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Research Article

Synthesis, Characterization, *In silico* and *In vitro* Studies of Transition Metal Complexes with Biologically Active Ligand as Antigout Agent Colchicine

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ABSTRACT

Colchicine is essentially useful in the treatment of gout. In the present work colchicine complexes has been prepared with transition metals viz., Copper(II) [Cu(II)], Zinc(II) [Zn(II)], Cobalt (II) [Co(II)], Nickel(II) [Ni(II)], and those checked for molecular docking. It has been observed that Zn(II), and Ni(II) complex have revealed good binding energy than the parent ligand, the increased binding energy of colchicine metal complexes indicates that the tubulin polymerization inhibitor tendency is enhanced; consequently antigout property is also increased. As transition metals have antimicrobial activity in themselves, complexes are also characterized for the antimicrobial activity, which is enhanced for Cu(II) and Co(II) metals.

INTRODUCTION

Metals have an important place in medicinal chemistry. They have been used in the treatments of diseases since ancient times.^[1] In the list of metals, transitions metals are identified to play a very important role in biological processes in the human body. Metal ions influence the complex form, particularly when the metal is necessary for the human body. Complex with the drug as the discovery of novel compounds having extra antioxidant, antimicrobial, and anti-inflammatory actions.^[2-4] The transition metal complex shows a broad application area in antimicrobial activities and antitumor.^[5] Colchicine, which is also known

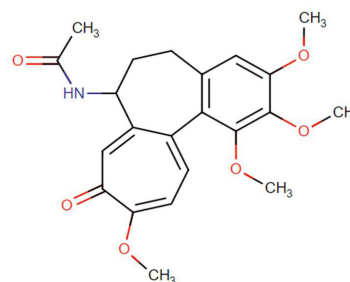


Fig. 1: Structure of Colchicine molecule.

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as mitogare acts as an antigout, antimitotic, antifibrotic, and anti-inflammatory drug (Fig. 1).

Gout is ordinary arthritis. It is due to the deposition of monosodium urate (MSU) crystals inside the joint behind a long-standing history of hyperuricemia. Overloaded uric acid in the blood is the basic reason of gout disease. Increased uric acid forms needle-like urate crystals, which accumulate on joints causing the inflammation and intense pain redness heat of gout attack. Metabolism of purine produces uric acid.

The normal small elimination of uric acid is 7–10%. While it reduces, it replicates a decrease of uric acid secretion in enhanced serum urate stage.^[6]

Colchicine is a tropolone alkaloid from autumnal used as gout suppressants and nonsteroidal anti-inflammatory drugs (NSAIDs).^[7] It is obtained from the dried seeds of colchicine autumnal known as meadow saffron, naturally occurs as a neutral molecule. All those drugs which bind to human tubulin bind to beta tubulin (β -tubulin). Initially, the tubulin was identified as the colchicine binding protein.^[8] These include padimate, colchicine, and vinca alkaloid. Colchicine is a tubulin polymerization inhibitor. Polymer inhibitor can be divided into two categories, destabilizing agents and microtubule-stabilizing agents. Colchicine binds to soluble tubulin to structure tubulin colchicine complexes, which after that, binds to the ends of micro-tubulin to avoid the elongation of the microtubule polymer and that is why it is also known as anti-microtubule (MT) drugs (microtubules α/β -tubulin dimer). It disrupts the polymerization of β -tubulin into microtubules in that way avoiding the degranulation, activation, and migration of neutrophils to sites of inflammation.^[9] Microtubules have been known as highly striking sites of cancer chemotherapy. Colchicine has not recognized as a commercial anticancer drug to date,^[10] because of its low therapeutic index due to high toxicity.^[11] Metabolism of colchicine take place throughout isoenzyme, cytochrome P450 3A4 (CYP3A4); therefore, taking the drug with an agent that inhibits the isoenzyme, and can construct elevated colchicine plasma concentrations, resulting in harsh and sometimes deadly adverse effects.^[12] It is observed in the case lesson of Familial Mediterranean fever (FMF). Natural grape juice, which is known as cytochrome P450 inhibitor, creates intoxication with colchicine because CYP450 is an enzyme required for the metabolism of drugs. Inhibition of this enzyme creates an increased level of a drug without metabolism, which leads to intoxication. Taking colchicine with CYP3A4 inhibitors (particularly clarithromycin) has given severe colchicine toxicity manifested by severe gastrointestinal harmfulness, and fatal effect.^[13] Although colchicine is one of the oldest medications so far, there is much more to study and find out its action of a mechanism.^[14]

Not a lot of study has been done on the development of complexes among colchicine and metal cations. In

the present work, we have chosen metals like zinc (Zn), nickel (Ni), copper (Cu), and cobalt (Co) metal ion to make complexes, with colchicine and characterized well and studied antimicrobial activities.

All four metal complexes are checked for molecular docking, it is observed that Zn and Ni show increased binding energy than colchicine itself, while Cu and Co have not shown good binding energy. This indicates that complexing with Ni and Zn increases the tendency of tubulin polymerization inhibitor than the parent ligand, which implies that; these two complexes have more antigout property than colchicine. These observations demonstrate that molecular docking has a very important role in this study.

The protein-ligand docking approach can be used to model the interaction between a small molecule and a protein at the atomic level, which permit us to differentiate the behavior of small molecules in the binding site of target proteins as well as to explain fundamental biochemical processes. The docking procedure involves two basic steps; one is a prediction of the ligand confirmation, as well as its position and orientation within these sites, and second, is the evaluation of the binding affinity. The field of drug designing is developing very rapidly and with the growing popularity of well-developed supercomputers and new softwares.^[15] The main objective of pre-clinical progress is the recognition and optimization of a lead compound for a targeted biological action in which the pharmacokinetic and pharmacodynamic exploration of the drug is involved and generally begins within silico analysis, which further leads to *in vitro* and eventually *in vivo* studies.

MATERIAL AND METHODS

All chemicals used are analysis grade colchicine is commercially available. The salts of nickel nitrate [$\text{Ni}(\text{NO}_3)_2$], zinc nitrate [$\text{Zn}(\text{NO}_3)_2$], cobalt nitrate [$\text{Co}(\text{NO}_3)_2$] and copper nitrate [$\text{Cu}(\text{NO}_3)_2$] was obtained from sigma-Aldrich.^[16] All the salts ligands are taken in the ratio of 2:1 and dissolved separately in ethanol and mixed together. The reaction blend was refluxed for at list 2 hours.^[17] The blend was filtered and dried in over to obtain the powder. All most all complexes have shown the change in color. Before reaction, the ligand was white after reaction with $\text{Cu}(\text{NO}_3)_2$. The color of the complex was green; with $\text{Ni}(\text{NO}_3)_2$, it was greenish-yellow in case of $\text{Zn}(\text{NO}_3)_2$. It was white and with $\text{Co}(\text{NO}_3)_2$, yellowish color. These changes in colors of all complexes are the indication of the first sign of complex formation.^[18-20]

Fundamentally the objective of protein-ligand docking is to present a calculation of the complex structure by using computation methods.^[21-22]

The docking method was achieved by Autodock Version 4.2.6 program, using the realized experimental free energy function and the lamarckian genetic algorithm (LGA). The grid map was designed using Autogrid step. During the



Table 1: Antimicrobial activity of Metal-Ligand complexes

		<i>S. aureus</i>		<i>B. subtilis</i>		<i>E. coli</i>		<i>K. pneumoniae</i>		<i>C. albicans</i>		<i>A. niger</i>	
		50	100	50	100	50	100	50	100	50	100	50	100
		µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL	µg/ mL
Concentration		Zone of Inhibition (mm)											
S. No	Compound Code	Zone of Inhibition (mm)											
1	Colchicine-Cu	10	14	12	17	12	16	10	17	12	19	12	18
2	Colchicine-Co	9	13	12	16	11	15	12	18	11	17	11	15
3	Ligand	9	13	12	16	11	15	9	13	11	17	11	15
4	Gentamicin (100 µg/ml)	12	17	13	17	11	14	10	18	11	19	12	18

* NCIM: National Collection of Industrial Microorganisms

* MTCC: Microbial Type Culture Collection and Gene Bank

process of dockings, a grid map with 40×40×40 points and a grid-point spacing of 0.481 Å was applied.

Antimicrobial Activity Synthesized Compound

The most commonly used of assay in identifying anti-microbial activity by using diffusion methods, which exploit the dispersion of antimicrobial compounds during agar media and shows inhibition of bacteria and fungi.

Test cultures as antimicrobial activity were screened by using six cultures, amongst which two were gram-positive (+ve) bacteria, two were gram-negative (-ve) bacteria, and two fungi. Gram-positive (+ve) bacteria are *Staphylococcus aureus* (*S. aureus*) NCIM 2901 and *Bacillus subtilis* (*B. subtilis*) NCIM 2063 (Table 1).

Gram-negative (-ve) bacteria are *Escherichia coli* (*E. coli*) NCIM 2256 and *Klebsiella pneumoniae* (*K. pneumoniae*) NCIM 2957. Fungi are *Candida albicans* (*C. albicans*) MTCC 3018 and *Aspergillus niger* (*A. niger*) MTCC 404.

RESULTS

Melting points are taken in open capillaries on a melting point apparatus. It observed that melting points of all complexes are above 350°C. The solubility of all complexes is checked; all are insoluble in water and partially soluble in dimethyl sulfoxide (DMSO), but solubility increases when the complexes are prepared in 1:1 ratio of metal and ligand. Infrared spectroscopy (IR), the harmonic vibrational study of some complexes are given below (Figs. 2-5).^[23] The heterocyclic compound N-H stretching vibration occurs in the range of 3500 to 3000 cm⁻¹. In recent work, N-H stretching vibrations are intended at 3454 cm⁻¹ for the parent ligand, and for the complexes prepared, almost all complexes are showing a decrease in the N-H stretching vibrations.

Table 2: N-H stretching values of metal-ligand complexes.

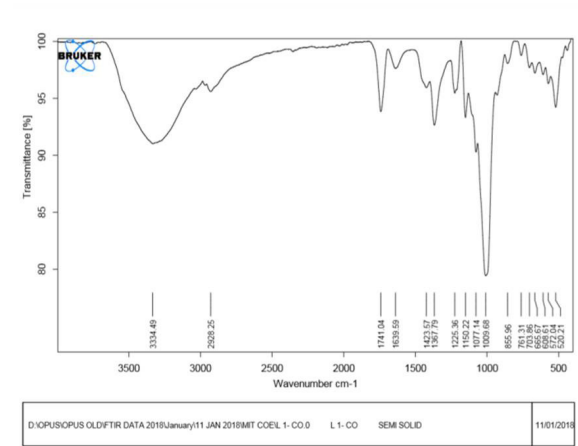
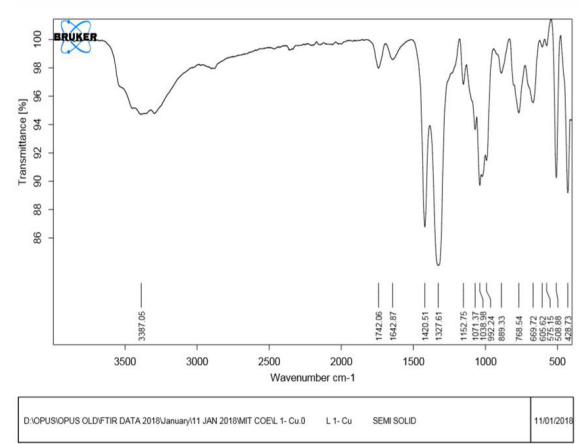
Compound	<i>U</i> (N-H) cm ⁻¹	<i>U</i> (M-N) cm ⁻¹
Colchicine	3454	
[Co(Colchicine)]	3334	520
[Zn(Colchicine)]	3387	439
[Ni(Colchicine)]	3266	431
[Cu(Colchicine)]	3338	428

The shifts are given below.

In the current study ligand, C-H stretching vibrations are observed at 3060 cm⁻¹, and there is no major shift change in the vibrations (Table 2). The same observation is obtained in the case of C₁₃ = O₄, so this indicates that the donor groups are N-H amino nitrogen.

Molecular Docking

AutoDock Version 4.2 uses a computationally inexpensive “hybrid” force field that covers terms based on the


Fig. 2: IR of colchicine-cobalt.

Fig. 3: IR of colchicine-copper.

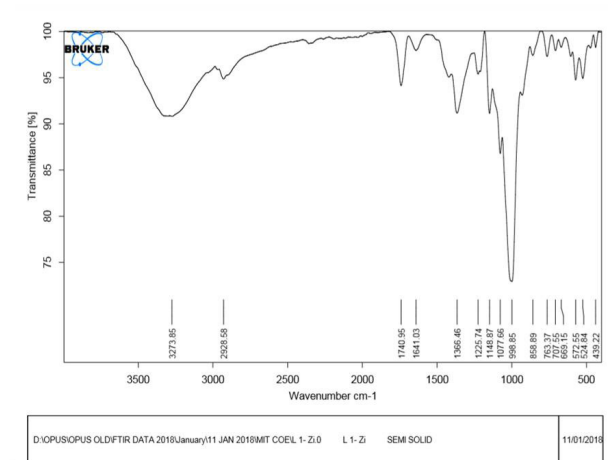


Fig. 4: Interventional radiology of colchicine-zinc.

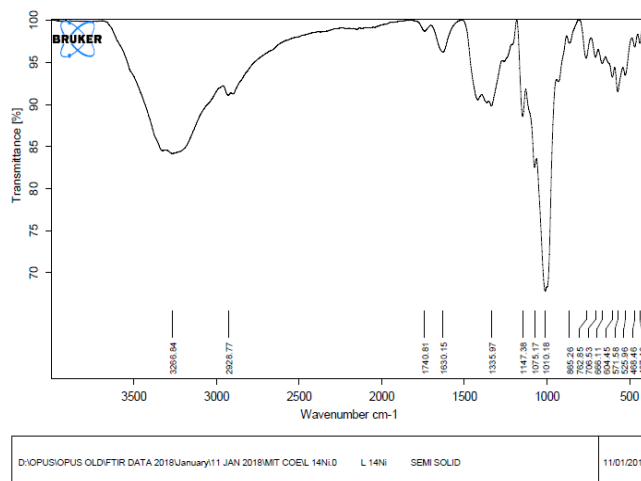


Fig. 5: Interventional radiology of colchicine-nickel.

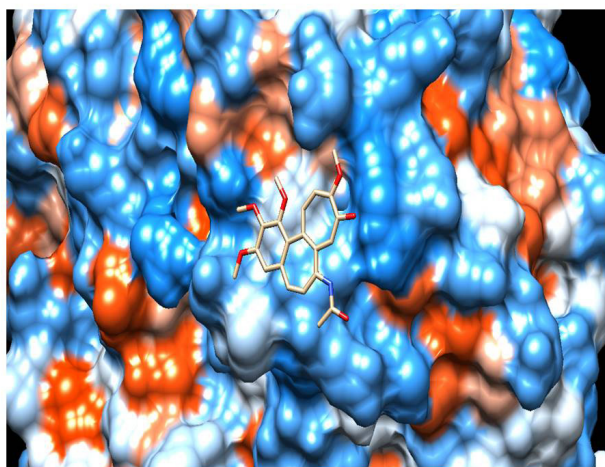


Fig. 6: Docking structure of beta tubuline protein and colchicine as a ligand.

molecular procedure as well as experiential terms.^[24-25] The calculation of absolute binding energies may be less precise compared to more computationally expensive, purely force field-based approaches, but this semi-

empirical approach is measured as well-suited for the relative rankings. The best confirmation with the lower dock energy was selected from the docking investigation. The interactions of complex protein-ligand conformations counting hydrogen bonds and bond lengths were analyze using Pymol software, University of California San Francisco (UCSF) Chimera, Molegro Molecular Viewer, and Accelrys Discovery Studio Visualizer software. The protein name is beta tubulin, and sequence length is 444. The protein organism is homo sapiens and gene names is TUBB5. The amino acid information of beta tubulin in which amino acids are 424 out of 444 (96%), favored amino acid is 395 (93%) and allowed amino acids is 29 (7%). This information is related with Ramachandran plot. On carrying out the docking analysis of the β -tubulin (Protein) with Colchicine and it detected that the binding energy shown by the β -tubulin and ligand is good at -8.557 kcal/mol (Figs. 6 and 7).^[26] This interaction is more stable as there is one hydrogen bonds formed at Arg164(H) (comparable binding energy, although lower binding energy indicates a good and stable communication). In conclusion, ligand showed better results on docking with the protein.

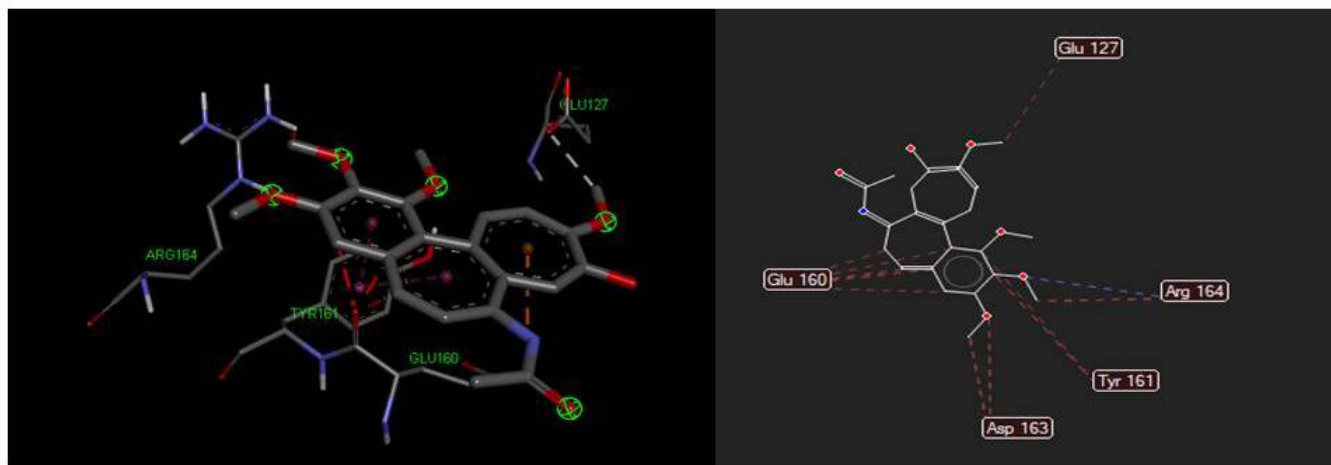


Fig. 7: Interaction of β -tubulin protein and colchicine.



Estimated loss of torsional free energy upon binding energy is +1.3720 kcal. Minimum electrostatic potential is -29.47 and maximum electrostatic potential is 30.19 (Table 3).

Nowadays, in-silico drug designing methods have been of enormous significance in target identification and in prediction of novel drugs. Molecular docking study of colchicine and its complexes has given fruitful information regarding binding energy of the drug. Colchicine is cytostatic drug; due to its toxic nature it can't be used as anticancer agent. Metals have good antimicrobial and anticancer activity so we have induced the metals with colchicine. The binding energy of Ni(II) and Zn(II) is -8.99 and -8.04, respectively (Figs. 8-11), which is more than the parent ligand this indicates that both complexes have good interaction with tubulin as beta tubulin inhibitor than the colchicine itself. This drug is antitumor and antiproliferative because of its tubulin inhibition property as its complexes are showing more binding energy than the parent ligand

which implies the two complexes would give good quality information in the pharmaceuticals of colchicine as antitumor as well as antimitotic agent.^[27-29] Cu(II) complex (Figs. 12 and 13) has shown binding energy -7.32, while Co(II) has shown no reaction with tubulin (Fig. 14).

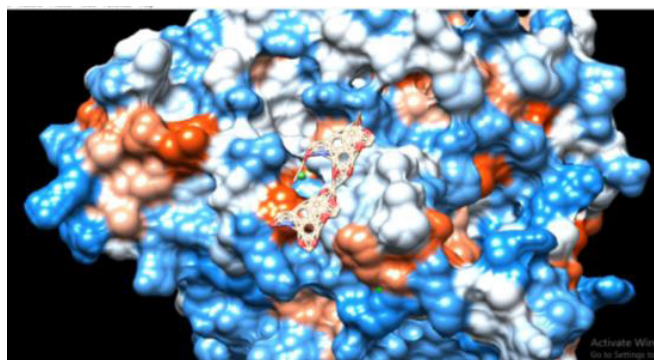


Fig. 8: Docking structure of β -tubulin protein and [Ni (Colchicine)] as a ligand.

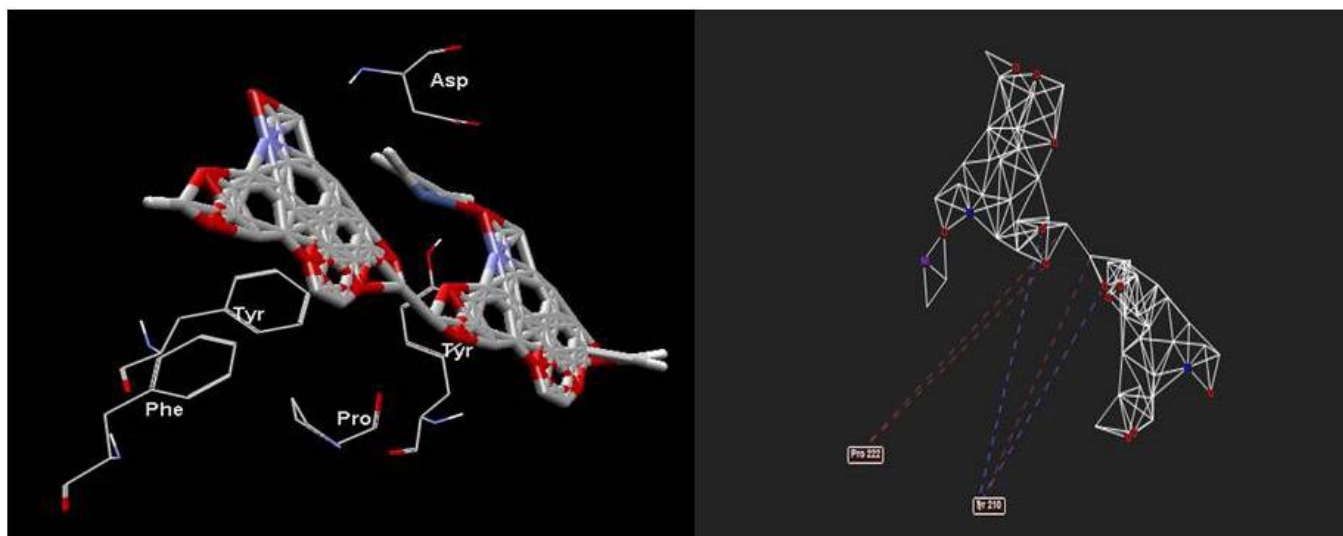


Fig. 9: Interaction of β -tubulin protein and [Ni (Colchicine)].

Table 3: Summary of Binding energy, Site Prediction, Hydrogen bond and Ligand Docking information results using AutoDock V4.2 software

Protein Name	Ligand Name	Binding Energy (kcal/mol)	No. of H Bonds	Interacting residue	Electrostatic Energy (Kcal/mol)	VdW + Hbond+ desolv Energy	Resolution
B-tubulin (Tubulin beta)	Colchicine	-8.557	01 (Distance= 3.36 Å, strength= -1.22)	Glu127 Arg164(H) Tyr161 Asp163 Glu160	-0.18	-9.00	3.6 Å
B-tubulin (Tubulin beta)	Colchicine + NiNO ₃ ⁻	-8.99	01 (Distance= 3.00 Å, strength= -2.50)	PRO 222 TYR 210 (H)	-0.21	-9.37	3.6 Å
B-tubulin (Tubulin beta)	Colchicine + NO ₃ Zn ⁺	-8.04	Nil	THR 276	+0.01	-10.44	3.6 Å
B-tubulin (Tubulin beta)	Colchicine + CuNO ₃ ⁺	-7.32	Nil	SER 77 TYR 224	+0.18	-9.59	3.6 Å
B-tubulin (Tubulin beta)	Colchicine + CoNO ₃ ⁻	Nil	Nil	Nil	-0.38	-11.28	3.6 Å

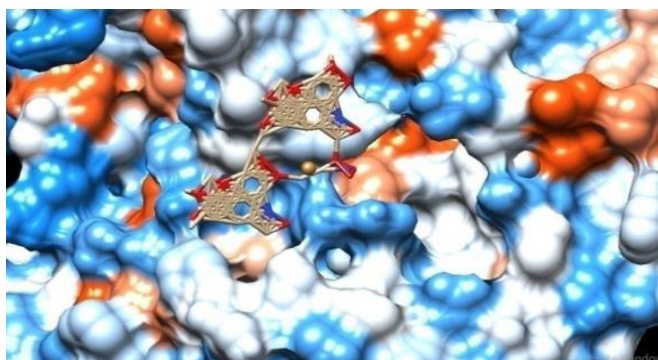


Fig. 10: Docking structure of β -tubulin protein and [Cu (Colchicine)] as a ligand.

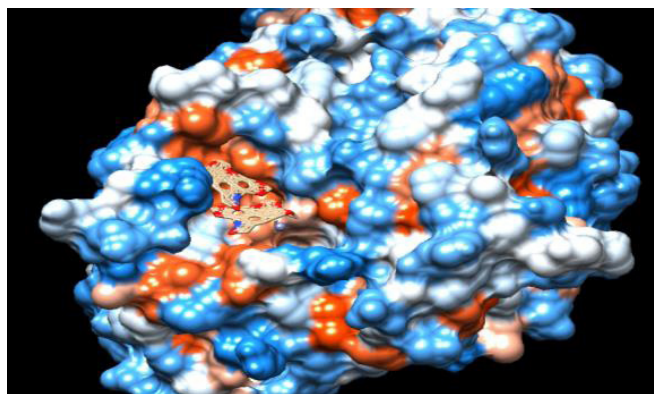


Fig. 12: Docking structure of beta tubulin protein and [Zn (Colchicine)] as a ligand.

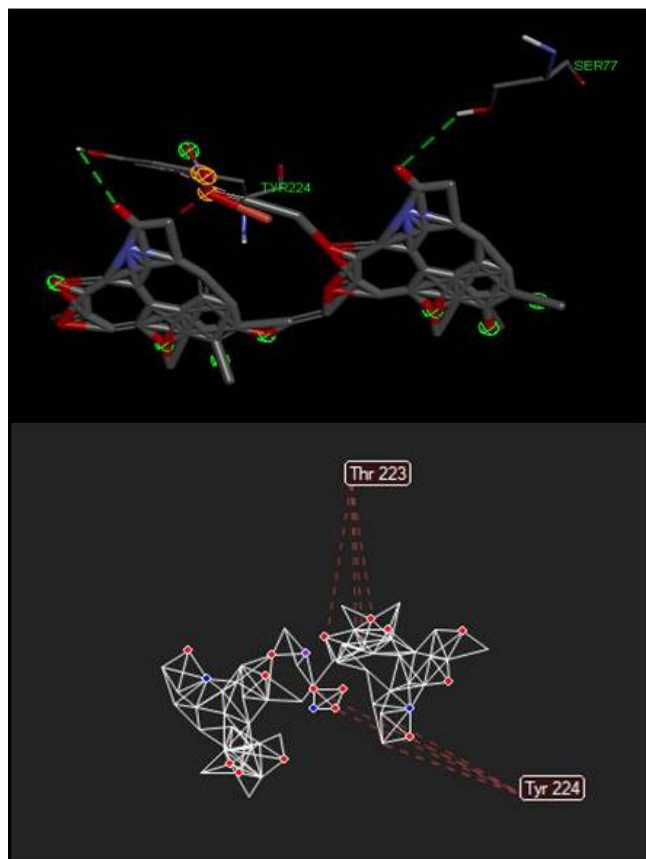


Fig. 11: Interaction of beta tubulin protein and [Cu (Colchicine)].

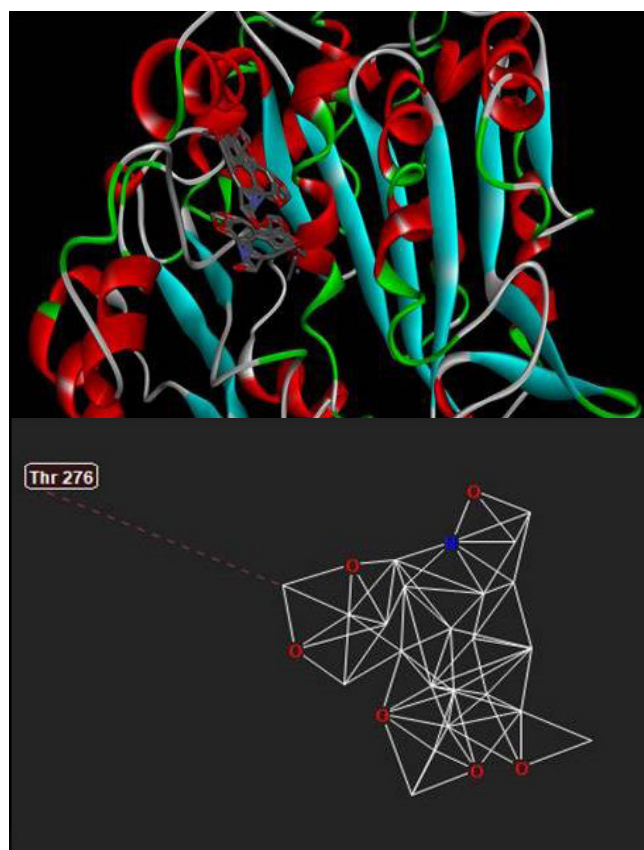


Fig. 13: Interaction of beta tubulin protein and [Zn (colchicine)].

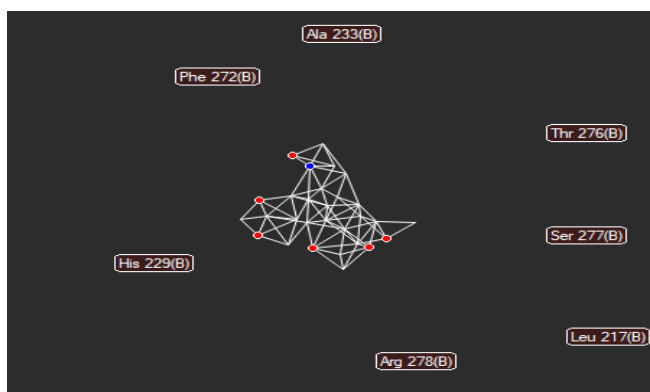


Fig. 14: No interaction between beta tubulin protein and [Co (Colchicine)].



DISCUSSION

The structures of known biologically active molecules are altered to obtain the innovative molecules known as metal coordinated complexes. The aim of such modifications is to get molecules that are improved in such way as stability, potency, reduced side effects antimicrobial activity, etc. We have been established some of these novel complexes and also observed that their molecular docking, antimicrobial activity and fungicidal activity is enhanced, there is always need of antimicrobial agents during the treatment of gout so this will also give some new property to the parent ligand.^[30] It is observed that the antimicrobial activity is enhanced for Cu and Co. This result may give the conclusion that the metals those are good enough in antimicrobial activity are not showing good binding energy in molecular docking, and vice versa, because increase in antimicrobial activity decreases the tubulin polymerization tendency, i.e., antigout property.

Results of molecular docking of Ni and Zn both metal complexes have shown greater binding energy than the ligand, while Cu and Co metal complexes have not shown good binding energy. This demonstrates that complexing with Zn and Ni increases the antigout property. This may give fruitful and important information in the further development of drug design of colchicine as antigout as well as antiproliferative drug, because complexing with these metals has given new property to the drug i.e. enhanced antimicrobial activity and antigout property.

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