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Research Article

EVALUATION OF ABORTIFACIENT ACTIVITY OF ROOT OF *LAWSONIA INERMIS* THROUGH *IN SILICO* DOCKING

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ABSTRACT

Objective: *Lawsonia inermis* known as henna is a branched glabrous shrub, belonging to family Lythraceae. To evaluate the abortifacient activity of root of *L. inermis* with progesterone receptor through *in silico* docking.

Methods: The molecular docking analysis of the 41 compounds which is derived from *L. inermis* with the progesterone receptor was carried out using the GOLD software. Further, the plant undergoes absorption, distribution, metabolism and excretion (ADME) analysis, and pharmacokinetic parameters have been done.

Results: The results showed that D-allose is having the highest binding affinity with the progesterone receptor having a GOLD score of 32.08. D-allose present in henna inhibits the activity of progesterone and induces abortion, and it also satisfies ADME parameters.

Conclusion: The findings concluded that *L. inermis* root exhibit abortifacient activity and further studies are suggested to isolate the active principles responsible for the activity.

Keywords: *Lawsonia inermis,* Progesterone receptor, D-Allose, Abortifacient activity, GOLD.

INTRODUCTION

Progesterone is a steroid hormone, plays an important role in pregnancy maintenance, expression of estrus, normal cyclic function, and in hypophyseal gonadal interrelationship. Progesterone, produced from the corpus luteum and in the placenta, is known to be essential for the maintenance of pregnancy. It acts to relax smooth muscle in many organs, including the pregnant uterus. Progesterone has immunosuppressive activity against the activation of T lymphocytes and blocks the effects of oxytocin on myometrium. Perhaps most importantly, progesterone is a potent inhibitor of the formation of gap junction between myometrial cells [1]. These intercellular communications are essential for the propagation of coordinated uterine muscle activity leading to labor. Herbal medicines are in great demand in the developed as well as developing countries for primary healthcare because of their wide biological and medicinal activities, higher safety margins, and lesser costs [2,3]. *Lawsonia inermis* commonly known as Henna or Mehandi are copiously available in tropical and subtropical areas. Arabic history of India depict its various uses and also plays a significant role in Ayurvedic or natural herbal medicines [4]. The plant has been report to have analgesic, hypoglycemic, hepatoprotective, immunostimulant, anti-inflammatory, antibacterial, antimicrobial, antifungal, antiviral, anti-parasitic, anti-trypanosomal, anti-dermatophytic, antioxidant, antifertility, tuberculostatic, and anticancer properties. It is now considered as a valuable source of unique natural products for the development of medicines against various diseases and also for the development of industrial products [5,6]. Traditionally, *L. inermis* state as an abortifacient but logically it is not publicized still thus the present study was intend to assess the abortifacient activity of *L. inermis*.

METHODS

According to gas chromatography-mass, spectrometry report of *L. inermis* root of ethanolic extract possess 41 phytochemicals. These compounds are believed to act as a good inhibitor of the progesterone receptor. The list of phytochemicals identified is shown in Table 1.

Ligand preparation

The chemical structures of all the 41 phytochemicals from *L. inermis* were taken from PubChem database. The two-dimensional structures of the 41 compounds were drawn using ACD Chemsketch (www.acdlabs.com/). The structures were then converted to three-dimensional; their geometries were optimized and saved in "MDL mol file" format.

Protein preparation

The X-ray crystallographic structure of progesterone receptor was obtained from the protein data bank (PDB). The crystal structure available in the PDB database with the PDB ID 1A28 and a resolution of 1.80 Å was taken for the molecular docking analysis. The crystal structure was found to be bound with the compound progesterone. The active site of the progesterone receptor was obtained from the PDBsum database. The Fig. 1 implies protein-chain branching ligand- ball and stick. Fig. 2 implies protein-schematic, ligand - ball and stick. Fig. 3 implies protein-tube, ligand - space full. Fig. 4 implies protein-surface density ligand- ball and stick

Active site identification

The active site of the crystal structure of progesterone receptor was obtained from the PDBsum database.

Molecular docking analysis

Docking approach is used to find the positive interaction at which a ligand binds to the receptor. GOLD is a program for calculating the docking modes of small molecules in protein binding sites and is provided as part of the GOLD Suite, a package of programs for structure visualization and manipulation (Hermes), for protein-ligand docking (GOLD), and for post-processing (GoldMine) and visualization of docking result. Modeling the intermolecular interactions in a ligand-protein complex is difficult because there are so many degrees of freedom and insufficient knowledge of the effect of solvent on the binding association [7].

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis

One of the main factor concerns with drug design is a pharmacokinetic parameter of a drug. The drug with valid absorption, metabolism,

Table 1: Phytochemicals of *L. inermis*

S. No	Name
1	Propanoica acid, 2-hydroxy-, ethyl ester, (S)-
2	Furfural
3	Phenol
4	Pantolactone
5	2,5-Dimethyl-4-hydroxy-3 (2H)-furanone
6	Phenol, 2-methoxy-
7	1-Penten-4-one, 2-acetyl-1-dimethylamino- ((Z)- or (E)-)
8	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-
9	Octanoic acid
10	Benzenecarboxylic acid
11	Dianhydromannitol
12	Isosorbide
13	2-Furancarboxaldehyde, 5-(hydroxymethyl)-
14	2-Methoxy-4-vinylphenol
15	Flucytosine
16	Phenol, 2,6-dimethoxy-
17	Hydroquinone
18	1,4-Naphthalenedione
19	1,4-Benzenediol, 2-methoxy-
20	2-Pyrrolidinecarboxylic acid-5-oxo-, ethyl ester
21	1,2,3-Benzenetriol
22	1,4-Naphthalenediol
23	D-Allose
24	3-Hydroxy-4-methoxybenzoic acid
25	Ethyl á-d-riboside
26	á-D-glucopyranoside, methyl
27	Benzyl benzoate
28	Quinolin-8-amine, 5,6-dimethoxy-4-methyl-
29	5-Amino-7,8-dimethoxyisoquinoline
30	Pentadecanoic acid, ethyl ester
31	3,5-di-tert-Butyl-4-hydroxybenzaldehyde
32	(E)-9-Octadecenoic acid ethyl ester
33	Hexadecanoic acid, ethyl ester
34	1,4-Dihydroxy-3-methylnaphthalene-2-carboxylic acid, methyl ester
35	9-Octadecenoic acid (Z)-, methyl ester
36	Tridecanoic acid, methyl ester
37	9,12-Octadecadienoic acid, ethyl ester
38	9-Octadecenoic acid, ethyl ester
39	6-Octadecenoic acid, (Z)-
40	3-t-Butyl-4,5-diphenyl-1H-pyrazole
41	Benzoic acid, 2-hydroxy-5-iodo-, methyl ester

L. inermis: Lawsonia inermis

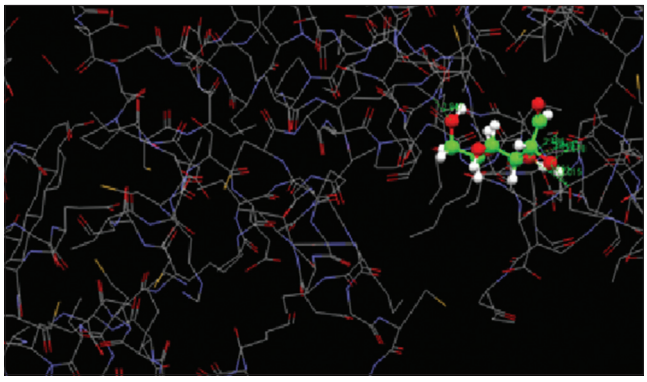

Fig. 1: Docking schematic pattern 1: Protein - chain branching, ligand – ball, and stick

distribution, and excretion/toxicity properties can easily pass through the clinical trials [8]. AdmetSAR is a tool used to evaluate the pharmacokinetic parameters of the compounds. AdmetSAR can predict about 50 ADMET endpoints by our recently development chemoinformatics-based toolbox, entitled ADMET-Simulator, which integrates high quality and predictive QSAR models. AdmetSAR will be helpful for *in silico* screening ADMET profiles of drug candidates

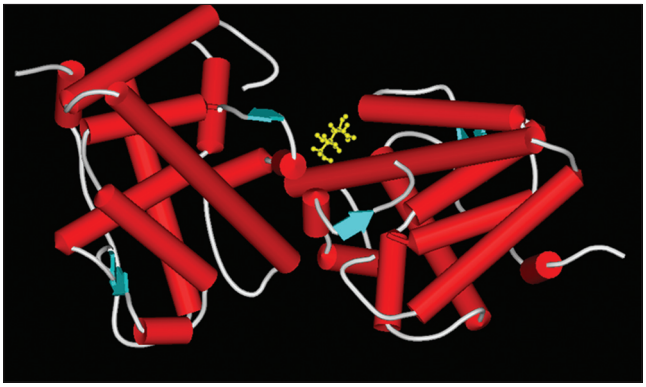

Fig. 2: Docking schematic pattern 2: Protein - schematic, ligand – ball, and stick

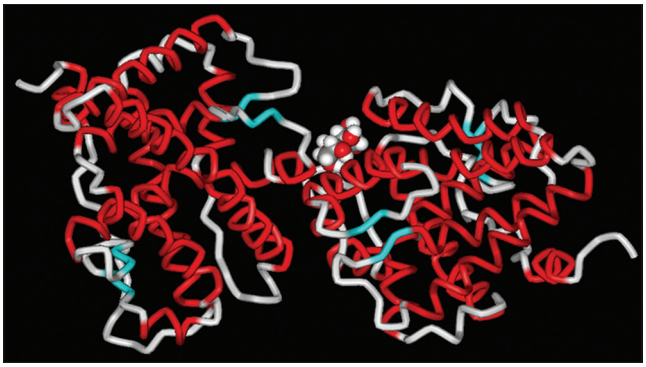

Fig. 3: Docking schematic pattern 3: Protein - tube, ligand – space full

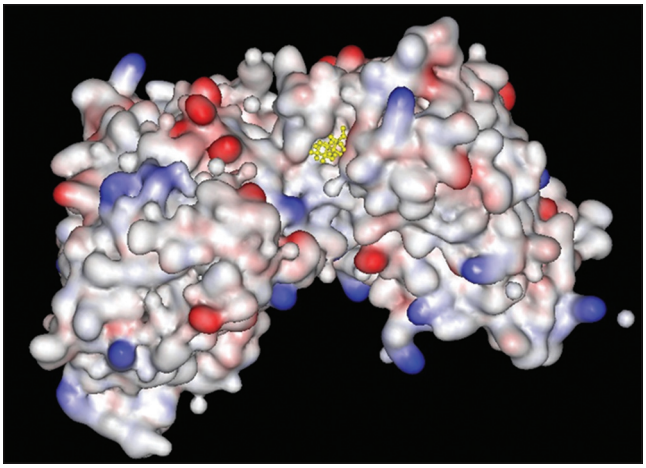

Fig. 4: Docking schematic pattern 4: Protein – surface density, ligand – ball, and stick

and environmental chemicals. AdmetSAR was engaged for the *in silico* screening of ADMET profiles for the active compounds derived from the plant *L. inermis.* The ADMET SAR server predicts the ADMET associated properties of the active compounds for different types of models, all of which shows the positive results [9,10].

RESULTS

Progesterone receptor is the drug target was selected based on a literature survey. The structure of the progesterone receptor was obtained from PDB. The residues involved in the active site are LEU718, ASN719, GLN725, MET759, ARG766, LEU797, MET801, TYR890, CYS891, THR 894, and MET 909 were obtained from PDBsum database.

The molecular docking analysis of the 41 compounds derived from *L. inermis* with the progesterone receptor was carried out using the GOLD software. The result indicates that the compound D-allose with the GOLD score of 35.04 has the highest inhibitory activity to the progesterone receptor. The GOLD score of phytochemicals present in *L. inermis* was shown in Table 2.

ADMET profiling

Absorption

ADMET-associated properties of the active compounds from *L. inermis* for different types of models such as blood-brain barrier (BBB) penetration, P-glycoprotein substrate, renal organic cation transporter, human intestinal absorption, and $Caco_2$ permeability showed positive results for almost all the compounds. The compounds 1,2,3-benzenetriol, 3-hydroxy-4-methoxybenzoic acid, and á-D-glucopyranoside, methyl alone showed negative results for BBB penetration. The compound á-D-glucopyranoside, methyl alone showed negative results for human intestinal absorption. The compounds dianhydromannitol, isosorbide, flucytosine, 2-pyrrolidinecarboxylic acid-5-oxo-, ethyl ester, D-allose, ethyl á-d-riboside, and á-D-glucopyranoside; methyl showed negative results for $Caco_2$ permeability. Table 3 which shows the predicted profile for active compound from L.inermis mainly in absorption.

Table 2: GOLD score of phytochemicals present in *L. inermis*

S. No	Name	GOLD score
1	Propanoic acid, 2-hydroxy-, ethyl ester, (S)-	23.86
2	Furfural	18.12
3	Phenol	21.22
4	Pantolactone	21.06
5	2,5-Dimethyl-4-hydroxy-3(2H)-furanone	24.19
6	Phenol, 2-methoxy-	24.33
7	1-Penten-4-one, 2-acetyl-1-dimethylamino- ((Z)- or (E)-)	11
8	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	24.69
9	Octanoic acid	26.83
10	Benzenecarboxylic acid	21.05
11	Dianhydromannitol	24.01
12	Isosorbide	25.04
13	2-Furancarboxaldehyde, 5-(hydroxymethyl)-	25.88
14	2-Methoxy-4-vinylphenol	26.33
15	Flucytosine	24.26
16	Phenol, 2,6-dimethoxy-	26.95
17	Hydroquinone	22.08
18	1,4-Naphthalenedione	23.76
19	1,4-Benzenediol, 2-methoxy-	24.68
20	2-Pyrrolidinecarboxylic acid-5-oxo-, ethyl ester	28.34
21	1,2,3-Benzenetriol	28.62
22	1,4-Naphthalenediol	29.13
23	D-Allose	35.04
24	3-Hydroxy-4-methoxybenzoic acid	26.36
25	Ethyl á-d-riboside	28.05
26	á-D-glucopyranoside, methyl	32.8
27	Benzyl benzoate	30.07
28	Quinolin-8-amine, 5,6-dimethoxy-4-methyl-	19.4
29	5-Amino-7,8-dimethoxyisoquinoline	28.37
30	Pentadecanoic acid, ethyl ester	18.34
31	3,5-di-tert-Butyl-4-hydroxybenzaldehyde	−0.18
32	(E)-9-Octadecenoic acid ethyl ester	25.7
33	Hexadecanoic acid, ethyl ester	14.88
34	1,4-Dihydroxy-3-methylnaphthalene-2-carboxylic acid, methyl ester	27.52
35	9-Octadecenoic acid (Z)-, methyl ester	10.46
36	Tridecanoic acid, methyl ester	19.74
37	9,12-Octadecadienoic acid, ethyl ester	25.74
38	9-Octadecenoic acid, ethyl ester	22.83
39	6-Octadecenoic acid, (Z)-	15.23
40	3-t-Butyl-4,5-diphenyl-1H-pyrazole	22.87
41	Benzoic acid, 2-hydroxy-5-iodo-, methyl ester	30.24

L. inermis: Lawsonia inermis

Distribution

Plasma protein binding and volume of distribution plays a major role. Table 4 shows the result of active compounds in distribution manner.

Metabolism

In the case of metabolism, various CYP substrate and inhibitor models are calculated, and the result shows that most of the active compounds are non-substrate and non-inhibitor of CYP enzymes. Table 5 shows the detailed description of metabolism reaction.

Toxicity

In case toxicity, all the compounds are found to be non-toxic. Table 6 represents the results that compounds which are docked are all non-toxic substances.

Table 3: ADMET predicted profile for active compound from *L. inermis* - absorption

Parameter	1	2	3	4	5	6	7	8	9	10
BBB	+	+	+	+	+	+	+	+	+	+
Human intestinal absorption	+	+	+	+	+	+	+	+	+	+
Caco-2 permeability	+	+	+	+	+	+	+	+	+	+

Parameter	11	12	13	14	15	16	17	18	19	20
BBB	+	+	+	+	+	+	+	+	+	+
Human Intestinal absorption	+	+	+	+	+	+	+	+	+	+
Caco-2 permeability	–	–	+	+	–	+	+	+	+	–

Parameter	21	22	23	24	25	26	27	28	29	30	31
BBB	–	+	+	–	+	–	+	+	+	+	+
Human intestinal absorption	+	+	+	+	+	–	+	+	+	+	+
Caco-2 permeability	+	+	–	+	–	–	+	+	+	+	+

Parameter	32	33	34	35	36	37	38	39	40	41
BBB	+	+	+	+	+	+	+	+	+	+
Human intestinal absorption	+	+	+	+	+	+	+	+	+	+
Caco-2 permeability	+	+	+	+	+	+	+	+	+	+

BBB: Blood-brain barrier, ADMET: Absorption, distribution, metabolism, excretion, and toxicity, *L. inermis: Lawsonia inermis*, BBB: Blood-brain barrier

Table 4: ADMET predicted profile for active compound from *L. inermis* – distribution

Parameter	1	2	3	4	5	6	7	8	9	10
P-glycoprotein substrate	NS	NS	NS	NS	NS	NS	NS	S	NS	NS
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	I	NI	NI	NI
	I	NI	NI	NI	NI	NI	NI	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

Parameter	11	12	13	14	15	16	17	18	19	20
P-glycoprotein substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

Parameter	21	22	23	24	25	26	27	28	29	30	31
P-glycoprotein substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	NI	I	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

Parameter	32	33	34	35	36	37	38	39	40	41
P-glycoprotein substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
P-glycoprotein inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Renal organic cation transporter	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

ADMET: Absorption, distribution, metabolism, excretion, and toxicity, *L. inermis: Lawsonia inermis*

Table 5: ADMET predicted profile for active compound from *L. inermis* – metabolism

Parameter	1	2	3	4	5	6	7	8	9
CYP450 2C9 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 substrate	NS	NS	NS	NS	NS	NS	S	NS	NS
CYP450 1A2 inhibitor	NI	I	NI	NI	NI	NI	NI	NI	I
CYP450 2C9 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2D6 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 3A4 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI

Parameter	11	12	13	14	15	16	17	18	19	20
CYP450 2C9 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 1A2 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	I	NI
CYP450 2C9 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	I	NI
CYP450 2D6 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	I	NI
CYP450 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 3A4 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI

Parameter	21	22	23	24	25	26	27	28	29	30	31
CYP450 2C9 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 substrate	NS	NS	NS	NS	NS	NS	NS	NS	S	NS	NS
CYP450 1A2 inhibitor	NI	NI	I	NI	NI	NI	NI	I	I	I	NI
CYP450 2C9 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	I	NI
CYP450 2D6 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI	I	I	I	NI
CYP450 3A4 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	I	I	NI

Parameter	32	33	34	35	36	37	38	39	40	41
CYP450 2C9 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 2D6 substrate	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CYP450 3A4 substrate	S	NS	NS	NS	NS	NS	NS	NS	NS	S
CYP450 1A2 inhibitor	I	I	I	NI	NI	I	NI	I	I	I
CYP450 2C9 inhibitor	NI	NI	NI	I	NI	NI	NI	NI	NI	I
CYP450 2D6 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
CYP450 2C19 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	I
CYP450 3A4 inhibitor	NI	NI	NI	NI	NI	NI	NI	NI	NI	I

ADMET: Absorption, distribution, metabolism, excretion, and toxicity, *L. inermis: Lawsonia inermis*

Table 6: ADMET predicted profile for active compound from *L. inermis* - toxicity

Parameter	1	2	3	4	5	6	7	8	9	10
Human ether-a-go-go-related gene inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI
AMES toxicity	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Carcinogens	C	NC	NC	NC	NC	NC	C	NC	NC	NC
Fish toxicity	HT	LT	HT	LT	LT	LT	HT	LT	HT	HT
Tetrahymena pyriformis toxicity	HT	HT	HT	LT	HT	HT	HT	HT	HT	HT
Honey bee toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Biodegradation	RB	RB	RB	RB	NRB	RB	RB	RB	RB	RB
Acute oral toxicity	III	II	II	III	III	III	III	III	IV	III

Parameter	11	12	13	14	15	16	17	18	19	20
Human ether-a-go-go-related gene inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI
AMES toxicity	NT	NT	NT	NT	NT	NT	NT	T	NT	NT
Carcinogens	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Fish toxicity	LT	LT	LT	HT	LT	HT	LT	HT	HT	LT
Tetrahymena pyriformis toxicity	LT	LT	HT	HT	HT	HT	HT	HT	HT	LT
Honey bee toxicity	HT	HT	HT	HT	LT	HT	HT	HT	HT	LT
Biodegradation	NRB	NRB	RB	RB	NRB	RB	RB	NRB	NRB	RB
Acute oral toxicity	IV	IV	III	III	III	III	II	II	III	III

Parameter	21	22	23	24	25	26	27	28	29	30	31
Human ether-a-go-go-related gene inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI
AMES toxicity	T	T	NT	NT	NT	NT	NT	T	T	NT	NT
Carcinogens	NC	NC	NC	NC	NC	NC	NC	NC	NC	C	NC
Fish toxicity	HT	HT	LT	HT	LT	LT	HT	LT	LT	HT	HT
Tetrahymena pyriformis toxicity	HT	HT	LT	HT	LT	LT	HT	HT	HT	HT	HT
Honey bee toxicity	HT	HT	HT	HT	HT	HT	HT	LT	LT	HT	HT
Biodegradation	RB	NRB	RB	RB	RB	RB	RB	NRB	NRB	RB	NRB
Acute oral toxicity	III	III	IV	III	IV	III	III	III	III	III	III

Parameter	32	33	34	35	36	37	38	39	40	41
Human ether-a-go-go-related gene inhibition	WI	WI	WI	WI	WI	WI	WI	WI	WI	WI
AMES toxicity	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Carcinogens	C	NC	NC	C	C	C	C	NC	NC	NC
Fish toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Tetrahymena pyriformis toxicity	HT	HT	HT	HT	HT	HT	HT	HT	HT	HT
Honey bee toxicity	HT	HT	HT	HT	HT	HT	HT	HT	LT	HT
Biodegradation	RB	RB	NRB	RB	RB	RB	RB	RB	NRB	NRB
Acute oral toxicity	III	III	III	III	III	III	III	IV	III	III

ADMET: Absorption, distribution, metabolism, excretion, and toxicity, *L. inermis: Lawsonia inermis*

DISCUSSION

Medicinal plants have provided plentiful leads to fight diseases, from the dawn of civilization. The extensive survey of the literature revealed that *L. inermis* is regarded as a common solution in the herbal medicine with varied pharmacological activity. *L. inermis* is having an exclusive source of various types of chemical compounds, which are responsible of the various activities of the plant. The GOLD docking of compounds of *L. inermis* are proved to be induced abortion by inhibiting the activity of progesterone. Toxicity analysis performed using admetSAR showed all the phytochemicals have shown to be non-toxic which shows they can become potent drugs. Docking studies gives fundamental information regarding effective receptor binding and further therapeutic action. Among the docking scores, the highest binding affinity was found to be 35.04 for D-allose with progesterone receptor.

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CONCLUSION

Henna imbibing a fabulous budding deserves an extraordinary notice of the scientific fraternity to come into view as a milestone for the medical science of this millennium due to its various medicinal uses. Further, evaluation desires to be accepted out on *L. inermis* in order to explore the hidden areas and their sensible clinical applications, which can be used for the welfare of the mankind. Hence, extensive investigation is needed to exploit their therapeutic utility to combat diseases.

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