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Review

An Evidence-Based Review on Selected Traditional Formulations against Pediculosis

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Abstract
Pediculosis is a growing social problem in both developed and undeveloped countries. Resistance to chemical treatments and toxicity of insecticidal compounds are reasons why alternative medications should be proposed for this parasitic infestation. This study attempted to investigate traditional anti-lice treatments, and draw together scientific insights into lice management through the study of Persian Medicine manuscripts. Lice infestation formulations were searched in seven traditional textbooks (*al-Manṣuri fi al-ṭibb, al-Qanun fi al-ṭibb, Kamil al-ṣina'ah al-ṭibbiyah, Qarabadin Kabir, Qarabadin Salehi, Makhzan al-Adviyeh, Eksir Azam*) pertaining to one millennium period, from the 9th to 19th century. Twenty multi-component medications were selected for the study of ingredients and their active compounds. PubMed, Google Scholar, and Scopus were searched to find pediculicidal or insecticidal evidence. *In vitro* studies and clinical trials reporting anti-lice and/or insecticidal activities were summarized. Formulations had four kinds of base (oil, vinegar, alcohol, or water). Oils act through occluding the respiratory spiracles of lice. Vinegar loosens the attachment between nits and hair shaft, improving the removal of nits from hair. Essential oil- and tannin-containing plants made up the majority of anti-lice components in the current study. Seventeen out of twenty-seven medicinal plants were reported to have pediculicidal and/or insecticidal activity. Considering the results, further investigation leads to the designing new treatments against pediculosis.

Keywords: *Pediculus humanus capitis*; Pediculosis; Medicinal plants; Persian medicine

Introduction
Louse infestation, pediculosis, existing for thousands of years and affecting millions of people each year, is caused by three blood-sucking human ectoparasites responsible for body louse, head louse, and pubic louse [1]. Head louse, *Pediculus humanus capitis* belonging to the order of Anoplura, is a social health problem worldwide. The infestation is more common in children aged 3 to 11 years particularly in girls, often transmitted by head-to-head contact [2-4]. According to the epidemiological studies, the prevalence of head lice infestation was reported 1.12% among children aged 1-5 in Kurdistan (Iraq), 11.14% among primary school girls in Turkey, and 72.2% among children aged 10-13 in Chiapas (Mexico) [5]. Previous studies in Iran have shown the prevalence of head lice between 2.3% to 17.5% [6]. Lice infestation might cause severe itchiness, excoriation, secondary

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bacterial infestation, and psychological distress, leading to absence from school [2,7-9]. Female louse lives 1 to 3 months and lays 8 to 10 nits (lice eggs) per day [1,10]. The nits are located near the scalp, stuck to the hair shaft [1,9,11]. The louse resides on hair and feeds from the scalp on average of 5 times per day, and this causes pruritus [1,4].

Mechanisms of topical anti-lice treatment and the examples include respiratory paralysis of lice in which the chemical interacts with sodium channels and depolarizes the membranes (e.g. Pyrethrins and permethrin); lice paralysis by neural hyperstimulation as a result of altering the transport of sodium and potassium (e.g. lindane as organochloride compound) or inhibition of cholinesterase of lice (e.g. malathion as an organophosphate compound); asphyxiation meaning blockage of the respiratory system of lice (e.g. benzyl alcohol and dimethicone); physical removal of lice by wet combing, and desiccation of lice by hot air treatment [4,7,12] Increasing resistance of head lice to neurotoxic agents such as lindane, malathion, pyrethrins, and permethrin has been reported in several countries [11,12]. Moreover, the concern over the safety of chemical anti-lice medications is rising [11]. Persian Medicine (PM) contains knowledge and practice in diagnosis, prevention and treatment in Persia [13]. Numerous topical treatments of herbal and mineral sources have been recommended for lice infestation. In current review, general structure of anti-lice formulations extracted from PM manuscripts was studied. Moreover, scientifically proven anti-lice and/or insecticidal effects of ingredients were presented.

Materials and Methods

Traditional anti-lice formulations were extracted from seven main textbooks using Persian keywords *Qaml*, *Qamqam*, *Shepesh* meaning lice and *Seyban* and *Reshk* meaning nits. The detailed information was listed in table 1. The formulations were found in the chapters considering skin and hair disorders or in herbal monographs or in the sections of topical dosage forms. For more certainty, electronic versions of *Qarabadin Kabir* and *Makhzan al-Advieh* were also searched. Totally, 290 formulations were found. Exclusion criteria were duplicated and/or complicated formulations, toxic or unknown contents, and/or non-domestic ingredients. Furthermore, formulations containing ingredients of animal sources (like cow bile) or minerals (like borax) were excluded. Formulations were categorized according to their bases including vinegar, oil, alcohol, or water. Twenty formulations (two or more-ingredient in definite solvent) were selected for further investigation. The insecticidal and/or pediculicidal potential of the ingredients was reviewed (Table 2). The indices of "*al-Aghrazotebie va al-Mabahesolalaiieh*" [15] and "*al-Saydanah fi al-Tibb*" [16] were applied for finding the scientific names, then being authenticated using "The Plant List" website. Supportive evidence for anti-lice or insecticidal effects of 27 medicinal plants administered in formulations was searched in PubMed, Google Scholar, and Scopus till October 2021. The keywords of lice, pediculicide, insect, and insecticide beside the scientific name of each plant were used for the search.

Table 1. The manuscripts searched for anti-lice compounds

Manuscript (century)	Author	No.*
al-Manṣuri fī al-ṭibb (9th)	Zakariya al-Razi	11
al-Qanun fi al-ṭibb (11th)	Ibn Sina	51
Kamil al-ṣina'ah al-ṭibbiyah (11th)	al-Majusi	8
Qarabadin Kabir (18th)	Aghili Shirazi	21
Qarabadin Salehi (18th)	Ghaeni Heravi	18
Makhzan al-Adviyeh (18th)	Aghili Shirazi	26
Eksir Azam (19th)	Hakim Azam Khan	155

*: Number of formulations

Results

Twenty traditional formulations were analyzed in terms of the pediculicidal or insecticidal effects of components. They were categorized into four groups according to the solvents applied (oil, vinegar, alcohol, or water). Seventeen out of twenty-seven medicinal plants had pediculicidal and/or insecticidal activities according to *in vitro* studies or clinical trials, summarized in table 3.

Sedanolide separated from methanolic extract of *Apium graveolens* showed 100% mortality on *Aedes aegypti*. The negative control contained 980 μL of degassed distilled water and 20 μL of DMSO solution [24]. The essential oil derived from the seeds of *Apium graveolens* revealed larvicidal activity against early fourth instars of *Aedes aegypti*, the major vector of dengue fever [25].

Insecticidal activity of the essential oil from *Artemisia pontica* on the insect *Acanthoscelides obtectus*, was evaluated by exposing the insects to 0-100 mg/g concentrations of the essential oil. In addition, non-treated insects were used as a control group. In addition, the insecticidal activity of the essential oil was contributed to the abundance of α-thujone and sabinyl acetate [26].

The toxicity of the essential oil for *Artemisia vulgaris* was evaluated against three stored product pests, *Callosobruchus maculatus*, *Rhizopertha dominica*, and *Tribolium castaneum* through a fumigant toxicity test.

The negative control jar contained no essential oil. Moreover, the insecticidal activity of the essential oil was associated with its camphene and α-Thujone content [27].

Table 2. Traditional anti-lice formulations and their bases

	Ingredients (part used)	Traditional names	Base	Ref.
1	*Melia azedarach* L. (l)	Azad derakht	Rose oil*	[17]
2	*Gypsophila struthium* Loefl. (r)	Kondosh	Olive oil	[18]
3	*Aristolochia longa* L. (r)	Zaravande tavil	Olive oil	[19,20]
4	*Rhus coriaria* L. (fr)	Sumaq	Olive oil	[20]
5	*Nerium oleander* L. (l)	Kharzahreh	Olive oil	[18]
6	*Aristolochia longa* L. (r), *Delphinium staphisagria* L. (s)	Zaravande tavil, Mavizaj	Olive oil	[21]
7	*Punica granatum* L. (l), *Rumex acetosa* L. (r)	Roman Hommaz	Olive oil	[18]
8	*Piper nigrum* L. (fr)	Felfel	Olive oil	[18]
9	*Myrtus communis* L. (l), *Rosa × damascena* Herrm (fl)	Murd, Gol-e sorkh	Safflower oil	[22]
10	*Usnea articulate* Ach. (ap), *Salsola kali* L. (ap), *Punica granatum* L. (p), *Piper nigrum* L. (fr),	Oshneh Oshnan Roman Felfel	Bitter almond oil	[18]
11	*Pimpinalla anisum* L. (fr)	Anison	Vinegar	[22]
12	*Delphinium staphisagria* L. (s)	Mavizaj	Vinegar	[18]
13	*Vicia faba* L. (s)	Baghela	Vinegar	[18]
14	*Lawsonia inermis* L. (l), *Nerium oleander* L. (l)	Hanna Kharzahreh	Vinegar	[18]
15	*Delphinium staphisagria* L. (s), *Nerium oleander* L. (l), *Saussurea costus* (Falc.) Lipsch. (r)	Mavizaj Kharzahreh Ghost	Almond oil & vinegar	[18]
16	*Apium graveolens* L. (s), *Liquidambar orientalis* Mill. (e)	Karafs Mieh	Rose oil & vinegar	[18]
17	*Aloe vera* (L.) Burm.f (e), *Myrtus communis* L. (l),	Sabr Murd	Alcohol**	[23]
18	*Artemisia pontica* L. (ap), *Artemisia vulgaris* L (fl).	Sheyh-e Armani Berenjasf	Water	[18,19]
19	*Veratrum album* L. (r), *Delphinium staphisagria* L. (s)	Kharbagh-e sefid Mavizaj	Water	[18]
20	*Veratrum album* L.(r), *Lepidium sativum* L.(s), *Lupinus angustifolius* L. (s)	Kharbaghe sefid Horf Tormes	Water	[18]

Abbreviations: ap: aerial part; b: bark; e: exudate; fl: flower; fr: fruit; l: leaf; p: peel; s: seed; r: root * rose petals macerated in sesame oil ** the alcoholic beverage, wine

Larvicidal activity of the essential oil of *Lepidium sativum* L. seeds was evaluated against *Anopheles gambiae*, a mosquito transmitting *Plasmodium falciparum*. Hexane solution 1% was applied as negative control. Furthermore, the effects against adult mosquito was performed. The negative control (1% acetone impregnated filter paper) and the positive control (bendiocarb 0.1% impregnated filter paper) resulted in 0% and 100% motility, respectively. It was concluded that the chemicals in the essential oil were responsible for respiratory blockage of larvae [28].

The pediculicidal bioassay of hydroalcoholic extract 50% of *Melia azedarach* was evaluated through different groups of insects. Permethrin lotion 1 % (10 mg/ mL) was applied as positive control, and distilled water was used as negative control. Hydroalcoholic extract 50% of *M. azedarach* showed 100% mortality of lice after 20 min. Mortalities of lice with water and permethrin were 25% and 100% in 24 h and 12 h, respectively [29].

Myrtle (*Myrtus communis*) essential oil containing lineol, α-pinene, and linalool has shown activity against *Pediculus humanis capitis* [30]. The essential oil from *Myrtus communis* showed activity against FcB1 (chloroquine-resistant) and Nigerian (chloroquine-sensitive) strains of *Plasmodium falciparum*. The essential oil was more effective against FcB1 than Nigerian strain [31].

Fumigant toxicity of *M. communis* essential oil against two stored-product pests, *Callosobruchus maculatus* and *Tribolium confusum*, was studied. The essential oil was more toxic against *C. maculatus* than *T.confusum*. The insecticide activity of major components of the essential oil including α-pinene, linalool, and 1,8-cineole had been investigated before; therefore, its toxic effects could be attributed to its major monoterpenes [32].

El-Shazy et al. evaluated the insecticide activity of ethanolic extract of *Nerium oleander* leaves, its active fraction, isolated crystals, and neriifolin (authentic sample) against western-banded blow fly, *Chrysomya albiceps*. The values of LC_{50} of the active fraction, isolated crystals, and neriifolin were 57, 35, and 36 ppm, respectively. The active fraction contained neriifolin, so it is the active chemical in the extract [33].

Pediculicidal effect of anise (*Pimpinella anisum*) essential oil was evaluated through pouring two concentrations of 0.25 and 0.5 mg/cm^2 anise oil over lice. Malathion solution 0.5% w/v was applied as positive control and coconut oil was negative control. KT_{50} values of malathion and coconut oil were 8.09 and >180 min, respectively [34].

In another study, head lice were immersed in a shampoo containing 10% (v/v) crude extract of *Piper nigrum* fruits for 30 seconds. Malathion shampoo was applied as positive control, and a commercial shampoo was used for negative control. At 60th second, the mortalities of 100% and 14% were reported for malathion and commercial shampoo, respectively [14]. The insecticidal activity of *P. nigrum* can be due to several phytochemicals of *Piper* species including piperine, pipericide, phenylpropanoids, dillapiol, guineensine, and pellitorine with toxic effects against mosquitos and their larvae [35].

Delphinium seeds have long been used against lice and fleas, but their harmful effects on humans have limited their application [36]. The mechanism of active components, diterpene alkaloids, is inhibition of the insect nicotinic receptors [37].

Based on one study on the anti-lice effect of alcoholic and aqueous extracts of *Punica granatum* leaves using filter paper diffusion test, 10% concentrations of both extracts exhibited the most pediculicidal activities, showing the most anti-lice activity by the alcoholic extract. However, 10% concentration of benzyl alcohol 25% (positive control) gave 100% mortality during the same exposure time [38].

For testing insecticidal activities of ethanolic peel extract of *Punica granatum* against larvae and adults of the red flour beetle, *Tribolium castaneum*, topical application bioassay was applied. The adults and larvae were treated with a 2% concentration of the extract and the control group received distilled water [39]. Essential oil obtained from *Saussurea costus* roots and its isolated constituents were tested for larvicidal activity against the Culicidae mosquito *Aedes albopictus*. Dehydrocostus lactone, and costunolide showed more larvicidal effect with LC_{50} values of 2.34 and 3.26 μg/mL, respectively than the essential oil with LC_{50} value of 12.41 μg/mL [40]. In chronic feeding tests on larvae of *Spodoptera littoralis*, survival of the larvae after applying different concentrations of three compounds isolated from *Usnea* spp. including usnic acid enantiomers (+ and -) and vulpiric acid in an artificial diet were assessed [41]. The results were summarized in the table 3.

Veratrum album has been applied for centuries for its effect as an insect repellant. Acetone, NH_4OH/benzene, and $CHCl_3$ extracts of the rhizome had toxic effects on Colorado potato beetle, *Leptinotarsa decemlineata*. Lambda cyhalothrin, a commercial insecticide as a positive control, showed LC_{50} value of 0.025 mg/mL. In addition, insecticide activity of six metabolites isolated from *V. album* extracts were tested against the beetle. Among the isolated compounds, oxyresveratrol, β-sitosterol 3-O-β-d-glucopyranoside, and jervine were classified as potent toxic compounds against *L. decemlineata* because of their lowest LC_{50} values [42].

The effectiveness of *Lawsonia inermis* mixed with mercury was tested on *pediculus humanus capitis* in a clinical trial. The mixture showed a high pediculicidal

Table 3. A summary of studies on pediculicidal and/or insecticidal activities of the components of formulation

Medicinal plant	Fraction	Insect	Study result	Ref.
Apium graveolens L. (s)	met ext.	*Aedes aegyptii* larvae	Mortality: 100% (at 50 µg/mL; after 24 h)	[24]
Apium graveolens L. (s)	e.o.	*Aedes aegypti* L. larvae	LC_{50}: 16.1 ppm (after 24h)	[25]
Artemisia pontica L. (ap)	e.o	*Acanthoscelides obtecus*	LD_{50}: 63.2 mg/g (after 72 h) LD_{50}: 28.5 mg/g (after 96 h)	[26]
Artemisia vulgaris L. (ap)	e.o.	*Callosobruchus maculatus* *Rhizopertha dominica* *Tribolium castaneum*	LC_{50}: 52.47 µL/L air (after 24 h; *C. maculatus*) LC_{50}: 75.56 µL/L air (after 24 h; *R.dominica*) LC_{50}: 279.86 µL/L air (after 24 h; *T. castaneum*)	[27]
Lepidium sativum L. (s)	e.o.	*Anopheles gambiae* larvae & adult	Mortality: 82.6 % (adult; 10% conc; 24 h recovery period) Mortality: 97 % (larvae; 100 ppm; 72 h post-exposure time)	[28]
Melia azedarach L. (l)	50% hydroethanolic ext.	*Pediculus humanus capitis*	Mortality: 100% (after 20 min exposure)	[29]
Myrtus communis L. (l)	e.o.	*Pediculus humanus capitis* *Plasmodium falciparum*	pediculicidal effect IC_{50}: 267µg/mL (*P. falsiparum*, FcB1, after 24 h) IC_{50}: 471 µg/mL (*P. falsiparum*, Nigerian, after 24 h)	[30, 31]
Myrtus communis L. (l)	e.o.	*Callosobruchus maculatus* *Tribolium confusum*	LC_{50}: 9.5 µL/L air (*C. maculatus*) LC_{50}: 260.7 µL/L air (*T. confusum*)	[32]
Nerium oleander L. (l)	eth.ext.	*Chrysomya albiceps* larvae	LC_{50}:164 ppm	[33]
Pimpinella anisum L. (fr)	e.o.	*Pediculus humanus capitis*	KT_{50}: 45.37 min (at 0.25 mg/cm^2) KT_{50}: 37.34 min (at 0.5 mg/cm^2)	[34]
Piper nigrum L. (fr)	ext. in shampoo	*Pediculus humanus capitis*	LT_{50}: 23.67 sec (at 10% v/v)	[35]
Punica granatum L. (l)	eth. ext aqu. ext.	*Pediculus humanus capitis*	Mortality: 65 % (eth. ext. 10%) Mortality: 20 % (aqu. ext. 10%)	[38]
Punica granatum L. (p)	eth. ext.	*Tribolium castaneum* larvae & adult	Mortality: 72 % (larvae; 2% top.; 21 days) Mortality: 44% (adults; 2% top.; 21 days)	[39]
Saussurea costus (Falc.) Lipsch (r)	e.o.	*Aedes albopictus* larvae	LC_{50}: 12.41 µg/mL	[40]
Usnea spp.	usnic acids vulpinic acid	*Spodoptera littoralis*	LD_{50}: 8.6 µM/g dry wt.; (-)-usnic acid LD_{50}: 90.8 µM/g dry wt; (+)-usnic acid LD_{50}: 111 µM/g dry wt; vulpinic acid	[41]
Veratrum album L. (rh)	Ace ext benzene/ NH_4OH ext. $CHCl_3$ ext.	*Leptinotarsa decemlineata*	LC_{50}: 8.30 mg/mL (ace. ext.) LC_{50}: 0.025 mg/mL (NH/ben. ext.) LC_{50}: 0.14 mg/mL (CH. ext.)	[42]
Lawsonia inermis L.(l)	+ mercury	*Pediculus humanus capitis*	(ct) 100% treatment; 2 h after the first use	[43]
Rhus coriaria L. (fr)	in olive oil & Soy lecithin	*Pediculus humanus capitis*	(ct) *R. coriaria* sol. was effective against permethrin-resistant lice	[44]
Liquidambar orientalis Mill. (ex)	e.o.	*Reticulitermes flavipes* Kollar *Coptotermes for mosanus* Shiraki	Storax eo. reduced mass losses at 10% concentration.	[45]

Abbreviations: IC_{50}: concentration inhibiting 50% of the parasite growth; KT_{50}: time in minute to 50% knockdown of exposed insects; LC_{50}: the concentration of a chemical in the air (for fumigant activity test of insecticides) or solution that kills 50% of test animals; LD_{50}: the amount of a chemical ingested, injected, or applied to the skin killing 50% of animals; LT_{50}: lethal time for killing 50% of population; ace: acetone; aqu: aqueous; ap: aerial part; ben: benzene; CH: CHC_{13}; conc: concentration; ct: clinical trial; eo: essential oil; eth: ethanolic; ex: exudate; ext: extract; fr: fruit; l: leaf; NH: NH_4OH; p: peel; r: root; rh: rhizome; s: seed; sol: solution; top: topical; wt: weight.

effect [43].

The efficacy of *Rhus coriaria* solution mixed with olive oil and soy lecithin was investigated against permethrin-resistant head lice in patients. The severity of infection and itching reduced significantly after treatment [44].

Different concentrations (1,3,5, and 10%) of the essential oil obtained from *Liquidambar orientalis* tree were tested against termites, *Reticulitermes flavipes* Kollar and *Coptotermes formosanus* Shiraki, using scots pine wood. The wood specimens were exposed to termites for 3 to 4 weeks and then mass losses were calculated after termite attack. The concentration of 10% from essential oil containing cinnamic acid reduced termite attack and showed toxic effects against the insects [45].

Discussion

The control of head lice is a global concern in the current time when the resistance of lice to neurotoxic insecticides is growing. The toxicity of chemical insecticides particularly for children is another limitation, so research on the safe and effective alternatives for pediculosis is of importance [46,47]. PM textbooks have suggested various herbal compounds against pediculosis. In this study, twenty traditional anti-lice formulations were introduced and proven evidence on pediculicidal or insecticidal of the components were presented. The majority of compounds had oily bases (rose oil, olive oil, safflower oil, or bitter almond oil). The mechanism of action for oils is believed to be suffocation by occluding the lice respiratory spiracles. Furthermore, oils facilitate combing and removing lice and nits by lubricating hair [48,49]. Vinegar with a specific effect on nits was the base of some formulations. The combination of vinegar and water loosens the attachment between nits and hair shafts, improving their removal [50].

According to the table 3, some parts of the plants such as seed of *A. graveolens*, aerial part of *Artemisia* species, seed of *L. sativum*, leaves of *M. communis, P. anisum* fruit, *S. costus* root, and *L. orientalis* exudate contain essential oils, showing pediculicidal or insecticidal effect [25-28,32,34,40,45].

R. coriaria fruit, *P. granatum* peel, and aerial parts of *Artemisia* species contain a high quantity of tannins which cause precipitation of membrane proteins and obstruction of lice respiratory system. Therefore, tannin content makes the plant extracts potential anti-lice agents [44,51-55]. Lethal activities of different extracts vary broadly, suggesting the preference of some solvents like ethanol rather than water. Comparing the toxicity of crude extracts or essential oils with their isolated compounds, it is concluded that special isolated compounds show a higher degree of toxicity (lower LC_{50} or higher mortality). Generally, seventeen out of twenty-seven plants have been reported as anti-lice or insecticide agents, so *in vitro* tests or clinical trials for efficacy evaluation and safety assessment for the rest of the plants are recommended. Traditional anti-lice compounds in PM textbooks can be a valuable source for suggesting effective new formulations against lice.

Conflict of Interests

None.

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