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Research Article

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Curcumin-Cobalt Complex: Theoretical, Software-Oriented Safety, and Pharmacokinetics Investigations

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ABSTRACT

Aim: To synthesize and evaluate a novel curcumin-cobalt complex to enhance curcumin's stability, solubility, and pharmacokinetics, thereby overcoming its limitations in clinical applications.

Methodology: The curcumin-cobalt complex was synthesized and subjected to theoretical investigations using molecular docking and density functional theory (DFT) to analyze binding interactions and electronic properties. In silico ADMET (absorption, distribution, metabolism, excretion, and toxicity) analysis was conducted using various software tools to assess the complex's pharmacokinetic profile and safety.

Results: The curcumin-cobalt complex demonstrated improved stability and solubility compared to curcumin alone. Molecular docking and DFT studies revealed strong binding interactions and favorable electronic properties. In silico ADMET analysis indicated enhanced pharmacokinetic parameters, including better absorption and distribution, along with low toxicity potential. These findings suggest the complex as a promising candidate for therapeutic use with reduced metabolic limitations.

Conclusion: The curcumin-cobalt complex successfully addresses curcumin's bioavailability and stability issues, offering enhanced pharmacokinetic properties and a favorable safety profile. This research highlights the potential of metal complexation to optimize curcumin's therapeutic efficacy. Future in vivo studies are necessary to validate these results and explore the complex's potential in managing chronic diseases, expanding curcumin's therapeutic applications.

Keywords: Curcumin-Cobalt Complex; Pharmacokinetics; Theoretical Investigations; Molecular Docking; ADMET Analysis; Bioavailability Enhancement

INTRODUCTION

The study of coordination compounds includes all facets of chemistry, from theoretical bonding research to the production of organometallic compounds. Lewis acids and bases form coordinate bonds in coordination compounds, which is their key characteristic. The Lewis bases are the ligands, while the Lewis acids are the metal atoms or ions. Forming coordination compounds are all metals. The kind of ligands, metal's atomic number, and oxidation state all affect a coordination compound's stability. The chelate effect is a particularly unique use of coordination chemicals.[1] Ethylenediamine is an illustration of a bidentate ligand; it forms a five-membered ring with the metal, two nitrogen atoms, and two carbon atoms. Hexadentate ligands, such as ethylenediamine tetraacetic acid (EDTA), wrap themselves around a metal cation and bite it simultaneously in six locations. This results in a chelated molecule that is incredibly powerful. Many different biological contexts contain chelated transition metal ions. Acute arsenic, copper, lead, and mercury poisoning are treated with dimercaprol, dimercaptosuccinic acid, dimercapto-propane sulfonate, penicillamine, EDTA, deferoxamine, and deferasirox. One of the most intriguing areas of coordination chemistry is the interaction of transition metal ions with biological molecules. Living things depend on chelated physiologically significant substances including hemoglobin, vitamin B_{12}, and chlorophyll.[2]

Transition metal complexes have been crucial in the biochemistry of pharmaceuticals. They are distinct oxidation states of neutral, cationic, or anionic substances having highly special interactions with living things. The pharmaceutical industry pays a lot of attention to the metal-based medications made from platinum, gold, ruthenium, osmium, silver, bismuth, and lithium. These complexes

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exhibit anticancer, anti-inflammatory, antibacterial, and other effects in addition to their anticancer properties. Due to Cisplatin's success in the medical sciences, there is a higher thrust for transition metal complexes. The discovery of anticancer medications is the result of extensive study on the effectiveness of transition metal complexes in slicing DNA. Schiff base ligand transition metal complexes of biological origin have powerful pharmaceutical uses with fewer adverse effects. Metallopharmaceuticals play an important role in contemporary society as therapeutic and diagnostic agents. Many metallopharmaceuticals have been developed to treat/cure a variety of cancers. Besides platinum compounds- cisplatin, carboplatin, oxaliplatin, tetraplatin, satraplatin etc., non-platinum compounds viz. NAMI-A, KP1019, KP46, auranofin and As_2O_3, etc. have shown promising results and many of them are in different phases of clinical trials. Traces of metals are essential for the proper functioning of enzymes in our body and also for the activity of many drugs of organic nature. Metal-based drugs have been used as therapeutic agents since ages. They are being used for the treatment of a variety of ailments viz. cancer, diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents. Many organic compounds used in medicine do not have a purely organic mode of action and require traces of metal ions directly or indirectly for activation or biotransformation.[3]

Schiff base (named after Hugo Schiff) is an organic compound with the general molecular formula $R_1R_2C=NR_3$, formed by the condensation of amine with carbonyl moiety. By reacting a substituted carbonyl molecule with a primary amine, these chemicals are created. Due to their stability, capacity to donate electrons, catalytic, liquid crystal, photochromic, optical nonlinearity, and biological accessibility qualities, they are very interesting in the realm of chemistry. These may perform a variety of tasks and operate as mono, di, tri, and polydentate ligands.[4] Because they are susceptible to polymerization processes, aliphatic Schiff bases (produced from aliphatic aldehydes or ketones) are often less stable. However, there is a considerable propensity for aromatic Schiff bases to form stable complexes with transition metals. Both the progress of coordination chemistry and inorganic biochemistry depend greatly on these kinds of chelates. Due to their extensive range of biological actions, which include anti-inflammatory, analgesic, non-ulcerogenic, anti-HIV, anticonvulsant, antitubercular, antioxidant, antibacterial, anthelmintic, anticancer, and cardiovascular activity, they are widely employed in the medical and pharmaceutical areas.[5] Schiff bases are useful in contemporary technology because of their favourable thermochromic and optical characteristics. To gauge and regulate the radiation's intensity in imaging systems and molecular memory storage, they are used in optical computers. Additionally, they are employed as organic materials in biological systems, reversible optical memory, photodetectors, and optical sound recording technologies. Schiff bases can be employed as stationary phase in gas chromatography because of their thermal stability.[6]

Due to the rise of several ailments and the lack of appropriate medical goods in various pharmaceutical industrial processes, drug development techniques are now necessary. One of the original approaches to drug discovery is the research and development process. In the past, humans made pure compounds in labs and utilised plants as medicines. On earth, there are 1.75 million species of recognised animals, plants, fungi, and microorganisms. Numerous chemical moieties make up each species. As long as humans have existed, plants have been used as a source of medicine. At least 120 different chemical compounds produced from plants are presently used in one or more nations throughout the world and are regarded as major medications. A number of the medications on the market today are straightforward synthetic adaptations or duplicates of the naturally occurring molecules. According to a study of plant-derived pure compounds used as medicines in nations with WHO-Traditional Medicine Centers, out of 122 compounds found, 80% were made from just 94 plant species and were used for the same or comparable ethnomedical uses.[7]

One of the most likely and encouraging alternatives to synthetic chemicals for the development of innovative gibbets with a diversity of biological functions is natural products. Antioxidant properties are acquired by medicinal plants. The plants that have this ability to treat a variety of ailments may also be able to treat other problems including cancer, Alzheimer's, atherosclerosis, diabetes, and other cardiovascular diseases. Herbal medicines' antioxidant properties are also effective at reducing the toxicity of other pharmaceuticals or harmful substances. To increase the medicines' bioavailability (pharmacokinetics) and reduce their toxicity, researchers created a variety of medications based on the chemical compounds' structure that were derived from plants. The primary focus of traditional Chinese and Indian remedies for the treatment of terrible illnesses is plant extracts. Natural substances have received more attention recently as innovative tactics. Many natural substances with plant origins have been suggested as viable alternatives to conventional cancer therapy. One of the plant-derived flavonoids has been linked to a number of diseases that can be prevented, including cancer, ageing, inflammatory disorders, coronary diseases, and neurological degeneration. This flavonoid also has a number of biological activities, including antiviral and antitumor properties.[8]

Indians have used turmeric since the Vedic era as dietary medicine as well as a spice for curries. It is regarded as a blessing from nature against terrible illnesses. Known also as diferuloylmethane, curcumin (1,7-bis-(4-hydroxy-

3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is an active, polyphenolic substance obtained from the root of Indian Golden spices turmeric (*Curcuma longa*). It is commonly grown in tropical South and South East Asian nations, especially in China and India. The ginger family, Zingiberaceae, includes *Curcuma longa*. It is the main component of three curcuminoids, which are used as food colouring, seasoning, and additives and give turmeric its distinctive yellow hue. Demethoxycurcumin and bis-demethoxycurcumin, which lack one or both of the -OMe functions at the outer phenol rings, are the minor curcuminoid components. It was initially isolated in 1815, and its first synthetic version appeared in 1910. It can be found in alkaline pH media as an enol and in acidic and neutral pH media as a keto form. It is widely known in the literature that curcumin exists in a stable crystalline form. However, two novel metastable polymorphs (enol form) of curcumin that are more soluble than the stable form have recently been identified.[9]

Because it functions as a safe and multitargeted chemosensitizer for cancer cells, curcumin has garnered a lot of attention during the past 20 years. It has a wide range of effects and can bind directly to a variety of receptors, including inflammatory molecules, cell survival proteins, protein kinases, protein reductases, histone acetyltransferases, histone deacetylases, glyoxalase I, xanthine oxidase, proteasome, HIV-1 Integrase, HIV-1 protease, sarcoendoplasmic reticulum Numerous preclinical and clinical investigations have demonstrated that it may effectively modify a variety of targets in cancer cells. Furthermore, numerous studies have demonstrated that curcumin is a potent chemosensitizer for a variety of chemotherapeutic drugs, including doxorubicin, 5-FU, paclitaxel, vincristine, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, and bortez Fascinatingly, a dosage escalation research was conducted to determine the maximum tolerated dose of curcumin with increasing doses from 500 to 12,000 mg. It was determined that curcumin was well tolerated and did not exhibit any negative side effects. Numerous studies have shown that curcumin protects healthy cells from chemotherapy. As a result, this substance has tremendous promise as a very effective chemosensitizer against many cancers.[10]

In contrast to acetylacetone, the unsaturated phenolic group (-CH-CH-C_6H_4(OH)(OMe)-3,4), which is sterically demanding, is present on both sides of the central β-diketone functionality. Its structure is broad and flat, similar to that of an eagle. With a number of different metal ions, curcumin forms very stable metal complexes thanks to the existence of the β-diketo-moiety (than the easily degraded curcumin itself). In 1997, researchers announced the discovery of the first compounds of curcumin with therapeutically useful transition metals, including Pd, Pt, Rh, and In. In general, the metal complexes showed increased biological activity against several molecular targets as compared to the parent ligands.[11]

The study involves computational research of novel curcumin metal complex using Swiss ADME online tool (for exploring pharmacokinetics, bioavailability, and drug-likeness studies) and Protox v.3.0 (for exploring toxicity).

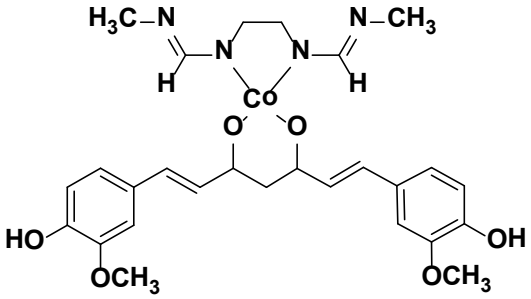

Figure 1: Structure of novel curcumin metal complex.

MATERIALS AND METHODS

In-silico ADMET study

Prediction study on pharmacokinetics, including absorption, distribution, metabolism, and excretion (ADME), bioavailability, and drug-likeness of ligands, was conducted using the SwissADME online tool. The bioavailability radar technique uses six physicochemical properties—lipophilicity, size, polarity, insolubility, flexibility, and saturation—to determine if a compound is drug-like. The BOILED-Egg model inside the tool identified positive or negative for the ADME features, including passive human gastrointestinal absorption (HIA), blood-brain barrier (BBB) penetration, and substrate or non-substrate of the permeability glycoprotein (P-gp). The generalized-born and solvent accessible surface area (GB/SA) model is used to determine the free energies of solvation in n-octanol and water, upon which the lipophilicity estimation (Log p/w) parameters iLOGP, XLOGP3, WLOGP, and MLOGP base their lipophilicity estimates. The Lipinski (Pfizer) filter was used to forecast drug-likeness; it is the first rule-of-five to be incorporated in a tool. Several physicochemical properties were employed in the bioavailability radar to make predictions about oral bioavailability. The ranges of each parameter was mentioned as LIPO = lipophilicity as -0.7 < XLOGP3 < +5.0; SIZE = size as molecular weight 150gm/mol < MV < 500gm/mol; POLAR = polarity as 20Å² < TPSA (topological polar surface area) < 130Å²; INSOLU = insoluble in water by log S scale 0 < Logs (ESOL) < 6; INSATU = insaturation or saturation as per fraction of carbons in the sp3 hybridization 0.3 < Fraction Csp3 < 1 and FLEX = flexibility as per rotatable bonds 0 < Number of rotatable bonds < 9.[12]

Toxicity study

Using Protox v.3.0 for new compound analysis involves a systematic process that integrates data input, model selection, prediction generation, and result interpretation. In this comprehensive guide, we'll walk through each step of using Protox v.3.0, covering key concepts, practical tips, and best practices for maximizing the utility of this in silico tool in chemical risk assessment and toxicology.[13]

Understanding Protox v.3.0

Before delving into the practical aspects of using Protox v.3.0, it's essential to understand the underlying principles and capabilities of the tool. Protox v. 3.0 is a computational platform based on quantitative structure-activity relationship (QSAR) modeling, which involves establishing mathematical relationships between chemical structures and their biological activities or toxicological effects. The tool leverages molecular descriptors, fingerprints, and predictive models to estimate the potential toxicity of chemical compounds across various endpoints, including acute toxicity, skin irritation, mutagenicity, carcinogenicity, and environmental hazards.[14]

Data Input

The first step in using Protox v.3.0 is to input the chemical structure of the compound you want to analyze. You can provide the structure in several formats, including SMILES notation, structure files (e.g. SDF, MOL), or drawn directly using the molecular drawing interface within the tool. Ensure that the structure is accurately represented to generate reliable predictions.[15]

Toxicological Endpoint Selection

Next, select the specific toxicological endpoints of interest for your analysis. Protox v.3.0 offers predictions for a wide range of endpoints, allowing you to assess various aspects of chemical safety comprehensively. Consider the regulatory requirements, research objectives, and intended applications of your analysis when choosing the endpoints. Common endpoints include acute toxicity, skin sensitization, genotoxicity, carcinogenicity, and environmental toxicity.[16]

Model Selection

Choose the appropriate predictive models within Protox v.3.0 based on the selected toxicological endpoints and the chemical properties of the compound. The tool may offer multiple models for each endpoint, each trained on different datasets or employing distinct modeling algorithms. Consider factors such as model performance metrics, applicability domain, and regulatory acceptance when selecting the most suitable model for your analysis.[17]

Data Processing and Prediction Generation

Submit the chemical structure of the compound along with the selected toxicological endpoints and predictive models to Protox v.3.0 for toxicity prediction. The tool will process the input data, extract relevant molecular descriptors, and apply the selected predictive models to generate toxicity predictions for the specified endpoints. This step involves computational algorithms and machine learning techniques to analyze the chemical structure and predict its toxicity profile based on the established QSAR relationships.[18]

Result Interpretation

Review the toxicity predictions generated by Protox v.3.0 and interpret the results in the context of your research objectives or regulatory requirements. Pay attention to the predicted toxicity scores or probability values, which indicate the likelihood of the compound exhibiting adverse effects for each endpoint. Compare the predictions against threshold values, regulatory guidelines, or benchmark data to assess the potential risks associated with the compound.[19]

Risk Assessment

Based on the toxicity predictions obtained from Protox v.3.0, perform a comprehensive risk assessment to evaluate the potential hazards posed by the compound. Consider additional factors such as exposure levels, intended use, population demographics, and environmental fate to assess the overall risk and inform risk management decisions. Integrate the toxicity predictions with exposure assessment to estimate the risk to human health and the environment accurately.[20]

Validation and Verification

Validate the predictions generated by Protox v.3.0 using experimental data or comparative analyses with other QSAR models and in vitro/in vivo studies. Assess the accuracy, reliability, and consistency of the predictions to ensure their relevance and applicability to real-world scenarios. Validate the predictions against external datasets, cross-validation techniques, or blind tests to verify the robustness and predictive power of the models.[21]

RESULTS AND DISCUSSION

In-silico ADMET study

Table 1 describes the predictive values for pharmacokinetics, bioavailability and drug-likeness data on novel curcumin-metal complex. The molecule showed high GIT absorption rate. Poor blood-brain permeability was obtained based on low LogP value (0.0) while low negative value (-7.35 cm/s) indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically cum solely inhibits CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55)

was obtained. Moderate water soluble characteristics were obtained for the novel curcumin-metal complex.

Table 1: Pharmacokinetics and physicochemical properties of novel curcumin-metal complex.

PROPERTIES	DATA
Physicochemical Properties	
Formula	$C_{27}H_{34}CoN_4O_6$
SMILES	[H]/C(N(C12OC(/C=C/C3=CC=C(O)C(OC)=C3) CC(/C=C/C4=CC(OC)=C(O)C=C4)O2) CCN1/C([H])=N/C)=N\C
Molecular weight (g/mol)	569.52
Number of heavy atoms	38
Number of aromatic heavy atoms	12
Fraction Csp^3	0.33
Number of rotatable bonds	8
Number of H-bond acceptors	8
Number of H-bond donors	2
Molar Refractivity	152.29
TPSA (A^2)	108.58
Lipophilicity	
Log Po/w (iLOGP)	0.00
Log Po/w (XLOGP3)	3.41
Log Po/w (WLOGP)	2.79
Log Po/w (MLOGP)	0.83
Log Po/w (SILICOS-IT)	2.29
Consensus Log Po/w	1.86
Water Solubility	
Log S (ESOL)	-5.22
Solubility	3.39e-03 mg/ml ; 5.96e-06 mol/l
Class	Moderate Soluble
Log S (Ali)	-5.37
Solubility	2.43e-03 mg/ml ; 4.27e-06 mol/l
Class	Moderate Soluble
Log S (SILICOS-IT)	-4.18
Solubility	3.74e-02 mg/ml ; 6.56e-05 mol/l
Class	Moderate Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log Kp (skin permeation) (cm/s)	-7.35
Drug-likeness	
Lipinski	Yes; 1 violation: MW>500
Ghose	No; 3 violations: MW>480, MR>130, #atoms>70
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	2 alerts: imine_1, imine_2
Lead-likeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	6.00

Bioavailability Radar Plot

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.33, FLEX as per number of rotable bond 8, INSOLU Logs (ESOL) as -5.22 (moderate soluble), SIZE as molecular weight (g/mol) of 569.52, POLAR as TPSA ($Å^2$) 108.58, and LIPO as XLOGP3 value of 3.41 (**Figure 2**). The study indicated that the molecule will have high oral bioavailability on administration.

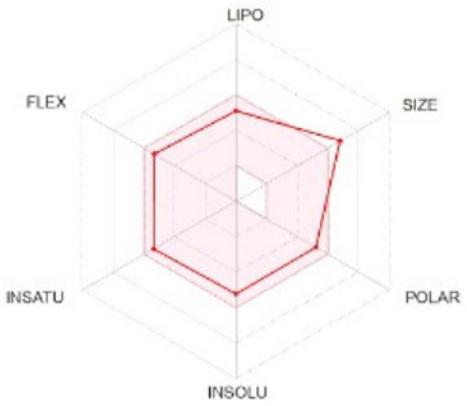

Figure 2: Bioavailability Radar Plot.

Boiled Egg Plot

In case of BOILED-Egg model (**Figure 3**), it was obtained that novel curcumin-metal complex has no ability of blood-brain barrier penetration but has a high gastrointestinal absorption. The molecule was found to be PGP positive as non-substrate in predictive model. Interestingly, the Brain Or xIntestinaLEstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which helps by computational prediction of the lipophilicity and polarity of small molecules.

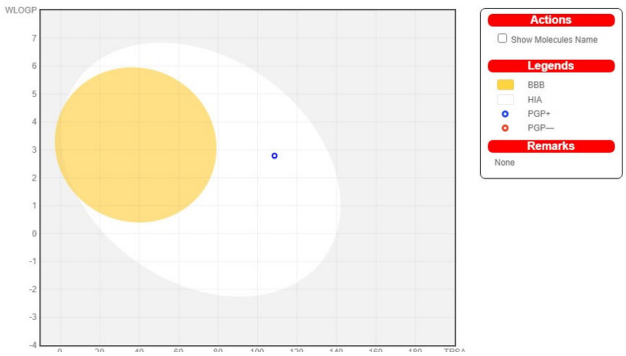

Figure 3: Boiled Egg Plot.

Protox toxicity studies

The synthesized compound may be neurotoxic in addition to respiratory harmful, as evidenced by the data set above. Exposure to the synthesized combination exhibited toxicity associated with the aromatase, estrogen receptor alpha, and estrogen receptor ligand binding domain. The compound that was created and showed toxicity towards aromatase, estrogen receptor alpha (ERα), and estrogen receptor ligand binding domain (ER LBD) implies that there is a complicated interaction with the endocrine system, particularly with elements from estrogen signaling pathways. The roles of aromatase, ERα, and ER LBD, their interactions, and the effects of their dysregulation on human health must all be further investigated in order to fully understand these discoveries.

Aromatase

One important enzyme in the manufacture of estrogens is aromatase. It is responsible for catalyzing the transformation of androgens, such testosterone, into estrogens, principally estradiol. The ovaries, placenta, testes, adipose tissue, and brain are among the tissues in which this conversion takes place. In order for the reproductive system, bones, heart, and brain to work properly, estrogens are essential. Unbalances in estrogen levels, which are linked to a number of health problems such as malignancies, heart illnesses, and reproductive abnormalities, can result from dysregulation of aromatase activity.

Estrogen Receptor Alpha (ERα) and Estrogen Receptor Ligand Binding Domain (ER LBD)

One of the primary estrogen receptors (the other being ERβ), ERα is found extensively in various parts of the body such as the brain, heart, bone, and reproductive tissues. Through its binding to estrogen and subsequent activation of gene transcription, it plays a crucial role in mediating the physiologic effects of estrogen. The activation function domains (AF-1 and AF-2) and the ligand-binding domain (LBD) are among the functional domains that make up ERα. The process of binding estrogen and starting subsequent signaling cascades is carried out by the LBD.

Interpretation of Toxicity

The synthesized complex's reported toxicity implies that it could interact with aromatase, ERα, and ERLBD, resulting in abnormal estrogen signaling and perhaps interfering with regular physiological processes. These are a few possible explanations:

Aromatase Inhibition

The produced complex may function as an aromatase inhibitor, preventing androgens from being converted to estrogens. This might lead to a drop in estrogen levels, which would cause hormonal imbalances and related health problems.

ERα Modulation

The complex may engage in direct agonist or antagonistic interactions with ERα to modify its function and associated signaling cascades. Numerous illnesses, such as breast cancer, osteoporosis, and cardiovascular disorders, have been linked to dysregulation of ERα signaling.

Disruption of ER LBD

Based on the toxicity associated with ER LBD, it is possible that the produced complex will obstruct the binding of estrogen to its receptor. Physiological disruptions may result from this malfunction, which could hinder ERα's capacity to start gene transcription and control target genes downstream.

Endocrine Disruption

The toxicity that has been seen suggests that the produced complex may have endocrine-disrupting effects. Chemicals known as "endocrine disruptors" can cause negative effects on development, reproduction, and general health by interfering with an organism's hormonal systems.

Potential Health Implications

The produced complex may be hazardous to human health, especially in terms of reproductive health, hormone-related

malignancies, and other disorders dependent on estrogen, as indicated by the toxicity linked to aromatase, ERα, and ER LBD.

Need for More Research

More research is necessary to determine the precise processes underlying the toxicity that has been observed and to evaluate the possible dangers of exposure to the synthesized complex. This could entail epidemiological research, animal studies, and in vitro experiments to assess its impact on human health and endocrine function.

Consequences for Chemical Safety Assessment

The results emphasize how crucial it is to include evaluations of endocrine-disrupting effects in chemical safety assessments. Determining possible risks and safeguarding the general public's health require an understanding of how substances interact with the endocrine system.

CYP Isoenzymes

CYP3A4

One of the most prevalent and adaptable enzymes in the human body for metabolizing drugs is cytochrome P450 3A4 (CYP3A4). Although it is expressed in other tissues as well, the small intestine is where it is most commonly found. About half of all pharmaceuticals used in clinical settings are among the many endogenous compounds, xenobiotics, and medications that CYP3A4 metabolizes. Because of the wide range of chemical structures that its substrates include, CYP3A4 is an essential factor in determining drug metabolism, bioavailability, and clearance.

CYP2C9

Mainly expressed in the liver, cytochrome P450 2C9 (CYP2C9) is an additional significant drug-metabolizing enzyme. Many medications are metabolized by it, such as NSAIDs, antiepileptic medications (like phenytoin), and anticoagulants (like warfarin). Genetic variations in CYP2C9 can cause inter-individual heterogeneity in treatment responsiveness and susceptibility to side effects. CYP2C9 plays a major role in the metabolism of medicines with narrow therapeutic parameters. Following are the results obtained from the Protox *In Silico* studies **(Figure 4)**:

ProTox-3.0 - Prediction of TOXicity of chemicals

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Active	0.69
Organ toxicity	Neurotoxicity	neuro	Active	0.87
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.90
Organ toxicity	Respiratory toxicity	respi	Active	0.98
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.77
Toxicity end points	Carcinogenicity	carcino	Inactive	0.62
Toxicity end points	Immunotoxicity	immuno	Active	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.97
Toxicity end points	Cytotoxicity	cyto	Inactive	0.93
Toxicity end points	BBB-barrier	bbb	Inactive	1.0
Toxicity end points	Ecotoxicity	eco	Active	0.73
Toxicity end points	Clinical toxicity	clinical	Inactive	0.56
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.74
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Active	1.0
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Active	1.0
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/ antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.88
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.88
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.70
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.96
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.99
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92
Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	mie_ampar	Inactive	0.97
Molecular Initiating Events	Kainate receptor (KAR)	mie_kar	Inactive	0.99
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Active	0.69
Molecular Initiating Events	Constitutive androstane receptor (CAR)	mie_car	Inactive	0.98
Molecular Initiating Events	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.92
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	mie_nadhox	Inactive	0.97
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.95
Molecular Initiating Events	Na+/I- symporter (NIS)	mie_nis	Inactive	0.98
Metabolism	Cytochrome CYP1A2	CYP1A2	Inactive	0.76
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.87
Metabolism	Cytochrome CYP2C9	CYP2C9	Active	0.56
Metabolism	Cytochrome CYP2D6	CYP2D6	Inactive	0.63
Metabolism	Cytochrome CYP3A4	CYP3A4	Active	0.71
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	0.98

Figure 4: Protox *In Silico* studies of the curcumin-metal complex.

Toxicity reports

The toxicity of the generated complex including CYP2C9 and CYP3A4 points to possible interactions that might change the pharmacokinetic profiles of medicines taken together and impact drug metabolism. Here are a few interpretations that could be made:

Enzyme Activity Inhibition

The produced complex may function as an inhibitor of CYP2C9 and CYP3A4 activity, resulting in a reduction in the metabolism of the corresponding substrates. Because these enzymes metabolize the co-administered medications, their inhibition may lead to higher plasma concentrations of those pharmaceuticals, raising the possibility of side effects or drug toxicity.

Induction of Enzyme Activity

On the other hand, the complex might stimulate CYP2C9 and CYP3A4 activity, which would improve the metabolism of their substrates. This induction may hasten the clearance of concurrently administered medications, diminishing their therapeutic benefits and efficacy.

Competitive Inhibition

When the complex binds to the active sites of CYP3A4 and CYP2C9, it may compete with substrates for binding, which will reduce enzyme activity. Changes in drug metabolic kinetics and unanticipated medication interactions may result from this competition.

Observed toxicity

The observed toxicity could suggest that the produced complex is inhibiting CYP3A4 and CYP2C9 in a time-dependent manner. Time-dependent inhibition is the gradual inactivation of an enzyme's activity after an inhibitor is exposed over an extended period of time. Therapeutic medication monitoring and drug dosage schedules may be affected by this phenomenon.

Potential for Drug-Drug Interactions

Given the toxicity associated with CYP3A4 and CYP2C9, it is possible that the produced complex will interact with concurrently administered medicines that are processed by these enzymes, producing drug-drug interactions. Careful attention in clinical practice is required since these interactions may show up as changes in drug efficacy, safety, and pharmacokinetics.

Risk of Adverse Drug responses

The manufactured complex may enhance the risk of adverse drug responses related to co-administered medications by dysregulating CYP3A4 and CYP2C9 metabolism. Increased drug exposure, the build-up of hazardous metabolites, and erratic pharmacological reactions are a few examples of this. Following are the summary of the results obtained from the Protox *In Silico* Studies in Network chart **(Figure 5)** format:

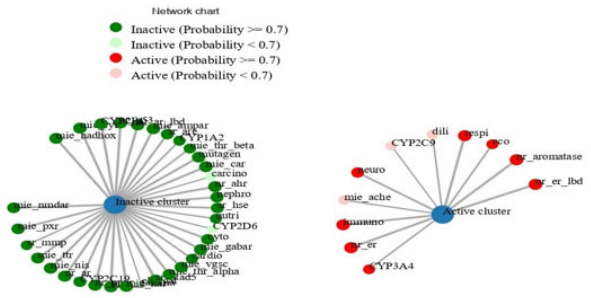

Figure 5: Network toxicity chart of the curcumin-metal complex.

Safety Pharmacology Assessments

It was performed thorough safety pharmacology assessments to appraise the synthesized complex's overall safety profile, taking into account any potential off-target effects on physiological systems other than drug metabolism. These evaluations can point up further safety issues and direct preclinical development risk-reduction tactics. As a result, it is critical to comprehend the toxicity of the generated complex including CYP3A4 and CYP2C9 and to minimize any potential negative effects on drug efficacy and metabolism. This is because the complex interacts with important enzymes involved in drug metabolism. Subsequent investigations ought to concentrate on clarifying the fundamental processes, refining the composition of compounds, and carrying out meticulous preclinical and clinical assessments to guarantee the security and effectiveness of innovative treatments. Through the use of a multidisciplinary strategy that includes pharmacokinetic evaluations, mechanistic research, in vitro screening assays, and clinical investigations, we can reduce the likelihood of toxicity and open the door to the creation of safer and more efficient medicines. The Radar chart **(Figure 6)** for the toxicity of the curcumin-metal complex is given below:

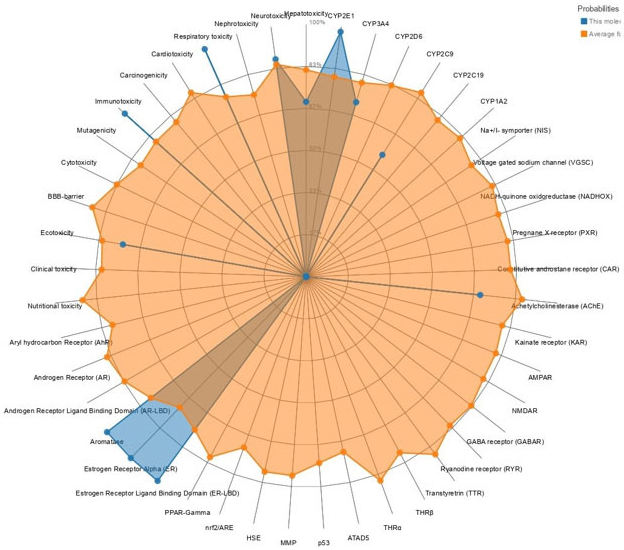

Figure 6: Radar chart for the toxicity of the curcumin-metal complex.

CONCLUSION

In conclusion, the toxicity detected in the produced complex including aromatase, ERα, and ER LBD emphasizes its ability to interfere with estrogen signaling and interfere with regular physiological functions. To determine the implications for human health and to clarify the underlying mechanisms, more research is necessary. Future researchers in this subject should focus on minimizing the toxicity, as indicated by the following data. Drug metabolism, efficacy, and safety may

be affected by possible interactions with important enzymes that metabolize drugs, as shown by the toxicity seen in the manufactured complex involving CYP3A4 and CYP2C9. We examined the functions of CYP3A4 and CYP2C9, their importance in drug metabolism, and the effects of their dysregulation on human health in order to fully interpret these data and specify future research directions to reduce toxicity; CYP3A4 and CYP2C9.

CONFLICT OF INTEREST

No conflict of interest is declared.

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ETHICAL STATEMENT

No animal was employed in this study.

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AUTHORS' CONTRIBUTION

Ravi Khatri: Analysis, Plagiarism correction, Revision

Khan Ziya Khan: Concept, Checking, Editing, Grammar correction, Literature Review, Formatting, Writing manuscript

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