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Antifungal Activity of Fagonia Bruguieri and Tamarix Dioica: A Review

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Abstract
Fungal infections are common around the globe and they occur when the immune system of the body fails to detect the invading fungi. Fungal infections can be uncomfortable or even painful. Medicinal plants are being used as therapeutic agents for various infectious diseases since ancient times. Medicinal plants act as significant antifungal agents due to the presence of a wide range of phytochemicals. Medicinal values of *Tamarix* and *Fagonia*genuses are affirmed by the presence of large number of phytoconstituents and the pharmacological properties. This review article highlighted the antifungal activities of *Fagoniabruguieri* and *Tamarix dioica* which will be beneficial for the future analysis of bioactive compounds of these plants qualitatively and quantitatively for drug analysis in herbal preparations. Nowadays, preference is given in advancing the healthcare with eco-friendly system. Therefore, the vast potentiality can provide the way in developing effective strategies through varied formulations and advanced studies which will be helpful for the treatment of various ailments. On the basis of detailed studies of published literature, *G. bruguieri* and *T. dioica* are the excellent options for the cure of a number of diseases including fungal infections in human beings and their significant biological activities make these plants favorable for developing variety of new pharmaceutical products. The herbs or medicinal plants grasp the attention in all aspects for detailed research works for comparative and comprehensive studies to explore the plants in much depth.

Keywords: Antifungal activity, *fagoniabruguieri, tamarixdioica;* fungalinfections, thal desert, infectious diseases, medicinal plants

Introduction

Fungi and Fungal Diseases

Many fungi live freely either in water or soil while some undergo symbiotic or parasitic interactions with plants, animals, and humans. Animal-host and plant-host species are estimated to be at higher risk of fungal diseases [1]. Fungi can be compared with all other living organisms concerning their vegetative growth mode and nutrient consumption as they digest organic matter external to their body before absorbing it into their mycelia. Fungi are exposed to human beings in several ways: symbiotic relationships, commensalism, latent or pathogenic interactions. Fungi affect the health, food, industry, and agriculture both positively and negatively, as they are associated with our lives. Fungal pathogens have been recognized to have an enormous influence on plants, animals, and human life. Fungal diseases characterize a significant example in immunology, resulting in either due to the lack of recognition by the immune system or hyper-activation of the inflammatory responses [2]. Globally, Fungal infections are considered the relevant cause of morbidity and can be associated with high mortality incidents despite the availability of antifungal drugs [3].

Epidemiology of Fungal Diseases

Over the past decade, the upsurge of fungal infections is prominent. Globally, the increased ratio of immuno-compromised hosts has eventually caused the epidemiological characteristics of fungal infections to undergo vast modifications [4]. Dermatophytes, the chief causative agents, have variable geographical distribution as they have been located in various regions in the world. Owing to different geographical distribution, drug therapy, and socioeconomic conditions, the incidence and distribution of dermatophyte infection are altered [5]. In recent years, over 1.6 million deaths are estimated annually due to fungal diseases, and over one billion people are reported to be suffering from serious fungal diseases [6]. In a recent research study, the overall prevalence of superficial fungal infections is stable in China. Still, the transmission route and incidence rate of *Tinea capitis*have been modified. While, recently in China, the incidence of Candida species except *Candida albicans* has been found greater than before. Marked propagation of Aspergillus infections has also been reported in recent past years, which is found to be associated with azole-resistant *Aspergillus fumigatus*.

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Superficial mycosis affects millions of people globally. Worldwide, superficial fungal infections are common, and their incidence rate gradually raised as they are reported to affect the world's population by 20-25% [7]. A previous study in the America discovered that the main agents of *Tinea capitis* are *Microsporumcanis* and *Trichophytontonsurans*. In the southern area of Brazil, *M canis* accounted for 60% of cases. While in the northeast region, *T.tonsurans* arer esponsible for 74% of infection cases. While, in Mexico, *M. canis* is the abundant fungal agent followed by *T. tonsurans* [8]. In a recent study in Northeast Brazil, researchers have reported a high incidence rate of *T. tonsurans* in cases of superficial fungal infection.

Moreover, they have found *Trichophyton rubrum* and *Candida parapsilosis* as the most abundant and prevalent dermatophyte fungal species [9]. The *Candida auris*hasto emerge as a multidrug-resistant infection as it has been recorded in many Asian countries. In an acquired candidemia study, *C. auris* candidemia had been documented at 5.3% of all candidemia cases in India. The mucormycosis accounted for a very high incidence rate in China and India particularly in patients with unchecked diabetes [10, 11].

Classification of Fungal Infections

Fungal infections called mycosis, are classified based on infection site, acquisition route, and virulence [12-14]. Fungal infections can be classified as subcutaneous, cutaneous, superficial, and deep based on the infection site [15-17]. Superficial fungal infections do not cause inflammation as they are just confined to the *stratum corneum* [18-21]. Cutaneous mycosis invades the integument as well as its appendages [22-24]. Cutaneous mycoses [25, 26] may be classified into two types, namely 1-dermatophytosis and 2-dermatocytosis (Table 1). While the subcutaneous mycoses [27] are classified into three general categories (Table 2) such as chromoblastomycosis, mycetoma and sporotrichosis. On the other hand, the deep mycosis (Table 3) is further classified into primary mycosis [28] and opportunistic mycosis [29].

Table 1: Cutaneous mycosis, their etiological factors, and site of infection

Classification	Causative Agents	Site of infection
Dermatophytoses	*Microsporum spp.*	Hair and skin
	Epidermophyton floccosum	Skin and nails
	Trichophyton spp.	Skin, hair, and nails
Dermatomycoses	*Candida*spp	Skin

Table 2: Subcutaneous mycosis, causative agents, and site of infection

Types	Causative Agents	Site of infection
Chromoblastomycosis	*Phialophora verrucosa* *Fonsecaea compacta* *Cladosporiumcarionii* *Fonsecaeapedrosoi*	Subcutaneous tissue not invades into bones, muscle, or tendon
Mycetoma	*Pseudallescheria boydii* *Nocardia brasiliensis*	Bone skeletal muscle tendon
Sporotrichosis	*Sporothrixschenckii*	Subcutaneous tissue at the traumatic inoculation site

Table 3: Deep mycosis, their etiological agents, and site of infection

Classification	Infections	Causative Agents	Site of Infection
Primary mycosis	Histoplasmosis	*Histoplasma capsulatum*	Pulmonary infection
	Tuberculosis	*Mycobacterium tuberculosis*	Lungs, bones
	Blastomycosis	*Blastomyces dermatitidis*	Pulmonary infection
	Coccidioidomycosis	*Coccidoioidesimmitis*	brain, bone, lungs
Opportunistic Mycosis	Candidiasis	*Candida albicans*	kidneys,eyes, liver, heart, brain, spleen
	Aspergillosis	Aspergillus	Lungs, paranasal sinuses

Moreover, pathogenic fungi have also been categorized based on the risk associated with a specific living agent [30].

- **Risk Group 1:** Includes microorganisms that are not likely to develop disease conditions in all living organisms.
- **Risk Group 2:** Includes microorganisms that may develop mycosis in living organisms but are not fatal, could be prevented and well-treated, and have less transmission rate.
- **Risk Group 3:** Includes fungi regarded as pathogens; capable of causing serious infections in humans and other living organisms, treatable but fatal.
- **Risk Group 4:** Includes pathogenic fungi that can cause life-threatening mycosis in humans and other organisms, have a high transmission rate and their effective cure is usually unavailable.

Fungal Infections and Humans

In humans, fungal diseases are generally considered hard to treat. Unlike bacteria, fungi being eukaryotes are unresponsive to traditional antibiotics. In compromised immune individuals, fungal infections may prove fatal. AIDS, candidiasis, Athlete's foot, etc. are considered important fungal infections in human beings. Each year, billions of people are infected by Fungi, however, their impact on the overall disease burden is generally unrecognized. Most infections are mild, but some can lead to death, such as malaria or tuberculosis. However, due to the lack of epidemiological data, exact mortality cases are unknown. Invasive fungal infections are reported to rise, followed by modern medical interventions and immunosuppressive illnesses, such as AIDS [31]. Above 600 different fungi have been stated to cause human infection, including mucosa diseases, nails, skin, hair, and other allergies that could range from mild to fatal [24, 32, 33].

Fungal pathogens can cause serious infections, which if left untreated may be fatal. These serious illnesses include aspergillosis, candidosis, histoplasmosis, cryptococcosis mucormycosis, coccidioidomycosis, mycetoma, and paracoccidio-idomycosis [34, 35]. Infections caused by *Candida* spp. have become opportunistic infections, which mostly affect the mucosal lining. In immunocompromised patients, *Candida* spp. generally cause oral, esophageal, and vaginal infections such as thrush is a mucosal lining of the oral cavity and vagina [19]. Fungal species such as *Candida, Fusarium,* and *Aspergillus* mostly cause infection in the

cornea of the eye and lead to cause around 1-6 million cases [24].

Candidiasis

Candida albicans, being an opportunistic pathogenic fungus, causes candidiasis in humans. The growth of *C. albicans* occurs in several different morphologies that can range from unicellular yeast to multicellular hyphae [36]. Unicellular *C. albicans* is a form of yeast and an oval-shaped diploid fungus [37]. Naturally, *C. albicans* colonizes, in 70% of the total population, in the genitourinary and gastrointestinal tract. Hyper-growth of this fungus usually leads to mycosis. Candidiasis can affect skin, mouth, blood, CNS, CVS, eye, throat, and genitals [38].

Pathophysiology of Mycosis

The incidence rate of fungal infection has been increasing extremely mostly in patients having compromised immune systems. Fungal infections may be of two types such as opportunistic or endemic. Generally, the endemic (pathogenic, fungi) caused infection in healthy persons, while the immunocompromised patients got the infection through opportunistic fungi. Inhalation of contaminants is considered the cause of most fungal infections, especially pulmonary/lung infections. In pulmonary tissues, the fungi provoke reactions, which could be ranged from severe exudative to granulomatous. Sustained chronic infection or dissemination to other adjacent or distant organs can result from resolving the pulmonary lesion, which could ultimately lead to systemic infections. Culture or histological examination of organisms such as serological testing can help to diagnose fungal infection or pathogen [39]. Different strains are used to identify Fungi including eosin and hematoxylin stains. Still, some special stains are also used, such as silver periodic acid-Schiff and Gomori's methenamine reagent, for diagnosis [40]. In patients with the impaired immune system, the effects of fungal infections depend on a multifaceted interaction between pathogen and host, and on treatment modalities. Usually, complications arise due to the host's weak protective response to infection as pathogen eradication is difficult, or when these host protective reactions become strong and could damage the host itself rather than protection [41].

Pathophysiology of Candidiasis

Abnormal or overgrowth of *C. albicans* caused by an imbalance in the environment, ultimately lead to candidiasis [42].

- After laparotomy, Candida species colonizing in the gut causes candidemia and localized or deep-seated infection such as peritonitis via translocation or anastomotic leakage.
- After entering in blood circulation, candida colonizes in the intravascular catheters indwelled in patients.
- In catheter, the candida form biofilm and causes persistent Candidemia after releasing from biofilm
- Once after developing Candidemia via either colonized intravascular catheter or any other route/source, the fungus may spread, lead to metastatic secondary infections in other organs such as the kidney (pyelonephritis), liver, lung (Infectious pulmonary abscess), bone, spleen (Infectious splenic abscess), or eye (Endophthalmitis).
- Candida may also get released from the bloodstream to the urine and may develop candiduria.
- Candiduria may lead to ascending pyelonephritis and ultimately secondary candidemia develops.

Several virulence factors are present in *C. albicans* that could injure its host, such as cell wall adhesions. Adhesion proteins via hydrophobic interactions promote attachment of organism with its host, which ultimately causes reduction in the yeast clearance level from the body via immune regulation. After penetration in host tissue, *C. albicans* secretes degrading enzyme entities such as phospholipases, aspartyl proteases, and proteinases.

Phenotypic remodeling enables the yeast to alter its adherence properties, expression of an antigen, and affinity with tissue. This remodeling enables the cell wall to become flexible and helps it adapt according to hostile conditions executed by host and antifungal drugs [43].

Sign and Symptoms

Tropical candida infection manifests clear red patches on the skin having Scabs and pustules at edges, itching, most often with fluid oozing out. These typical symptoms usually appear in body parts having a warm and moist environment including the groin, under the breasts line, between toes and fingers, buttocks folds, and navel [44]. While, generalized cutaneous candidiasis, a rare form of candidiasis, is characterized by the diffuse eruption on the trunk and peripheral regions [45]. Vaginal candidiasis may develop as thick and white discharge causes itches, pain, discomfort, and burning during urination or intercourse. Pain or discomfort during intercourse is common [46, 47]. *Candida albicans* is the most frequent cause of tropical infections of the skin and the nails. *Candida paronychia,* an infection of finger nails, often develops consistently in wet hands, characterized by red and painful inflamed regions around the finger nail. Dry intact skin has high potent to resist fungal invasion than the hydrated epidermis. A yellow or white nail bed is revealed in more severe cases due to a separated fingernail. Oral thrush caused by candidiasis is characterized by white patches, having a curd-like appearance inside the buccal cavity [48] such as (palate, lips, and tongue).

Blurred vision, scotoma, floaters, and blindness are the characteristics of candida eye infection including endophthalmitis or chorioretinitis [49]. Central nervous system candidiasis affects brain tissue or meninges which have different manifestations including fever, altered consciousness, impaired mental status (coma), and/or focal disabilities depending on size and location of the candida abscess in the brain [50].

Risk Factors of Candidiasis

In recent years, the count of immunocompromised patients has elevated remarkably. Opportunistic infections, specifically fungal infections, are a high risk for patients having impaired immune systems. Candidiasis is among the most common fungal infections detected in the immune suppressed hosts [51]. Following conditions may serve as an opportunistic ground for candida [52-54]:

- Critical illnesses with a long-term stay in ICU
- Abdominal surgeries, including repetitive laparotomies
- Acute necrotizing pancreatitis
- Malignant disease with hematologic origin
- Carcinoma patients and the patients having an organ transplant
- Rational use of broad-spectrum antibiotics, hemodialysis

Diagnosis of Fungal Infections

Diagnostic shortcomings of fungal infections hinder the management of diseases, mostly in patients with an impaired immune system. Due to unspecific signs and symptoms, false-negative blood cultures, and the patient's inability to go through the invasive diagnostic techniques, diagnosis of mycosis is facing a consistent problem. Although a variety of laboratory tests are conducted on body fluids (blood, sputum) to be familiar with the appearance of many fungi in body tissues. Molecular identification, antibody, and antigen-based assays, and metabolite or DNA detection are listed among the category of non-culture diagnostic procedures [55]. Histopathology, tissue or wound biopsy, and other available serological assays are applied to diagnose fungal infections.

Culture studies, being a time taken, are either insensitive or sometimes unreliable due to contamination. They can detect a specific pathological agent or pave the path to perform a susceptibility test [56-58].

At present, most Point-of-Care rapid diagnostics use lateral flow immunoassay (LFIA). These assays can be applied to detect host antibodies that are meant to target antigens. Hence, the host antibody is detected using a labelled report (the second antibody, and the target antigen is kept immobilized). For example, serological assays for HIV-1/2 or hepatitis C virus [59].

Non-culture Diagnostic Methods

Non-culture procedures are meant to detect proteinase, glucan, enolase, or mannan in various antibody and antigen assays. These assays are applied for the diagnosis of fungal infections. Moreover, some metabolite detection assays include the detection of arabinitol and mannose. The PCR technique is used for Molecular identification that can amplify fungal DNA from tissue, hence could be a reliable source of infection diagnosis. DNA or RNA probes with the potential for a prompt diagnosis can be used forexo-antigen testing to detect diffused metabolites and antigens in agar. The broad-spectrum detection test for fungal infection which detects (1, 3)-β-D-glucan, a chemical found in the cell wall of most fungi, is known as G-test. Being sensitive, this assay can detect a limit of 1pg/mL. A clinical study reported that healthy individuals have <10 pg/mL (1, 3)-§-D-glucan in blood, with a mean value of c. 2.7 pg/mL. While, patients with mycosis have >20 pg/mL concentration, which provides a significant cut-off between normal and infected patient's levels [60]. To rule out Candidemia (deep-seated), the T2 Candida panel test is used which can detect fungal DNA in blood with a 1 CFU/mL detection limit [61, 62]. Likewise, different Immuno-chromatographic techniques including lateral flow devices/dipsticks are applied to detect pulmonary aspergillosis. These procedures detect components of cell walls in urine and serum. Aspergillus proximity ligation assay is utilized to detect cell wall component mannoprotein [63, 64]. Loop-mediated isothermal amplification assay, lateral flow device, and various ELISA techniques are applied to identify histoplasmosis [65, 66]. While, Cryptococcosis can easily be detected by using different lateral flow formats designated to find out cryptococcal polysaccharide antigen in cerebrospinal fluid (CSF), saliva, and whole blood [67, 68].

Diagnostic Procedures for Candidemia

Candidemia is a bloodstream infectious disease characterized by the presence of a Candida species in blood. Regardless of low sensitivity (50-60%), blood culture procedures are considered the gold standard for diagnosing candidemia. Different Candida species have a different time for positivization of blood cultures [69]. Blood cultures methods are useful only during the period of pathogen stay in the bloodstream. While the host with deep-seated infection yields negative culture results because of clearing candida from the bloodstream [70]. The primary invasive candidiasis has surrogate markers such as β-d-glucan, Candida mannan antigens, and anti-mannan antibodies. Researchers have also evaluated in-house PCR tests to detect invasive candidiasis (figure 1). However, limited validation and standardization have hindered their acceptance and implementation. PCR assay with a sensitivity of 89% was reported in deep-seated candidiasis that was detected negative on blood cultures [71]. The T2Candida Panel, a commercial PCR test, was used for its promising results as this technique does not require culture or nucleic acid extraction to detect the pathogen (Candida). It can directly detect Candida in whole blood.

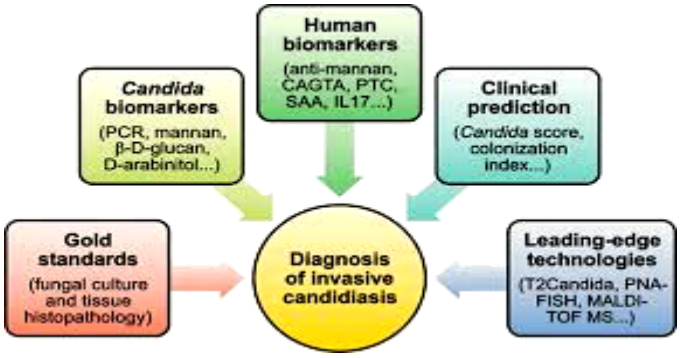

Fig 1: Diagnostic tools and techniques for Candidiasis [72]

The Candidiasis Treatment

Cutaneous candidiasis can be treated with a range of antifungal topical gels and creams. While Deep candidiasis is usually treated with fluconazole via intravenous administration. Patients having very low WBC counts may require other intravenous antifungal drugs as an alternate, such as micafungin or caspofungin. For candidiasis, commonly used antifungal agents include amphotericin B (AmB), fluconazole, itraconazole, polyenes, pyrimidine, and flucytosine. Amphotericin B attaches itself with ergosterol to cause fungal death via forming a transmembrane channel that causes leakage of monovalent ions [73-76] such as Na^+, H^+, K^+, and Cl^-.

Herbal Medicine

Pakistanis have wonderful trust in traditional medicine, which has a longtime history. The training/medication is usually temporarily interrupted from time to time, with little heeding the time of ups and downs. The main explanations for using herbs in therapeutic drugs are

1. Multifaceted, evidence-based use,
2. Synergistic, and constituent-limiting reactions [77, 78].

There is further emphasis on the ruinous impacts of the plastics produced. Hence, designs evolve into signature treatments. Internationally there are new examples of the transfer of resources from allopathic systems to standard social security systems. The global market for elective drugs is projected to reach $ 5,000 billion by 2050. The government has shown an interest in incorporating him into the human administration structure while ignoring the various challenges the Traditional, Complementary and Alternative Medicine (TCAM) is facing. A demonstration called "Tibb-e-Unani, Ayurvedic, Homeopathic, Herbal and Biochemical Medicines

Sedate 2010" to control the assembly, storage, import, and customs of conventional medicine has been certified by the Federal Cabinet and the Standing Committee of the National Assembly. Over 300 Pakistani green plants are used in or for the human service system, roughly 12% of the social security system. Ten driving Dawakhanas (herbalists) from Pakistan ate more than 2 million kg of 200 crops each year in the 1990s, while their use has increased many times over the past two decades. In 1990, 22 therapeutic herbs were traded valued at Rs 14.733 million, while that amount had grown to over Rs 122 million by 2002, an eight and a half percent increase. According to one report, an increase in the use of conventional herbal remedies by 600% compared to 1999 was observed [79]. Pakistan Therapeutic Plants Picture Guide describes more than 500 types of germinating plants used as medicinal products. It has also been shown that about 37% (266 species) originated from restoration facilities. Local species can be similarly searched for Ethnobotanical, pharmacological, and drug studies.

In this way, there is a general need to grow and screen crops. In 2006, the Pakistani government launched production of medicinal herbs in collaboration with private sector (PMHPS) to promote spices and herbal medicine (HM) for harvest in Pakistan. Efforts have focused the therapeutic spice era commercially through research-based advances in line with WHO guidelines on agriculture and conservation strategies [80, 81]. The NIH, Islamabad, Pakistan, coordinated various workshops to blend the regions' Western biomedical and conventional medicine sectors. In 2002, an exhibition of HMs was held in Islamabad, attended by more than 150 members from Pakistan and the South Asian Association for Regional Cooperation (ASACR) region. About 20 local prescription organizations were interested in the presentation. There are many problematic small businesses in Pakistan dealing in conventional and HMs.

Herbal Preparations Standardization

Medicinal plants are a term used to represent plants or their parts, which have been converted into plant protection products using basic procedures such as collection, drying, and capacity. The standardization of herbal products is a method of observing the entire process of green plant bioprospecting, assortment, extraction, bioactivity-based fractionation, and drug development using specialized guidelines accessible. Unfortunately, no official guidelines are available for the standardization and quality control of herbal products. Manufacturers use their limits for testing items. The limits included are dynamic rules (to discover a certain bioactivity profile), dynamic markers (to determine viability), logical markers (to characterize a certain component), negative markers (to filter toxicological issues), and so right now. However, the standardization process may include the possibility that one or a significant amount of markers can detect the quality control of HMs. The various test methods used by pharmacopeia guidelines are explicit gravity, drying unhappiness, minute rating, microbial control, refractive index, thickness, consistency, softening point, molecular structure, extraction value, heavy metals. The infinitesimal assessment is performed to obtain recognizable evidence and the initial detection of contaminants in HMs. The extraction value test is performed to determine the severity of the extractable component in various solvents. Microbial entrapment helps identify unknown particles in the unrefined drug. Reference standard based on parts for individual ingredients (to maintain profile), nutritional standards (used in addition to a health guide), and a recovery guide (to decide the suitability of the composite plan). The phytochemical investigation based on the markers uses dynamic rules, storage markers, normalization of the soluble frame, chemotype, pharmacopeia standard for the reference compound, chromatography, infrared (IR), ultra violet (UV), and nuclear magnetic resonance (NMR).

Protection conventions for unrefined drugs include a range of samples and taxonomically recognizable evidence. During the entire capacity, the metabolites of the division remain stable until the end. The finite element capacity guidelines relate to stability, realistic use, subject attributes, and labeling principles. Group examinations, identification tests, quality test standards for harmful/contamination influences, start and stop times, normal operation tests are the markers of process control. Since ancient times, plants are used to treat various ailments. In the 21st century, instead of having many synthetic drugs, plants remain an integral part of the health care system of various countries, especially the developing nations. The role of plants for their medicinal properties on the earth is undeniable. About 20 plants are used as medicinal drugs by 80% of the world population because, unlike modern medicine, plants show a synergistic effect and have no side effects.

Currently, the world is changing its consequences of using plant-based products. As many microorganisms develop resistance to various synthetic drugs, plant-based medicine can be used as alternative to these synthetic drugs due to their synergistic effects in treating infectious diseases. Worldwide, since ancient history, a variety of medicines have been provided by the plant kingdom. Nowadays, plants contribute as major sources of analgesics, antiarrhythmic agents, anti-inflammatories, medicines for asthma, antineoplastic drugs, and anti-hypertensives. In the previous decade, antifungal medicinal plants were least analyzed for their antifungal activity, but now numerous plants with antimicrobial activity. Globally, the researchers are directed towards the medicinal and antimicrobial properties of plant extracts. Modern conventional medicine has both advantages and adverse effects. That's why plant-origin medicines are gaining popularity because of their safe use, being comparatively cheap and easily available [82]. Plant extracts and essential oils are also found to be effective against plant pathogens. Therefore, plant-based medicines are being used both as a medicine and for plant protection [83].

In the recent past, antifungal drugs are reported to induce a significant reduction in death rate and morbidity caused by infectious diseases. Although, the incorrect and irrational use of antifungals has led to the rise in resistant microbial populations. Pathogenic fungi usually adopt different strategies to develop resistance to antifungal drugs such as target site alteration, drug efflux, or enzymatic degradations [84]. About 25-50% of current pharmaceuticals have a plant-based origin, which has increased the researcher's interest in medicinal plants. Crude extracts of medicinal plants are rich in secondary metabolites that can be an alternative source of resistance modifying agents. Alkaloids, polyphenols, tannins, etc. are reported to possess potential antimicrobial agents and resistance modifiers. Plant extracts can inhibit or modify protein-protein interactions owing to their capability to bind with protein domains. This property facilitates the herbs or medicinal plants to represent various cellular processes such as signal transduction, immune response, apoptosis, and mitosis as effective modulators. Hence, these plant extracts hinder the pathogenicity of microbes by killing them and

retard major steps of the pathogenic mechanism. This significant property of plant extract, in turn, decreases the ability of the microorganism to develop resistance to them.

Since ancient times, the majority of medicinal plants are used due to their therapeutically effects against various disorders. Due to the lack of reported adverse effects and being cost-effective and easily available, medicinal plants have become a therapeutic agent among patients [82]. The World health Organization (WHO) reported that an enormous proportion of the world population, about 80%, are directly or indirectly depends on medicinal plants [85]. Phytochemical constituents are reported to act as immunomodulator to boost the body's oxidant state or anti-oxidant compounds, prevent microbial attachment, or cease microbial multiplication and proliferation, but the exact pharmacological action against specific diseases is still unknown [86]. These miscellaneous medicinal plant activities are attributed to numerous phytochemical constituents, i.e. alkaloids, flavonoids, anthraquinones, saponins, glycosides, steroids, phenols, and tannins anthraquinone, terpenoids, sesquiterpenes, triterpenoids, phlorotannins, phenols, etc. Whole plants or different parts such as flowers, bark, leaves, seeds, and fruit could treat several diseases. Moreover, whole plants or their parts could be used as a single formulation or as a mixture with other drinks and foods (milk, juices, honey, black pepper or water). Sex, age, and health status of patients could affect the dose of herbal preparations [87]. In previous clinical studies, plants extracts have been documented to elicit antifungal therapeutic potential *in vitro* trials. In particular, wild plants have useful metabolites and could be a favorable source [88, 89].

Published literature shows that *Fagoniabruguieri* and *Tamarix dioica* have a wide range of pharmacological activities, and due to these properties, they are used in various plant-based medicine to treat different diseases. Several phytochemicals are present in these plants that enable them to have such therapeutic effects. However, to treat various diseases, a comprehensive study is needed to develop their medicinal usage. Both plants have different therapeutic properties, so it deserves special consideration by researchers and scientists to develop a novel drug for this time. That's why further assessment is required to explore the hidden potentials of *Fagoniabruguieri* and *Tamarix dioica* and their therapeutic applications for human wellbeing.

Fagoniabruguieri DC

Fagoniabruguieri is a tiny, erect under shrubs that are spiny and somehow glandular. The scientific name and local name were reported in Table 4. Its branches are slender, glabrous, triate and terete. While this branching and the erect herb is woody at the base.

Table 4: Scientific name, local name and family of *Fagoniabruguieri.*

Scientific Name	***Fagoniabruguieri* DC**
Local Name	Damasa
Family	Zygophyllaceae
Parts used	Whole plant

The Stem

The stems of *Fagoniabruguieri* are manifestly angular. However, the angular pattern could be defined as thicker and thinner ridges on the stem, while "terete" is termed as stems having uniform ridges [90].

The Stipules

Fully free stipules are possessed by *Fagoniabruguier*i that are spiny or pointed at the apex. Stipules are in form of two pairs of sharp slender thorns with a length of 12 mm. Spine of stipules is usually recurved and somehow lengthier (6-12 mm) than the leaves [90].

The Leaves

Fagoniabruguieri possess simple and opposite leaves having flat or rarely terete leaflets ranging from 2-7 in number. Usually, the leaflets are flashy, and their count remains constant within species. Leaflets are ovate to oblong having 4-12 m in length. The leaves are petiolate and the leaflets are petiolulate in *Fagoniabruguieri*. Usually, the basal leaves are mostly petiolate such as upper unifoliolate and trifoliolate. Upper leaves are sessile and subsessile possessing a 5 mm long petiole. Leaves are arranged in an alternate manner having1 to 3 foliate. Their petioles are of various lengths ranging from 3-30 mm long and are slender and deeply striated. Leaflets of the plant are sessile, linear, and acute, having very small petiolules [90].

The Trichomes

Trichomes are present *in Fagoniabruguieri* as they could be present sparsely on some parts of the plant, including pedicels, young stems, and sepals. Unicellular secretory cells with multicellular stalks are present within mature glands. While the immature glands only possess a single cellular stalk. The epidermal cells separation from mesophyll leads to the formation of the trichome-stalk. One of the unique features of Fagonia is the formation of an intercellular space under the raised epidermal cells [90].

The Flowers

The inflorescence of Fagonia is usually helicoid or asymmetrical as one lateral branch is originated from each flowering branch. Flowers have the same count of sepals and petals i.e. five of each. While the petals are twice the length of sepals. Flowers are purplish or pale-pink, usually small (8-10 mm across), shortly pedunculated, and have pedicel (5 mm). Sepals are 2-2.5 mm in length, pubescent, acute-acuminate, persistent, and morphologically lanceolate-ovate. While the petals are 3.5-4 (-6) mm in length, the obtuse having long filaments and are broad at the apex and tapered to the base [90].

The Fruit

The fruit Fagonia is capsular and inverted cone shape with persistent style and possesses hairs. Length measurement of mature hairs is used for the quantification of Trichome size. The capsule is usually opened with the splitting of the endo & exo-carp. This splitting mostly happens at the base when the pedicel bends down. Fruits are globulicidal. From each locule, shedding of seeds occurs before the ripened fruits drop. These features of *Fagoniabruguieri*are very distinct [90].

The Seeds

The seeds of *F. bruguieri* are small, and the hilum is even shorter than seeds. The outer and inner testa of *Fagoniabruguieri* comprises uniform layers formed by cells without having any specified internal structures [90].

The Pollen Grains

The Fagonia possesses tricolpate, reticulate pollen grains that are morphologically prolate to prolate-spheroidal. The Sexine of pollen grains is thicker than the endexine. Pollen size in

Fagoniabruguieri DC is characterized by 28-32 µm length and 16-20 µm width [90].

Geographical Distribution and Habitat

The *F. bruguieri* is geographically distributed in Africa from Mauritania to Egypt (west to east) and the south of Sahel, a regional transition zone (15•-20•N). In the east, it is distributed to Pakistan and Afghanistan from Israel/Palestine, and towards the south, it spread out to Yemen[78]. Gypsum or limestone-rich gravel or sand is favourable for the growth of *F. bruguieri*. Mostly, it is seen on a stony slant, in wadis and grassland at an altitude of 2300 m from sea level. It normally forms a leading part of the vegetation. In Pakistan, it is found from west to north [90].

Chemical Composition

Fagonia sp. have been documented to possess different phytochemicals such as terpenoids, saponins, coumarins, sterols, alkaloids, proteins, flavonoids, amino acids, and trace elements [91]. In a study, *F. bruguieri* was reported to contain about seven flavonol glycosides including kaempferol 3-O-rhamno-galactoside, Quercetin 3-galactoside, and Quercetin-3-rhamnogalactoside were reported for the first time in the genus *Fagonia*L. The flavonoids were found to be based on isorhamnetin, kaempferol and quercetin [92]. Aerial parts of *Fagoniabruguieri* were found to have diterpenes of erythroxan-type such as 16-O-acetylfagonone and 15, 16-dihydroxy-7-oxo-cis-ent-erythrox-3-ene (fagonone). Spectroscopic and crystal X-ray diffraction studies were conducted to determine these diterpene structures. Moreover, Five substituted 8-methoxyflavones were also discovered [93]. In a study in Libya, *F.bruguieri*wascontended of alkaloids, flavonoids, and saponins, while tannins, terpenes, coumarins, and anthraquinones were absent. The IC50 value of *F. bruguieri* was 12.50± 1.15 compared to that of ascorbic acid. Moreover, total polyphenols (TPC) and total flavonoids (TFC) concentrations of leaves of *F. bruguier*i were 249.28±54.48 and 349.28±54.48, respectively [94]. Likewise, in another study, *F. bruguieri* was reported to have the highest value of ascorbic acid [95].

Medicinal Properties

Conferring to the previous researches on *Fagonia*, a genus comprised of 45 species is acknowledged as a potent medicinal plant effective against various diseases. Although, this species is not subjected to any research or clinical study in Pakistan. Extensive studies on the medicinal uses of *Fagonia* sp. uncovered its potential use as an analgesic, antitumor, astringent and antioxidant. In local regions of Pakistan, *Fagonia sp*. were reported to use for cancer treatment as well as in toothache, stomachache, renal diseases, asthma, and fever [91]. In a research study, *Fagoniabruguieri* was reported to possess strong free radical scavenging activity with an IC50 value of 32.7332 µM, total antioxidant activity of 130 µg AA equivalent/mg methanol extract, and total reducing power of 141 µg AA equivalent/mg methanol extract [96].

In another study, an aqueous extract of *Fagoniabruguieri* was claimed to have anti-allergic activity and found to possess LD50 values of 10.75 & 11.5 g/kg in rats and mice, respectively. An intravenous dose of 200 mg/kg, plant extract has developed bronchoconstriction in albino guinea pigs. The plant was documented to be used as a febrifuge and tonic in Peshawar Valley. Moreover, it is administered as a prophylactic drug for smallpox in children. The leaves and twigs are thought to have exhilarating effects. Methanol extract of *Fagoniabruguieri* was reported to possess anti-fungalproperties against four fungal strains i.e. *Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, and *Mucor mycosis*[96]. In a previous study, *Fagoniabruguieri* was reported to have phytoestrogens i.e., Daidzein, Quercetin, Genistein, and Kaempferol. *F. bruguieri*wasdocumented to possess significant proliferative activity on MCF-7 cells [97].

Aqueous extract of Fagonia was reported to exhibit significant anti-cancer activity, individually or in association with other anti-cancer agents to hunk the proliferative tendency of breast cancer cells through expression of p53 and DNA damage-induced FOXO3a [98]. The wound healing and anti-inflammatory effect of the alcoholic plant extract were reported to induce paw oedema in rats and the excision wound model. The anti-allergic effect of freeze-dried extract of *Fagoniabruguieri* was also reported in a research study. The plant is being utilized by desert natives to treat skin diseases, sores, otitis, skin eruptions, and venereal diseases and as an antipyretic and analgesic [99].

Ethanolic leave extract of plant species also possesses analgesic and anti-microbial activity [100]. Antitumor and cytotoxic activity of Fagonia was observed at lab-based study via performing antitumor, cytotoxic, and DNA damage assay [101].

Traditionally, the Fagonia species are recognized to cure inflammation, leprosy, haemorrhoids, open wounds, fever, and sores. The other plant of this species, *F. schweinfurthii* (whole plant), reported healing skin eruptions and boils. *Fagoniacretica* methanolic extract is documented as a potent antimicrobial treatment and has significant free radical scavenging activities against nitrogen and reactive oxygen species. Moreover, the medicinal effects of Fagonia spp. comprise thrombolytic, analgesic, anti-inflammatory and antipyretic activities.

Botanical Characteristics

T. dioica (*Tamaricaceae*) is locally known as ban jhau (Table 5). This is a perennial shrub or small tree (1-18 m height) characterized by reddish bark, sheathed leaves (1.5 to 3 mm long), and purple fluorescence [102] as highlighted in Table 6.

Table 5: *Tamarixdioica* Roxb. ex Roth

Scientific Name	***Tamarix dioica* Roxb. ex Roth**
Local Name	Lal, Jhau
Family	Tamaricaceae
Parts used	Areal Part

Table 6: Leaves, flowers, petals, sepals and stamens of *T. dioica* (*Tamaricaceae*)

Leaves	• 1.5-3 mm long • Glabrous • Vaginate • Abruptly acuminate • Broad whitish margins
Flowers	• Pentamerous • Purplish pink to purple • Subsessile
Sepals	• 5 in number, 2 mm long, 1.5 mm broad • Obtuse • Orbicular • Ovate to broadly ovate
Petals	• 5 in number • mm long and 1-1.25 mm broad • Obovate • Free • Obtuse
Stamens	• 5 in count and 1.75-2 mm long • Filiform filaments • Emarginated notches • Obtuse anthers • Abortive in female flowers
Styles	• 3 in count, • Long as ovary or slightly short • Triquetrous Ovary 1-1.5 mm long • Absent/abortive in male flowers

Geographical Distribution and Habitat

Tamarix, genus, belongs to the family *Tamaricaceae* and is commonly known as "tamarisk" or "salt cedar". The genus is comprised of about 60 species whose plants can be grown nearly worldwide. The needle-like leaves of these halophyte plants are covered with salt, usually secreted from the salt glands. The habitat of these plants in hot and dry climates, although these plant species can also be grown in temperate climates [103]. *Tamarix*plant species are favorably cultivated in dry climates than in wet climates as being an invasive plant that hinders the growth of other plant species [104]. *Tamarix* species are deep-rooted and groundwater-dependent for their water supply. These plant species are facultative as they can acclimatize to different available salt and dry conditions [105].

The tree is native to Pakistan, India, Afghanistan, Kashmir, Iran, Myanmar, Bhutan, Nepal, and Bangladesh. *T. dioica* is abundantly found throughout Pakistan especially in Sindh and Khyber Pakhtunkhwa (KPK) provinces.

Chemical Composition

Tamarix species has been subjected to several phytochemical studies, which discovered the phytochemicals series including important polyphenols such as flavonoids, phenolic acids, and tannins. Naturally, *Tamarix* is grown in India, Pakistan, Algeria, and Iran and is famous for its medicinal applications. Phytochemical analysis of *T. dioica* shown that phlorotannins and steroids are present in all parts of the plant. Leaves, flowers, and roots contain tannins, phenols, and flavonoids are found abundantly in roots, leaves, and flowers, while terpenoids and saponins are more frequent in flowers, stems, and leaves. In this research study, flower oil was determined as mixture of different chemical constituents such as octadecane (5.60%), 1-hexadecene (6.93%), *E*-15-heptadecenal (4.98%), dodecanoic acid (5.22%), and hexahydrofarnesyl acetone (5.64%). While, leaves oil [106] was reported to contain phytochemicals such as dihydroactindiolide (10.27%), 2-methoxy-4-vinylphenol (17.70%), 1-hexadecene (5.10%), and megastigmatrienone (5.53%).

Flavonoids: Flavonoids, a polyphenol, constitute a major portion of the human diet and are further categorized into six sub-groups called flavanols, flavonols, flavones, flavanones, anthocyanins, and isoflavones. A significant ratio of flavonoids has been discovered from *Tamarix* species. The flavonoids mostly possess a fixed 3-hydroxyflavone structure (flavonol structure) compared to other flavonoid structures. *Tamarix* was reported to contain quercetin in the form of various glycosides. Tamarixetin and rhamnetin are also found in *Tamarix* species having diverse glycosylation patterns [107].

Tannins: Tannins, a subgroup of polyphenols, bind complex proteins and are known of having astringent activity. These are further categorized into ellagic acid and gallic acid derivatives, tannins, and proanthocyanidins. Hydroalcoholic, aqueous, and aqueous-acetone plant extracts of *Tamarix* reported yielding tannins. Ellagitannins are found in abundance as compared to gallotannins. Aerial parts, stem callus, and shoots of *Tamarix* are found to have tamarixinins and Hirtellins [108].

Terpenes: Terpenes, secondary metabolites, are volatile compounds responsible for the aroma of plants. Several triterpenoids and triterpenes i.e. β-amyrin, β-sitosterol, and ursolic acid are present in *Tamarix* species. *T. dioica* was reported to contain series of volatile monoterpenes (camphene, sesquiterpenes, iso-carveol, and safranal). Although, volatile terpenes are not among major constituents responsible for *T. dioica* biological activities [106] because their yield is comparatively low (0.07-0.57%).

Medicinal Properties

Moreover, *Tamarix dioica* is familiar as an astringent in some medical conditions such as vaginal discharge and leucorrhea. Antifungal activity of three microbes [109, 110], including *Aspergillus fumigatus, Candida glabrata,* and *Trichophyton rubrum, was* inhibited by *Tamarix dioica*. It was also found to hinder bacteria [111] such as *K. pneumonia* and *P. aeruginosa* [111].

In another study, the high antibacterial activity of leaves, and flower essential oils were recorded against*E. coli*as compared to that of *S. aureus.* The results demonstrated a significant reduction in *E. coli* colonies than that of *S. aureus*. [106].

Conclusion

Medicinal values of *Tamarix* genus and the *Fagonia* genus are affirmed by the presence of large number of phytoconstituents and the pharmacological properties vehicles ride out over recent years. Extracts of various kinds separated from these plants proved the presence of numerous phytoactive constituents with their clinically verified pharmacological effects. This review article highlighted the antifungal activities of *F.bruguieri* and *Tamarix dioica* which will be beneficial for the future analysis of bioactive compounds of these plants qualitatively and quantitatively for drug analysis in herbal preparations. Nowadays, preference is given in advancing the healthcare with eco-friendly system. Therefore, the vast potential can provide the way in developing effective strategies through varied formulations and advanced studies which will be helpful for the treatment of various ailments. The herbs or medicinal plants grasp the

attention in all aspects for detailed research works for comparative and comprehensive studies to explore the plants in much depth.

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