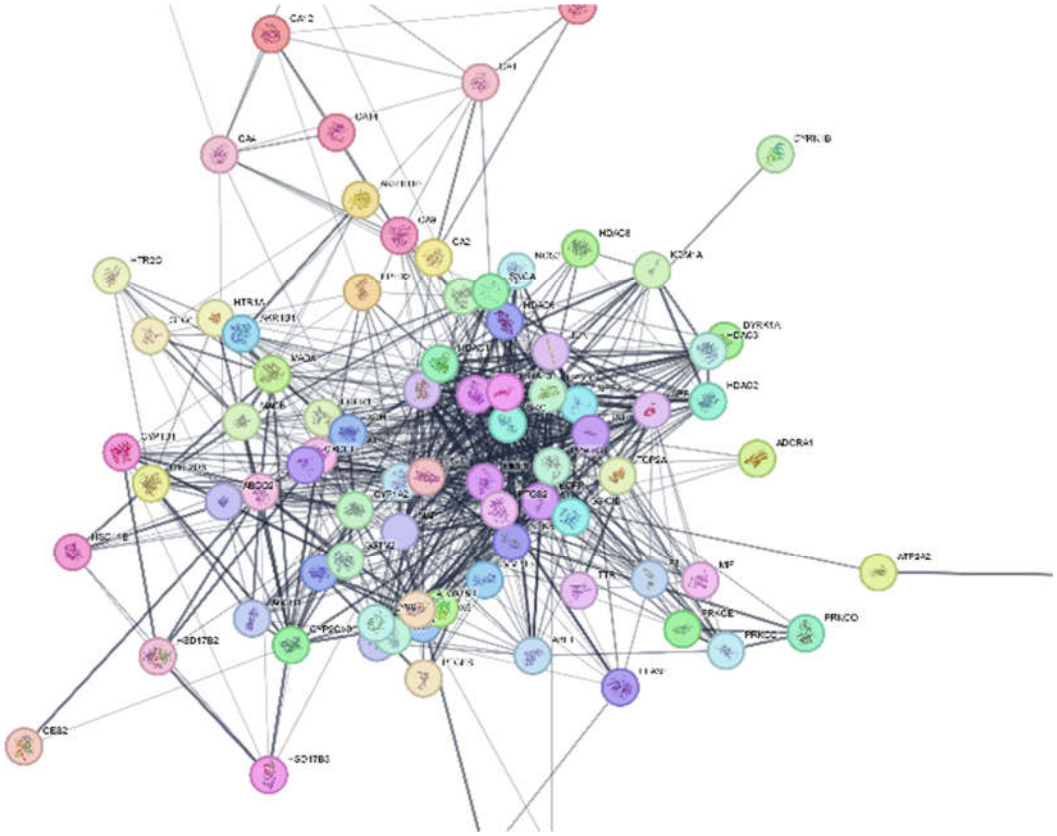

Fig. 3 PPI Network of Common targets between UCMSC and Curcumin

In Cytoscape an extensive associative interrelationship exists among the set of interconnected genes involved in the construction of the PPI model. In particular, the hub genes connected within the interaction network were seen to have an extremely high degree of connectivity: SRC, STAT3, EGFR, TNF, NF-KB1, PPARG, PTGS2, JUN, EP300, and NFE2L2 (Z. Yang et al., 2022). These proteins play important roles in many biological processes, including but not limited to cell growth/proliferation; the regulation of inflammation; and the response to oxidative stress as well as the maintenance of stem cells and the repair/regeneration of tissues. Given these findings, it would not be surprising to see curcumin's many functional effects on UCMSCs through the simultaneous modulation of multiple pathways in a coordinated fashion (Shannon et al., 2003) (Szklarczyk et al., 2018)

3.3 DOCKING ANALYSIS:

Table 5. Binding Affinity of Targets against Curcumin

Microorganism	Target Gene/Protein	Binding Affinity (kcal/mol)	Binding Strength
Escherichia coli	DNA Gyrase	-7.0	Moderate Binding Affinity
	Topoisomerase IV (ParC)	-9.3	Very Strong Binding Affinity
Klebsiella pneumoniae	MurA	-8.4	Strong Binding Affinity
Staphylococcus hominis	FabI	-7.8	Moderate Binding Affinity
Staphylococcus aureus	PBP2	-7.7	Moderate Binding Affinity
	SorA	-7.1	Moderate Binding Affinity
Candida albicans	ERG11	-7.4	Moderate Binding Affinity
	HSP90	-8.1	Strong Binding Affinity

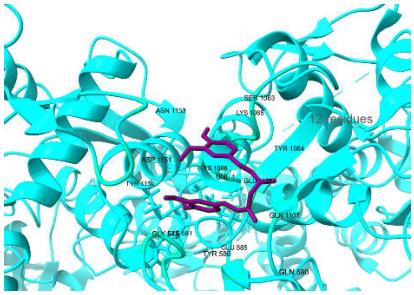

Fig.4 Curcumin and DNA Gyrase

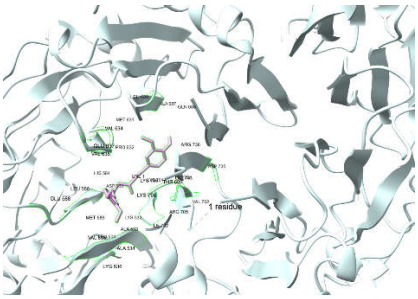

Fig.5 Curcumin and Topoisomerase IV

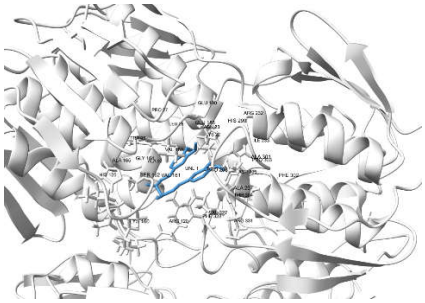

Fig.6 Curcumin and MUR A

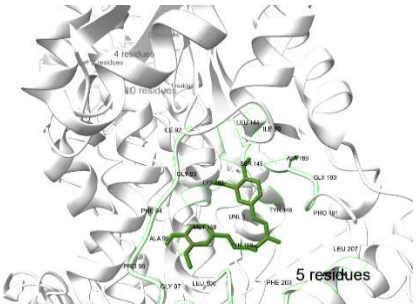

Fig.7 Curcumin and FABI

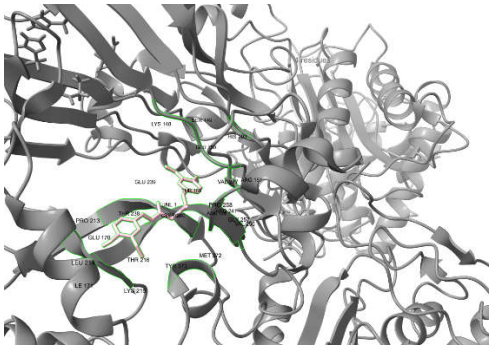

Fig.8 Curcumin and PBP2

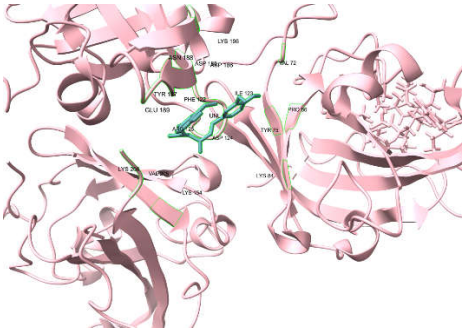

Fig.9 Curcumin and SOR A

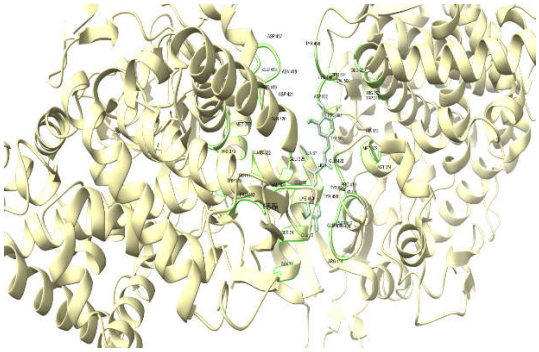

Fig.10 Curcumin and ERG11

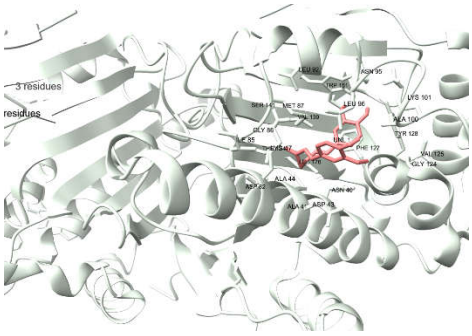

Fig.11Curcumin and HSP90

Molecular docking analyses found an affinity for curcumin to bind with several critical microbes' targets. Curcumin had binding affinities ranging from -7.0 to-9.3 kcal/mol across the target microbes. The most significant binding interaction between curcumin and E. coli Topoisomerase IV (ParC) with -9.3 kcal/mol occurred; the second highest was with MurA (-8.4 kcal/mol) followed by HSP90 from Candida albicans (-8.1). These results suggest curcumin could have possible antibacterial effects via the simultaneous alteration of many critical viral proteins; therefore, there could be a valuable role for curcumin in using natural antimicrobial methods within UC-MSC culture system(s).

4. CONCLUSION

The results of this study conclude that curcumin has a suitable pharmacokinetics profile, including good bioavailability, a high degree of drug-likeness, and a high level of safety. Toxicological studies had consistently identified curcumin as being low in acute toxicity and having no significant mutagenic or carcinogenic potential, good biodegradability, and limited environmental toxicity. Network pharmacology analysis revealed that curcumin has 89 common targets to UC-MSC associated genes, with common key hub proteins that are associated with stem cell proliferation, regulation of oxidative stress, inflammatory response control, and tissue regeneration. In addition, molecular docking showed that curcumin has significant interactions with multiple bacterial and fungal proteins, suggesting a wide range of antibacterial and antifungal actions for curcumin. Therefore, together, these findings provide evidence that curcumin can potentially be a safe, biologically compatible natural alternative to traditional antibiotics in culture systems for UC-MSCs. In-vitro and in-vivo studies are needed

to confirm the results from the current in-silico study and to determine how curcumin can realistically fit into regenerative medicine with respect to stem cell therapy.

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