The traditional uses, phytochemistry, pharmacological, and botanical description of *Quercus infectoria galls* (Mazuphal): A review

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**Abstract**

Ethno-pharmacological relevance- In Unani system of medicine *Quercus infectoria galls* (QIG) (known as Mazuphal), have a long history of use in the management of many human ailments like diarrhea, hemorrhage, skin diseases, and many other. The QIG is a protective product of small shrub *Quercus infectoria* and its medicinal applications of have become increasingly popular in Greece, Syria, Iraq and Iran.

**Aim**- The aim of the present paper is to provide a contemporary reviewed on the traditional uses and its toximomy, phytochemical, analytical methods, pharmacological activities, toxicology, and drug interactions of QIG to assess the ethnopharmacological uses, explore its therapeutic potential, and identify future opportunities for research.

**Materials and methods**- Information on studies of QIG was collected from the Internet (using Google Scholar, Baidu Scholar, Elsevier, ACS, Pubmed, Web of Science, CNKI, and EMBASE) and libraries. Additionally, information was also obtained from local books and PhD and M.D.'s dissertations.

**Results**- QIG has played an important role in traditional Unani medicine. The main bioactive metabolites of QIG include tannins, phenolic acids, flavonoids, triterpenoids, steroids etc. Scientific studies on the QIG extract and its components have shown its extensive range of pharmacological activities, such as cholinesterase and monoamine oxidase-inhibitory, antitumor, anti-hyperpertension, antidiabetic, antimicrobial, insecticidal, antiparasitic, antioxidant, and anti-inflammatory.

**Conclusions**- In this review the traditional knowledge, ethnopharmacological, phytochemical, pharmacological, and analytical methods of QIG were highlighted, which gives the proper information for future studies and business exploration. QIG has a huge potential for pharmaceutical and nutraceuticals applications. Moreover the toxicity studies of QIG be reported for the enduring the safety. Additional investigations are recommended to transmute the ethnopharmacological claims of this plant in folklore medicines into scientific rationale-based information. Research on pharmacokinetics studies and potential drug interactions with standard care medications is still limited, which calls for additional studies particularly on humans. Further assessments and clinical trials should be performed before it can be integrated into medicinal practices.

**Keywords**: *Quercus infectoria galls*, Ethnopharmacology, Phytochemistry, Pharmacology

1. INTRODUCTION

The flora is a valuable creation of nature which acts as a vital gift for mankind by providing a potent source of therapeutic materials to handle the medical conditions and maintain human wellbeing. Indian traditional systems of medicine like Ayurveda, Siddha and Unani, mainly based on plant medicine which managed many ailments effectively for ancient times1-2.

*Quercus Infectoria* Olivier is a small shrub, widely distributed in Greece, Iran, Iraq, Syria and the Galls (QIG) is its protective product. The QIG is popular traditional (Unani) herbal medicines that can be used as a decoction (Joshanda) or rinse the mouth because relieved the tonsillitis, directly applied on the inflamed skin diminishes swelling and restores the contractibility of the uterine wall after parturition as a sitz bath (aabzan)3-4.

Besides the medicinal value, the QIG have become increasingly popularity in nutraceuticals and cosmetics as an anti-aging agent. It also known for producing many secondary metabolites with antibacterial5-6, Anti-inflammatory activities5,6,7, antitumor, and anti-viral8-

*Mazu* (*Quercus infectoria* Olivier), the oak galls is a special natural outgrowth on the new branches on the oak tree. These are formed through the irritation of larva of the *Adleria gallae tinctoria*, of genus *Cynips*, and order *Hymenoptera*. The gall development is commenced by a female insect that has an ovipositor, known as Latrelle/ the *borer* (*terebrarum*), with lateral teeth. Employing this arrangement, they are enabled to hole the laminae, cortical parts of a plant to deposit their eggs, along with acrid material. The egg grows as a larva, and the larva possibly excites the outgrowth as a result of infection and encircled by the soft cells of emerging galls as a response.
By using plant materials like carbohydrates the larva gradually grown into the pupa by making a central cavity. The dimension of galls also going to be reduced due to the disappearance of feeding materials. The size of the galls also depends upon that the egg or larva reached its maturity and change into a chrysalis. The mature gall wasp or chrysalis escapes out into the outer environment by bores the gall with its mandible11,12.

The collection of galls is always take place before the escape of insect because at that time the medicinal property of galls is maximum. During the process of gall formation, the complexion changes from a bluish-grey to olive green and finally appears as white. Fully matured dry galls are flat and shiny as if varnished and chestnut brown, but more usually rough and of greyish-brown colour. After drying the gall, classified into two varieties. Out of which the first have outer bluish surface, non-perforated and weightier, it reflected the best quality and more effective. Even though the second one have outer white surface, perforated and light weightier, consider as a low quality. The actual time at which the gall is collected when it has inner tissue is soft, deep greenish-yellow in colour, very stringent in taste and feel sweet after taste11,12.

2. BOTANICAL DESCRIPTION

2.1 Classification17,18,19,20,21

Kingdom

Plantae

Subkingdom

Tracheobionta - Vascular plants

Super division

Spermatophyta – Seeded plants

Division

Magnoliophyta – Flowering plants

Class

Magnoliopsida - Dicotyledons

Subclass

Hamamelidae

Order

Fagales

Family

Fagaceae – Beech family

Genus

Quercus L. - Oak

Species

Quercus infectoria Olivier – Aleppo oak

2.2 Plant Description

*Quercus infectoria* is a deciduous, semi-evergreen medium-sized tree about 2 meters high, and have up to 4 cm long leaves on drooping branches. It grows up to 6 feet with a medium rate in low land, moist soil and mountain valleys. The root is cylindrical, branched, and shows a fibrous fracture, 6-10 cm long and 4-8 mm in thickness. The bark: The bark is slightly grey. Leaves: The leaves are 4-6 cm long, very rigid, often 5 glabrescent with spinous teeth, short petiole, elongate and sinuate. Flowers: The flowers are unisexual. The male flowers are tangled into hanging, axillary catkins with 6-8 tepals perigone and 6-10 stamens. The female sessile flowers are single or in small groups in the leaf axis of dropping stipules. The perigone is 6 tipped with an inferior 3 walled parenchyma, a ring of sclerenchymatous cells, and a small inner zone of radially walled parenchyma surrounding the central cavity. The parenchymatous tissues contain abundant starch, masses of tannin, rosettes and prisms of calcium oxalate, and the rounded so-called ‘Lignin bodies’, which give a red colour with phloroglucinol and hydrochloric acid17,18,19,20,21.

2.6 Organoleptic Properties of QIG

Colour: Bluish green or olive green externally and pale buff internally.

Odour: Odourless.

Taste: Astringent followed by the sweet taste.

Shape: Spherical in shape with short basal stalk.

Size: 10 – 30 mm

Weight: 2 – 4 gram

Powder: Yellowish-white to light brown shining colour17,18,19,20,21.

3. TRADITIONAL USES OF QIG

In the Unani system of medicine, QIG have been used for ages to treat various diseases. The drug has pharmacological actions such as analgesic, anti-inflammatory, antipyretic, antiseptic, hemostatic, deodorant, desiccant, powerful astringent, germicidal sedative, expectorant, hypnotic, local anaesthetic and it is used in epistaxis, gingivitis, leucorrhoea, rectal prolapse, uterine prolapse, wounds etc. as shown in Table.1 17,18,19,20,21,22,23.

According to Vaid’s, Mazu is used as an antidote in many plants poisoning. It is also added in ingredients of medicine for a health tonic. It is used to cure fevers which are frequent and irregular. Its powder mixed with water is applied on breast wounds and in the haemorrhoids. It helps to treat leucorrhoea and gonorrhoea23.
3.1 According to Unani Literature 24,25,26,27,28

3.1.1 Af’āl (Action)
Hābis-i-Haiz, Qābīd (Astringent), Mane Ruqāf(Antiepistaxis), Hābis-i-Dam (Hemostyptic), Dāh-i-Ta’affun (Antiseptic), Mujaffīf (Desicent), Muqawwī (Astringent), Mane Ruaqf(Antiepistaxis).

3.1.2 Istʻemāl (Therapeutic use)
‘Irq-i-mufrit, Qurū’ al-am’a’(Intestinal ulcers), Ishāl al k hon(Blood stained Stools), Quā’ dahan (stomatitis), Waram al-Litha (Teeth and Gum tonic)

3.1.3 Parts used: Galls

3.1.4 Mizāj (Temperament): The Unani physicians have unanimously described the Temperament of Mazu as Bārid 2° and Yābis 2° (Cold and Dry in the second degree)

3.1.5 Muzir (Adverse effect): Harmful for throat and chest.

3.1.6 Musleḩ (Corrective): Kateetra (Astragalus tragacanth L.), Samag-e-arabi (Acacia arabica L.)

3.1.7 Badal (Substitute): Post-e anar (Bark of Prunus domestica L.)

3.1.8 Dose: 3-5 gram

3.1.9 Mashur Unani Murrakabāt (Important Unani formulations)
Majoon muqawwi Rahem, Safoof-e hābis, Safoof-e muʻallif, Sanoon-e zarad, Sunoon-e muqawwi dandān, Qurs-e bandish Khoon, Majoon-e hamal ambarī Alvi khan

4. PHYTOCHEMICAL COMPOSITIONS
The gall contain about 50-70% tannic acid and a small amount of free gallic acid 2-4%, ellagic acid, nytcanthic acid, rubric acid. The galls contain 50-70% of the tannin known as gallotannic acid. This is a complex mixture of phenolic acid glycosides varying greatly in composition. Galls were also found to contain gum, sugar, volatile oil, anthocyanins, Methyl betulate, methyl linoleate, sitosterol, beta-sitosterol, amentoflavone, hexamethyl ether and isocryptomerin.22,29,30.

5. ELEMENTAL COMPOSITION OF MAZU SABZ (QUERCUS INFECTORIA)
The Elemental composition of Quercus infectoria indicated the presence of important minerals such as calcium (Ca), magnesium (Mg), phosphorus (P), oxygen (O2), potassium (K), aluminium (Al), carbon (C), zinc (Zn), iron (Fe), manganese (Mn), nickel (Ni) and silica (Si) (Table 2).

| Elements (in ppm) | Quercus infectoria (in 5% HCl) |
|------------------|---------------------------------|
| Calcium (Ca)     | 12,700                           |
| Phosphorus (P)   | 11,100                           |
| Potassium (K)    | 2,23,633                         |
| Magnesium (Mg)   | 20,933                           |
| Iron (Fe)        | 3,587                            |
| Manganese (Mn)   | 100                              |
| Zinc (Zn)        | 329                              |
| Nickel (Ni)      | 213                              |

Table 2: Elemental composition of QIG by using atomic absorption spectrophotometer
Table 3: Recent clinical and animal studies of Quercus infectoria gall.

| 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 |

Table 4: 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 | 35 |
| 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 CCl4 in rat | (7×5), 28 days, p.o. C: DW (1 mL/kg/day), P: silymarin (100 mg/kg/day), CCl4-treated control: DW (1 mL/kg/day), gall (500, 1000 and 2000 mg/kg/day), gall (2000 g/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: MMC (1% w/v), P: Silymarin (100 mg/kg), CCl4 (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. Entamoeba histolytica (fecal samples) | Cure in 26% and 13% of mice at a concentration of 500 and 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 | (4×6), P: Solc Oseryl® jelly, 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 CaCl2-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)+ CaCl2] | Spasmolytic but less than loperamide and verapamil | 43 |
| Antibacterial efficacy of an ellagitannin from gall (Q4) in mice | (3×5), Streptomycin pretreated (streptomycin-resistant E. coli STEC) mice, C: PBS, infected group, Q4 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 (10 mg/kg), N: normal saline (10 mL/kg), Met Ext (20 mg/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 | Potent chemopreventive agent and Fe-NTA-induced renal carcinogenesis and oxidative and inflammatory responses 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, O2−) and lytic enzymes | 47 |
### Table 5: Recent in vitro studies about *Quercus infectoria* gall.

| Assessment                                             | Extract(s) / Tested items                                                                 | Outcomes                                                                 | Ref. |
|--------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------|
| Antibacterial activity against dental pathogens        | Pet, Chl, Met and Aq Ext / *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 Ext / *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 Ext / *S. aureus, MRSA*                                                      | Significant antibacterial activity against all strains of MRSA            | 50   |
| Growth inhibition of pathogenic bacteria                | Met, Eth, Hex, Chl and Aq Ext / *E. coli, B. subtilis, S. aureus*                        | Superior antimicrobial activity of Met Ext                                | 51   |
| Cell surface hydrophobicity and cell survival of *H. pylori* | Eth Ext / hydrophobicity of 10 clinically-isolated *H. pylori* strains                  | Significant increase of hydrophobicity, bacteriostatic & bactericidal activities | 52   |
| Cell surface properties of Shiga toxigenic *E. coli*    | 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 *E. faecalis*            | Met Ext / P: sodium hypochlorite (2%) and chlorhexidine (2%), N: dimethyl sulfoxide       | Antibacterial property against *E. faecalis*                             | 54   |
| Antibacterial activity against wound bacteria           | Aq, Met and Eth Ext / *S. aureus, P. aeruginosa, E. coli, Enterobacter spp., P. mirabilis, K. pneumonia, K. oxytoca and C. freundii | Beneficial effect as an antiseptic                                        | 55   |
| Antibacterial activity                                  | Pet, Eta and Eth Ext / successive extraction with Ace followed by Met, Aq extraction / *S. aureus, S. epidermidis, B. subtilis, E. coli, S. typhimurium, S. enteritidis, P. aeruginosa | The highest inhibition zone diameter against *S. aureus* by Met Ext        | 56   |
| Antibacterial activity                                  | Aq and Ace Ext / *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 *S. aureus* by resulting in hypersensitivity to low and high osmotic pressure | 58   |
| Antimicrobial activity                                  | Crude Ext / *E. coli, K. pneumoniae, 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 Ext / *S. aureus*, coagulase negative *Staphylococcus, Acinetobacter* spp., *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 Ext / *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   |
| In vitro antifungal activity of a 29-kDa glycoprotein purified from the gall | Treated 29-kDa protein with NaI04 and pronase                                         | Inhibition of mycelial growth of *R. solani*                             | 65   |
| Antifungal activity                                     | Met and Aq Ext / *C. albicans, C. krusei, C. glabrata, C. parapsilosis and C.*          | Displaying substantial anti-Candida activity                              | 66   |
## Evaluation of antifungal activity
|        |      | Good antifungal activity as compared to other extracts |
|--------|------|-------------------------------------------------------|
| **Chl, Eth, Ace, Eta and Aq Exts /C: clotrimazole, Penicillium spp., Aspergillus spp.** | **Antifungal activity** | **Aq and Eth Exts / C. albicans and C. glabrata** | **Eth Ext: more effective against C. albicans while Aq Ext more effective against C. glabrata** |
| **Eta, Met, Ace, Nbu Exts / Anopheles stephensi Liston** | **Larvicidal activity** | **The most larvicidal activity by Eta Ext** |
| **Hex, Dic and Met Exts / Blastocystis hominis, C: Metronidazole** | **Effects on growth of intestinal protozoa parasite** | The highest anti-protozoa activity by Met Ext |
| **Met Ext / C: Kojic acid** | **Cytotoxicity and the effect on melanin synthesis in B16/F10 melanoma** | Inhibition of melanogenesis in non-toxic concentrations |
| **Met Ext (Pet, Chl, Eta and Met fractions)** | **Tyrosinase inhibitory activity** | Potent antityrosinase effect by Eta-Met fraction |
| **Met, Eth and Aq Exts / HeLa and Caov-3 cancer cell lines (nonmalignant cell line)** | **Cytotoxic effects towards cervical (Hela) and ovarian (Caov-3) cancer cell lines** | Anticancer effect (a novel antiproliferative agent) |
| **Aq Ext** | **Proliferation and activity of human fetal osteoblast cell line** | Enhancing Cell proliferation and increasing ALP and osteocalcin levels |
| **Eth Ext** | **Two new compounds from the gall with nitric oxide and superoxide inhibiting ability** | Exhibiting NO and O2•− (related to pathophysiology of almost all ailments) inhibitory effect |
| **Gallotannin of gall** | **Salivary amylase inhibition** | Inhibitory effect on HSA |
| **Eth Ext** | **Antioxidant activity** | Potent antioxidant activity in chemical and biological models |
| **Treated macrophages with Aq Ext** | **In vitro immunomodulatory activity** | An increase in phagocytic activity of macrophages |
| **Eth Ext** | **Lipase inhibitory activity** | A potential for treatment of obesity |

### CONCLUSION

Mazu (Gall of Quercus infectoria) has been widely used in Unani system of medicine as a safe and effective medicine, to treat wide range of indications since times immemorial. It belong to temperament cold 1<sup>st</sup> grade and dry 2<sup>nd</sup> grade of the group of drug classification by Unani Physician. It has been subjected to quite extensive phytochemical, experimental and clinical investigations. Experimental studies have established its analeptic, antibacterial, anti-carcinogenic, anti-inflammatory, antioxidant, larvicial and wound healing effect etc. These scientific studies have widen the scope of its application for therapeutic purposes in clinical practice. In the present health consequences, search for newer medicines is going on. These findings may be helpful and show the way in the development of newer and standard medicines. Rigorous experimental studies and clinical trials may be designed to generate evidences for human use.

### Conflict of Interest

The authors declare to have no conflicts.

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