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A Comprehensive Review about *Quercus infectoria* G. Olivier Gall

Sayyede Fatemeh Askari¹, Amir Azadi², Bahia Namavar Jahromi^{3,4}, Mojgan Tansaz⁵, Asghar Mirzapour Nasiri⁶, Abdolali Mohagheghzadeh^{1,7}, Parmis Badr^{7,8*}

¹Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

²Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran. ³Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

⁴Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

⁵Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

⁶Department of Natural Resources and Water Management, Khorramabad, Iran.

⁷Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

⁸Phytopharmaceutical Technology and Traditional Medicine Incubator, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Due to an interaction between gall wasp *Andricus sternlichti* Bellido and *Quercus infectoria* G.Olivier from Fagaceae, the oak galls with a wide range of industrial and pharmaceutical applications are produced. *Quercus infectoria* galls have been well-known by both ethnopharmacology and traditional medicine of Iran. The aim of current study was a comprehensive collection of Persian scholars' notions and recent findings about medicinal effects of this gall. Sixteen traditional manuscripts of one millennium were sought by two keywords ("Afs" and "Mazu". Arabic and Persian names of *Quercus* gall, respectively), and relevant articles till October 2018 were reviewed. In traditional manuscripts, three main dosage forms from gall including decoction, powder, and poultice were found. They had been prescribed for about of thirty disorders. Except for one clinical trial, other articles described related to animal studies and antimicrobial effect evaluation. Since *Quercus infectoria* gall as an endemic natural product of Iran is a valuable source for export, ethnic usages and pharmaceutical applications, the outcomes of this study can be beneficial for researchers involved in development of natural medications.

Keywords: ethnopharmacology; plant tumors; Quercus infectoria G.Olivier; traditional Iranian medicine

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Introduction

Plant galls or cecidia are hypertrophic or hyperplasic cells, tissues, or organs induced by parasitic organisms [1]. One of the most important hosts prone to such abnormal outgrowth is *Quercus infectoria* G.Olivier from family Fagaceae. Grown vastly in Middle Eastern countries like Cyprus, Syria, Turkey, Iraq and Iran, *Q. infectoria* is a small tree about 2.5 m high with 4-6 cm long leaves, and acorn fruits that are narrow scaly and cylindrical [2-4]. One habitat rich in *Q. infectoria* trees is Zagros forests of Iran, particularly in West Azerbaijan,

^{*}Corresponding author: badrp@sums.ac.ir

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Kurdistan and Lorestan (figures 1a, 1b and 1c) [5]. Originated from Celtic language, *Quercus* means "beautiful tree", and *infectoria* refers to the process of producing galls as an infection [6-8]. Gall wasps such as *Diplolepis rosae* L., *Asterodiaspis quercicola* Bouche, *Chionaspis lepineyi* Balachowsky, *Andricus curtisii* Mueller, *Cynips quercus* Fourcroy and *Andricus sternlichti* Bellido (the gall-inducer in Iran) are responsible for this process (figure 1d and 1e) [9-11].



Figure 1. a) Habitat of *Quercus infectoria* trees in Lorestan province of Iran; b) One *Q. infectoria* tree; c) Leaves and fruits of *Q. infectoria*; d) A gall wasp, e) A larva living inside the gall (all captured by the author)

Proliferation and development of host cells are changed after laying eggs by female wasps. When the larva is growing, the gall is formed simultaneously. Circular tunnels in galls show that the mature wasp has emerged (figure1e) [6,12]. Application of Q. infectoria galls dates back to ancient times when people used them as dyeing agents to provide permanent paintings in their natural surroundings. Some old drawings painted using a combination of the gall, common madder (Rubia tinctorum L.) extracts, blood and bear fat have remained on stones (figure 2a) [13]. Moreover, *Q. infectoria* gall has been one of the essential ingredients of natural dyes for carpet varns to increase their quality and durability (figure 2b) [14,15]. This industrial usage in addition to medicinal indications has been mentioned in medieval manuscripts. So-called "Afs" or "Mazu" (Arabic and Persian names of Quercus gall, respectively) in Traditional Iranian Medicine, galls cold (in first degree) and dry (in second degree) temperament shows intensive astringent effect [16,17]. Ethnic applications of gall are emollient for napkin rash, anti-infective after circumcision, pain killer for toothache, and protection from evil eye (figure 2c and 2d) [18].

The current study was conducted to cover a comprehensive review on both traditional applications in a millennial timespan and recent findings.



Figure 2. Ethnic applications of the gall in Lorestan province; a) An ancient pictograph on mountain stone colored by a mixture containing gall extract, Koohdasht, Lorestan, Iran (Cultural Heritage in Handicrafts and Tourism Organization of Iran, Registration No. 14300) [13];
b) The custom of application gall as a natural dye for carpet yarns in Lorestan; c) Ethnic belief of using a string of gall for new-born babies to protect them from evil or harm; d) A string of gall, one type of talisman as a way to ward off misfortune by evil eye (all captured by the author)

Methods

In order to collect applications of Q. infectoria gall, sixteen traditional references, highlyreferred texts of medieval era written by the most credible scholars of Materia Medica from one millennium (10th to 20th century) were studied. "Afs" and "Mazu" were sought as keywords in "Ketab al-Abnia an Haqaeq al-Adwia" (10thAD), "Al-Mansuri fi-Tib" (10thAD), "Al-Hawi" (10thAD), "Zakhire Kharazmshahi' (11thAD), "Al-Aghraz al-Tibbia wa-al Mabahess al-Alaiia" (11thAD), The Canon of Medicine (vol.2) (11thAD), "Umdat al-Tabib fi Marifat al-Nabat" (12thAD), "Kitab al-Jami li-Mufradat al-Adwiya wa al-Aghdhiya" (13thAD), "Ikhtiarat Badiee" (13thAD), "Al-Shamel fi al-Sanaate al-Tibiye al-Adwia wa al-Aghziye" (13th AD), "Hadiqat al-Azhar fi Mahiyyat al-Ushb wa-l-Aggar" (16thAD), 'Tadhkira'' (17thAD), "Tohfata al-Momenin' (17thAD), "Makhzan-al Adviyeh" (18thAD), "Khazaen Al-Molouk" (19thAD), and Useful Plants of Iran and Iraq (20thAD) [16-31]. References Latin equivalents names were chosen according to previous publication [32] were checked manually. Recent studies by October 2018 were found by searching in Google Scholar "Quercus infectoria and PubMed, using G.Olivier gall" as the keyword. Review articles papers related to multi-component and formulations were excluded.

Results and Discussion

Desired galls have been described as green, jagged, and perforation-free, but medicallyunusable galls are yellow, flattened, light and perforated [16]. The gall with cold and dry temperament had been provided in three main dosage forms (decoction, powder, and poultice), targeting different tissues like gastrointestinal tract, oral cavity, nose, eye, anus, vagina and skin (table 1) [17]. Moreover, the processed gall (burnt and then extinguished in alcohol or salty vinegar) was suggested for special indications like hair dying and stopping hemorrhage. Daily dosage of the gall is one "Deram" (approximately 3.5 g) to one "Misqal" (approximately 4.5 g). If there is no access to gall for preparations, six natural products can be used as substitutes: Punica granatum L. (peel), Q. infectoria (fruit, fruit hull), Tamarix gallica L. (fruit), Terminalia citrina Roxb. ex Fleming (fruit), Myrtus communis L. (fruit), and Juniperus sabina L. (fruit). The gall worsens lung and throat disorders like hoarseness and cough. Long-term intake of hydrolysable tannins with astringent effect had similar adverse effects like irritation of gastric mucosa, nausea, and vomiting on mucous membranes [33]. Application of Astragalus tragacantha L. (exudate), or Acacia nilotica (L.) Delile (exudate), or Apium graveolens L. (seed) can relieve or modify disadvantages of gall [19,25,26,30]. Recent relevant articles have been summarized in tables 2 and 3 divided into clinical, animal and in vitro studies.

 Table 1. Traditional dosage forms and indications of Quercus gall

Dosage form	Administration	Indications
Decoction	Hair dye (Khazab ¹)	Hair greying
	Mouthwash (Mazmazeh ²)	Aphtha, dental cavity, pus
	Oral	Diarrhea, erysipelas, hemorrhage, herpes, hypermenorrhea, leprosy, pemphigus, psoriasis, ulcerative colitis, umbilical hernia, vaginitis
	Rectal	Abscess, inflammation, prolapse
	Vaginal	Prolapse, vaginitis
Powder	Ocular (Kohl ³)	Blepharitis, epiphora, scabies
	Nasal (Nafoukh ⁴)	Epistaxis
	Buccal (Sanoun ⁵)	Aphtha, dental cavity, pus, toothache, wound
Poultice	Topical (Zemad ⁶)	Hyperhidrosis, malodor
Founde	Rectal	Abscess, inflammation

¹Traditional cosmeceutical for changing hair color; ²liquid medication for gargling; ³powder-like formulation for ocular disease; ⁴fine-particle powder as an inhaler; ⁵buccal formulation for tooth and gum applications; ⁶semisolid formulation for topical applications

Gall with great potential for treatment of disorders was the main focus of the current study.

Based on traditional Iranian medicine (TIM), gall is a dying agent for grey hairs, and its topical preparation eliminates malodorous sweat and heavy perspiration. Wound healing, anti-bleeding, and antibacterial properties of gall reflect to the astringency. The powder of gall ("Nafoukh", as a kind of TIM nasal powder from which is used without adding any liquid) controls nasal bleeding. Its decoction has been suggested for diarrhea, hemorrhage, and hypermenorrhea. As effective as Povidone Iodine, wound dressings of gall has been used in animal studies [40-42]. Treatment of many inflammation-related diseases like ulcerative colitis, vaginitis, blepharitis, and rectal abscess is justifiable, because gall has a significant effect on function of macrophages and neutrophils, causing release of inflammatory mediators and lytic enzymes [47]. One clinical study on gall mouthwash has shown promising result for chronic gingivitis [34]. The extracts were traditionally used for aphtha, dental cavity, toothache, and oral wounds. Anti-bacterial effect of gall methanol extract has been proved against oral pathogens such as Streptococcus mutans, Streptococcus salivarius, Staphylococcus aureus, Lactobacillus acidophilus, Streptococcus sanguis, Porphyromonas gingivalis and Fusobacterium nucleatum which cause dental caries and periodontitis [48,49]. Vaginal decoction of gall, both aqueous and in vinegar, has been prescribed for vaginitis [30]. Recent studies have shown antifungal effect of its ethanol extract against C. albicans [70]. Animal studies have proved the cardiovascular effect. antidiabetic activity. hepatoprotective, and anti-inflammatory effects [37-40,49]. Oral preparations of gall [18-31], have been suggested for herpes ('Namle" [21,80]), erysipelas ("Homra" [21,80]), leprosy ("Akeleh" [81]), pemphigus ("Ghorouh-e-saive" [31,82]), and psoriasis ("Ghooba" [83, 84]), all of which are among challenging diseases. Presence of flavonoids, alkaloids, and phenols, particularly tannins, in gall has been reported through preliminary phytochemical screenings [85]. Its anti-inflammatory properties, antibacterial and anti-fungal effects are the result of such compounds. The astringency caused by tannins leads to the cure of diarrhea, hemorrhage, oral wounds, and hypermenorrhea.

Clinical trial	D (***)	T / /	0.4	D (
Method	Participants	Intervention	Outcome	Ref
Randomized controlled, double-blind, cross-over	n=20, (20-30 YO) with generalized chronic gingivitis	Gall Aq Ext and Listerine mouthwash, 10 ml, once daily, 30 seconds, 7 days	Efficient but less than of Listerine	[34]
Animal studies				
Assessment		Method	Outcome	Ref
Cardiovascular effects of Met Ext in rabbit	(4×6), 45 days, C: normal rabbit chow, normal chow + 1.5 g/kg gall, high-fat diet, high fat diet + gall		Decrease in total cholesterol, LDL, TG, and atherogenic indices of plasma in high fat diet	
Antidiabetic activity of Met & Aq Ext in rat	(5×6), p.o, C: DW, P: acarbose (50 mg/kg), N: glucose (sucrose) solution, Met Ext, Aq Ext		Blood glucose lowering effect of Met & Aq Ext at 500 mg/kg	[36
Hepatoprotective effect of gall Aq Ext against liver injury induced by CCl ₄ in rat	(7×5), 28 days, p.o, C: DW (1 mL/kg/day), P: silymarin (100 mg/kg/day), CCl ₄ -treated control: DW (1 mL/kg/day), gall (500, 1000 and 2000 mg/kg/day), gall (2000 mg/kg/day)		Prevention of free radical- mediated disorders including inflammation and hepatotoxicity	[37]
Hepatoprotective effect of Aq-Eth Ext in rat	(6×6), p.o, C: CMC (1% w/v), P: Silymarin (100 mg/kg), CCl ₄ (2 ml/kg), gall Ext 200, 400, 600 mg/kg		Hepatoprotective effects of gall	[38
Effects on caecal amoebiasis in mouse	(7×15), C: DW, P: metronidazole (62.5, 125 mg/kg/day), (125,250, 500, 1000 mg/kg/day), 6 days, p.o, <i>Entamoeba histolytica</i> (fecal samples)		Cure in 26% and 13% of mice at a concentration of 500 and of 250 mg/kg/day, respectively	[39]
Wound healing activity in rat	(5×6), p.o, C: gum acacia 2%, Aq Ext (Pet, Etr and Eta fractions 100 mg/kg)		Significant wound healing property (incision, excision and dead space)	[40
Wound healing property in rat	C: 0.9% NaCl, P: povidone iodine, gall water (0.1, 1 and 10 mg/mL) and organic suspension (0.1, 1 and 10 mg/mL)		Significant wound healing property as povidone iodine and saline	[41
Wound healing activity in rat		N: Vaseline [™] Petroleum jelly, 10% Eth Ext, 10% Aq Ext	Gall as a potential antibacterial source and a wound dressing	[42
Spasmolytic activities of Met Ext in rat ileum and pig ileum	Inhibitory effects on spasmogen-induced contractions [loperamide (0.3-10 μg/mL), verapamil (4.9-49 ng/mL), gall (0.1-10 mg/mL)]. Inhibitory effects on the KCl (30 mM)-induced contractions Inhibitory effects of the plant Ext and Loperamide on CaCl ₂ -induced contractions, (12×5), [loperamide (0.1, 3, 1 μg/mL), verapamil (4.9, 14.7, 49 ng/mL), gall (1, 3, 10 mg/mL)]+ CaCl ₂		Spasmolytic but less than loperamide and verapamil	[43
Antibacterial efficacy of an ellagitannin from gall (Qi 4) in mouse	(3×5), Streptomycin-pretreated (streptomycin-resistant <i>E. coli</i> : STEC) mice, C: PBS, infected group, Qi 4 treatment		Effective eradication of colonization of STEC in intestinal tract & prevention renal injury	[44
Analgesic activity in rat	(4×6), i.p, P: morphine sulfate and sodium salicylate (10mg/kg), N: normal saline (10 mL/kg), Met Ext (20mg/kg)		Analgesic activity in hot plate and tail-flick models	[45
Chemopreventive effect against chemically-induced renal toxicity and carcinogenesis in rats	(5×6), kidney tissue &blood & serum Gavage of normal saline, 7 days; a single dose of Fe-NTA on 20 th day; pretreated with gavage of gall (75, 150 mg/kg), 20 days, followed by administration of Fe-NTA on 20 th day; gavage of gall (150 mg/kg), 20 days		Potent chemopreventive agent and Fe-NTA-induced renalcarcinogenesis and oxidative and inflammatory response suppressant	[46
Anti-inflammatory evaluation after oral or topical administration in rat and mouse	Eth Ext Carrageenan induced paw oedema [(4×6), C: saline, P: indomethacin (25 mg/kg), gall Ext (300 and 600 mg/kg, p.o.)], histamine, serotonin and PGE2 induced paw oedema [(5×6), C: saline, P: indomethacin (25 mg/kg), gall Ext (200,400 and 600 mg/kg, p.o.)], PMA induced mouse ear (5×4), C: saline, P: indomethacin (0.5 mg), gall Ext (0.5, 1 and 2.5 mg per ear)		Inhibitory effect on functions of macrophages and neutrophils, release of inflammatory mediators (PGE2, NO, O_2^{-}) and lytic enzymes	[47

(n×m): (n: number of group and m: the number in each group), Aq: Aqueous, C: Control group, DW: Distilled water, Eta: Ethyl acetate, Eth: Ethanol, Etr: Ether, Ext: Extract, i.p: Intraperitoneally, Met: Methanol, N: Negative control group, p.o: Per-oral, P: Positive control group, Pet: Petroleum ether, YO: years old.

Table 3. Recent in	vitro	studies	about	Ouercus	infecto	oria gall.

Assessment	Extract(s) / Tested items	Outcomes	Ref
Antibacterial activity against dental pathogens	Pet, Chl, Met and Aq Exts / S. mutans, S. salivarius, S. aureus, L. acidophilus, S. sanguis	Maximum antibacterial activity against all bacteria by Met Ext	[48]
Antibacterial activity against oral bacteria	Met and Ace Exts / S. mutans, S. salivarius, P.gingivalis, F. nucleatum	Similar antibacterial activity against oral pathogens causing dental caries and periodontitis	[49]
Antibacterial activity	Aq and Eth Exts / S. aureus, MRSA	Significant antibacterial activity against all strains of MRSA	[50]
Growth inhibition of pathogenic bacteria	Met, Eth, Hex, Chl and Aq Exts / E. coli, B. subtilis, S. aureus	Superior antimicrobial activity of Met Ext	[51]
Cell surface hydrophobicity and cell survival of <i>H. pylori</i>	Eth Ext/ hydrophobicity of 10 clinically-isolated <i>H. pylori</i> strains	Significant increase of hydrophobicity, bacteriostatic & bactericidal activities	[52]
Cell surface properties of Shiga toxigenic <i>E. coli</i>	Eth Ext / 5 strains of STEC	Modifying hydrophobic domains, partition the lipids of the bacterial cell membrane, rendering the membrane more permeable and allowing leakage of ions and other cell contents, leading to cell death	[53]
Antibacterial property against <i>E. faecalis</i>	Met Ext / P: sodium hypochlorite (2%) and chlorhexidine (2%), N: dimethyl sulphoxide	Antibacterial property against E. faecalis	[54]
Antibacterial activity against wound bacteria	Aq, Met and Eth Exts / S. aureus, P. aeruginosa, E. coli, Enterobacter spp., P. mirabilis, K. pneumonia, K. oxytoca and C. freundii	Beneficial effect as an antiseptic	[55]

Assessment	Extract(a) / Tested items	Outcomer	Det
Assessment	Extract(s) / Tested items	Outcomes	Re
Antibacterial activity	Pet, Eta and Eth Exts / successive extraction with Ace followed by Met, Aq extraction / S. aureus, S. epidermidis, B. subtilis, E. coli, S. typhimurium, S. enteritidis, P. aeroginosa	The highest inhibition zone diameter against <i>S</i> . <i>aureus</i> by Met Ext	[56
Antibacterial activity	Aq and Ace Exts / S. aureus, S. epidermidis, B. subtilis, E. coli, S. typhimurium, P. aeruginosa	Similar antimicrobial activity on bacterial species	[57
Antimicrobial activity against MRSA	Eth Ext / C: S. aureus, MRSA	Effective on MRSA and <i>S. aureus</i> by resulting in hypersensitivity to low and high osmotic pressure	[58
Antimicrobial activity	Crude Ext / E. coli, K. pnuemoniae, S. typhi, S. marcescens, V. cholerae, V. parahaemolyticus, E. faecalis, P. aeruginosa	Antimicrobial activity and an alternative way for human treatment	[59
Antibacterial activity	Aq and Eth Exts / S. aureus, coagulase negative Staphylococcus, Acinetobacter sp., E. coli, K. pneumoniae	Potential use as one of the effective phytotherapeutic agents against MDR bacteria	[60
Morphological and ultrastructural changes in cell structure	Eth Ext / Enterohaemorrhagic E. coli	Complete loss of surface appendages and disruption of the cytoplasmic membrane and leakage of the internal contents	[61
Comparative proteomic analysis of differential proteins	Aq Ext / MRSA	Dose-dependent bactericidal (by involving in energy metabolism and protein stress)	[62
Biofilm removal activity	Met, Eth and Ace Exts / S. mutans	Potentially good sources of antibacterial and biofilm disinfection agent	[63
Inhibition of virulence factor	Met Ext/quorum sensing-controlled of P. aeruginosa	Down regulating the production of virulence factor	[64
<i>In vitro</i> antifungal activity of a 29-kDa glycoprotein purified from the gall	Treated 29-kDa protein with NaIO ₄ and pronase	Inhibition of mycelial growth of R. solani	[65
Antifungal activity	Met and Aq Exts / C. albicans, C. krusei, C. glabrata, C. parapsilosis and C. tropicalis	Displaying substantial anti-Candida activity	[66
Evaluation of antifungal activity	Chl, Eth, Ace, Eta and Aq Exts /C: clotrimazole, Penicillium sps., Aspergillus sps.	Good antifungal activity as compared to other extracts by Chl Ext	[67
Antifungal activity	Aq and Eth Exts / C. albicans and C. glabrata	Eth Ext: more effective against <i>C. albicans</i> while Aq Ext more effective against <i>C. glabrata</i>	[68
Larvicidal activity	Eta, Met, Ace, Nbu Exts / Anopheles stephensi Liston	The most larvicidal activity by Eta Ext	[69
Effects on growth of intestinal protozoa parasite	Hex, Dic and Met Exts /Blastocystis hominis, C: Metronidazole	The highest anti-protozoa activity by Met Ext	[70
Cytotoxicity and the effect on melanin synthesis in B16/F10 melanoma	Met Ext / C: Kojic acid	Inhibition of melanogenesis in non-toxic concentrations	[71
Tyrosinase inhibitory activity	Met Ext (Pet, Chl, Eta and Met fractions)	Potent antityrosinase effect by Eta-Met fraction	[72
Cytotoxic effects towards cervical (Hela) and ovarian (Caov-3) cancer cell lines	Met, Eth and Aq Exts / HeLa and Caov-3 cancer cell lines and MDCK (nonmalignant cell line)	Anticancer effect (a novel antiproliferative agent)	[73
Proliferation and activity of human fetal osteoblast cell line	Aq Ext	Enhancing Cell proliferation and increasing ALP and osteocalcin levels	[74
Two new compounds from the gall with nitric oxide and superoxide inhibiting ability	Eth Ext	Exhibiting NO and O ₂ (related to pathophysiology of almost all ailments) inhibitory effect	[75
Salivary amylase inhibition	Gallotannin of gall	Inhibitory effect on HSA	[76
Antioxidant activity	Eth Ext	Potent antioxidant activity in chemical and biological models	[77
In vitro immunomodulatory activity	Treated macrophages with Aq Ext	An increase in phagocytic activity of macrophages	[78
Lipase inhibitory activity	Eth Ext	A potential for treatment of obesity	[79

Ace: Acetone, Aq: Aqueous, B. subtilis: Bacillus subtilis, C: Control group, C. albicans: Candida albicans, C. freundii: Citrobacter freundii, C. glabrata: Candida glabrata, C. krusei: Candida krusei, C. parapsilosis: Candida parapsilosis, C. tropicalis: Candida tropicalis, Chl: Chloroform, Dic: Dichloromethane, E. coli: Escherichia coli, E. faecalis: Enterococcus faecalis, Eta: Ethyl acetate, Eth: Ethanol, Ext: extract, F. nucleatum: Fusobacterium nucleatum, H. pylori: Helicobacter pylori, Hex: Hexane, K. oxytoca: Klebsiella oxytoca, K. pneumoniae: Klebsiella pneumoniae, L. acidophilus: Lactobacillus acidophilus, MDR: multidrug resistant, Met: Methanol, MRSA: Methicillin-resistant S. aureus, N: Negative control group, Nbu: N-butanol, P: Positive control group, P. aeruginosa: Pseudomonas aeruginosa, P. gingivalis: Porphyromonas gingivalis, P. mirabilis: Proteus mirabilis, Pet: Petroleum ether, R. solani: Rhizoctonia solani, S. aureus: Staphylococcus aureus, S. enteritidis: Salmonella enteritidis, S. epidermidis:Staphylococcus epidermidis, S. marcescens: Serratia marcescens, S. mutans: Streptococcus mutans, S. salivarius: Streptococcus salivarius, S. sanguis: Streptococcus sanguinis, S. typhi: Salmonella typhi, S. typhimurium: Salmonella typhimurium, V. cholera: Vibrio cholera, V. parahaemolyticus: Vibrio parahaemolyticus

Conclusion

The traditional usages of *Q. infectoria* gall have been mentioned in the present study. Since no clinical study supporting these ideas was found, they are considered as notions for further studies, leading to potential new drugs from this endemic natural product.

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Author contributions

Sayvede Fatemeh Askari participated in designing the work, reviewing recent and traditional literature, and drafting the manuscript. Asghar Mirzapour Nasiri prepared data about Lorestan. Abdolali Mohagheghzadeh, Amir Azadi, Bahia Namavar Jahromi, Mojgan Tansaz and Parmis Badr contributed in conception of the work and revised the manuscript critically and also Parmis Badr designed the work, contributed in drafting, and critical revision.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

TIM: traditional Iranian medicine