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Isolation and Characterization of Berberine from *Tinospora Cordifolia* Leaf Extract and *In Silico* Analysis of Fts-Z Binding

Prajwala B[1], Raghu N[1], Gopenath TS[2], Raviraja S[3], Nagalambika Prasad[4] and Kanthesh M Basalingappa[1*]

[*1]Division of Molecular Biology, School of Life Science, JSS Academy of Higher Education & Research, Mysore, Pin code: 570015, Karnataka, India
[2]Division of Biotechnology, School of Life Science, JSS Academy of Higher Education & Research, Mysore, Pin code: 570015, Karnataka, India
[3]Division of Cognitive Neurosciences, School of Life Science, JSS Academy of Higher Education & Research, Mysore, Pin code: 570015, Karnataka, India
[4]Division of Microbiology, School of Life Sciences, JSS Academy of Higher Education & Research, Mysore, Pin code: 570015, Karnataka, India

ABSTRACT

Fts-Z is the major cytoskeletal protein in the bacterial cytokinesis machine, and it is the first protein to move to the division site and is essential for recreating other proteins that produce new cell walls between dividing cells. The cellular concentration of Fts-Z regulates the frequency of division and genetic studies have indicated that it is the target of several endogenous division inhibitors. Antibiotic resistance has the potential to affect people at any stage of life. Since drug resistance too many antibiotics have been known hence it is essential to develop new drugs. Herbs can be antibiotics too, *Tinospora cordifolia* is a well-known medicinal plant used to cure plenty of diseases. The plant having anti-bacterial, anti-cancer, anti-diabetic, anti-inflammatory, antioxidant, anti-spasmodic, anti-pyretic, anti-allergic, anti-leprotic immunomodulatory activity, etc. Berberine is a natural plant alkaloid having many medicinal properties including anti-bacterial. In the present study, berberine was isolated by preparative HPLC and characterized by sophisticated instruments such as LC-MS, NMR, and IR. The isolated compound was tested on *E. coli*; berberine successfully inhibited the bacterial growth. Molecular docking was done to check the interaction of berberine with Fts-Z protein. Berberine docks well with Fts-Z protein and *In silico* analysis showed berberine as a good inhibitor of Fts-Z protein.

Keywords: Berberine, HPLC, LC-MS, Fts-Z, *In silico*

INTRODUCTION

Berberine is a plant alkaloid, is a member of naturally occurring protoberberine class, it is present in plants of *Menispermaceae, Ranunculaceae, Papaveraceae, Berberidaceae* families. Berberine has been isolated from various parts of the plants such as root, stem, leaf, bark, and rhizome [1]. Extraction is an essential step for the analysis of medicinal plants because it is necessary to extract the desired compound from plant material for further separation and characterization. Usually, plant extracts occur as

[*]**Corresponding Author:**
kantheshmb[at]jssuni.edudotin

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a combination of various types of phytochemicals or bioactive compounds with different polarities, separation of the desired compound is still a big challenge for the process of identification and characterization [2]. TLC, column chromatography, HPLC are the common separation techniques used to obtain pure compounds. Pure compounds are then used for the determination of structural and biological activity [3]. Column chromatography is the most frequently used method among other chromatographic methods. This technique is used for the purification of biomolecules and it is one of the most commonly used methods of protein purification [4]. TLC can provide the light images and fluorescence images which is one more visual parameter than chromatograms and it also gives different levels of profiles and corresponding integral data with chromatography scanning and digital processing and it is the major advantage of TLC [5]. High-Performance Liquid Chromatography (HPLC) is a versatile, robust and widely used technique for the isolation of natural products. HPLC can separate a mixture of compounds and it is used in phytochemical and analytical chemistry to identify, quantify and purify the individual components of the mixture [6]. Among various analytical techniques, HPLC is gaining popularity and it is the main choice for fingerprinting study for the quality control of herbal plants [7]. Modern HPLC uses a non-polar solid phase, like C-18 column and a polar liquid phase, generally a mixture of water and another solvent [8]. One of the advantages of HPLC is many detectors like UV, DAD, ELSD, FLD, RID; MS and NMR, etc can be connected to it which supplies many more possibilities for detecting different constituent types [9]. Mass Spectroscopy [MS] provides information about the molecular mass and fragmentation pattern of the analyte. Ionization performed in the positive and negative ion mode, anthocyanins are analyzed in the positive mode and other groups are analyzed in the negative mode [10]. Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful technique for the structure elucidation of an organic molecule. The field where multidimensional NMR spectroscopy has most impressively been used is its use in the determination of protein. The NMR method provides data that are in many ways complementary to those obtained from X-ray crystallography and thus promises to widen our view of protein molecules, giving a clearer insight into the relationship between structure and function [11]. Molecular docking is a type of bioinformatics modeling which involves the interaction of two or more molecules to give the stable adduct. Depending upon binding properties of ligand and target, it predicts the three-dimensional structure of any complexity. To attain a ligand-receptor complex with optimized confirmation and to possess less binding energy is the main objective of molecular docking [12].

As the issues of anti-bacterial resistance continue to grow, there is a renewed interest in deriving anti-bacterial products from natural compounds, particularly extracts from plant material [13]. The present study describes the isolation of natural compound called berberine from *Tinospora cordifolia* leaf by preparative HPLC method and it was structurally elucidated by appropriate methods such as LC-MS, NMR, and IR. Molecular docking studies were conducted with berberine and Fts-Z protein to find the interaction of berberine with Fts-Z. The chemical structure of Berberine (2D) is showing below (Figure 1).

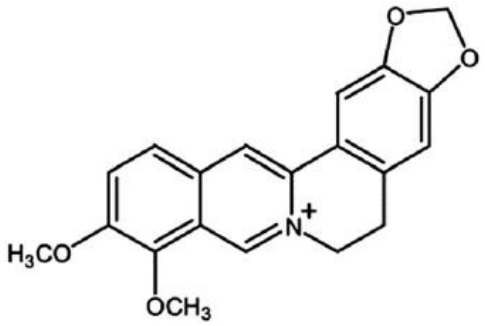

Figure 1: Chemical Structure of Berberine (2D)

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- Molecular formula: $C_{20}H_{18}NO_4$ +
- Molecular weight: 336.4g/mol
- IUPAC name: 16, 17-dimethoxy-5,7-dioxa-13azoniapentacyclo [$11.8.0.0^{2,10}.0^{15,20}$] henicosa-1(13),2,4(8),9,14,16,20-octaene.

MATERIALS AND METHODS

I. Extraction, Purification, and Isolation of Berberine

a) Plant extraction: Extraction is an essential and initial step for the analysis of medicinal plants. *Tinospora cordifolia* leaves were washed, dried, powdered and Soxhlet method was used for the preparation of crude extract for 48 hours with methanol [14].

b) HPLC analysis: Berberine standard was purchased from Sigma-Aldrich, Bangalore and it was run against methanolic extract. Qualitative analysis of HPLC was carried out using Shimadzu HPLC to find the presence of berberine from the methanolic extract of *Tinospora cordifolia* leaf. The retention time of methanolic extract matches with berberine standard.

c) Purification: Qualitative analysis of HPLC confirmed the presence of berberine in the methanolic extract of *Tinospora cordifolia* leaf. Berberine was purified by Column chromatography.

d) Isolation of Berberine: Initially, berberine was purified by Column chromatography then it was subjected to isolation. Berberine was isolated by Preparative HPLC. HPLC analysis was carried out using Waters 2545 Binary Gradient Molecule (BGM), C-18 column with the mobile phase of Formic acid (0.1%) and acetonitrile at a flow rate of 1ml/min with Photo Diode Array (PDA) detector at 264 nm.

II. Characterization of Berberine

e) Liquid Chromatography-Mass Spectra (LC-MS): Pure compound or berberine obtained from preparative HPLC and it was subjected to LC-MS. Berberine was analyzed by LC-MS to get the molecular mass, berberine standard was used as a reference. Time of Flight Mass Spectrometry (TOFMS) method is used to characterize berberine by LC-MS using a Diode Array Detector (DAD). TOFMS is a method of mass spectrometry in which an ion's mass to charge ratio is determined through a time of flight measurement [15].

f) Nuclear Magnetic Resonance (NMR): NMR is an analytical chemistry technique used in research for determining the content and purity of a sample as well as its molecular structure [16]. Here berberine was subjected for NMR spectroscopy (^1H and C^{13} NMR) to get the molecular structure of berberine. NMR was carried out by Agilent VNMRS-400 using CDCl3 solvent with ambient temperature.

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H^1 NMR

Pulse sequence	Observation	Data processing
Relax. Delay -1.000 second **Pulse- 45.0 degrees** **Acquired time- 3.722 second** **Width- 8802.8 HZ** **Repetitions- 16**	H^1,399.8257242	Line broadening- 1.0 HZ FT size-65536 Total time: 1 minute

C^{13} NMR

Pulse sequence	Observation	Data processing
Relax. Delay -1.000 second **Pulse- 45.0 degrees** **Acquired time- 1.022 second** **Width-32051.3 HZ** **Repetitions- 10000**	C^{13}, 100.5362583 Decouple- H1, 399.8277233 Power- 39 Db Continuously on WALTZ -16 modulated	Line broadening 2.5 HZ FT size- 65536 Total time- 5.6 hours

g) Infrared Spectroscopy (IR): IR deals with the infrared region of the electromagnetic spectrum. It was used to identify and study chemical substances in the berberine compound. IR spectrum can be visualized in a graph of infrared light absorbance on the vertical axis vs. frequency or wavelength on the horizontal axis [17]. Berberine was also characterized by IR spectroscopy using Perkin Elmer spectrum version 10.03.09.

III. Anti-Bacterial Test: To evaluate the antibacterial activity of berberine against *Escherichia coli,* we studied the inhibitory effect of berberine on bacterial growth. Agar well diffusion method was employed for anti-bacterial test [18]. Isolated berberine was tested against *E. coli;* anti-bacterial activity was interpreted from the size of the zone of inhibition.

IV. *In silico* Analysis of Fts-Z Binding

- **Binding site prediction**
  - The binding site of the procured protein structure was analyzed through ligand explorer of the RCSB PDB server.

- **Preparation of Ligand**
  - The 2D structure of berberine was generated using the Chemsketch tool. The generated 2D structure was saved as .mol file and the same was used to generate 3D structure where the hydrogens were added and 3D coordinates were generated using Open Babel tool and saved in PDB format.

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- **Molecular Interaction studies**
  - The procured crystal structure of the cell-division protein Fts-Z (PDB ID: 1fsz) from RCSB PDB was further refined by removing water residues, followed by addition of gasteiger charges, and were further refined by merging non-polar hydrogens using Auto dock V.4.0

- **Auto grid Generation**
  - Upon refinement of protein, the protein structure was selected for a rigid molecule and the 3D structure of the ligand was selected for map type. Based on the binding site residues the grid box was set, where all the binding site residues fit inside the grid box and hence the grid box was set with X:53, Y:61 and Z:61 dimensions. Upon saving the grid the grid parameter file (gpf) was generated and saved. The saved grid parameter file was used to run using Autogrid4.
  - On successful completion of the autogrid, molecular docking of the ligand was carried out using a genetic algorithm using Autodock4, followed by generation of docking parameter file (DPF). The saved docking parameter file was used to run Autodock4.

RESULTS AND DISCUSSION

I. Isolation of Berberine

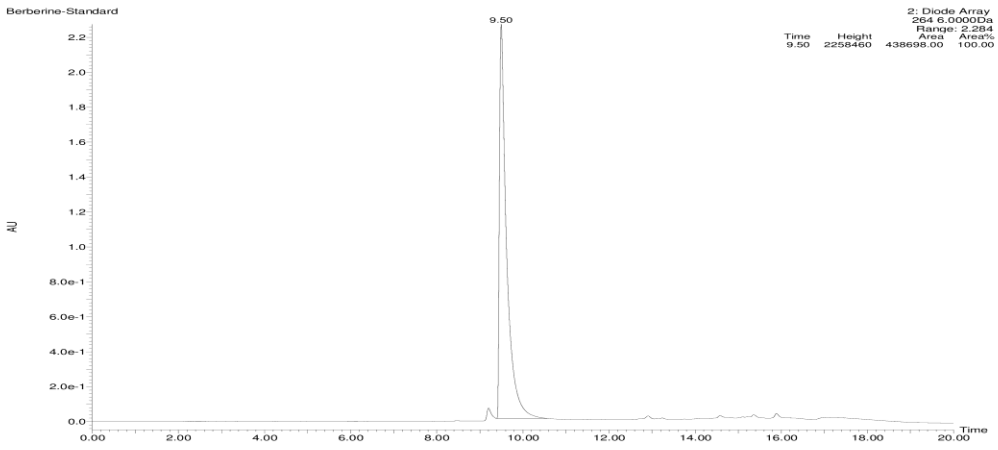

Figure 2: Berberine Standard

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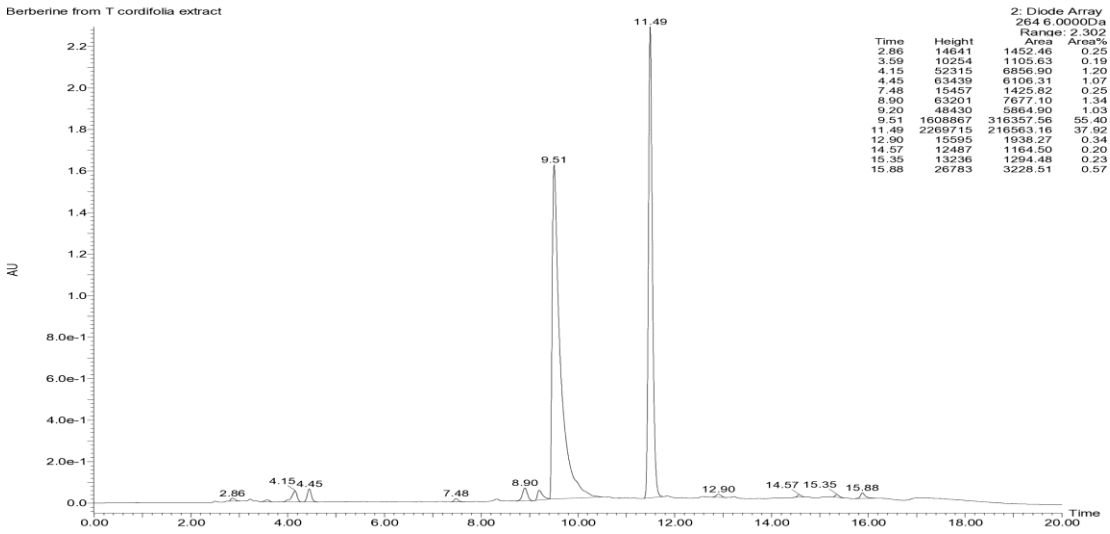

Figure 3: Berberine Isolated from *T. cordifolia*

Berberine standard showed a peak at the retention time of 9.50 (Figure 2), *T. cordifolia* leaf extract showed a peak at the retention of 9.51 (Figure 3), hence it can be concluded that the peak at retention time 9.51 corresponded to berberine. Area percentage showing 55% of berberine concentration at the retention time 9.51 (Figure 3), hence the yield of berberine is **55%**.

Table 1: Peak Table of Berberine

Time	Height	Area	Area %
2.86	14641	1452.46	0.25
3.59	10254	1105.63	0.19
4.15	52315	6856.90	1.20
4.45	63439	6106.31	1.07
7.48	15457	1425.82	0.25
8.90	63201	7677.10	1.34
9.20	48430	5864.90	1.03
9.51	**1608867**	**316357.56**	**55.40**
11.49	2269715	216563.16	37.92
12.90	15595	1938.27	0.34
14.57	12487	1164.50	0.20
15.35	13236	1294.48	0.23
15.88	26783	3228.51	0.57

II. Characterization of Berberine

Isolated berberine was characterized through LC-MS, NMR and IR spectroscopy.

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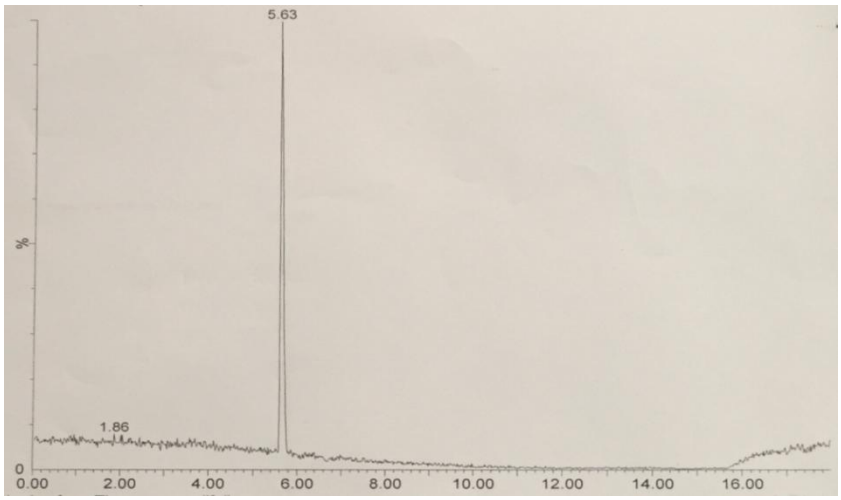

Figure 4: LC-MS of Berberine Standard

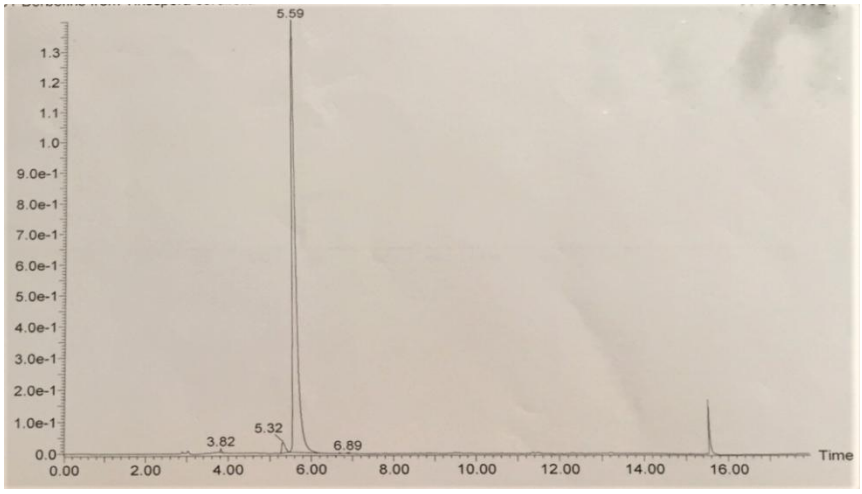

Figure 5: LC-MS of Isolated Berberine

Table 1: Peak table of LC-MS

Time	Height	Area	Area %
3.82	12148	390.38	0.26
5.32	32669	3115.70	2.10
5.59	**1400089**	**1445562.75**	**97.42**
6.68	2017	115.70	0.08
6.89	3219	205.35	0.14

LC-MS of berberine from *T. cordifolia* leaf extract showed molecular peak at 5.59 (Figure 5) retention time which is good agreement with the berberine standard (5.63) (Figure 4).

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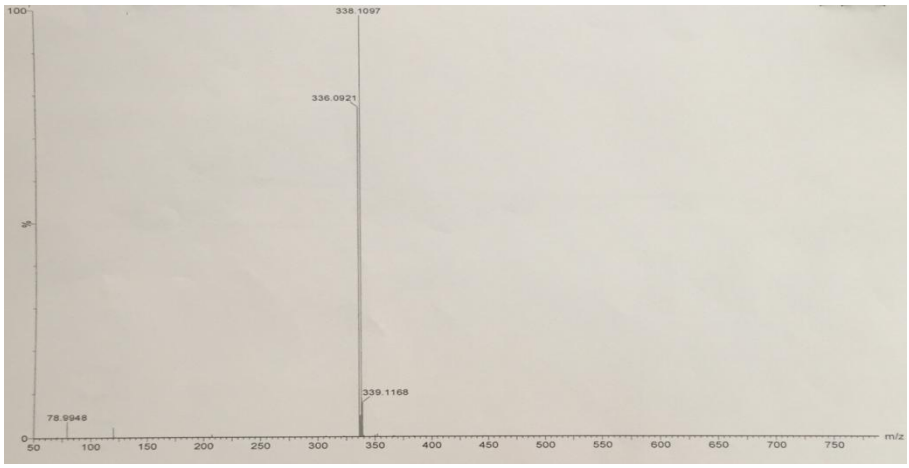

Figure 6: Mass Spectra of Berberine

Calculated (m+1) m/z value for the compound $C_{20}H_{18}NO_4$ is 337.3739, obtained value is **336.0921** (Figure 6)

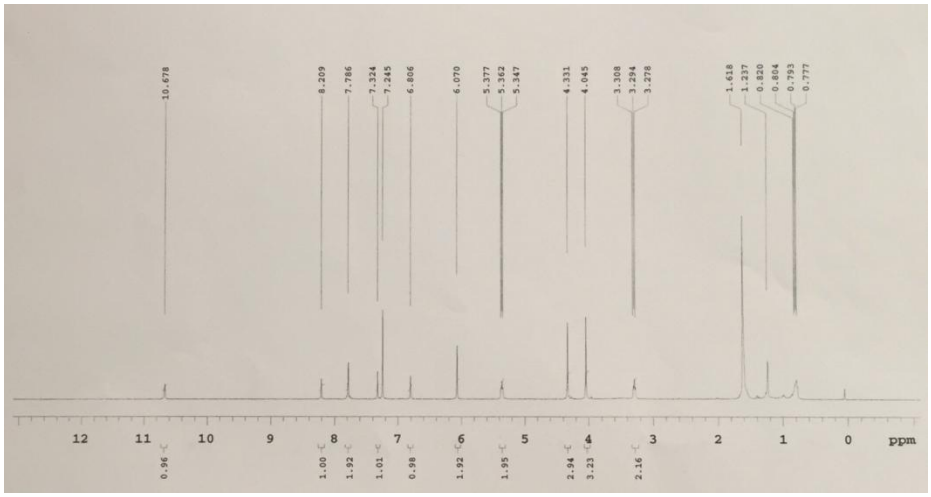

Figure 7: Proton NMR or ^{1}HNMR

^{1}HNMR: (400 MHz, CdCl3): *δ* 10.67 (s, 1H, ArH), 8.21 (s, 1H,ArH), 7.79 (s, 2H, ArH), 7.32 (s, 1H, ArH), 6.81 (s, 1H, ArH), 6.07 (s, 2H, -CH_2-), 5.36 (t, *J* = 6.0 Hz, 2H, -CH_2-), 4.33 (s, 3H, -OMe), 4.04(s, 3H, -OMe), 3.29 (t, *J* = 6.4 Hz, 2H, -CH_2-), total 18H, 12H aliphatic compound, 06 aromatic compounds (Figure 7).

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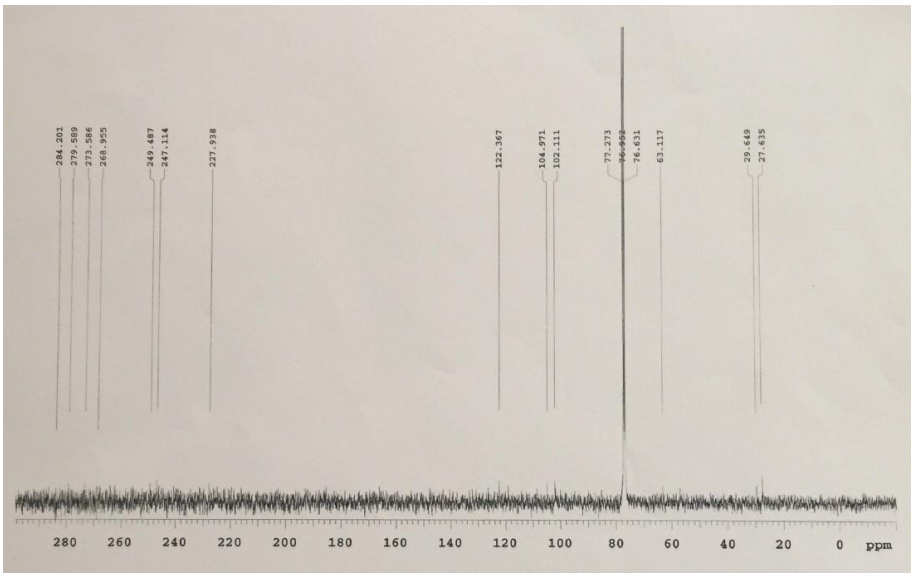

Figure 8: C^{13} NMR

C^{13} NMR: Aromatic-15 Carbon, aliphatic-05 Carbon (Figure 8)

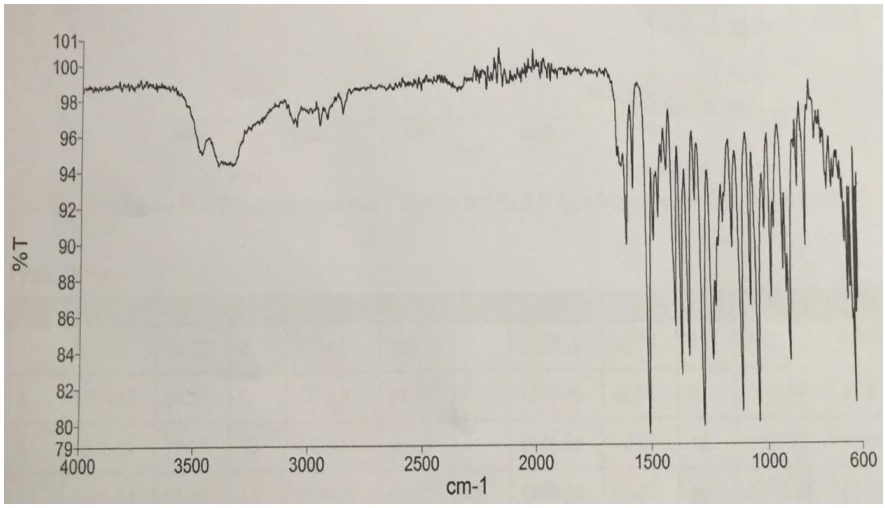

Figure 9: IR spectroscopy of Berberine

Table 2: Peak Table of IR Spectroscopy of Berberine

Peak	X(cm-1)	Y(%)	Peak	X(cm-1)	Y (%)	Peak	X(cm-1)	Y(%)	Peak	X(cm-1)	Y(%)
1	3393.9	94.38	2	2154.5	100.94	3	2138.15	98.75	4	2003.14	100.84
5	1598.52	89.85	6	1578.9	97.57	7	1568.59	92.95	8	1545.66	98.9
9	1505.35	79.36	10	1489.51	94.05	11	1481.03	90.04	12	1467.23	93.86
13	1460.04	91.35	14	1435.23	96.27	15	1423.24	93.97	16	1412.36	97.35
17	1389.42	85.27	18	1376.24	95.23	19	1363.62	82.59	20	1345.92	93.95

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21	1331.54	83.64	22	1311.01	96.08	23	1301.44	92.25	24	1291.31	95.39
25	1271.3	79.79	26	1248.41	93.88	27	1228.83	83.44	28	1188.32	93.04
29	1181.59	91	30	1154.62	95.55	31	1143.35	89.61	32	1127.58	94.92
33	1105.77	80.58	34	1080.5	95.9	35	1065.73	86.38	36	1055.1	94.81
37	1035.22	80.02	38	1011.77	93.61	39	1003.07	90.6	40	987.17	95.84
41	976.69	86.82	42	942.21	96.33	43	924.05	88.36	44	917.72	92.51
45	910.89	87.06	46	906.13	89.11	47	897.66	83.35	48	865.35	96.55
49	859.02	92.9	50	845.05	97.54	51	827.2	89.63	52	801.36	98.78
53	731.87	92.71	54	718.81	95.58	55	711.07	92.84	56	685.76	94.83
57	660.02	89.81	58	656.41	91.93	59	646.68	86.62	60	641.75	92.78
61	637.62	87.33	62	633.77	92.77	63	621.25	81.02	64	615.7	94.97
65	612.01	85.91	66	608.84	92.79	67	605.37	86.65			

IR DATA(cm^{-1}): 3393.9 (– CH), 1598.5 (–C=N), 1578.9 (-C=C), 1376.2 (-CH), 1271.3 (-O-C) (Figure 9)

III. Anti-Bacterial Test

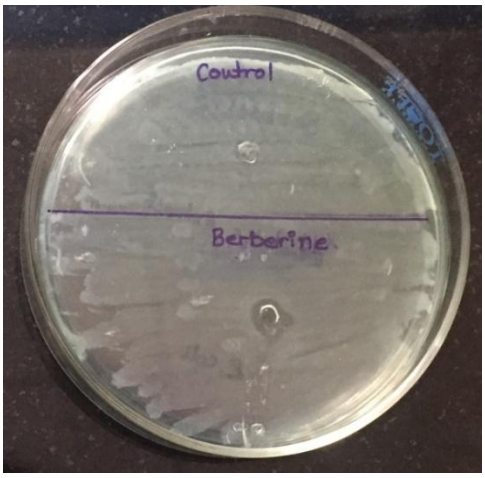

Figure 10: Anti-bacterial Activity of Berberine

IV. *In Silico* analysis of Fts-Z Binding

Interaction of Berberine with cell division protein Fts-Z

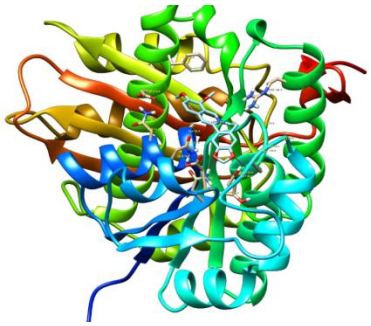

Figure 11: Image Showing Berberine Bound to Cell Division Protein Fts-Z

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Berberine dock very well with Fts-Z protein with 2 Hydrogen bonds (indicating in red color) and also it shows hydrophobic interaction with residues (Figure 11).

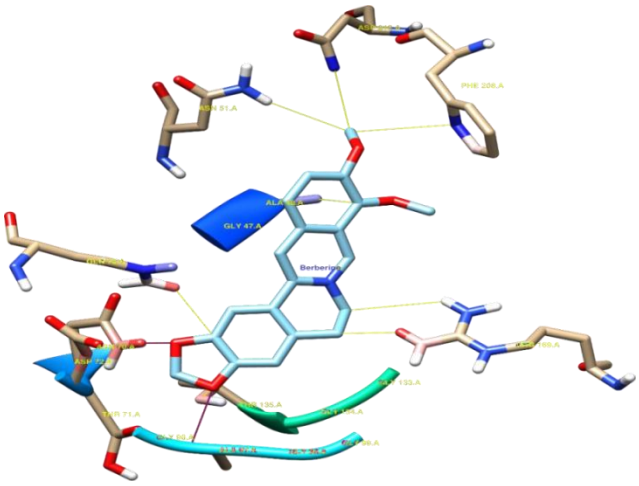

Figure 12: Image Showing Interaction of Berberine with Binding Site Residues

Figure 12 showing interaction of Berberine with binding site residues such as GLY47, ALA48, ASN51, ASN70, THR71, ASP72, GLN75, GLY96, ALA97, GLY98, GLY99, GLY133, GLY134, ARG169, PHE208 and ASP212. Berberine has 16 binding sites with Fts-Z protein. Berberine bind with ASP70 and GLY47 with hydrogen bond, remaining amino acid residues showed hydrophobic interaction.

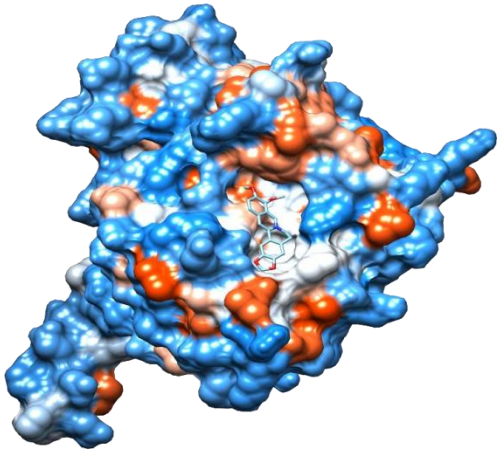

Figure 13: Image Showing Hydrophobic Binding of Berberine in the Binding Pocket of Fts-Z protein

Berberine showed hydrophobic interaction with the binding pocket of Fts-Z (Figure 13). If Berberine shows hydrophilic interaction, it doesn't bind with Fts-Z protein. Berberine form perfect fit inside the binding pocket of Fts-Z.

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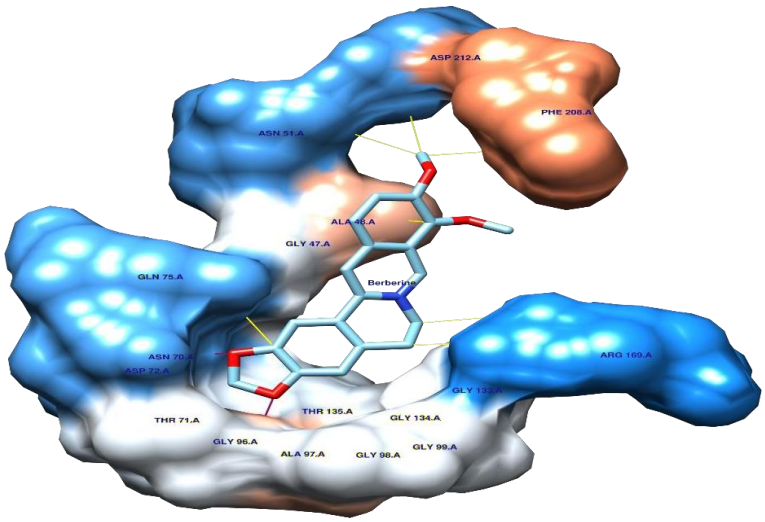

Figure 14: Image Showing Hydrophobic Interaction of Berberine with Binding Site Residues of Fts-Z

Figure 14 is showing that Berberine molecule binds to cell division protein Fts-Z with binding energy -**5.25Kj/mol.**

DISCUSSION

Berberine is a natural plant alkaloid found in several medicinal plants including *Tinospora cordifolia*and has been used in Indian and Chinese medicines having a wide range of pharmacological actions against many diseases [19]. Berberine is one of the main compounds in this plant and its concentration is more in root, stem, and leaves [20]. In this study we have used leaves of *T. cordifolia*; HPLC analysis confirms the presence of Berberine in the methanolic extract of *T. cordifolia*. HPLC analysis showed 55.40% yield of berberine in *T. cordifolia* leaf extract. The isolated compound was structurally determined by LC-MS, NMR, and IR spectroscopy. LC-MS of berberine showed a peak at retention time 5.59 and it was compared with berberine standard. Mass spectra of berberine standard showed 337.3739 and the value of isolated compound was 336.0921. ^{1}H NMR showed a total of 18H, 12H aliphatic compound, 06 aromatic compounds, and C^{13} NMR showed 15 Carbon of romatic, 05 Carbon of aliphatic compounds. An isolated compound called berberine was tested against *E. coli* bacteria to determine the antibacterial activity of berberine. Berberine successfully inhibited the bacterial growth on an agar plate and showed a zone of inhibition. Berberine inhibited the *E. coli* growth by targeting cell division protein called Filamenting temperature-sensitive mutant Z (Fts-Z). Because during bacterial cell division Fts-Z is the first protein to move to the division site and is essential for recreating other proteins that produce new cell walls between dividing cells [21]. In *Escherichia coli*, the Z ring recruits at least ten other proteins, all of which are required for the progression and completion of cytokinesis [22]. Hence berberine may target Fts-Z protein to inhibit bacterial growth. In one of the studies, molecular docking simulations suggested that berberine bind into the C-terminal interdomain cleft of Fts-Z [23]. Hence, we have done the molecular docking study with berberine. We have checked the interaction of berberine with cell division protein Fts-Z. The binding site of the Fts-Z structure was analyzed through ligand explore of the RCSB PDB server. Berberine docks very well with Fts-Z protein with 2H bond and showed hydrophobic interactions with residues. Berberine binds with Fts-Z protein with binding energy -5.25 Kj/mol. Negative values indicate free energy and spontaneity. Higher the value of -10 higher the affinity. If it has a positive value, extra energy would be required for binding. But berberine showed -5.25 Kj/mol hence no need of extra energy to bind.

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CONCLUSION

Berberine is a natural plant alkaloid that can be extracted from different plants including *Tinospora cordifolia. Tinospora cordifolia* is known for its immense application in the treatment of various diseases. Studies suggest that berberine has a "harmonious distribution" into several targets in the body, which allows it to fight certain conditions while causing minimal side effects. Berberine was purified and isolated from methanolic extract of *Tinospora cordifolia;* berberine inhibited the *E. coli* growth by targeting Fts-Z protein. *In silico* analysis of Fts-Z binding concluded that berberine is a good inhibitor of Fts-Z protein. Hence *Tinospora cordifolia* can be used as a source of berberine and berberine can be used as a natural antibiotic.

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