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Comparative Assessment of Compounds in *Lawsonia Inermis* L. - A Potent Antileishmanial Plant

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Abstract

Lawsonia Inermis L. plant, traditionally known as henna, played a svital role in the daily lives of ancient cultures, offering medicinal and psychological benefits, in addition to being used for personal beautification. The medicinal role of *Lawsonia Inermis* L. plant was known since ages and several isolated compounds from this plants plays an important role in the treatment of several tropical disease including *Leishmaniasis*. A large number of active compounds are present in this plant which could be used for the efficient treatment of this disease. Active compounds were collected from data bank of The Royal library/Copenhagen University library, PubMed, Scifinder, Reaxys, and Google Scholar etc. More than 161 compounds are identified, well-studied along with their molecular characterization from *Lawsonia inermis* L. plant out of which 20 compounds possess antileishmanial activity whereas 12 compounds were similar between *Lawsonia inermis* L and other plants that have Antileishmanial activities.. Although many studies reported the pharmacological activities of compounds isolated from *Lawsonia Inermis* L. plant in several diseases but the anti-leishmanial roles of compounds have not been widely investigated. The goal of present study was to evaluate the potential of the isolated compounds from *Lawsonia Inermis* L. plant in terms of their anti-leishmanial activity. The present review provides valuable information about compounds isolated from the *Lawsonia Inermis* L. plant, which could be considered in the future experimental and clinical trials for the treatment of leishmaniasis and other diseases.

Keywords: *Lawsonia inermis* L; Leishmaniasis; Anti-leishmanial Active Compounds; Natural Compounds

Introduction

Leishmaniasis is an infectious neglected parasitic disease, caused by the intracellular parasite which is transmitted via the bite of female sand fly and belong to the genus *Leishmania*. It has been extended in five continents with high endemicity in developing countries [1]. The disease has widespread clinical spectrums ranging from self-limiting cutaneous to fatal visceral form which depends on the parasite strain and host immune response. World Health Organization (WHO) highlights on leishmaniasis as one of the seven significant diseases [2]. Approximately, 1.5 million new

cases of leishmaniasis are reported annually and 12 million people are affected. Moreover, nearly 350 million people are at the risk of disease in 98 countries. Almost, 90% cases of leishmaniasis occur in Saudi Arabia, Iran, Afghanistan, Syria, Peru, Iraq and Brazil [3]. Pentavalent antimonials are mostly used for leishmaniasis from 1959 but it is a toxic drug with life-threatening side effects and needs prolong injections. The emergence of resistance has further decreased the efficacy of antimonials and limits their usage [4]. Other drugs including pentamidine and amphotericin B are used as second line agents, but have severe side effects. The absence of vaccines further deteriorates the situation due to complexity of immunity to parasites and technical challenges. Therefore, there is an urgent need for the supplementation or replacement of current drugs with new and more effective anti-leishmanial drugs. WHO suggests the use of traditional medicine for neglected diseases in societies with poor health facilities. Plant extracts or biochemical active compounds isolated from plants are likely to offer a beneficial source of new medicinal drugs. The crucial requisite for substituting medications has led to screening of natural compounds in leishmaniasis. The data acquired from reviewing isolated active compounds from plants could result in the emergence of safer and effective natural compounds with valuable anti-leishmanial activity. Moreover, it could also be an efficient approach for the production of new synthetic compounds [5]. *Lowsonia inermis* L pant (commonly known as Mehndi or Henna) belongs to the family Lythraceae. It is widely cultivated in tropical and subtropical areas, and native to the Southern-western Asia and Northern Africa. It is chemically well explored and many active compounds have been reported [6], including napthalenes, flavonoids, coumarins, naphthoquinones, terpenes (both volatile and non-volatile), alkylphenones, alkaloids and aliphatic hydrocarbons. It is extensively used for various medicinal purposes, and preserve a variety of pharmacological activities, including antibacterial, antioxidant, antiviral, antifungal, antiparasitic, cytotoxic, antidiabetic and anti-leishmanial efficacy [5]. Dichloromethane and methanol extracts acquired from the leaves displayed antiparacidal activity against *Trypanosoma brucei*, *plasmodium falciparum*, Nematoda and *Leishmania donovani* [7].

The present study attempts to offer a summary on the bioactive compounds isolated from the *Lawsonia Inermis* L. plant and the assessment with other plants, which could offer a valuable treatment option compound against *Leishmania* parasites. To best of our knowledge, the present study is first to summarize potential of active compounds isolated from *Lawsonia Inermis* L. plant for leishmaniasis.

Methods

Search method

An exclusive search was executed through all major scientific databases from 1976 to December, 2017 including five English databases, including Scopus, PubMed, Google Scholar, SciFinder and Reaxys. All articles which are related to the *Lawsonia Inermis* L plant and leishmaniasis were selected having at least GC-MS and/or NMR data. Moreover, the bibliography lists of all the articles were assessed for prevention of missing pertinent data. The search terms were: "medicinal plants", "*Lawsonia Inermis* L", "Leishmaniasis", "anti-leishmanial agents", "natural and synthetic compounds" "herbal extract", "phytopharmaceuticals" and "isolated active compounds" alone or in combination together. Other relevant topics including *Leishmania* parasite, half-maximal inhibitory concentration (IC_{50}) values, chemical name, class, structure of isolated compound, part of *Lawsonia Inermis* L plant and *in vitro*/*in vivo* evaluation of isolated active compounds were also evaluated and incorporated if the appropriate outcomes were recovered.

Paper selection

The papers selected for inclusion were reviewed thoroughly. The studies with poor methodology, papers on plants other than *Lawsonia Inermis* L and repetitive studies were excluded. The following data were obtained: parasite species, the structure of pure isolated compound, GC-MS, NMR data, chemical name, phytochemical class, part of plant used for extraction and research outcomes. Two referees individually examined studies recognized for inclusion and established study eligibility (Kapp index displayed an agreement 91% between two referees). Disagreements were settled by the third party interpretation.

Phytochemicals

Almost a hundred of phytochemical compounds, demonstrating a number of classes, have been recognized from all parts of *Lawsonia Inermis* L. plant. This abundance of pharmacologically active compounds suggests that this plant has could have active compounds which can be used for the treatment of several ailments including Leishmaniasis. Previous literature is lacking the in-depth details of anti-leishmanial compounds present in *Lawsonia Inermis* L.

S/No.	Antileishmanial Compounds Isolated from *Lawsonia Inermis* L.	*Leishmania* Strain	References
1	Lawsone (2-hydroxy-1,4-naphthoquinone)	*L. Mexicana*	[8]
2	Scopoletin	*L. donovani,*	[9,10]
		L. amazonensis,	
		L. infantum and	
		L. braziliensia,	
3	tannic acid	*L. donovani*	[11]
4	4-methoxyapigenin (linarisenin, acacetine or linarigenin)	*L. donovani*	[10]
5	luteolin-7-O-glucoside	*L. donovani*	[12,13]
6	7-hydroxyflavone	*L. donovani*	[3]
7	diosmetin-7-rutinoside	*L. donovani*	[3]
8	Betulin	*L. donovani*	[14]
9	Lupeol	*L. donovani*	[14]
10	isocaryophllene	*L. donovani*	[15]
11	ethyl hexadecanoate	*L. donovani*	[15]
12	Harmaline	*L. donovani*	[16]
13	Harmine	*L. donovani*	[16]
14	24-ethylcholest-ol	*L. major*	[6]
15	Apigenin	*L. tropica*	[5]
16	Luteolin	*L. tropica*	[5]
17	Lalioside	*L. tropica*	[5]
18	Luteolin-4-O-beta-D-glucopyranoside	*L. tropica*	[5]
19	Apigenin-4-O-beta-D-glucopyranoside	*L. tropica*	[5]
20	Apigenin	*L. tropica*	[5]

Table 1: Antileishmanial activities of compounds from *Lawsonia Inermis* L.

S/No.	Antileishmanial Compounds Isolated from other Plants (also existed in *Lawsonia Inermis* L.)	*Leishmania* Strain	References
1	Linalool	*L. amazonensis*	[17]
2	Apigenin	*L. donovani*	[10]
3	Apigenin 7-O-glucoside	*L. donovani*	[10]
4	Luteolin 7-O-glucoside	*L. donovani*	[10]
5	Quercetin	*L. donovani*	[10]
6	Catechin	*L. donovani*	[10]
7	Gallic acid	*L. donovani*	[10]
8	p-Coumaric acid	*L. donovani*	[10]
9	p-cymene	*L. major*	[18]
10	Beta-pinene	*L. major*	[18]
11	Alpha-pinene	*L. major*	[18]
12	1,8-cineole	*L. major*	[18]

Table 2: Similar Compounds between *Lawsonia Inermis* L. and other Plants having Antileishmanial activities.

The anti-leishmanial compounds reportedly produced by the plant have been characterized according to main classes as following:

Phenolic compounds

Napthoquinones: A number of naphthoquinones are present in the leaves of the *Lawsonia Inermis* L. including 2-hydroxy-1,4-naphthoquinone (lawsone). This compound is the dyeing principle of this plant and is particularly found in the leaf petioles [19]. Moreover, this compound is unstable when exposed to light or high temperature, making it necessary to use appropriate means to dry it. The anti-leishmanial activity of lawsone has been reported and displayed that this compound is active against *L. mexicana* parasites [8].

Coumarins: In the case of coumarins, scopoletin was identified in the leaves part of the *Lawsonia Inermis* L. plant [20,21]. It was displayed in several studies that scopoletin is active against different types of Leishmania parasites, including *L. donovani, L. amazonensis, L. infantum* and *L. braziliensia*, whereas IC_{50} values were reported to be 30, 41, 44 and >50 µg/ml, respectively [9,10].

Tannins: The hairy root of *Lawsonia Inermis* L. yields tannic acid which is one of the main constituents of this plant and show good efficacy for Leishmaniasis [11].

Flavonoids: A large number of flavonoids have been isolated from the aerial parts of the *Lawsonia Inermis* L plant. These include 4-methoxyapigenin also known as linarisenin, acacetine or linarigenin. This compound is shown to be active against *L. donovani*, having IC_{50} value of 19 µg/ml [10]. The other compounds included luteolin-7-O-glucoside and several studies indicated the anti-lesihmanial activity this compound [12,13]. This compound displayed most potent anti-lesihmanial activity (IC_{50} 0.8 µg/ml) when tested *in vitro* against *L. donovani* promastigotes. 7-hydroxyflavone and diosmetin-7-rutinoside are compounds is isolated from the leaves of the plant and exhibited efficacy against L. donovani, having IC50 value of 4.1 and 2.6 µg/ml, respectively [3].

Terpenes

Non-volatile terpenoids: Betulin and lupeol are the two-known non-volatile terpenoids that have been identified in the seeds of *Lawsonia inermis* [21]. These compounds show anti-leishmanial activity when evaluated against the intra-macrophage model of amastigotes [14].

Volatile terpenes: A clear essential oil with deep fragrance is isolated from the flowers. The smell of this oil resembles a combination of roses, chocolate and cigars. The oil comprises mainly isocaryophllene and ethyl hexadecanoate, which are active against the *Leishmania* parasites [16].

Alkaloids

Harmaline and harmine are the two major alkaloids which are isolated from the extract of seeds of *Lawsonia inermis*. A study displayed that when administered in experimental model of leishmaniasis, it decreased the parasitic load and could be used in combination with other anti-leishmanial synthetic compounds [16].

Steroids

Till now, only one steroid, 24-ethylcholest-ol has been isolated from the roots of the plant and a study shows that it could be effective when used against the promastigotes of *L. major* parasites [6].

Miscellaneous

Many other constituents are known anti-leishmanial compounds which are isolated from leaves and stems of this plant including oleamide and 2-butoxysuccininc acid [22]. (Supplementary material)

Conclusion

To summarize, the present review it is the first time to present complete information about isolated compounds, antileishmanial activity and compounds similar between *Lawsonia Inermis* L. and other plants, this offers a valuable evidence about the biologically active compounds present in the *Lawsonia inermis* L. plant having anti-leishmanial activities and could be used alone or in combination with marketed synthetic compounds for clinical and experimental therapy studies. There is a need to exploit and explore more anti-leishmanial compounds, and potential adverse effects that would lead to developing safe and well-tolerated drugs for leishmaniasis. This serves a valid statement that *Lawsonia inermis* L. is a potent antileishmanial plant.

S/No	Name of Compound	References
1	Harmine	[16]
2	Harmaline	[16]
3	1,2,4-trihydroxynapthalene-1-O-beta-D-glycopyranoside	[23]
4	D-glucopyranose	[23]
5	D-Mannitol	[23]
6	Methyl pheophorbide	[23]
7	Oleamide	[23]
8	2-Butoxysuccinic acid	[23]
9	Geistein	[23]
10	Lawsochylin A	[23]
11	Lawsonaphthoate A	[23]
12	Lawsonaphthoate B	[23]
13	Lawsonaphthoate C	[23]
14	Luteolin	[23]
15	Luteolin 7-O-beta-D-glucopyranoside	[23]
16	Luteolin 4-O-beta-D-glucopyranoside	[23]
17	Apigenin 7-O-beta-D-glucopyranoside	[23]
18	Apigenin 4-O-beta-D-glucopyranoside	[23]
19	Apigenin	[23]
20	Luteolin 7-O-rutinoside	[23]
21	Diosmetin 7-O-rutinoside	[23]
22	3-Amino-2-methoxycarbonyl-1,4-naphthoquinone	[23]
23	(4S)-4hydroxy-alpha-tetralone	[23]
24	3alpha,4alpha-dihydroxy-alpha-tetralone	[23]
25	9-hydroxy-4-megostigmen-3-one	[23]
26	(+)-dihydrodehydrodiconiferyl alcohol	[23]
27	4-dihydroxybenzaldehyde	[23]
28	Isoplumbagin	[24]
29	p-coumaric acid	[25]
30	2-methoxy-3-methyl-1.4-naphthoquinone	[25]
31	Apiin	[25]
32	Cosmosin	[25]
33	Lalioside	[26]
34	Lawsoniaside	[26]
35	2,4,6-trihydroxyacetophenone-2-O-beta-D-glucopyranoside	[26]
36	1,2,4,-trihydroxynaphthalene-1-O-beta-D-glucopyranoside	[26]
37	Lawsochrysin	[27]
39	Lawsochrysinin	[27]
40	Lawsonaringenin	[27]
41	3',4'-dimethoxyflavone	[27]

42	7-hydroxyflavone	[27]
43	3,3',4',7-tetrahydroxyflavonone	[27]
44	Dodecane	[28]
45	Tridecane	[28]
46	1-(1,5-dimethyl-4-hexenyl-4methyl-benzene	[28]
47	Tetradecane	[28]
48	2-methyl-decane	[28]
49	3-methyl-decane	[28]
50	3-methyl-hexasecane	[28]
51	Heptodecane	[28]
52	2-methyldodecane	[28]
53	Pentadecane	[28]
54	Hexadecane	[28]
55	Octadecane	[28]
56	Hexahydropseudoionone	[28]
57	Eicosane	[28]
58	2-hexyle-1-decanol	[28]
59	Isophytol	[28]
60	Dibutyl phthalate	[28]
61	Heptafluorobutyric acid, n-tetradecyl ester Phytol	[28]
62	Isoctyl phthalate	[28]
63	8-heptyl pentadecane	[28]
64	Dotriacontane	[28]
65	Octacosane	[28]
66	7-hexyl-eicosane	[28]
67	Linalool	[29]
68	Alpha-terpineol	[29]
69	Etherphenylvinyl	[29]
70	1.3-indandione	[29]
71	Eugenol	[29]
72	Cis-hexahydro-8a-methyl18[2H,8H]naphthalenedione	[29]
73	Oxirane-tetradecyl	[29]
74	Hexadecanoic acid	[29]
75	Phytol	[29]
76	Acacetin	[30]
77	Acacetin 7-glucoside	[30]
78	Laxanthone I	[30]
79	Laxanthone II	[30]
80	Lawsone	[30]
81	Beta-sitosterol (-Glucoside)	[30]
82	D-mannitol	[31]

83	Benzaldehyde	[15]
84	2-heptanone	[15]
85	Amyl isobutyrate	[15]
86	Undecane	[15]
87	Naphthalene	[15]
88	Methyl salicylate	[15]
89	Decane	[15]
90	(Z)-alpha-damascenone	[15]
91	Alpha-copaene	[15]
92	Beta-elemene	[15]
93	Isocaryiphyllene	[15]
94	(E)-alpha-ionone	[15]
95	Neryl acetone	[15]
96	(E),-beta-famesene	[15]
97	Gamma-muurolene	[15]
98	Alpha-pinene	[32]
99	Beta-pinene	[32]
100	Alpha-phellandrene	[32]
101	p-cymene	[32]
102	Limonene	[32]
103	1,8-cineole	[32]
104	Alpha-terpineol	[32]
105	Beta-caryophyllene	[32]
106	Aromadendrene	[32]
107	Alpha-humulene	[32]
108	alloaromadendrene	[32]
109	2H-Pyran-2,6(3H)-Dione	[33]
110	4H-Pyran-4-one,2,3 dihydro 3,5-dihydroxy-6-methyl-	[33]
111	Benzene	[33]
112	1.4-Naphthalenedione,2-hydroxy (Henna)	[33]
113	Methyl alpha-D-Glucopyranoside	[33]
114	n-hexadecanoic acid	[33]
115	Lawsoniasides A	[34]
116	Lawsoniasides B	[34]
117	Dihydroxylupene	[35]
118	Dihydroxylupane	[35]
119	Gallic acid	[36]
120	2-hydroxy-1,4-naphthoquinone	[36]
121	1,3-hydroxy-naphthoquinone	[36]
122	1,4-naphthoquinone	[36]
123	1,2-DIhydroxy-4-Glucosyloxynaphthalene	[37]

124	Lacoumarin	[38]
125	Lawnermis acid	[39]
126	Lawsaritol	[40]
127	Catechin	[41]
128	Antocyanins	[41]
129	Quercetin	[41]
130	1-hydroxy-3,7-dimethoxy-6-acetoxy xanthone	[42]
131	Bicoumarin A	[43]
132	Biflavonoid A	[43]
133	Biquinone A	[43]
134	Lawsonicin	[44]
135	Lawsonadeem	[44]
136	Vomifoliaol	[44]
137	1,2,4-trIhydroxynaphthalene-4,4-di beta-D-glucopyranoside	[45]
138	2,3,4,6-tetrahydroxyacetophenone-2- beta-D-glucopyranoside	[45]
139	n-triacontyl n-tridecanoate	[46]
140	n-triacontanol	[46]
141	Beta-sitosterol	[46]
142	Lupeol	[46]
143	3o-norlupan-3-beta-ol-20-one	[46]
144	Betulinic acid	[46]
145	Betulin	[46]
146	Rosamutin	[47]
147	Euscaphic acid	[47]
148	1beta,2beta,3beta,19alpha-tetrahydroxyurs-12-en-28-oic acid	[47]
149	Ursolic acid	[47]
150	Arjunic acid	[47]
151	12-[2'-(1'.4'-doxin-5'.6'-dione)]-8"E-undecenyl-dodecanoate	[48]
152	5-[1'-(docosa-2'E.5'E-dienyl)]-1.4-doxin-2,3-dione	[48]
153	Lawsorosemarinol	[49]
154	Lawsofructose	[49]
155	2-(beta-D-glucopyranosyloxy)-1,4-naphthoquinone	[49]
156	3-(4-hydroxyphenyl)-tricontyl-(Z)-propenoate	[49]
157	4-hydroxy coumarine	[49]
158	3-(4-hydroxy-3-methoxyphenyl)-tricontyl-(Z)-propenoate	[49]
159	4-hydroxy-4-methyl coumarine	[49]
160	1,3-dihydroxy-6,7-dimethyoxyxanthione	[50]
161	1,hydroxy-3,6-diacetoxy-7-methyoxyxanthione	[50]

Table 3: Supplementary material**:** Complete list of Isolated Compounds from *Lawsonia Inermis* L.

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