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Original Article

Fifty Selected Phytoconstituents of *Datura metel* (Indian Thorn Apple) as Anti-Inflammatory Agents: An *in silico* Study

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ABSTRACT

Background and Objectives: *Datura metel* (Indian thorn apple) has been known for various biological activities. In the present investigation, we aimed to study fifty chosen phytoconstituents of *D. metel* (Indian thorn apple) as potent inhibitory agents of Human Neutrophil Elastase (hNE), Human Matrix Metalloproteinase 2 (hMMP 2) and Human Matrix Metalloproteinase 9 (hMMP 9) using docking approach. **Materials and Methods:** The fifty chosen constituents of *D. metel* (Indian thorn apple) were studied on the docking behaviour of hNE, hMMP 2 and hMMP 9 by using the Swiss dock method. **Results:** The docking investigation showed that Daturametelin F, Daturafoliside F and Daturametelin B of *D. metel* (Indian thorn apple) has exhibited the maximum binding energy (-8.85, -9.56 and -9.53 kcal/mol) with the hNE, hMMP 2 and hMMP 9 respectively. **Conclusion:** Thus, the present finding gives new information about the fifty selected ligands of *D. metel* (Indian thorn apple) as potent inhibitory agents of human neutrophil elastase (hNE), Human Matrix Metalloproteinase 2 (hMMP 2) and Human Matrix Metalloproteinase 9 (hMMP 9), which will help in managing cancer, inflammation, photo-aging and wounds.

Keywords: *Datura metel*, Indian Thorn Apple, Human Neutrophil Elastase, Human Matrix Metalloproteinase 2 and 9, Daturametelin F, Daturafoliside F, Daturametelin B.

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INTRODUCTION

Datura metel (Indian thorn apple) belongs to Solanaceae (potato) family and is commonly distributed throughout the world.[1] Till date fourteen *Datura* species have been reported these includes *Datura ceratocaula, Datura discolor, Datura ferox, Datura inoxia, Datura kymatocarpa, Datura lanosa, Datura leichhardtii, Datura metel, Datura pruinosa, Datura quercifolia, Datura reburra, Datura stramonium, Datura velutinosa*, and *Datura wrightii*.[2,3]

Among above mentioned *Datura* species, *Datura metel* (Indian thorn apple) is one the well-known species used in the Indian traditional (Ayurveda) medicine.[1,4] The vernacular names for *Datura metel* (Indian thorn apple) are "Dhutura" in Bengali, "Jozmathel" in Arabic, "Yang Jinhua" in Chinese, "Sadadhatura" in Hindi, "Huindogmaipul" in Korean, "Burbiaca" in Portuguese, "Buriadora" in Spanish and "Indisk Spikklubba" in Sweden.[4,5]

Different plant parts of *Datura metel* (Indian thorn apple) are traditional used as follows i) leaves are used to relieve pain; ii) flowers are used to treat skin inflammation and psoriasis; iii) dried flowers are used for smoking; iv) seeds are used as sedative agent; v) whole plant is used for treating asthma; vi) plant extracts are used as anesthesia agent and to treat chronic bronchitis.[4]

Datura metel (Indian thorn apple) has been reported to possess various pharmacological activities such as i) analgesic, ii) anti-bacterial, iii) anti-cancer, iv) anti-diabetic, v) anti-fertility, vi) anti-fungal, vii) anti-gout, viii) anti-inflammatory, ix) anti-microbial, x) anti-nociceptive, xi) anti-neuroinflammatory, xii) anti-oxidant, xiii) anti-proliferative, xiv) anti-psoriasis, xv) anti-spasmodic, xvi) anti-viral, xvii) herbicidal, xviii) insecticidal, xix) neuroprotective and xx) wound healing.[4,5]

The previous reports engaged us to carry out the present investigation on fifty chosen constituents which includes Daturafoliside A-I; Daturafoliside K-P; Daturafoliside R-W; Daturametelin A-G; Daturametelin I, J; Baimantuoluoside A-H; Baimantuoluoside J; Baimantuoluoline A, C, D, E, K; Daturataturin A; Hyoscyamilactol; Acnistoferin; Atropine; Scopolamine and Hyoscyamine.

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These above said *Datura metel* (Indian thorn apple) phytoconstituents were aimed to investigate on the docking analysis of Human Neutrophil Elastase (hNE), Human Matrix Metalloproteinase 2 (hMMP 2) and Human Matrix Metalloproteinase 9 (hMMP 9) by using the swissdock method.

MATERIALS AND METHODS

Ligand preparation

The chemical structures of fifty (Indian thorn apple) ligands namely 1) Daturafoliside A (CID 102139042); 2) Daturafoliside B (CID 102139043); 3) Daturafoliside C (CID 102139044); 4) Daturafoliside D (CID 102139045); 5) Daturafoliside E (CID 102139046); 6) Daturafoliside F (CID 102139047); 7) Daturafoliside G (CID 102139048); 8) Daturafoliside H (CID 102139049); 9) Daturafoliside I (CID 102139050); 10) Daturafoliside K◊; 11) Daturafoliside L◊; 12) Daturafoliside M◊; 13) Daturafoliside N◊; 14) Daturafoliside O◊; 15) Daturafoliside P◊; 16) Daturafoliside R◊; 17) Daturafoliside S◊; 18) Daturafoliside T◊; 19) Daturafoliside U◊; 20) Daturafoliside V◊; 21) Daturafoliside W◊; 22) Daturametelin A (CID 101592187); 23) Daturametelin B (CID 11968398); 24) Daturametelin C (CID 11762427); 25) Daturametelin D (CID 101588714); 26) Daturametelin E (CID 5316311); 27) Daturametelin F (CID 5316312); 28) Daturametelin G-AC (CID 11968399); 29) Daturametelin I (CID 91895479); 30) Daturametelin J (CID 102139051); 31) Baimantuoluoside A (CID 101482744); 32) Baimantuoluoside B (CID 101482745); 33) Baimantuoluoside C (CID 101482746); 34) Baimantuoluoside D◊; 35) Baimantuoluoside E◊; 36) Baimantuoluoside F◊; 37) Baimantuoluoside G◊; 38) Baimantuoluoside H (CID 102236867); 39) Baimantuoluoside J◊; 40) Baimantuoluoline A (CID 101434809); 41) Baimantuoluoline C (CID 101434811); 42) Baimantuoluoline D (CID 101862358); 43) Baimantuoluoline E (CID 101862359); 44) Baimantuoluoline K (CID 102236868); 45) Daturataturin A (CID 146156957); 46) Hyoscyamilactol (CID 100942617); 47) Acnistoferin (CID 268947); 48) Atropine (CID 174174); 49) Scopolamine (CID 3000322) and 50) Hyoscyamine (CID 637577) were downloaded from PubChem compound database. The unavailable◊ Indian thorn apple ligands structures were drawn and prepared by using ChemDraw 2D and 3D software tools.[6,7] Thus, these prepared three-dimensional structures were used for further studies (swissdock).

Preparation of target enzymes

The three-dimensional (3-D) structure of human neutrophil elastase [hNE] (PDB◘ ID: 1H1B with a resolution of 2.0 A°), human matrix metalloproteinase 2 [hMMP 2] (PDB◘ ID: 1QIB with a resolution of 2.80 A°) and human matrix metalloproteinase 9 [hMMP 9] (PDB◘ ID: 4H1Q with a resolution of 1.59 A°) was downloaded from ◘Protein Data Bank (PDB). 'A' chain of these three enzymes were prepared independently by deleting other chains, ligands, and even the crystallographically observed 'water' (H_2O) molecules by using UCSF Chimera software tool.[8]

Docking study

A docking analysis was carried out for fifty chosen phytoconstituents of *Datura metel* (Indian thorn apple) with three target enzymes (hNE, hMMP 2 and hMMP 9) using the Swissdock free online server.[9] Finally, PyMOL software was utilized to analysis the binding site of best-docked pose for each ligand.[9]

RESULTS

The present Swissdock investigation showed that Daturametelin F has shown the Highest Binding Energy [HBE] (-8.85 kcal/mol) with the Human Neutrophil Elastase (hNE) enzyme. On the other hand, Daturafoliside D has exhibited the minimum binding energy (+103.58 kcal/mol) with the hNE enzyme (Table 1).

In the current study ten ligands (Daturafoliside B, Daturafoliside K, Daturafoliside L, Daturafoliside M, Daturametelin A, Daturametelin D, Daturametelin E, Daturametelin J, Acnistoferin and Hyoscyamine) have shown interactions with Ser195 amino acid residue of Human Neutrophil Elastase (hNE) enzyme (Table 1). Similarly, seven ligands (Daturafoliside C, Daturafoliside P, Daturafoliside R, Daturafoliside S, Daturametelin D, Baimantuoluoside G and Hyoscyamilactol) have shown interactions with His57 amino acid residue of hNE enzyme (Table 1).

The present Swissdock investigation showed that Daturafoliside F has exhibited the Highest Binding Energy [HBE] (-9.56 kcal/mol) with the human matrix metalloproteinase 2 (hMMP 2) enzyme. On the other hand, Daturametelin G has exhibited the minimum binding energy (-6.18 kcal/mol) with the hMMP 2 enzyme (Table 2).

In the present study eleven ligands (Daturafoliside A, Daturafoliside M, Daturafoliside O, Daturafoliside U, Daturafoliside V, Daturafoliside W, Daturametelin D, Daturametelin F, Daturametelin J, Baimantuoluoside C and Baimantuoluoline E) have shown interaction with Gln213 amino acid residue of Human Matrix Metalloproteinase 2 (hMMP 2) enzyme (Table 2). Similarly, three ligands (Daturafoliside D, Daturafoliside P, Baimantuoluoside A) have shown interaction with His211 amino acid residue of hMMP 2 enzyme (Table 2).

The present docking analysis showed that Daturametelin B has exhibited the Maximum Binding Energy [MBE] (-9.53 kcal/mol) with the human matrix metalloproteinase 9 (hMMP 9) enzyme. On the other hand, Daturametelin G has shown the minimum binding energy (-6.11 kcal/mol) with the hMMP 9 enzyme (Table 3).

In the current study eleven ligands (Daturafoliside F, Daturafoliside H, Daturafoliside N, Daturafoliside O, Daturafoliside R, Daturametelin A, Daturametelin J, Baimantuoluoside C, Baimantuoluoside H, Baimantuoluoside J

Table 1: The Swissdock binding energy analysis of 50 selected *Datura metel* (Indian thorn apple) ligands with the Human Neutrophil Elastase (hNE) enzyme using Swissdock method.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (A°)
1	Daturafoliside A	8.08	His25, Arg75, Asn117	3.5, 3,2 and 3.2, 2.1
2	Daturafoliside B	7.52	Arg177, Ser195	3.2, 2.1 and 2.1
3	Daturafoliside C	6.33	His57, Asn61, Pro98	3.4, 2.8, 1.9
4	Daturafoliside D	+103.58	Ile16, Arg20, Asn159, Arg187	2.3, 2.7, 2.8, 3.0
5	Daturafoliside E	8.14	Arg147	3.0 and 3.1
6	Daturafoliside F	8.19	Arg36, Arg65A	3.2, 3.3 and 3.3
7	Daturafoliside G	8.08	His25, Arg75, Asn117	3.5, 3.2 and 3.2, 2.1
8	Daturafoliside H	7.71	No binding	-
9	Daturafoliside I	8.06	Cys58	2.5
10	Daturafoliside K	8.80	Asn61, Arg147, Ser195, Val216	2.6, 3.2, 3.3 and 3.4, 3.3, 2.7
11	Daturafoliside L	7.61	Ser195	3.1
12	Daturafoliside M	7.25	No binding	-
13	Daturafoliside N	7.79	Ser195	3.0 and 3.1
14	Daturafoliside O	7.27	No binding	-
15	Daturafoliside P	8.09	His57, Cys58, Arg147	2.1, 2.7, 3.3
16	Daturafoliside R	8.58	His57	3.2
17	Daturafoliside S	7.72	His57, Asn61	3.3, 3.0
18	Daturafoliside T	7.01	Leu35	2.8
19	Daturafoliside U	6.91	Phe41	2.7
20	Daturafoliside V	Failed to dock	-	-
21	Daturafoliside W	Failed to dock	-	-
22	Daturametelin A	7.19	Asn61, Ser195	3.0 and 3.6, 3.4
23	Daturametelin B	8.32	Arg147, Phe192	3.1, 3.2 and 3.5, 3.1
24	Daturametelin C	7.93	Val216	2.5
25	Daturametelin D	7.27	His57, Arg177, Ser195	3.3, 3.3, 3.1
26	Daturametelin E	8.46	Ser195	3.2
27	Daturametelin F	8.85	Arg147, Cys220	3.3, 2.0
28	Daturametelin G	7.49	Asn62A, Arg63	3.0, 3.3
29	Daturametelin I	6.57	No binding	-
30	Daturametelin J	7.74	Gly193, Ser195	3.3, 3.2 and 3.2
31	Baimantuoluoside A	7.03	Asn61, Val216	2.9, 3.3
32	Baimantuoluoside B	7.19	Leu73, Arg80	2.9, 3.0 and 3.2
33	Baimantuoluoside C	8.12	Arg147	3.1 and 3.4
34	Baimantuoluoside D	7.02	No binding	-
35	Baimantuoluoside E	7.80	Phe41	3.3
36	Baimantuoluoside F	8.09	His40	1.9
37	Baimantuoluoside G	7.27	His57	3.4
38	Baimantuoluoside H	6.97	Val62B, Arg63, Ile88	2.9, 3.3, 3.5
39	Baimantuoluoside J	7.55	Arg23, His25, Ala116, Gln122	3.3 and 3.3, 2.5, 2.2, 3.2

40	Baimantuoluoline A	6.72	Asn99A, Arg177	3.1, 3.5
41	Baimantuoluoline C	6.51	Cys220, Ser222	2.1, 3.1
42	Baimantuoluoline D	7.84	Cys220, Ser222	2.1, 3.1
43	Baimantuoluoline E	7.92	No binding	-
44	Baimantuoluoline K	6.84	No binding	-
45	Daturataturin A	6.67	No binding	-
46	Hyoscyamilactol	6.78	His57	3.4
47	Acnistoferin	6.33	Asn61, Ser195	3.3, 3.5 and 3.5
48	Atropine	7.57	Phe41	3.2
49	Scopolamine	7.86	Arg147	3.0
50	Hyoscyamine	7.07	Ser195	3.1

Table 2: The Swissdock binding energy analysis of 50 selected *Datura metel* (Indian thorn apple) ligands with the Human Matrix Metalloproteinase 2 (hMMP 2) enzyme using Swissdock method.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (A°)
1	Daturafoliside A	8.27	Lys91, Ser212, Gln213, Asp214	3.0, 3.2, 3.0, 3.1
2	Daturafoliside B	8.10	Pro215, Arg233, Leu234	3.3, 2.9, 2.4
3	Daturafoliside C	7.33	Tyr193	2.3
4	Daturafoliside D	8.57	Lys89, Glu210, His211, Glu244	3.1 and 3.2, 1.8, 3.1, 2.0
5	Daturafoliside E	9.19	Lys91	2.9 and 3.2
6	Daturafoliside F	9.56	Arg88, Asp237	3.6, 1.9
7	Daturafoliside G	7.66	His25, Arg75, Asn117	3.5, 3.0 and 3.2, 2.1
8	Daturafoliside H	7.82	Thr229	3.3
9	Daturafoliside I	7.90	Leu234	3.2
10	Daturafoliside K	8.11	Arg88	3.1, 3.2 and 3.4
11	Daturafoliside L	7.66	Asp214, Gln236	1.8, 2.9
12	Daturafoliside M	7.27	Ser212, Gln213, Thr227	2.4, 3.5, 3.2 and 3.4
13	Daturafoliside N	7.31	Gly216, Arg233	3.3, 3.0
14	Daturafoliside O	9.32	Arg88, Lys89, Gln213, Lys240	3.5, 3.4, 3.2, 3.1
15	Daturafoliside P	9.09	Arg88, His211, Asp237	3.0, 3.1 and 3.3, 2.2, 1.8 and 1.9
16	Daturafoliside R	7.94	Gly208	1.9
17	Daturafoliside S	8.58	Lys89, Lys91	1.8, 3.3
18	Daturafoliside T	8.46	Arg88, Lys89, Asp237	3.1, 3.1, 2.3
19	Daturafoliside U	9.15	Arg88, Lys89, Gln213, Asp237	2.9, 3.0 and 3.5, 3.4, 2.0 and 2.1
20	Daturafoliside V	8.28	Asp115, Gln123, Arg233	2.1, 3.0, 3.1
21	Daturafoliside W	9.08	Arg88, Lys89, Lys91, Gln213	2.9, 3.3, 3.5, 2.4
22	Daturametelin A	7.24	Phe132, Arg134	3.3, 3.3
23	Daturametelin B	8.62	Asp237, Glu244	3.1 and 3.3, 2.5
24	Daturametelin C	7.98	Ile222, Thr229	2.7 and 3.1, 3.0 and 3.2
25	Daturametelin D	7.81	Gln213	3.0
26	Daturametelin E	8.15	Glu244	2.4

27	Daturametelin F	8.43	Ser212, Gln213	3.4, 3.6
28	Daturametelin G	6.18	No binding	-
29	Daturametelin I	8.09	Arg88, Lys89	2.9, 3.2
30	Daturametelin J	8.69	Arg88, Ser212, Gln213, Asp237	2.9, 3.2 and 3.5, 3.2, 2.3
31	Baimantuoluoside A	7.64	His211, Ser212, Glu244, Asp237	3.5, 3.4, 3.0, 2.2
32	Baimantuoluoside B	8.68	Arg88, Lys89, Gly208	3.5, 3.1, 3.4
33	Baimantuoluoside C	8.79	Ser212, Gln213, Lys240	3.0 and 3.5, 3.1, 3.2
34	Baimantuoluoside D	9.13	Lys240	3.4
35	Baimantuoluoside E	8.55	Pro215, Gly216, Thr227, Arg233	2.4, 2.3, 3.4, 3.2
36	Baimantuoluoside F	8.53	His40	`1.9
37	Baimantuoluoside G	8.09	Thr227, Gln236	3.6, 3.5
38	Baimantuoluoside H	8.75	Ser212, Asp237, Lys240, Glu244	3.1, 1.9, 2.0 and 2.4, 3.5, 1.9 and 3.0
39	Baimantuoluoside J	7.40	Tyr223	2.8
40	Baimantuoluoline A	8.98	No binding	-
41	Baimantuoluoline C	8.95	Arg88, Lys89, Asp237	3.0, 3.2, 2.0 and 2.5
42	Baimantuoluoline D	8.11	No binding	-
43	Baimantuoluoline E	8.23	Arg88, Lys89, Gln213	2.9, 3.3, 3.2
44	Baimantuoluoline K	8.59	Gly208	2.1
45	Daturataturin A	7.94	Thr229, Arg233	3.4, 2.5
46	Hyoscyamilactol	7.92	Arg88, Lys89, Gly241	2.8, 3.0, 2.5
47	Acnistoferin	6.84	Asn231, Phe232	3.3, 2.0
48	Atropine	7.08	Ser212, Asp237, Glu244	3.6, 1.9 and 2.7, 3.1
49	Scopolamine	6.94	Lys89, Glu210	3.1, 3.1
50	Hyoscyamine	7.07	Ser212, Asp237, Glu244	3.2, 2.6 and 2.7, 3.1

and Baimantuoluoline C) have shown interaction with Ala191 amino acid residue of Human Matrix Metalloproteinase 9 (hMMP 9) enzyme (Table 3). Similarly, three ligands (Daturafoliside M, Daturafoliside P and Baimantuoluoside G) have shown interaction with His226 amino acid residue of hMMP 9 enzyme.

DISCUSSION

According to Hiraoka and co-workers,[10] *Datura metel* plants are cultivated for ornamental purpose which has been reported to possess various varieties like i) alba, ii) fastuosa, iii) rubra, iv) metel, and v) muricata. *Datura metel* has been reported to play a vital role in the Indian traditional systems of medicine as a i) narcotic, ii) anodyne, and iii) anti-spasmodic drug agents which is similar to Belladonna and Stramonium.[4] *Datura metel* (Indian thorn apple) has been reported to inhibit enzymes like i) acetyl cholinesterase;[11] ii) alpha glucosidase;[12] iii) beta secretase; [12] iv) mushroom tyrosinase;[13] and v) xanthine oxidase[14] activities. Recently, Ruksiriwanich and colleagues[15] had reported that *Datura metel* leaf extract (using Supercritical Carbon Dioxide ($scCO_2$) extraction method) showed to suppress the expression of matrix metalloproteinase 2 (MMP 2) activity. Thus, in the present investigation, three target enzymes namely i) Human Neutrophil Elastase (hNE), ii) Human Matrix Metalloproteinase 2 (hMMP 2) and iii) Human Matrix Metalloproteinase 9 (hMMP 9) were chosen for the docking study.

In the current dock study, two Indian thorn apple ligands namely Daturafoliside V and Daturafoliside W fail to dock with the first target enzyme. Moreover, Daturafoliside D has exhibited the minimum binding energy (+103.58 kcal/mol) with the hNE enzyme. This positive (+) binding energy might be due to 'unfavourable affinity' as demonstrated by Castro and colleagues (2009).[16] The chosen *Datura metel* (Indian thorn apple) ligands have shown interaction with Asn61, His57, Arg80, Arg147, Ser195 and Gly193 amino acid residues of Human Neutrophil Elastase (hNE) enzyme. This result showed good correlation with earlier report.[17]

All the chosen *Datura metel* (Indian thorn apple) ligands have docked successful with the second target enzyme (Human Matrix Metalloproteinase 2 (hMMP 2)). Interestingly, eleven Indian thorn apple ligands have shown interaction with Gln213 amino acid residue of hMMP 2 enzyme (Table 2). This result showed good agreement with previous report. [18] Three ligands of Indian thorn apple have shown interaction with His211 amino acid

Table 3: The Swissdock binding energy analysis of 50 selected *Datura metel* (Indian thorn apple) ligands with the Human Matrix Metalloproteinase 9 (hMMP 9) enzyme using Swissdock method.

Sl. No.	Ligand name	Swissdock binding energy (-kcal/mol)	Interactions of amino acids residues	Bond distance (A°)
1	Daturafoliside A	8.07	Trp116, His117, Tyr268	1.9, 2.6 and 3.2, 1.9
2	Daturafoliside B	8.05	Gly186	1.8
3	Daturafoliside C	8.21	Tyr218	3.1 and 3.5
4	Daturafoliside D	8.87	Tyr179, Ala189, Gln227, Tyr248	3.1, 2.2, 3.1, 2.2
5	Daturafoliside E	9.18	Tyr218	3.3
6	Daturafoliside F	8.54	Ala191, Tyr248	3.0, 3.3
7	Daturafoliside G	8.73	Tyr248	3.4
8	Daturafoliside H	8.59	Ala191, Leu234	1.9, 2.3
9	Daturafoliside I	8.41	Pro246, Tyr248	3.2, 3.0
10	Daturafoliside K	8.78	Asp185, Gln227	2.2, 3.0
11	Daturafoliside L	8.69	Gly186, Tyr248	3.0, 3.1
12	Daturafoliside M	8.44	Ala189, His226, His230, His236	1.8, 3.2, 3.4, 3.0
13	Daturafoliside N	8.20	Ala191	3.1 and 3.3
14	Daturafoliside O	8.01	Tyr179, Ala191, Gln227	3.5, 3.2, 3.2
15	Daturafoliside P	8.09	His226, Tyr248	3.1, 3.0
16	Daturafoliside R	8.05	Ala191, Pro246	2.1, 2.4
17	Daturafoliside S	9.23	Tyr179, Tyr248	3.6, 2.9
18	Daturafoliside T	7.90	Tyr218, Tyr248	3.2, 3.2
19	Daturafoliside U	8.56	Gln227, Pro246	3.6, 1.9
20	Daturafoliside V	8.40	Gly186, Tyr218	3.2, 2.1
21	Daturafoliside W	8.92	Gly186, Leu188, Tyr218	2.4, 3.6, 3.3
22	Daturametelin A	7.72	Ala191	2.5
23	Daturametelin B	9.53	Tyr218, Pro246	2.1, 2.6
24	Daturametelin C	8.75	No binding	-
25	Daturametelin D	7.10	Gly215, Gly217	2.9, 3.3
26	Daturametelin E	8.58	No binding	-
27	Daturametelin F	8.46	No binding	-
28	Daturametelin G	6.11	Tyr248	2.8 and 3.3
29	Daturametelin I	7.66	No binding	-
30	Daturametelin J	8.14	Leu188, Ala191, Gln227	3.5, 3.1 and 3.5, 3.0
31	Baimantuoluoside A	6.71	Gly112, Lys115, His117	3.1 and 3.3, 3.2, 2.9 and 3.4
32	Baimantuoluoside B	7.93	No binding	-
33	Baimantuoluoside C	8.19	Gly186, Ala191	3.0, 2.3 and 3.5
34	Baimantuoluoside D	8.33	Leu234	1.9
35	Baimantuoluoside E	7.95	Gly186, Tyr248	3.3, 3.4
36	Baimantuoluoside F	8.91	No binding	-
37	Baimantuoluoside G	8.42	His226, His230, His236, Tyr248	3.4, 3.3, 3.5, 2.0
38	Baimantuoluoside H	8.00	Ala191	3.2

39	Baimantuoluoside J	8.55	Leu188, Ala189, Ala191, Gln227, His230, His236	2.9, 3.1 and 3.5, 3.4, 3.4, 3.2, 3.1
40	Baimantuoluoline A	8.04	Leu188, Ala189	2.9, 3.2 and 3.5
41	Baimantuoluoline C	7.71	Leu188, Ala189, Ala191, His236	2.8, 3.5, 3.3, 3.1
42	Baimantuoluoline D	7.95	No binding	-
43	Baimantuoluoline E	8.22	Tyr248	3.0
44	Baimantuoluoline K	7.75	No binding	-
45	Daturataturin A	7.27	Gln227, Pro246	3.1, 3.3
46	Hyoscyamilactol	7.52	Arg143	3.2 and 3.4
47	Acnistoferin	7.40	No binding	-
48	Atropine	7.09	Gly186	2.6
49	Scopolamine	7.29	Leu256	1.9
50	Hyoscyamine	8.08	Tyr248	3.2 and 3.2

residues of hMMP 2 enzyme. This result showed good correlation with earlier report.[19] Similarly, the chosen *Datura metel* (Indian thorn apple) ligands have shown interaction with Pro215, Gly216, Tyr223 and Thr227 amino acid residues of hMMP 2 enzyme. This result showed good correlation with earlier report.[20]

All the chosen *Datura metel* (Indian thorn apple) ligands have docked successful with the third target enzyme (Human Matrix Metalloproteinase 9 (hMMP 9)). Interestingly, eleven Indian thorn apple ligands have shown interaction with Ala191 amino acid residue of hMMP 9 enzyme (Table 2). This result showed good agreement with previous report.[21] Three ligands of Indian thorn apple have shown interaction with His226 amino acid residues of hMMP 9 enzyme. This result showed good correlation with earlier report.[22] Similarly, the chosen *Datura metel* (Indian thorn apple) ligands have shown interaction with Leu188, Ala189, Gln227 and Tyr248 amino acid residues of hMMP 9 enzyme. This result showed good correlation with earlier report.[23]

The current finding is only based on molecular docking (*in silico*) approach which provides new understanding about the fifty chosen *Datura metel* (Indian thorn apple) constituents and their interactions with three target enzymes namely i) Human Neutrophil Elastase (hNE), ii) Human Matrix Metalloproteinase 2 (hMMP 2) and iii) Human Matrix Metalloproteinase 9 (hMMP 9). However, further *in vitro* enzyme (biochemical) assay studies are needed to confirm their enzyme inhibition activities of chosen Indian thorn apple phytoconstituents.

CONCLUSION

In the present investigation, the fifty chosen *Datura metel* (Indian thorn apple) phytoconstituents have shown the potential to dock with two targeted human enzymes (hMMP 2 and hMMP 9) and two ligands fail to dock with the first target enzyme (hNE) respectively. Moreover, eight ligands of Indian thorn apple (Daturafoliside H, Daturafoliside M, Daturafoliside O, Daturametelin I, Baimantuoluoside D, Baimantuoluoline E, Baimantuoluoline K and Daturataturin A) do not exhibit any interaction with amino acid residues of hNE enzyme. Thus, the present finding give new information about the fifty chosen ligands of *Datura metel* (Indian thorn apple) as potent inhibitory agents of hNE, hMMP 2 and hMMP 9, which will aid in managing cancer, inflammation, photo-aging, and wounds.

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ABBREVIATIONS

hNE: Human Neutrophil Elastase; **hMMP 2:** Human Matrix Metalloproteinase 2; **hMMP 9:** Human Matrix Metalloproteinase 9; **2D:** Two Dimensional; **3D:** Three Dimensional; **PDB:** Protein Data Bank; **HBE:** Highest Binding Energy; **MBE:** Maximum Binding Energy.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

In the present study, fifty chosen constituents of *Datura metel* (Indian thorn apple) were studied on the docking behaviour of Human Neutrophil Elastase (hNE), Human Matrix Metalloproteinase 2 (hMMP 2) and human Matrix Metalloproteinase 9 (hMMP 9) by using the Swiss dock method. The docking investigation showed that Daturametelin F, Daturafoliside F and Daturametelin B of D. metel (Indian thorn apple) has exhibited the maximum binding energy with the hNE, hMMP 2 and hMMP 9 respectively.

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