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Research Article

MOLECULAR DOCKING STUDIES AND ADMET PROPERTIES OF COMPOUNDS FROM *PHYSALIS MINIMA* L. LEAVES, ROOT AND FRUIT

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ABSTRACT

Objective: Lung cancer is the most common and fatal disease in the world. The major activity of phytochemicals from plant parts is crucial in finding potential new drug molecules for therapeutic use. The aim of our study was to find drug target for lung adenocarcinoma using the plant parts of *Physalis minima* L. *P. minima* L. is an important medicinal plant of Indian System of Medicine. The *P. minima* L. plant parts which are leaves, root, and fruit have been found to be useful in the treatment of cancer.

Methods: Molecular docking, absorption, distribution, metabolism, excretion, and toxicity studies were performed for those plant compounds to evaluate and analyze the anti-lung cancer activity. Docking experiments were carried out between biocompounds from leaves, Root and Fruit with the target protein (human Mms2/Ubc13 [4ONM]) using Accelry's Discovery Studio 4.0.

Results: Compounds present in leaves and roots were found to have efficient activity against 4ONM. All the compounds had interaction with the target protein out of which hexaethylene glycol monododecyl ether present in leaves had maximum no. of interactions and minimum binding energy. In the root, compound "2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy)" showed maximum no. of interactions with minimum binding energy. Hence, these molecules have been identified as lead.

Conclusion: This study it may be concluded that more compounds from this plant has to be explored for its potential use in lung cancer therapeutics.

Keywords: *Physalis minima* L. Plant parts, Molecular docking, Lung cancer, Lung adenocarcinoma.

INTRODUCTION

The *Physalis minima* L. commonly known as Gooseberry and also as Tottakkali in Tamil. It is an annual herbaceous, upright plant that grows to a height of 15-45 cm and belongs to the family Solanacea. It may be seen growing on the borders of cultivated fields and waste lands [1]. Leaves are used to externally treat yaws and measles. The leaves are used for cattles' stomach complaint and crushed leaves applied over snake bite [2]. *P. minima* L. contains compounds such as phenols and alkaloids, physalins, steroids, and flavonoids [3]. Dihydroxyphysalin B, a new physalin, was extracted from *P. minima* leaves [4]. *P. minima* L. leaves extracts exerted inhibitory properties against human T-47D breast carcinoma cells, inducing apoptotic cell death. These anti-cancer properties and cytotoxic activities were also noticed on NCI-H23 (human lung adenocarcinoma). It is believed that extracts of *P. minima* L. could be used in future to develop anticancer drugs [5-7].

The fruit is edible, yellowish, and encapsulated in papery cover. The fruit is a good source of vitamin C and is considered to be a diuretic, purgative and used to relieve pain (analgesic action) and cure spleen disorder. The root extract decoction is taken to cure fever, headache, stomach trouble, smoke treatment, hypertension, cancer, and diabetes.

Lung cancer cells start to grow in an uncontrolled way and form tumors. Adenocarcinoma is the dominant histological type of lung malignancy in women; thus, it can be stated that gender and risk factors other than cigarette smoking appear to play an important role in the pathogenesis of lung adenocarcinoma. Studies have demonstrated associations between lung adenocarcinoma and a variety of risk factors including cigarette smoking; exposure to cooking fumes, air pollution, second-hand smoke, asbestos, and radon; nutritional status; genetic susceptibility; immunologic dysfunction; tuberculosis infection; asthma. Lung cancer cells spread to distant sites including liver, bone, brain, and other organs. Lung adenocarcinoma is a form of non-small cell lung cancer. Non-small cell lung cancers account for 80% of lung cancers, and of these, roughly 50% are adenocarcinomas.

METHODS

Compounds identified from *Physalis minima* L. leaves, root and fruit

The compounds from *P. minima* L. leaves, root and fruit were taken from Articles, PubChem database, and was analyzed using binding database through which Lung adenocarcinoma was found to be susceptible (current therapeutic target for cancer) (Tables 1-3) [6].

Molecular docking studies

Protein preparation

The molecule taken is (human Mms2/Ubc13) PDB ID -4 ONM, with resolution factor of 1.60Å and the method of incorporation is X-ray diffraction method. The ligand and crystallographic water molecules are removed from the protein, and the chemistry of the protein was corrected for missing hydrogen.

Table 1: Seven compounds identified n the leaves of *Physalis minima* L.

Peak	Retention time	Compound identified	Percentage
1	13.14	Acetamide, 2,2,2-trifluoro-N-methyl-	7.20
2	30.28	2-Cyclopenten-1-one, 2-methyl-	3.83
3	36.20	Phytol	17.88
4	40.50	n-Hexadecanoic acid	29.81
5	43.76	Octadec-9-enoic acid	3.55
6	45.05	Hexaethylene glycol monododecyl ether	5.60
7	45.36	9,12,15-Octadecatrienoic acid, (Z, Z, Z)	14.63

Ligand preparation

The compounds were taken from articles containing gas chromatography-mass spectrometry analysis results of leaves, root and fruit from *P. minima* L. Hydrogen bonds were added, and the energy was minimized using CHARMm force field. Lipinski properties such as AlogP98, blood brain barrier, CYP2D6 and polar surface area for the compounds were obtained while assessing absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties (Tables 4-6).

RESULTS AND DISCUSSION

The retrieved crystal structure from (PDB ID 4ONM) has the structural weight as 16779.4. This protein is a homodimer with two chains, namely, A and B. Each chain has 149 amino acid residues. Different compounds (ligands) from the plants' leaves, root and fruit were docked with the lung cancer proteins' target residues out of which one compound from each plant part showed the best interaction with the active site receptors. Docked pose of the different compounds with protein is presented in Figs. 1-3. The ADMET properties of the compounds with analyzed results is described in Figs. 4-6. The values of the compounds include Cdocker Energy, Lig score 1 and 2, piecewise linear potential (PLP) - PLP1 and PLP 2, Jain, potential of mean force - (PMF) presented in Tables 7-9. The LibDock score, binding energy, hydrogen bond

Table 2: Four compounds identified in the root of *Physalis minima* L.

Peak	Retention time	Compound identified	Percentage
1	40.50	n-Hexadecanoic acid	4.06
2	45.17	2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy)	1.43
3	59.30	O-Methyl-DL-serine, N-dimethylaminomethylene-, ethyl ester	63.20
4	59.47	Ethyl dl-(1-naphthyl) glycolate	4.94

Table 3: Seven compounds identified in the fruit of *Physalis minima* L.

Peak	Retention time	Compound identified	Percentage
1	13.16	Acetamide, 2,2,2-trifluoro-N-methyl-	3.90
2	30.26	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	8.40
3	34.22	5-Hydroxymethylfurfural	14.07
4	39.55	(Z)-3-Phenyl-2-propenoic acid	3.33
5	43.38	Octadecanoic acid	3.35
6	45.07	2-Isopropoxyethyl propionate	9.28
7	45.35	9,12,15-Octadecatrienoic acid, (Z, Z, Z)-	3.47

Table 4: Physiochemical properties of leaves compounds identified in *Physalis minima* L.

Compound name	Alogp98	BBB*	CYP2D6	PSA[1]
Acetamide, 2,2,2-trifluoro-N-methyl-	0.462	2	–6.59687	30.111
2-Cyclopenten-1-one, 2-methyl-	1.281	2	–2.9027	17.3
Phytol	7.337	4	–1.06037	20.815
n-Hexadecanoic acid	4.918	0	0.924467	34.601
Octadec-9-enoic acid	5.386	0	1.55352	34.601
Hexaethylene glycol monododecyl ether	3.834	2	2.45614	74.396
9,12,15-Octadecatrienoic acid, (Z, Z, Z)	4.497	1	0.915842	34.601

*BBB: Blood brain barrier, [1]PSA: Polar surface area

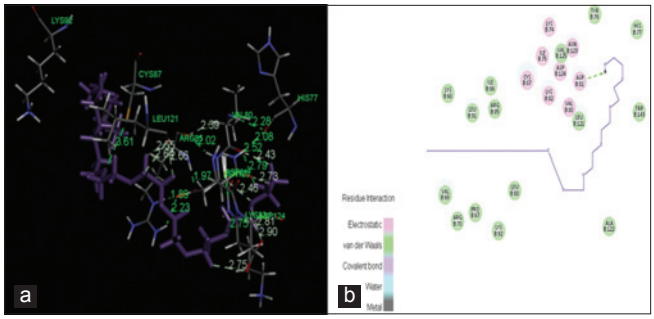

Fig. 1: (a) *Physalis minima* L. Leaves docked pose of compound (hexaethylene glycol monododecyl ether) with lung cancer. (b) Leaves compound of 2D diagram

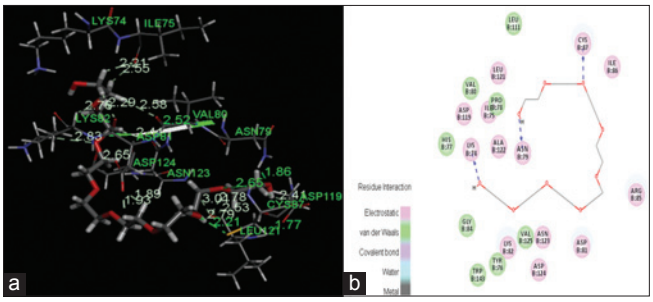

Fig. 2: (a) *Physalis minima* L. root docked pose of compound (2-[2-[2-[2-[2-[2-[2-[2-(2-hydroxyethoxy) with lung cancer. (b) Root compound of 2D diagram

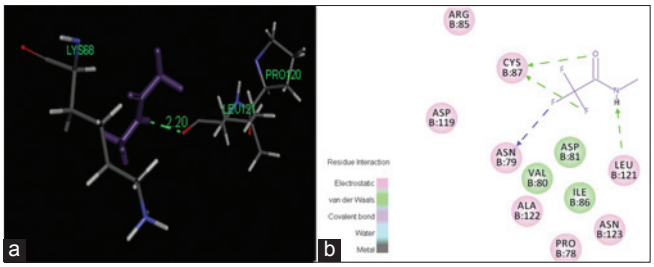

Fig. 3: (a) *Physalis minima* L. fruit docked pose of compound (acetamide, 2, 2, 2-trifluoro-N-methyl-) with lung cancer. (b) Fruit compound of 2D diagram

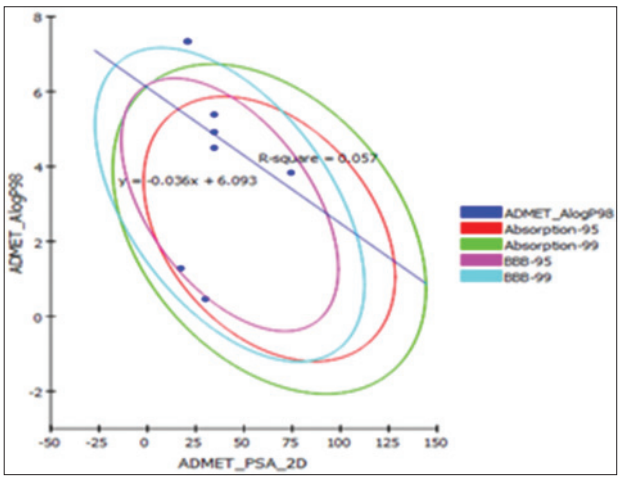

Fig. 4: Absorption, distribution, metabolism, excretion, and toxicity properties of bioactive compounds from *Physalis minima* L. leaves

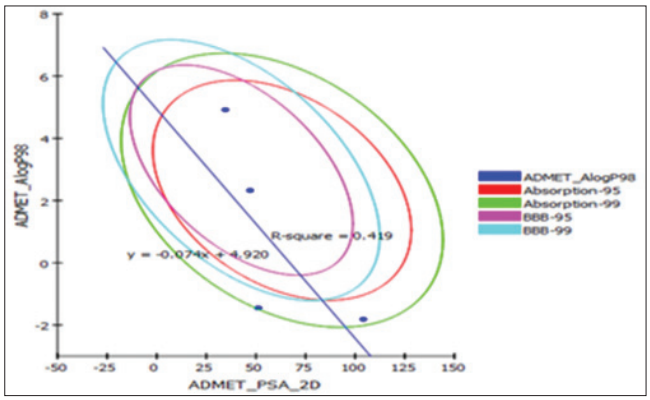

Fig. 5: Absorption, distribution, metabolism, excretion, and toxicity properties of bioactive compounds from *Physalis minima* L. root

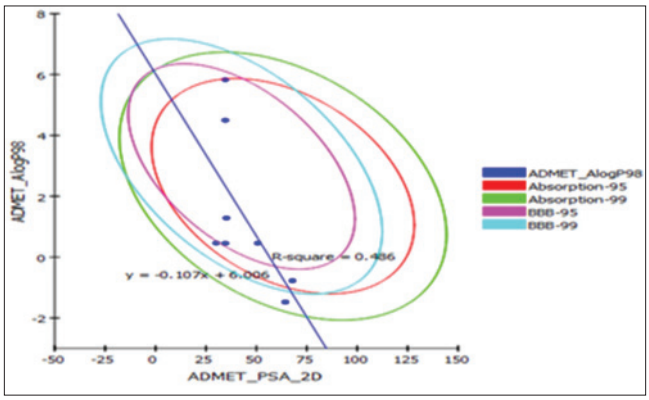

Fig. 6: Absorption, distribution, metabolism, excretion, and toxicity properties of bioactive compounds from *Physalis minima* L. fruit

Table 5: Physiochemical properties of root compounds identified in *Physalis minima* L.

Compound name	Alogp98	BBB	CYP2D6	PSA
n-Hexadecanoic acid	4.918	0	0.924467	34.601
2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy)	−1.814	4	−0.23333	104.141
O-Methyl-DL-serine, N-dimethylaminomethylene-, ethyl ester	−1.453	4	−4.60316	51.175
Ethyl dl-(1-naphthyl) glycolate	2.325	2	0.697339	47.046

PSA: Polar surface area, BBB: Blood brain barrier

Table 6: Physiochemical properties of fruit compounds identified in *Physalis minima* L.

Compound name	Alogp98	BBB	CYP2D6	PSA
Acetamide, 2,2,2-trifluoro-N-methyl-	0.462	2	−6.59687	30.111
4H-Pyran-4-one, 2,3-dihydro-3, 5-dihydroxy-6-methyl-	−0.775	3	−7.56977	67.861
5-Hydroxymethylfurfural	0.458	3	−6.7906	50.67
(Z)-3-Phenyl-2-propenoic acid	0.453	3	−6.41932	34.601
Octadecanoic acid	5.831	0	1.32951	34.601
2-Isopropoxyethyl propionate	1.283	2	−4.86727	35.16
9,12,15-Octadecatrienoic acid, (Z, Z, Z)-	4.497	1	0.915842	34.601

PSA: Polar surface area, BBB: Blood brain barrier

Table 7: *Physalis minima* L. leaves results for protein-ligand interaction

Name	-C Docker energy	Ligscore 1	Ligscore 2	-PLP 1	-PLP 2	Jain	-PMF
Acetamide, 2,2,2-trifluoro-N-methyl-	13.911	1.86	3.23	18.29	30.18	−0.68	−36.56
2-Cyclopenten-1-one, 2-methyl-	−6.99	−0.03	1.76	33.91	28.74	1.63	−14.59
Phytol	−3.785	2.19	3.93	35.02	38.94	−1.33	28.88
n-Hexadecanoic acid	34.12	0.68	2.15	38.68	37.99	0.38	−0.66
Octadec-9-enoic acid	17.142	2.6	2.97	65.64	64.58	2.32	19.79
Hexaethylene glycol monododecyl ether	43.178	2.81	3.77	84.09	77.73	0.02	57.99
9,12,15-Octadecatrienoic acid, (Z, Z, Z)	−9.954	2.22	3.83	58.7	53.32	−0.03	5.87

PMF: Potential of mean force, PLP: Piecewise linear potential

Table 8: *Physalis minima* L. root results for protein-ligand interaction

Name	-C Docker energy	Ligscore 1	Ligscore 2	-PLP 1	-PLP 2	Jain	-PMF
n-Hexadecanoic acid	35.131	1.23	3.19	49.85	47.23	0.13	-8.59
2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy)	44.496	3.04	3.06	103.09	93.32	3.61	45.14
O-Methyl-DL-serine, N-dimethylaminomethylene-, ethyl ester	36.118	1.39	3.48	30.63	28.5	0.34	48.79
Ethyl dl-(1-naphthyl) glycolate	4.507	1.60	3.37	46.69	47.5	1.81	50.13

PMF: Potential of mean force, PLP: Piecewise linear potential

interaction, and distance obtained using the LigandFit protocol of Discovery Studio 4.0 is presented in Tables 10-12, respectively.

The ligands (Hex ethylene glycol monododecyl ether, 2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy), Acetamide, 2,2,2-trifluoro-N-methyl) from leaves, root and fruit, respectively, showed the highest dock score and hydrogen bond interaction with lung cancer protein target when compared to other ligands.

To ensure that the ligand orientation obtained from the docking studies was likely to represent valid and reasonable binding modes of the inhibitors, the ligand fit program docking parameters had to be first

Table 9: *Physalis minima* L. fruit results for protein-ligand interaction

Name	-C Docker energy	Ligscore 1	Ligscore 2	-PLP 1	-PLP 2	Jain	-PMF
Acetamide, 2,2,2-trifluoro-N-methyl-	9.97	2.28	1.82	16.42	30.67	0.32	–46.33
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	–9.425	–1.65	–5.68	–14.29	–2.06	2.26	–56.29
5-Hydroxymethyl furfural	22.622	2.95	3.46	53.08	55.38	2.13	35.02
(Z)-3-Phenyl-2-propenoic acid	5.017	1.57	2.82	28.43	25.99	0.42	–13.58
Octadecanoic acid	35.529	1.04	2.43	24.61	29.65	–0.85	–2.12
2-Isopropoxyethyl propionate	19.388	1.46	2.63	41.89	39.93	3.25	–19.47
9,12,15-Octadecatrienoic acid, (Z, Z, Z)-	–12.581	0.65	1.75	29.8	24.4	–0.18	–11.89

PMF: Potential of mean force, PLP: Piecewise linear potential

Table 10: *Physalis minima* L. leaves results for hydrogen bond interaction

Name	Lib dock score	Binding energy	Hydrogen bond interaction	Distance (Å)
Acetamide, 2,2,2-Trifluoro-N-Methyl-	46.31	–27.3894	[CYS87] N-H…F	2.86
			N-H…O [LEU121]	2.17
			[ASN123] N-H…F	2.69
			[VAL80] C-H…O	2.86
			[ASP81] N-H…F	2.58
2-Cyclopenten-1-One, 2-Methyl-	46.853	14.9959	[ASN123] N-H…O	2.44
			[ASN123] N-H…O	2.65
Phytol	56.072	–29.181	[ARG85] C-H…O	2.59
N-Hexadecanoic acid	69.449	35.1038	[ASN123] N-H…O	2.65
			[ASN123] N-H…O	2.45
			[VAL80] C-H…O	2.95
			[ASP81] N-H…O	2.68
Octadec-9-Enoic acid	80.951	44.8594	[CYS87] N-H…O	2.91
Hexaethylene glycol monododecyl ether	93.074	–58.9886	[CYS87] C-S…O	3.61
			C-H…O [LEU121]	2.66
			C-H…O [LEU121]	2.55
			C-H…O [LEU121]	2.64
			C-H…O [ASP124]	2.75
			C-H…O [ASP124]	2.81
			C-H…O [ASP124]	2.90
			[ASP81] C-H…O	2.46
			O-H…O [VAL80]	2.79
			C-H…O [VAL80]	2.43
9,12,15-Octadecatrienoic acid, (Z, Z, Z)	80.133	18.382	[ASN123] N-H…O	2.37
			[CYS87] N-H…O	2.72

Table 11: *Physalis minima* L. root results for hydrogen bond interaction

Name	Lib dock score	Binding energy	Hydrogen bond interaction	Distance (Å)
n-Hexadecanoic acid	59.951	29.6487	[ASP81] N-H…O	2.78
			[ASN123] N-H…O	2.31
			[ASN123] N-H…O	2.97
			[ASN79] C-H…O	2.66
2-[2-[2-[2-[2-[2-[2-(2-Hydroxyethoxy)	72.197	–60.324	C-H…. O [ASP124]	2.65
			[LYS82] C-H…O	2.83
			C-H…O [ASN123]	2.41
			[LYS82] C-H…O	2.76
			C-H…O [ASP81]	2.29
			C-H…O [ASP81]	1.93
			C-H…O [ASP81]	1.89
			C-H…O [VAL80]	2.58
			C-H…O [ILE75]	2.55
			C-H…O [ILE75]	2.21
			C-H…0 [LEU121]	2.78
			C-H…0 [LEU121]	3.01
			C-H…0 [LEU121]	2.79
			C-H…0 [LEU121]	2.51
			[ASN79] N-H…O	1.86
			[CYS87] C-S…O	2.21

(Contd)…

Table 11: ***(Continued)...***

Name	Lib dock score	Binding energy	Hydrogen bond interaction	Distance (Å)
O-Methyl-DL-serine, N-dimethylaminomethylene-, ethyl ester	49.028	–248.983	N-H…O [ASP119]	1.92
			C-H… [ASP119]	2.56
			C-H…O [CYS87]	2.48
			C-H…O [CYS87]	2.67
			C-H…O [CYS87]	2.46
			C-H…O [CYS87]	2.56
Ethyl dl-(1-naphthyl) glycolate	55.563	–62.6901	C-H…O [ASP124]	2.46
			C-H…O [ASP124]	2.68
			C-H…O [ASN123]	2.16
			[LYS82] N-H…O	1.83

Table 12: ***Physalis minima*** **L. fruit results for hydrogen bond interaction**

Name	Lib dock score	Binding energy	Hydrogen bond interaction	Distance (Å)
Acetamide, 2,2,2-trifluoro-N-methyl-	38.748	45.5103	N-H….O (LEU 121)	2.20
4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	44.284	81.324	-	-
5-Hydroxymethyl furfural	63.119	–18.6036	-	-
(Z)-3-Phenyl-2-propenoic acid	45.408	68.7172	-	-
Octadecanoic acid	74.178	27.2618	-	-
2-Isopropoxyethyl propionate	48.697	9.3247	-	-
9,12,15-Octadecatrienoic acid, (Z, Z, Z)-	70.004	85.5707	-	-

validated for the crystal structure's active site. Protein utilities and health protocol of Discovery Studio was used to find out if the active site contains amino acids such as PRO 78, ASN 79, VAL 80, ASP 81, ARG 85, ILE 86, CYS 87, LEU 121, ALA 122, ASN 123. Results of docking showed that the compound binds to the active site residue which indicates that these compounds can inhibit the lung cancer protein. Further clinical trials are required to validate these compounds.

CONCLUSION

Discovery studio offers variety of features in the drug discovery process. Molecular docking gives the promising contributions in identification and optimization of protein and ligand interactions. The combination of the chemical information of the plant product under study with docking-based virtual screening plays an important role as more and more new potential targets emerge from the functional genomics studies. The present study indicates that the bioactive compounds from *P. minima* L. plant parts shows a strong affinity toward lung cancer protein target. Thus, this study is a step taken to unravel the potential of the compounds from roots, leaves and fruits against lung cancer. Looking into results obtained during the present study it may be concluded that more compounds from this plant has to be explored for its potential use in cancer therapeutics.

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REFERENCES

1. Angamuthu J, Ganapathy M, Evanjelene VK, Ayyavuv N, Padamanabhan V. Evaluation of phytochemical analysis and antimicrobial activity of leaf and fruit extract of *Physalis minima*. Int J Emerg Technol Adv Eng 2014;4(1):462-5.
2. Chothani DL, Vaghasiya HU. A phyto-pharmalogical overview of *Physalis minima* Linn A phyto-pharmalogical overview of *Physalis minima* Linn. Indian J Nat Prod Resourc 2012;3(4):477-82.
3. Nathiya M, Dorcus D. Preliminary phytochemical and anti-bacterial studies on *Physalis minima* Linn. Int J Curr Sci 2012;???:24-30.
4. Khan MA, Khan H, Khan S, Mahmood T, Khan PM, Jabar A. Anti-inflammatory, analgesic and antipyretic activities of *Physalis minima* Linn. J Enzyme Inhib Med Chem 2009;24:632-7.
5. Karpagasundari C, Kulothungan S. ???. J Med Plants Stud 2014;2(4):59-64.
6. Subhashini V, Swamy AV. ???. Int J Innov Res Sci Eng Technol 2013;(2):9.
7. Shariff N, Sudarshana MS. Antimicrobial activity of *Rauvolfia tetraphylla* and *Physalis minima* leaf and callus extracts. Afr J Biotechnol 2006;5(10):946-50.