WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 17, 195-206. Review Article ISSN 2277– 7105

QUERCUS INFECTORIA GALLS: PHYTOMEDICINE PROMISSING FOR TREATING CANDIDIASIS - AN AREVIEW

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Article Received on
31 October 2017,
Revised on 21 Nov. 2017,
Accepted on 11 Dec. 2017
DOI: 10.20959/wjpr201717-10475

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ABSTRACT

There are global problems of multiple antifungals resistance as well as emergence of new and resurrection of previously eradicated diseases. Most of the current antimicrobial drugs simply reduce the level of growth of bacteria or fungi and some of them are very toxic to the kidney, the hematopoietic and central nervous system. With the rising problems of side effects and limited efficacy of antifungal drugs, there is an urgent need for the development of alternative antifungal substances and researchers are nowadays turning to natural products from plants, as their main source of bioactive compounds with antifungal and antimicrobial properties, to complement the existing synthetic antifungal drugs that are gradually becoming less potent against pathogenic micro-organisms. Medicinal plants remain a rich source of novel therapeutic agents. Many plant species are still unevaluated chemically or biologically. Several studies regarding the action of plant extracts against some pathogenic fungi have been performed. The Gall of *Quercus infectoria* is described in detail in ethnobotanical and literature to possess various pharmacological actions such as analgesic, antidote, antiinflammatory, antipyretic, antiseptic, antistomatitis, expectorant, germicidal, hypnotic, hypoglycaemic, powerful astringent, sedative, styptic, tonic, tonic to teeth and gum, and wound healing, antibacterial, antiviral, antifungal and many more. The galls have been documented to possess stringent and antimicrobial properties. The stringent properties are mainly derived from tannin, the main compound constituting 50-70% of QI. Tannin has displayed their antifungal action by several mechanisms. This review thus provides a useful database of the therapeutic bioactivity of *Quercus Infectoria* Galls, Thus effort must be making for isolation, standardization and clinical evaluation of such phytochemicals in order to obtain lead compounds for further new drug discovery and different formulations can be

made in form of gels, ointments, mouth washes and powder to be effectively used for the treatment of different form of candidiasis.

KEYWORDS: *Quercus Infectoria* Galls, phytochemicals, ethno botanical, bioactivity, Candidiasis.

INTRODUCTION

The development of strategies to control fungal infections may be an effective means for therapeutic interventions. The majority of clinically used antifungals have various drawbacks in terms of toxicity, efficacy and cost and their frequent use has led to emergence of resistance strains. Antifungals based on synthetic chemicals cause severe and long-term medical problems are highly and acutely toxic. The primary benefits of using plant derived medicines are that they are relatively safer than synthetic alternatives, offering profound therapeutic benefits and more affordable treatment. Consequently, the aim of new antifungal strategies is to develop drugs that combine sustainability, high efficacy, restricted toxicity, safety for humans with low production cost. Since antifungals of biological and natural origin have been demonstrated to be specifically effective on target organisms and are also safe. For millions of people traditional medicine serves as the only opportunity for health care. Safety and lower side effects of many herbal extracts have also suggested them as sources of new pharmaceuticals.[1] Most of the current antimicrobial drugs simply reduce the level of growth of bacteria or fungi and some of them are very toxic to the kidney, the hematopoietic and central nervous system. With the rising problems of side effects and limited efficacy of antifungal drugs, there is an urgent need for the development of alternative antifungal substances and researchers are nowadays turning to natural products from plants, as their main source of bioactive compounds with antifungal and antimicrobial properties, to complement the existing synthetic antifungal drugs that are gradually becoming less potent against pathogenic micro-organisms. Phytotherapy is referred to as the study of the use of plant extracts from natural origin as medicines or health-promoting agents. The main difference between phytotherapy medicines and the medicines containing the herbal elements lies in the methods of plants processing. The preparation of medicines containing herbal elements involves the extraction of the chemically clean active substances, while in the case of phytotherapy medicines all complex active substances of plant are incorporated in the crude natural form. Phytotherapeutic medicines do not include drugs from medicinal plants made for homeopathy, anthroposophic medicine, as well as non-standardized mixture of plant

and synthetic bioactive substances or isolated in a pure form from natural bioactive substances. The study of plants used in traditional medicine requires the effective integration of information on chemical composition of extracts, pharmacological activities of isolated compounds, as well as indigenous knowledge of traditional healers. The acquisition of ethnobotanical information remains an empirical aspect in any such study.[2] The process of isolating and identifying lead compounds from a complex mixture requires a number of specific resources, including comprehensive knowledge, specialised equipment and skill. The urgency of the discovery of new agents is a result of impenetrable factors that come into play, including the emergence of new killer diseases, known antimicrobial drug-resistance, the inefficiency of synthetic drug discovery and the high cost of bringing to market a single drug. A shift towards natural product research, which is further driven by remarkable advances in plant extract technology, biotechnology and analytical chemistry, is therefore inevitable.

CANDIDA ALBICANS AND ITS PATHOGENESIS

Fungi are eukaryotic organisms with approximately 300 000 different species. Of these, about 200 are potential parasites, with only a few of these affecting humans. Fungal diseases of mammals, mycoses, range from the common mild cutaneous or subcutaneous skin infections, such as athletes foot, to the potentially lethal acute or chronic infection of deep tissues that are typically caused by *Candida species*. Of the *Candida species* afflicting humans, *Candida albicans* is by far the most common. *Candida albicans* belongs to the class *Ascomycetes* and the family, *Saccharomycetaceae*. This yeast can live as harmless commensal in many different body locations and is carried in almost half of the population. However, in response to a change in the host environment, *C. albicans* can convert from a benign commensal into a disease-causing pathogen, causing infections in the oral, gastrointestinal and genital tracts. The infection caused by *C. albicans* can be defined in two broad categories, superficial mucocutaneous and systematic invasive, which involves the spread of *C. albicans* to the blood stream (candidemia) and to the major organs. Systemic candidemia is often fatal. Superficial infections affect the various mucous membrane surfaces of the body such as in oral and vaginal thrush. *C. albicans* is the primary causative agent of candidiasis, the most common form of mycotic infection. Risk factors that may increase the incidence of *Candida* infection include compromised immunity, hormonal imbalances, use of broad spectrum antibiotics and use of oral contraceptives, pregnancy, metabolic and nutritional disorders and poor oral hygiene. Infections caused by *C. albicans* may include oral thrush, vulvar rash, vaginitis, conjunctivitis, endophthalmitis, diaper rash and infections of the nail, rectum and

other skin folds. Yeasts which are part of the genus *Candida* consist of 150-200 species.[3] They are imperfect unicellular dimorphic fungi which multiply mainly by budding similar cells from their surface and form hyphae and/or pseudohyphae.[4] They were earlier assigned to the family deuteromycetes, indicating a lack of sexual reproduction. However, several pathogenic and non-pathogenic *Candida species* have been identified to have a sexual stage.[5] *Candida albicans* is the most common species isolated from the oral cavity in both healthy and diseased (in 60 - 80% of the cases).[6,7] Other species responsible for oral infections have also been identified including *C.glabrata, C. krusei, C. parapsilosis, C. dubliniensis, C. tropicalis, C. kefyr and C. guilliermondii*.[7,8,3] Also species such as *C. inconspicua, C. lusitaniae, C. norvegensis* and *C. rugosa* have been isolated occasionally from patients.[4] Yeasts not belonging to the genus *Candida* such as *Rhodotorula glutinis* and *Saccharomyces cerevisae* are sometimes found in the oral cavity but these are not known to cause oral infections.[9] However, colonization of *Candida* in the oral cavity does not indicate infection in the absence of clinical lesions or other symptoms. All the *candidal* species cause the same kind of mucositis but there are differences in the invasiveness and antifungal susceptibilities among species.[6] The role of these other species also referred to as *non-albicans species* have become increasingly important, especially in high-risk patients. Oral candidiasis is the one of the most treatable oral mucosal infections seen in immuno-deficient patients such as those with diabetes, infants, HIV or AIDS…ect.[4] Oral candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste and aversion to food.

ANTIFUNGAL RESISTANCE AMONG CANDIDA SPECIES

The most commonly used antifungal agents are azoles (fluconazole, itraconazole, and ketaconazole) and polyenes (amphotericin B). Some *Candida species* have intrinsic resistance and some develop resistance to azoles. The widespread use of fluconazole and itraconazole as therapeutic or prophylactic doses has increased recently[10] and is most often associated with the HIV infected with oropharyngeal *candidiasis.*[11] This has lead to the increase of reports of resistance.[12] *C. krusei, C. inconspicua* and *C. norvegenesis* are by nature resistant to fluconazole and *C. glabrata* possesses the ability to rapidly develop resistance to fluconazole.[10] It is believed that prolonged or repeated exposure to low-dose fluconazole may be associated with resistant isolates of *C. albicans* and to the selection of resistant *non- Candida albicans* species in the patient.[13] Antifungal drugs should be used as high doses only for the treatment of oral candidiasis, not for prophylaxis.[14] In study by Bagg et al.[15] of the 270 Candida isolates from patients receiving treatment for advanced cancer

25% were not susceptible to fluconazole at standard doses and 66% of the *C. glabrata* isolates were fluconazole-resistant.[15] However, in a study by Kuriyama et al.[16] from a total of 618 clinical *Candida* isolates from patients with different oral diseases almost all were susceptible to fluconazole. Only 6.8% of the *C. glabrata* strains and none of the *C. krusei, C. paralopsilosis* and *C. tropicalis* strains were resistant to fluconazole. Itroconazole resistance was found in 23.7% of the *C. glabrata* 3.14% of the *C. krusei*, 7.7% of the *C. tropicalis* and 1% of the *C. albicans* strains. Amphotericin B is the most commonly used polyene antifungal. It has been in use since the 1950s.[10] It has a broad spectrum of activity. There have only been few reports on resistant *C. albicans* isolates. Recently there have been reports on resistant *C. glabrata* and *C. krusei* isolates.[10] Resistant isolates have also been found in *C. tropicalis, C. parapsilosis* and *C. lusitaniae*. *C. glabrata* is considered as intermediate or susceptible dependent upon dose.[17] Voriconazole is a wide-spectrum azole which is susceptible to most of the isolated strains[18] but reduced susceptibility to this antifungal has also been reported.[15]

QUERCUS INFECTORIA

ETHANOBOTANICAL DESCRIPTION

Quercus infectoria Oliv (Family – *Fagaceae*) is a small tree or shrub about 2 m high[19], with many spreading branches. The bark is slightly grey in[20] colour. The leaves are 4-6 cm long, very rigid, often[20,21] glabrescent with spinous teeth, short petiole, elongate and sinuate.[22] The flowers are unisexual.[20] The male flowers are tangled into hanging, axillary catkins, with a 6-8 tepaled perigone and 6-10 stamens. The female sessile flowers are single or in small groups in the leaf axils of dropping stipules. The perigone is 6 tipped with an inferior 3 chambered ovary surrounded by an initially inconspicuous and then 6later cup shaped cupula.[22] The fruit is up to 4 cm long, cylindrical, shiny brown and is 3 times longer than the cupula, which is 6covered with narrow scales.[22] The galls are globular in shape and from 10 to 25 mm in diameter. They have a short, basal stalk and numerous rounded projections on the surface. The galls are hard and heavy, usually sinking in water. The so called 'blue' variety is actually of a grey or brownish-grey colour. These and to a lesser extent the olive-green 'green' galls, are preferred to the 'white' variety, in which the tannin is said to have been partly decomposed.

DISTRIBUTION

The plant is found in Turkey, Syria, Persia, Cyprus and Greece.[19] The various *Quercus species* originated in Iran, Iraq and Turkey, but are now widespread and particularly common in Asia Minor, Europe and North Africa.[22]

VERNACULARS

The Gall is known by different vernacular names: Ifas, Uffes, Swadul Quzat (Arabic); Maayaaphala (Ayurvedic); Majuphala, Majuphal (Bengali); Gall Nut, Oak Galls, Magic Nuts, Galls, Aleppo Galls, Mecca Gall (English); Mazyan, Mai phala (Gujrati); Majuphul, Majuphal, Mazu, Muphal (Hindi); Gala (Latin); Mai Phal, Majuphala (Maharashtra); Manja Kani, Mashikkay, Majakani (Malyalam); Mazu (Persian); Machkam, Majuphul, Keetavasa (Sanskrit); Mochakai, Mashikkai (Siddha); Aafsi (Siryani); Machakai, Mashikai (Tamil); Mashikaya, Machikaya (Telgu); Maaju phal, Maazu, Feetus, Falees, Maaphala, Iqaqualees (Unani) and Mazu (Urdu).[23,24, 25, 26]

FORMATION OF GALLS

These galls are the vegetable growths formed on the young twigs of the dyer's oak, *Quercus infectoria* (Fagaceae), as a result of the deposition of the eggs of the gall-wasp Adleria gallectinctoriae among the leaf buds of the plant.[19,20,21,22,27] Abnormal development of vegetable tissue round the larva is due to an enzyme-containing secretion, produced by the young insect after it has emerged from the egg, which by the rapid conversion of starch into sugar stimulates cell division. As starch disappears from the neighbourhood of the insect, shrinkage occurs and a central cavity is formed in which the insect passes through the larval and pupal stages. Finally if the galls are not previously collected and dried, the mature insect or imago bores its way out of the gall and escapes. During these changes color passes from a bluish-grey through olive green to almost white.[19,24]

PHYTOCHEMISTRY

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. It is prepared by fermenting the galls and extracting with water-saturated ether. The galls also contain gallic acid (about 2-4%), ellagic acid, sitosterol, methyl betulate, methyloleanolate, starch and calcium oxalate. Nyctanthic, roburic and syringic acids have more recently been identified as the CNS active component of the methanolic extract of galls. Tannic acid is hydrolysable tannin yielding gallic acid and glucose and having the minimum complexity of pentadigalloyl glucose.

Solutions of tannic acid tend to decompose on keeping with formation of gallic acid, a substance which is also found in many commercial samples of tannic acid. It may be detected by the pink colour produced on the addition of a 5% solution of potassium cyanide.[19] The main constituent of tannin is pentadigalloyl-glucose.[28] The galls also contain gum, sugar and essential oil.[21] Pure gallic acid assumes the form of white or nearly colourless feathery crystals of a beautiful silky luster. The commercial acid, however, is usually of a pale yellow colour. It is soluble in alcohol and also, sparingly in ether. Its solution in water undergoes decomposition when exposed to air. When strongly heated, gallic acid is converted into meta-gallic acid.[26]

THERAPEUTIC POTENTIAL OF TANNINS

The tannins may present mineral, synthetic or vegetable origins. Mineral tannins are obtained from inorganic salts based on chromium or zirconium.[29] Synthetic Tannins are derived from the condensation of phenol, cresol and naphthalene with an aldehyde, such as furfuraldehyde.[29] The natural tannins, in turn, can be found in various parts of a plant, such as the bark, leaves, heartwood, fruits, seeds and sap. They are known, therefore, as vegetable tannins and are extracted mainly from the bark, stem or heartwood of the plant. Their properties may vary between different species or within the same species depending on the plant tissue, age, time or even the place where it was collected.[30,31] Tannins are produced by plants in adverse environmental conditions, being responsible for their protection against herbivores and pathogenic diseases and are essential for the growth and reproduction of the plants.[31] Tannins or tanning agents are natural occurring phenolic plant compounds. Their main operation area is to support the healing process of inflammations, abscesses, incinerations, wounds[32], atopic skin[33] as well as quinsy.[34,35] The effect of tannins is antibacterial, antiviral[36], antifungal[37] anti-inflammatory, astringent and toxin neutralizing. Tanning agents are divided into three groups: gallotannins, algae tanning agents and catechol tanning agents. Gallic acid, also known as 3,4,5-trihydroxybenzoic acid, is a component of the gallotannins and found highly concentrated in gallnuts and oak bark. Tannic acid is a specific commercial form of tannin. The chemical formula for tannic acid is often given as C76H52O46, which corresponds with decagalloyl glucose, but in fact it is a mixture of polygalloyl glucoses or polygalloyl quinic acid esters with a varying number of galloyl moieties per molecule. Tannins are commonly defined as water–soluble polyphenolic compounds ranging in molecular weight from 500 to 3000 Daltons that have the ability to precipitate proteins.[38] Due to the fact that this plant is very useful, as found by the

mentioned researches, there is a need to find out more about the potentiality of this plant as an antimicrobial agent. High amounts of tannin present in the galls of *Q. infectoria* implied that tannin is the active compound for the antimicrobial activity.[39,40]

ANTICANDIDAL ACTIVITY

Methanol and aqueous extracts of *Q. infectoria* galls were tested for *anti-candida* activity against *Candida albicans*, *Candida krusei*, *Candida glabrat*, *Candida parapsilosis* and *Candida tropicalis*. Results showed that both methanol and aqueous extracts displayed substantial *anti- candida* activity and pyrogallol was the major component of both crude extracts. Pyrogallol has been reported to have various biological activities such as *candidicidal* and fungicidal activities.[41] Pyrogallol is the extracted compound from QI that potentially possesses *anti*‑*Candida* properties.[42] In recent years, numbers of studies have been reported on the antifungal activity of phenolic compounds from natural sources. The site(s) and number of hydroxyl groups on the phenol group are thought to be related to their relative toxicity to microorganisms, with evidence that increased hydroxylation results in increased toxicity.[43] In addition, it was also reported that more highly oxidized phenols are more inhibitory.[44,45] The mechanisms thought to be responsible for phenolic toxicity to microorganisms include enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups or through more nonspecific interactions with the proteins.[46]

CONCLUSION

The galls of the *Quercus infectoria* (QI) traditionally used as a medicine in the treatment of different illness. The galls of *Q. infectoria* have also been pharmacologically documented to possess astringent, antidiabetic, antitremorine, local anaesthetic, antiviral, antibacterial, antifungal, larvicidal and anti- inflammatory activities. These pharmacological activities of gall extracts were reported to be due to its excellent antioxidant activity with phytochemicals constituents of phenolic compounds. The galls have been documented to possess stringent and antimicrobial properties. The stringent properties are mainly derived from tannin, the main compound constituting 50-70% of QI. Tannin has displayed their antifungal action by several mechanisms.

This review thus provides a useful database of the therapeutic bioactivity of *Quercus Infectoria* Galls, Thus effort must be making for isolation, standardization and clinical evaluation of such phytochemicals in order to obtain lead compounds for further new drug

discovery and different formulations can be made in form of gels, ointments, mouth washes and powder to be effectively used for the treatment of different form of *candidiasis* in particular and other fungal infections.

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