Terminalia genus as source of antimicrobial agents

O. Silva* and **R. Serrano**

RESEARCH INSTITUTE FOR MEDICINES (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Av. Professor Gama Pinto, 1649-003 Lisbon, Portugal
* Corresponding author: email: osilva@campus.ul.pt

Species of *Terminalia* L. genus (*Combretaceae*) were worldwide used in traditional medicine to treat different kind of diseases. In Africa, 30 *Terminalia* species were described and the traditional uses of most of it as antimicrobial agents were reported by different authors. In the present work a summary of the principal studies and results concerning the evaluation of the potential of 11 *Terminalia* species from Africa, America, Asia and Oceania as antibacterial, antiviral, antifungal and antiprotozoal agents or source of these will be presented. In detail, results obtained by our team concerning the antimicrobial activity of *Terminalia macroptera* Guill & Perr., a tree widely distributed in the savannahs and woodlands of Tropical Africa and used in Guinea-Bissau to treat infectious diarrhoeal diseases and venereal diseases, will be presented and discussed. Extracts of *T. macroptera* leaf and/or root have been found to be slight active against *Candida albicans*, and showing an interesting profile of activity against *Campylobacter* sp., *Shigella dysenteriae*, *Vibrio cholerae*, *Neisseria gonorrhoeae*, *Helicobacter pylori* and HIV-1. Obtained results corroborate total or partially with the traditional usages of *T. macroptera*. Also referred are species like *Terminalia arjuna*, *Terminalia bellerica* and *Terminalia chebula*.

Keywords: Antimicrobial; *Combretaceae*; Ethnopharmacology; *Terminalia arjuna*; *Terminalia bellirica*; *Terminalia chebula*; *Terminalia macroptera*

1. Introduction

Terminalia L. genus bellows to *Combretaceae* and consists of trees, often large and sometimes provided with buttresses on the base, and devoid of shrubs scales. Spiral leaves or sub-opposite sometimes grouped in end of the branches, often with glandular petioles and whole limbo or sub entire sometimes gland at the base of the bottom page and, sometimes, with translucent scores. Flowers in spikes or racemes, usually axillary, sessile or pedicellate, in men's rule, to the apex of the inflorescence, and bisexual to the base, mere 5-(4-sometimes not merely species African), devoid of petals; stamens 10, arranged in two whorls; ovary inferior with 2 (rarely 3) eggs and simple stylus, exert generally pubescent. Very variable fruit, indehiscent, drupaceous or samaroide, 2 wings more or less well developed, to ovoid and roughly angular. Seed with contorted cotyledons [1]. According to Stace, to this pantropical genus have been attributed 400 specific names, corresponding possibly to 100-150 species [1]. Species of this genus were worldwide used in traditional medicine to treat different kind of diseases, including diabetes, inflammatory diseases, malaria and hepatic, venereal and infectious gastrointestinal diseases. Three species of this genus were already considered on British Pharmacopoeia as herbal substances for use in Europa as traditional herbal medicinal products, namely *Terminalia chebula* Retz. fruit, *Terminalia arjuna* stem bark and *Terminalia bellirica* fruit [2]. "Triphala", an Ayurvedic herbal traditional preparation integrating two of these herbal substances (*T. chebula* and *T. bellirica*) among others, is considered the "Ayuervedic wonder" and is traditionally used to the treatment of different types of disease including infectious, since antiquity. The antibacterial activity of these constituents against different strains was already confirmed [3].

A literature research made on Science Citation Index Expanded, Thomson Reuters [4] since 1900 to July 1st 2015, allowed the identification of antimicrobial studies involving 24 species of *Terminalia* genus namely, *Terminalia alata* Heyne ex Roth, *Terminalia albida* Scott-Elliot, *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn., *Terminalia australis* Cambes., *Terminalia avicennioides* Guill & Perr., *Terminalia bellirica* (Gaertn.) Roxb., *Terminalia brachystemma* Welw. ex Hiern, *Terminalia brownii* Fresen., *Terminalia catappa* L., *Terminalia complanata* K.Schum., *Terminalia glaucescens* Planch. Ex. Benth., *Terminalia ivorensis* A. Chev., *Terminalia laxiflora* Engl & Diels, *Terminalia macroptera* Guill & Perr., *Terminalia mollis* M.A.Lawson, *Terminalia muelleri* Benth., *Terminalia nigrovenulosa* Pierre, *Terminalia pallida* Brandis, *Terminalia phanerophlebia* Engl. & Diels, *Terminalia sericea* Burch. ex DC., *Terminalia spinosa* Engl., *Terminalia stuhlmannii* Engl., *Terminalia superba* Engl. & Diels and *Terminalia triflora* (Griseb.) Lillo.

Among the studied species: 14 are of African origin, namely *Terminalia albida*, *Terminalia avicennioides*, *Terminalia brachystemma*, *Terminalia brownii*, *Terminalia glaucescens*, *Terminalia ivorensis*, *Terminalia laxiflora*, *Terminalia macroptera*, *Terminalia mollis*, *Terminalia phanerophlebia*, *Terminalia sericea*, *Terminalia spinosa*, *Terminalia stuhlmannii* and *Terminalia superba*; 2 are of American origin, namely *Terminalia australis* and *Terminalia triflora*; 6 are of Asian (India) origin, namely *Terminalia alata*, *Terminalia arjuna, Terminalia bellirica*, *Terminalia chebula*, *Terminalia nigrovenulosa* and *Terminalia pallida*; and 2 are of Oceanian (Australia) origin, namely *Terminalia complanata*, and *Terminalia muelleri*. Although attributed to Asia, the nature range of *T. catappa*, one of the most important medicinal plants of *Terminalia* genus, is uncertain. In fact, it has long been naturalized in a broad belt

extending from Africa to northern Australia and New Guinea through Southeast Asia and Micronesia into the Indian Subcontinent. More recently, the plant has also been introduced on America [5].
Polyphenols and triterpenoids are the most common classes of compounds in *Terminalia* genus. Among the polyphenols, flavonoids and hydrolysable tannins (gallotannins and ellagitannins) are predominant, while oleanolic acid derivatives are the major constituents of the triterpene saponins (triterpenoids class of compounds). Besides these classes of compounds, it is also common the presence of high amounts of mucilage and calcium salts (carbonate and oxalate) in this botanical genus (*Terminalia* L.) [6].

The antimicrobial studies on 11 *Terminalia* species, representative of the geographical distribution of this genus in the four Continents and including *Terminalia arjuna*, *Terminalia bellerica* and *Terminalia chebula* were presented and discussed on this work. Obtained data confirm to be the African continent, where 30 species of the genus *Terminalia* are described, the holder of most species of this genus whose antimicrobial activity was determined.
During the last 20 years our team has been devoted to the study of *Terminalia macroptera* and it has been chosen as representative species of the African continent, in the present work.

2. Antimicrobial studies on *Terminalia* genus

2.1 African *Terminalia* species

2.1.1 *Terminalia macroptera*

Terminalia macroptera was described by Guillemin & Perrotet [7] and its synonyms *Terminalia elliotii* Engl. & Diels, *Terminalia adamauensis* Engl. & Diels and *Terminalia chevalieri* Diels [8].

This species is a shrub or small tree 8-10 m tall with a dark-gray rhytidome, deeply fissured and hairless twigs (Fig. 1). This has natural distribution in Western Africa, occurring from Senegal, southward to Nigeria and east to Sudan and Uganda. It is a tree of wooded savannas, usually in situations more or less moist [8].

This species at Guinea-Bissau is known under the name of fadi, fadih (balanta); macêta, macête, macete, masete, masiti (creole of Portuguese matrix) and in French as badamier du Sénegal [9-13].

Fig 1 *Terminalia macroptera*, general aspect.

Ethnomedical uses: The traditional use of *T. macroptera* is described mostly the countries of West Africa, where it was identified (Fig. 2). For medicinal purposes leaves stems, roots and bark of this species are used [12-14].
The main internal uses, described for *T. macroptera* are the treatment of hepatitis, gonorrhea, syphilis, respiratory tract diseases and fever [15].

Externally, *T. macroptera* is used essentially in treatment of wounds as hemostatic and healing, and treatment of skin diseases [11,16,17]. This species is also used in combination with one or more other medicinal plants belonging to different botanical families [15].

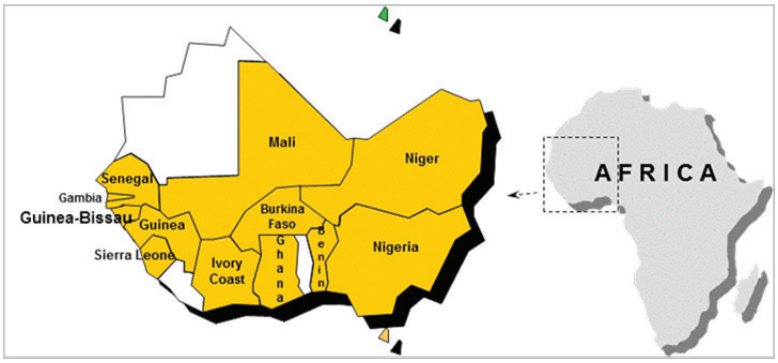

Fig. 2 West African countries where it is described the use of *Terminalia macroptera*.

Traditional herbal preparations: Four main recipes used to administrate *T. macroptera* as medicine, according to pathologies are given:

Gonorrhea and syphilis: Remove the rind and cut the root into small pieces, dried in the sun and grind. Boil a portion with water (10 g / L; cooking), add salt and strain with a cloth. Taking a glass until symptoms disappear, once a

day; Guinea-Bissau [18]. Wounds, first apply baking the stem bark, and then, apply a poultice of root bark (hemostatic and wound healing); Guinea-Bissau [11].

Wounds and conjunctivitis: Stepping in the bark of roots and pestle in the presence of water, placing the pulp obtained in a clean cloth and squeezing fluid to the wound or on the eye; Senegal [13].

Jaundice: Burn the bark of roots, tread the mortar and mix the powder in water; drink the liquid; Togo [15].

Diabetes, diabetic foot sores: Leaves and decoction in equal amounts, 1 teacup drunk twice daily for 5–7 days. Mali [18].

Antimicrobial activity studies: The *in vitro* antimicrobial activity of a ethanolic extract (95%) obtained by percolation (10ml ethanol / g dry plant) of leaves, bark and roots of *Terminalia macroptera* against *Bacillus subtilis*, *Staphylococcus aureus* and *Aspergillus niger* was first determinated by others. The extract of the leaves showed activity against *Bacillus subtilis* (inhibition zone greater than 15 mm at the concentration of 50 mg/mL) and against *Staphylococcus aureus* (inhibition zone greater than 15 mm at the concentration of 5 mg/mL); The extract of the bark has also shown to be active against *Bacillus subtilis* (inhibition zone less than 15 mm at 50 mg/mL) and against *Staphylococcus aureus* (inhibition zone greater than 15 mm at the concentration of 5 mg/mL); the root extract (50 mg/mL) was shown to be inactive against the 3 microorganisms tested [19].

After a preliminary *in vitro* antimicrobial screening using different reference bacterial strains and *Candida albicans* [20], the antimicrobial activity of the *T. macroptera* roots hydroethanol (80% V/V) extract and liquid-liquid partition fractions was evaluated by out team first against 7 reference bacterial strains *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* ATCC 43971, *Shigella dysenteriae* ATCC 13313, *Staphylococcus aureus* ATCC 25923, *Streptococcus faecalis* ATCC 10541 and *Vibrio cholerae* ATCC11623, and against *Candida albicans* CIP 3153A. Extract and fractions showed some activity against all strains except *Candida albicans* and *Escherichia coli*. The lowest minimum inhibitory concentrations (MICs) for the extract were obtained with *Shigella dysenteriae* (313 µg/mL), *Staphylococcus aureus* (1250 µg/mL) and *Vibrio cholerae* (less than 156 µg/mL). Similar MICS were obtained with the most active fractions (diethyl ether and water fractions) against the same bacterias. This active extract has been tested against a total of 97 strains of *Escherichia coli*, 106 strains of *Campylobacter* sp., 100 strains of *Salmonella* (*S. enteritis*, *S. typhimurium*) and 100 strains of *Shigella* (*Sh. dysenteriae*, *Sh. flexneri*) isolated from sporadic cases of gastro-enteritis in Portugal, and against 91 strains of *Vibrio cholerae* isolated in Portugal (23 strains), Brazil (38 strains) and Angola (30 strains) Results showed an interesting profile of activity against *Campylobacter* sp. with MIC50 and MIC90 of 25 µg/mL and 50 µg/mL, respectively [21].

Also evaluated was the *in vitro* activity of *T. macroptera* roots hydroethanol (80% V/V) extract and liquid-liquid partition fractions against nine reference and clinical *Neisseria gonorrhoeae* strains, including penicillin- and tetracycline-resistant and susceptible strains. This extract showed MIC values between 100 µg/mL and 200 µg/mL to all tested strains. The most active fractions of this extract were the diethyl ether fraction and water fractions. Ellagic acid, gallic acid, punicalagin, terchebulin, 3,3´-di-*O*-methylellagic acid, 3,4,3´,4´-tetra-*O*-methylellagic acid and terflavin A were isolated and identified in the extract and active fractions and also showed activity against *N. gonorrhoeae* strains tested [22, 23].

As referred, *Terminalia macroptera* roots is widely used in African traditional medicine to treat various infectious diseases, including stomach-associated diseases. In a study also conducted by us the *in vitro* activity of the *T. macroptera* roots hydroethanol (80% V/V) extract against 3 standard strains and 62 clinical strains of *Helicobacter pylori* and attempt to localize the extract bioactivity. 20% of the used *H. pylori* strains were clinical isolates resistant to at least two of the three antibiotics belonging to the main groups of antibiotics used in multi-therapy to eradicate *H. pylori* infections. The extract showed anti-*H. pylori* activity against 92% of the tested strains (MIC50 and MIC90 = 200 µg/mL). Water soluble fractions from this extract showed a MIC50 of 100 µg/mL. The main compounds of the extract and active fractions were the ellagitannins terchebulin and punicalagin [24].

In another study an ethanol extract of *T. macroptera* root has shown to be virucidal *in vitro* against a clinical strain of Herpes simplex virus type I (HSV-1) and innactive agianst a strain of African swine fever virus (ASFV) [25].

Concerning *T. macroptera* leaves the activity of a hydoethanol extract (80%) V/V and liquid-liquid partition fractions were also evaluated by us against 7 reference bacterial strains and against *Candida albicans*. In the range of tested concentrations (3200 to 50 µg/mL), the extract was active against all tested microorganisms. The best results were obtained against *Shigella dysenteriae* and *Vibrio cholerae (*MIC=200µg/mL for both) [26].

In pursuit of our studies, the evaluation of the antimicrobial activity of the hydroethanol extract from the leaves of *T. macroptera* and their Liquid-Liquid fractions against the nine strains *Neisseria gonorrhoeae* used to test the activity of the roots of this species was also perfomed. The results confirmed the antibacterial activity of the leaves extract (MICs between 200 µg/mL and 100 µg/mL) and of the liquid-liquid fractions against all tested strains. Diethyl ether fraction is the most active fraction (MIC between 50 µg/mL and 25 µg/mL). Chebulagic acid, chebulinic acid, isoorientin. gallic acid, ellagic acid and 3,4,5-trimethyl-3'acid, 4'-dioxoloflavelagic acid were among the constituents of the active extract. Gallic acid, ellagic acid and 3,4,5-trimethyl-3'acid, 4'-dioxoloflavelagic acid were simultaneously the main constituents of the most active fraction [27].

A hot aqueous extract from the root bark of *T. macroptera* has shown *in vitro* antiprotozoal activity against *Plasmodium falciparum* W2, a strain resistant to chloroquine (IC50 = 1 mg/mL) [28].

2.2 American *Terminalia* species

2.2.1 *Terminalia australis*

The methanol and aqueous extracts of *T. australis* aerial part showed to be active *in vitro* against to a strain of: *Candida albicans*, with MIC of 180 and 259 μg/mL, respectively; *Candida kruzzei* with MIC of 250 and 300 μg/mL, respectively; *Aspergillus fumigatus* with MIC of 0.3 and 0.8 μg/mL, respectively and the methanol extract to *Aspergillus flavus* (1.8 μg/mL). MICs of methanol extract against *Aspergillus* sp. were lower than the MIC of amphotericin B used as positive control. According to the authors, this plant part is not used in traditional medicine [29]. No data correlating the antimicrobial activity with the chemical composition were found.

2.2.2 *Terminalia triflora*

Despite the absence or few reports related with the ethnomedical uses for *Terminalia triflora*, the *in vitro* antimalarial activity of a methanol extract of the aerial parts of this species, from Panama, was evaluated. This extract showed an IC50 value of 9.0 μg/mL against a chloroquine resistant *P. falciparum* strain (W2 Indochina) [30].

At Argentina, results of an *in vitro* antifungal activity study using a methanol extract of this plant part showed its moderate activity against one clinical strain of *Microsporum gypseum*, *Trichophyton rubrum* and *Trichophyton mentagrophytes* (MIC of 250 μg/mL, 100 μg/mL and 100 μg/mL, respectively) [31]. An interesting *in vitro* antifungal activity result was also obtained by Gaitan et al. 2011 [32] using and ethanol extract of the dried leaves of this species. In fact, the extract showed to be active against *Sporothrix schenckii* and *Fonsecaea pedrosoi,* with MIC's of 25 μg/mL, for both fungi. These microorganisms are usually resistant to most of available antibiotics, and this kind of activity is not commonly studied in medicinal plants [32]. Concerning the antibacterial activity of this species no studies were described. However, and aqueous extract of *T. triflora* leaves showed to inhibit the polymerase and ribonuclease activities of HIV reverse transcriptase at IC50 between 1.6 μg/mL and 1.8 μg/mL, respectively [33] and the ellagitannins punicalin and 2-*O*-galloylpunicalin were identified as the main compounds responsible for this activity [34].

2.3 Asian *Terminalia* species

2.3.1 *Terminalia alata*

This species is described in the Agroforestry Database [35] as "a medium-sized to fairly large deciduous tree up to 35 m tall, bole up to 200 cm in diameter, bark surface with deep vertical fissures and transverse cracks, dark grey to blackish, inner bark reddish. It is known as "laurel or Indian laurel" and is native from India, Myanmar, Nepal and Thailand.

Fresh bark juice (3 spoonfuls, 3 times a day for as long as necessary) is taken for diarrhoea and dysentery at Nepal. A methanol extract obtained from dried bark showed to be active *in vitro* against Sindbis virus, Human poliovirus 1, and Herpes simplex virus-l with MICs of 100 μg/mL, 50 μg/mL (partial inhibitory effect) and 25 μg/mL, respectively [36]. The same kind of extract, tested *in vitro* at 1 mg using the agar disc diffusion method showed to be active against *Bacillus subtilis*, *Staphylococcus aureus*-methicilin sensitive, *Staphylococcus* aureus-methicillin resistant; *Streptococcus faecalis*; *Pseudomonas aeruginosa*-sensitive; *Pseudomonas aeruginosa*-wild type, *Mycobacterium phlei*, *Saccharomyces cervisiae*, *Candida albicans* and *Trichophyton mentagrophytes*. The activity against *S. aureus*-methicillin sensitive was enhanced by UV light, and *S. cervisiae* and *C. albicans* seems to be the less sensitive microorganisms among the tested [37]. However, only one strain of unknown origin of each kind of microorganism was used in this study. Betulic acid, arjunic acid, arjunolic acid, arjunetin and ellagic acid were identified from the trunk bark of this specie [38]. In a ethanol extract of the roots, 3,3'-di-*O*-methylellagic acid 4-*O*-β-D-glucopyranosyl-(1--> 4)-β-D-glucopyranosyl-(1-->2)-α-L-arabinopyranoside, 5,7,2'-tri-*O*-methylflavanone, 4'-*O*- α-L-rhamnopyranosyl-(1-->4)- β-D-glucopyranoside), and 2α,3β,19 β,23-tetrahydroxyolean-12-en-28-oic acid 3-*O*-β-D-galactopyranosyl-(1 -->3)- β-D-glucopyranoside-28-*O*-β-D-glucopyranoside were identified for the first time [39]. No data correlating the antimicrobial activity with the chemical composition were found.

2.3.2 *Terminalia arjuna*

This species, well known as "white marudah" and considered a sacred medicinal plant, is one of the most important herbal medicines on India and traditionally used as cardio protective and to treat different pathologies including infectious diseases. It is a large tree, up to 6-15 (-25) m tall with smooth, pale greenish to whitish grey bark, distributed throughout the greater part of India, Burma and Sri Lanka [40]. Dried bark is the most used *T. arjuna* plant part and is a cardiac stimulant and cardiotonic herbal medicine. Major constituents responsible for these activities are triterpenoids like arjunolic acid, and arjunic acid, but hydrolysable tannins like arjunin, punicalin, casuarinin, galloylglucose and hexahydroxidephenyl-1-galloyl glucose derivatives, flavon-3-ols such as (+)-catechin, (+)-gallocatechin and (-)-

epigallocatechin and phenolic acids such as gallic acid, ellagic acid and its derivatives like 3-*O*-methyl-ellagic acid 4-*O*-beta-D-xylopyranoside and 3-*O*-methyl ellagic acid 3-*O*-rhamnoside were also found in *Terminalia arjuna* [41, 42].

Aqueous and methanol extracts of *T. arjuna* bark showed to be active against multidrug resistant *Escherichia coli* Dk1 and *Staphyllococus aureus* MRS901 tested by agar well diffusion method. The maximum Zone of Inhibition was 9-13 mm for both extracts [43]. However, according to Kan et al. a crude ethanol extract of *T. arjuna* bark was not active against a clinical multidrug resistant strain of *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans* and against ATCC strains of *Streptococcus mutans*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus bovis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans* [44]. A methanol extract of this plant and of Triphala (a mixture containing *T. chebula*, *T. arjuna* and *Emblica officinalis*) showed to be active against multi-drug resistant *Salmonella typhi* strain [45]. Previous studies on this plant part also showed: the antimicrobial activity (1,000–5,000 ppm) of dichloromethane and aqueous extracts against *Escherichia coli* [46]; and of the crude drug against *Bacillus subtilis* and *Staphyloccus aureus* [47].

An anti-Herpes simplex virus effect (HSV) was verified and attributed to the presence of hydrolysable tannins on the bark of *T. arjuna* [41]. The extract of this medicinal plant is effective at early stage of HSV infection to hinder viral attachment and penetration [48]. The *in vitro* antiviral activity of casuarinin, one of the hydrolysable tannin isolated from this plant part, was also determined. Results showed that this compound inhibit the viral attachment and penetration, and also disturb the late event(s) of infection [49]. *In vitro*, *T. arjuna* bark also strongly suppressed the secretion of hepatitis B virus (HBV) surface antigen (HBsAg) [50]. At Pakistan, the antihelmintic *in vitro* and *in vivo* activity of a methanol extract of *T. arjuna* bark against *Haemonchus contortus* was also determined. It is active in egg hatch and larval development (645.65 μg/mL and 467.74 μg/mL, respectively) and effective in the adult motility assay (mortality of *H. contortus* at different hours post exposure). In sheep treated with this extract (3 g/kg) a maximum (87.3%) egg count percent reduction was obtained on day 11 post-treatment [51].

Methanol and aqueous extracts of *T. arjuna* leaves also showed antihelmintic activity *in vitro* against *Trichostrongylus colubriformis*, with a lethal concentration 50 (LC50%) of 1.502 and 3.002 , respectively [52].

2.3.3 *Terminalia bellirica*

A native species on Bangladesh, Bhutan, Cambodia, China, Indonesia, Laos, Malaysia, Nepal, Pakistan, Sri Lanka, Thailand, Vietnam, and according to Orwa et al. 2009 it "is a large deciduous tree to 50 m tall and a diameter of 3 m with a rounded crown. The frequently buttressed bole at the base is branchless up to 20 m. The bark is bluish or ashy-grey covered with numerous fine longitudinal cracks, the inner bark yellowish "[35]. The fruit rind (pericarp) is used in traditional medicine to treat different diseases including infections and inflammations [35].

As referred, this medicinal plant is commonly used in combination with the fruits of *Terminalia chebula* and *Emblica officinalis* is (equal parts of each) in a traditional Ayurvedic herbal preparation called Triphala used to treat different diseases, including gastrointestinal disorders, since antiquity. This preparation has been object of different studies concerning the evaluation of its antimicrobial potential [53]. Aqueous extracts of these plants were prepared and antibacterial activities were evaluated by agar well diffusion method against *Escherichia coli* and *Staphylococcus aureus* [54]. Ethanol and aqueous extracts of each component of this preparation and also the total traditional herbal preparation revealed to be active against most of the tested clinical strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae*, *Shigella sonnei*, *Shigella flexneri*, *Staphylococcus aureus*, *Vibrio cholerae*, *Salmonella paratyphi-B*, *Escherichia coli*, *Enterococcus faecalis*, *Salmonella typhi*) isolated from HIV infected patients [55]. The same kind of extracts of each of these three species and of Triphala were also tested against strains of *Staphylococcus aureus* and *Helicobacter pylori* isolated from different HIV infected patients. These samples showed and minimal inhibitory concentration between 0.1 and 100 μg/mL to the different tested strains [56]. Other study concerning and ethanol extract of Triphala and the ointment of this extract (10% w/w) revealed *in vivo* the antibacterial and wound healing capacity of this preparation and its usefulness in the management of infected wounds [57]. Methanol and aqueous extracts of Triphala also showed antibacterial activity against multi-drug resistant *Salmonella typhi* wounds [58].

Interesting antimicrobial results were also obtained with *T. bellerica* in other studies. In one of them, made with different medicinal plants used in Thai traditional medicine, the anti-quorum sensing activity a bio monitor strain, *Chromobacterium violaceum* DMST 21761 was evaluated. *T. bellirica* was one of the active medicines showing a significant inhibitory activity [59]. In other, the antibacterial activity of *T. bellerica* fruits against 4 clinical strains of methicillin resistant *Staphylococcus aureus* (MRSA) and a strain of methicillin sensitive *S. aureus* (MSSA) isolated from diseased human eyes was determined and these medicinal plants showed broad-spectrum antibacterial activity against all MRSA and the MSSA strains with inhibition zone size of 17–27 mm and a minimum inhibitory concentrations between less than 1500 μg/mL to 8200 μg/mL [60].

The vibriocidal activity against 12 isolates of *Vibrio cholerae* non-O1, and one reference strain of each *Vibrio cholerae* and *Vibrio parahaemolyticus* was also determined on *Terminalia bellirica* fruits aqueous, acetone, and ethanol extracts. Ethanol extracts showed a MIC between 2500-20000 μg/mL [61]. A *T. bellirica* fruits ethanol extract showed also some activity against *Candida albicans* (MIC of 7000 μg/mL) A *T. bellirica* fruit ethanol extract was tested *in vitro* using growth inhibition assay for resistance modifying agents (RMAs) of novobiocin against *Acinetobacter baumannii*,

an important nosocomial pathogen. At 250 μg/mL the extract showed a low antibacterial activity but significantly enhanced the activity of novobiocin at 1 μg/mL against this pathogen [62].

2.3.4 *Terminalia chebula*

This species is a medium size to large tree, up to 25-30 cm tall with many spreading branches with pale greenish, gray and smooth bark, expontanea on India, Ceylon, Burma, Malayan peninsula, Siam an cultivated in Pakistan. In English is known as black myrobalan or chebulic myrobalan. Two varieties of this species are recognized - *Terminalia chebula* var. *chebula* and *Terminalia chebula* var. *tomentella* [40]. It is called the "king of medicines" and is the most important medicinal plant in the Ayurvedic materia medica due to its general use. The fruit of this species is one of the constituents of Triphala, a popular traditional herbal preparation used also for diferent chronic diseases like diabetes [63].

The dried ripe fruit of *T. chebula* is the plant part traditional used in Indian traditional medicine as homeostatic, antitussive, laxative, diuretic and cardiotonic agent, and to treat chronic ulcers and wounds. The principal class of compounds present on this herbal medicine are triterpenoids (oleanolic acid derivatives) and hydrolysable tannins, like tannic acid, as deifined strutures like chebulic acid, chebulagic acid, chebulinic acid, corilagin, punicalagin, chebulanin, corilagin, neochebulinic acid, 1,2,3,4,6-penta-*O*-galloyl-H-D-glucose, 1,6-di-*O*-galloyl-D-glucose, casuarinin, 3,4,6-tri-*O*-galloyl-D-glucose and terchebulin and phenol acids like gallic acid and ellagic acid [63].

T. chebula fruit ethanol and water extracts showed to be active against *Bacillus subtilis* ATCC 6051, *Salmonella typhimurium* ATCC 23564, *Pseudomonas aeruginosa* ATCC 25619, and *Escherichia coli* K-12 and *Staphylococcus aureus* clinical strains. The water extract was also active against *Proteus vulgaris* ATCC 6380 using a modified agar well diffusion method. At a concentration of 200 mg/mL this extract was disproved of cellular toxicity (fresh sheep erythrocytes) [64].

Results from another antibacterial activity study made with an ethanol extract of *T. chebula* fruits showed the activity of this herbal medicine against both gram-positive and gram-negative bacteria. This extract was effective against *Salmonella typhi* SSFP 4S, *Staphylococcus epidermidis* MTCC 3615, *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* MTCC 441 and *Pseudomonas aeruginosa* ATCC 27853 [65]. Gallic acid and its ethyl gallate were identified as 2 of the main constituents responsible for the antibacterial activity of *T. chebula* fruit against methicillin-resistant *Staphylococcus aureus* [66].

An aqueous extract and powdered *T. chebula* fruits showed to be active against ten clinical isolates of *Helicobacter pylori* - MICs of 125 μg/mL and 150 μg/mL, respectively and minimum bactericidal concentration of 150 μg/mL and 175 mg/L, respectively. The aqueous extract (1-2.5 mg/mL) also inhibited urease activity of *H. pylori* [67]. This kind of extract also inhibited the growth, sucrose-induced adherence and glucan-induced aggregation of *Streptococcus mutans* [68]. The aqueous extract of black myrobalan also showed antifungal activity against dermatophytes and *Candida albicans* [69].

In vitro and *in vivo* antiviral activity of this medicinal plant against HSV and human cytomagalovirus (CMV) was also demonstrated. This medicinal plant is active against human immunodeficiency virus-1 reverse transcriptase [70] and from this gallic acid and derivatives were isolated as immunodeficiency virus type 1 (HIV-1) integrate inhibitors [71] and other hydrolysable tannins as hepatitis C inhibitors [72]. In combination with acyclovir *T. chebula* showed a stronger *in vitro* antiviral activity against herpes simplex virus type 1 [73].

2.3.5 *Terminalia nigrovenulosa*

This species is a tree or shrub to 15 m tall with a trunk to 0.5 m dbh (diameter at breast height) and a bark gray-white, gray, yellowish brown, gray-brown, or brown, spotted. It is described on Hainan [Cambodia, Laos, Malaysia (NW Peninsular Malaysia and Lankawi Islands), Myanmar, Thailand, Vietnam] [40].

A methanol extract of *T. nigrovenulosa* bark tested by disk diffusion method, showed *in vitro* antifungal activity against the phytopathogens *Phytophthora capsici* KACC 40157, *Fusarium solani* KACC 40384, *Fusarium oxysporum* KACC 40032 and *Rhizoctonia solani* KACC 40111. The methanol leaves extract is also tested and showed to be inactive against *P. capsici* and less active against *R. solani* [74].

2.3.6 *Terminalia pallida*

This species is a semi-evergreen tree recorded from the States of Andhra Pradesh and Tamil Nadu in India and well known as "white gali nut" tree. It is harvested for its fruits and it has been estimated that 40% of the wild population had declined over three generations (87 years). Therefore this species is actually referred by IUCN on The IUCN Red List of Threatened Species and assessed as Vulnerable by this organization [75].

Traditionally, the bark is used has mild diuretic and the fruits are used in the treatment of ulcers, diarrhea and in venereal diseases. An *in vitro* antimicrobial screening using a methanol extract of fruit powder of this species at a concentration range of 625-5000 μg/mL by cup-plate method showed that this extract exhibited activity against one

clinical strain of each *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Escherichia coli*, *Salmonella typhi*, *Shigella dysenteriae*, *Vibrio cholerae*, *Aspergillus niger* and *Candida albicans* [76].

2.4 Oceanian *Terminalia* species

2.4.1 *Terminalia complanata*

A rainforest species described on Australian Flora as a "tree to 45 m, deciduous or partly so. Branchlets sericeous, glabrescen", occurring in Australia from Iron Ra. and McIlwraith Ra., Qld, but extending through New Guinea to the Solomon Islands [77].

No data related with medicinal traditional uses of this species were found in the literature. *T. complanata* leaf, root and stem bark methanol extracts were tested against bacteria, protozoan and fungi (*Aspergillus niger*, *A. rubrum*, *A. versicolor*, *A. vitis*, *Candida albicans*, *C. tropicalis*, *Cladosporium cladosporiodes*, *Trychophyton mentagrophytes*, *T. tronsurum* by disk diffusion method (20 mg/disc). The extracts were inactive against all tested moulds but active against all other microorganisms tested (*Bacillus cereus*, *B. coagulans*, *B. megatarium, B. subtilis*, *Lactobacillus casei*, *Micrococcus luteus*, *M. roseus, Staphylococcus albus, S. aureus, S. epidermidis*, *Streptococcus faecalis*, *St. mutans, St. pneumonia, Agrobacterium tumefaciens*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Escherichia coli, Klebsiella pneumonia*, *Neisseria gonorrhoeae*, *Proteus mirabilis, P. vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Sa. typhymurium*, *Serratia marcescens* and *Trichomonas vaginalis*) [78]. Arjunolic acid and asiatic acid were found in *T. complanata* wood [79].

2.4.2 *Terminalia muelleri*

This species is described on ABRS Flora of Australia (2015) as a "tree to 10 m, deciduous. Branchlets appressed pubescent, glabrescent. Occur from Rockhampton to Cape York, Qld, extending a small distance S along the western side of Cape York Peninsula. Common in low closed-forest on stabilised dunes and occasionally on sandstone on the coast." [80].

This plant is known in Indonesia as "ketapang kencana". The ethanol extract of the leaves has shown antimicrobial activity against *Escherichia coli*, *Staphyloccoccus aureus* and *Candida albicans*. Additionally, non-identified constituent of ethylacetate extract of this plant part has shown inhibit a *methicillin-resistant Staphylococcus aureus* strain [81-83].

3. Final remarks

The studies described clearly show the interest of the botanical *Terminalia* genus as source of medicines with antimicrobial activity. Most studies were performed *in vitro* and focus primarily the determination of the antibacterial activity of the target species. In fact, few antiviral and antimalarial activity studies were made until now on this botanical genus.

The majority of the antimicrobial activity studies were conducted in non-standardized extracts and even of unknown composition. In addition the constituents responsible for the antimicrobial activity were not determined. Thus, taking into account the possible variability in the vegetable starting material and the different methods used for the production of the plant extracts tested it may be justifiable the variability between the results obtained in different studies involving the same medicinal plants and the same microorganisms. Hydrolysable tannins is one of the classes of chemical compounds that can be correlated with the demonstrated antimicrobial activity demonstrated by the different *Terminalia* medicinal plants.

Studies made with *Terminalia macroptera* decorticated root showed antimicrobial activity relevant against *Neisseria gonorrhoeae*, consistent with the traditional use in the treatment of venereal diseases. Additionally, this medicinal plant was shown to be active against *Staphylococcus aureus* and *Enterococcus faecalis*, which is consistent with the traditional use for the treatment of conjunctivitis and wounds, and urinary problems in other West African countries This part of the plant showed large activity against bacteria commonly associated with the onset of diarrhea (*Salmonella typhimurium, Shigella dysenteriae*) and cholera (*Vibrio cholerae*), infectious diseases of high incidence in Africa. In addition, this herbal medicine proved to have virucidal activity against HSV-1. The major constituents of the active herbal preparation were identified and correlated with the biological activity. The same correlation was verified on *Terminalia macroptera* leaves studies.

Acknowledgements The support by iMed.ULisboa (UID/DTP/04138/2013) from Fundação para a Ciência e a Tecnologia (FCT), Portugal, is gratefully acknowledged.

References

[1] Stace CA. The significance of the leaf epidermis in the taxonomy of the *Combretaceae*, I. A general review of tribal, generic and specific characters. The Journal of the Linnean Society. 1965; 59:229-52.

[2] MHRA British Pharmacopoeia, 8th ed. MHRA Regulation Medicines and Medical Devices. UK: BP Publications; 2014.

[3] Baliga MS, Meera S, Mathai B, Rai MP, Pawar V, Palatty PL. Scientific Validation of the Ethnomedicinal Properties of the Ayurvedic Drug Triphala: A Review. Chinese Journal of Integrative Medicine. 2012; 18 (12):946-54.

[4] Thomson Reuters; 2015 [cited 2015 Jun 14]. Available from: http://ip-science.thomsonreuters.com/cgi-bin/jrnlst/jlsubcatg.cgi?PC=D

[5] USDA United States Department of Agriculture. Agricultural Research Service, Beltsville Area. Germplasm Resources Information Network (GRIN); 2015 [cited 2015 Jun 14]. Available from: http://www.ars-grin.gov/cgi-bin/npgs/html/taxon.pl?36334

[6] Hegnaüer R. Chemotaxonomie der Pflanzen, vol. VIII, Berlin, Birkhäuser Verlag; 1989. p. 254-60.

[7] Guillemin JBA, Perrottet GS, Richard A. Florae Senegambiae Tentamen, seu Historia Plantarun in Diversis Senegambiae Regionibus a Peregrinatoribus et Leprieur Detectarum, part 7, Paris; 1832, Pl. 63.

[8] Hutchinson J. Flora of West Tropical Africa, 1st ed., vol 1, London, Crown Agents for the Colonies; 1927, part 1, 226.

[9] Gomes ET, Diniz MA. Plantas Usadas na Medicina Tradicional na Região de Contúboel, Comunicações - Instituto de Investigação Científica Tropical. Série das Ciências Agrárias. 1993; 13:153-65.

[10] Espírito Santo J. Nomes Vernáculos de Algumas Plantas da Guiné Portuguesa. Lisboa, Junta de Investigações do Ultramar; 1963. p. 116.

[11] Feijão RO. Elucidário Fitológico: Plantas Vulgares de Portugal Continental, Insular e Ultramarino. Lisboa, Instituto Botânico de Lisboa; 1960. p. 164-5.

[12] Burkill HM. The Useful Plants of West Tropical Africa - Families *A-D*. 2nd ed.,vol. 1, Kew, Royal Botanic Gardens; 1985. p. 421-3.

[13] Kerharo J, Adam JG. La Pharmacopée Sénégalaise Traditionnelle – Plantes Médicinales et Toxiques. Paris, Vigot; 1974. p. 359-60.

[14] Baerts M, Lehmann. *Terminalia macroptera* Guill. & Perr. In: A Few Medicinal Plants Used in Traditional Veterinary and Human Medicine in Sub-saharan Africa – Database Prelude, web ed., Belgique, Laboratoire de Botanique Médicale de Louvain-la-Neuve; 2002 [cited 2014 Jun 7]. Available from: http://www.fynu.ucl.ac.be/users/j.lehmann/.

[15] Adjanohoun E, Cusset G, Issa lD, Keita A, Le Bras M, Lejoly J. *Terminalia macroptera* Guill. & Perr. In: Banque de Données de Médecine Traditionnelle et Pharmacopée (Pharmel), 2éme ed., Paris, Agence de Coopération Culturelle et Technique; 1994.

[16] Berhaut J. Flore Illustrée du Sénégal: Dycotylédones, Tome II: Balanophoracées à Composées, Dakar, Gouvernement du Sénégal: Ministère du Développement Rural – Direction des Eaux et Forêts; 1974. p. 409-11.

[17] Pobéguin H. Les Plantes Médicinales de la Guineé, Paris, A. Challame; 1912. p. 27.

[18] Phama AT, Dvergsnesa C, Togolab A, Wangensteena H, et al. *Terminalia macroptera*, its current medicinal use and future perspectives. Journal of Ethnopharmacology. 2011; 137:1486-91.

[19] Grand AL, Wondergen PA, Verpoorte R, Pousset JL. Anti-Infectious Phytotherapies of the Tree-Savannah of Senegal (West-Africa). II. Antimicrobial Activity of 33 Species. Journal of Ethnopharmacology. 1988; 22:25-31.

[20] Silva O, Duarte A, Cabrita J, Pimentel M, Diniz A, Gomes E. Antimicrobial activity of Guinea-Bissau traditional remedies. Journal of Ethnopharmacology. 1996; 50 (1): 55-9.

[21] Silva O, Duarte A, Pimentel M, Viegas S, Barroso H, Machado J, Pires I, Cabrita J, Gomes E. Antimicrobial activity of *Terminalia macroptera* root. Journal of Ethnopharmacology. 1997; 57 (3):203-7.

[22] Silva O, Ferreira E, Vaz Pato M, Gomes E. Guinea-Bissau's plants: In vitro susceptibility studies on *Neisseria gonorrhoeae*. International Journal of Pharmacognosy. 1997; 35, 5: 323-8.

[23] Gomes ET, Silva O, Diniz MA, Martins ES. Macete. In: Plantas Medicinais da Guiné-Bissau – Manual Prático, Guiné-Bissau, Acção para o Desenvolvimento; 2003. p. 45-8.

[24] Silva O, Viegas S, de Mello-Sampayo C, Costa MJP, Serrano R, Cabrita J, Gomes ET. Anti-*Helicobacter pylori* activity of *Terminalia macroptera* root. Fitoterapia. 2012; 83(5):872-6.

[25] Silva O,Barbosa S, Diniz A, Valdeira ML, Gomes E. Plant extracts antiviral activity against Herpes simplex virus type 1 and african swine fever virus. International Journal of Pharmacognosy. 1997; 35(1):12-6.

[26] Silva O, da Silva G, Taniça M, Serrano R, Vital J, Gomes ET. *In vitro* antimicrobial activity screenning of *Terminalia macroptera* leaf. Planta Medica. 2010; 76-P466.

[27] Silva O, Ferreira E, Pato MV, Canica M, Gomes ET. *In vitro* anti-*Neisseria gonorrhoeae* activity of *Terminalia macroptera* leaves. FEMS Microbiology Letters. 2002; 211(2):203-6.

[28] Sanon S, Ollivier E, Azas N, Mahiou V, Gasquet M, Ouattara CT et al. Ethnobotanical Survey and *in vitro* Antiplasmodial Activity of Plants Used in Tradicional Medicine in Burkina Faso. Journal of Ethnopharmacology. 2003; 86:143-7.

[29] Carpano SM, Spegazzini ED, Rossi JS, Castro MT, Debenedetti SL. Antifungal activity of *Terminalia australis.* Fitoterapia. 2003; 74:294-7.

[30] Calderon AI, Simithy-Williams J, Gupta MP. Antimalarial natural products drug discovery in Panama. Pharmaceutical Biology. 2012; 50(1):61-71.

[31] Muschietti L, Derita M, S¨ulsen V, de Dios Muñoz J, Ferraro G, Zacchino S, Martino V. *In vitro* antifungal assay of traditional Argentine medicinal plants. Journal of Ethnopharmacology. 2005; 102:233-8.

[32] Gaitan I, Paz AM, Zacchino SA, Tamayo G, Gimenez A, Pinzon R, Caceres A, Gupta MP. Subcutaneous antifungal screening of Latin American plant extracts against *Sporothrix schenckii* and *Fonsecaea pedrosoi*. Pharmaceutical Biology. 2011; 49(9): 907-19.

[33] Martino VS, Lopez P, Martinez Irujo J J, Sanroman M, Cuevas MT, Santiago E, Lasarte JJ, Font M, Coussio JD, Monge A. Inhibitory effect against polymerase and ribonuclease activities of HIV-reverse transcriptase of the aqueous leaf extract of *Terminalia triflora*. Phytotherapy Research. 2002; 16:778-80.
[34] Martino VS, Morales J, Martinez-Irujo J J, Font M, Monge A, Coussio J. Two ellagitannins from the leaves of *Terminalia triflora* with inhibitory activity on HIV-1 reverse transcriptase. Phytotherapy Research. 2004; 18:667-9.
[35] Orwa C. Mutua A, Kindt R, Jamnadass R, Anthony S. Agroforestree Database: a tree reference and selection guide version 4.0. World Agroforestry Centre, Kenya; 2009 [cited 2015 Jun 20]. Available from: http://www.worldagroforestry.org/resources/databases/agroforestree
[36] Taylor RSL, Hudson, JB, Manandhar NP, Towers GHN. Antiviral activities of medicinal plants of southern Nepal. Journal of Ethnopharmacology. 1996; 53:97-104.
[37] Taylor RSL, Edel F, Manandhar NP, Towers GHN. Antimicrobial activities of southern Nepalese medicinal plants. Journal of Ethnopharmacology. 1996; 50:97-102.
[38] Mallavarapu GR , Babu Rao S , Syamasundar KV. Chemical Constituents of the Bark of *Terminalia alata.* Journal of Natural Products. 1986; 49 (3):549-50.
[39] Srivastava SK, Srivastava SD, Chouksey BK. New antifungal constituents from *Terminalia alata*. Fitoterapia. 2001; 72(2):106-12.
[40] *Terminalia arjuna*; *Terminalia chebula*; *Terminalia nigrovenulosa*. In Flora of Pakistan @ efloras.org [cited 2015 Jun 29]. Available from: http://www.eFloras.org
[41] Jain S, Yadav PP, Gill V, Vasudeva N, Singla N. *Terminalia arjuna* a sacred medicinal plant: phytochemical and pharmacological profile. Phytochemistry Reviews. 2009; 8:491-502.
[42] Saha A, Pawar VM, Jayaraman S. Characterisation of Polyphenols in *Terminalia arjuna* Bark Extract. Indian Journal of Pharmaceutical Sciences. 2012; 74(4):339-47.
[43] Kumar S, Singh AK, Verma SK, Misra R, Seniya C. Antibacterial and Phyto-chemical Analysis of Some Medicinal Plants and their Efficacy on Multidrug Resistant Bacteria. Journal of Pure and Applied Microbiology. 2013; 7(3):2191-204.
[44] Khan R, Islam B, Akram M, Shakil S, Ahmad A, Ali SM et al. Antimicrobial Activity of Five Herbal Extracts Against Multi Drug Resistant (MDR) Strains of Bacteria and Fungus of Clinical Origin. Molecules. 2009; 14(2):586-97.
[45] Rani P, Khullar N. Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant *Salmonella typhi*. Phytotherapy Research. 2004; 18(8):670-3.
[46] Aggarwal RR, Dutt S. Chemistry, pharmacology and therapeutic actions of *Terminalia arjuna*. Proceedings of the National Academy of Sciences. 1936; 6:305.
[47] Samy RP, Ignacimuthu S. Antibacterial effects of the bark of *Terminalia arjuna*: Justification of folklore beliefs. Pharmaceutical Biology. 2001; 39(6):417-20.
[48] Cheng CL, Ng KY, Xu HX. Recent Advances in the Discovery of Novel Anti-Herpetic Agents from Chinese Herbal Medicines. Current Organic Chemistry. 2010; 14(16):1714-26.
[49] Cheng HY, Lin CC, Lin TC. Antiherpes simplex virus type 2 activity of casuarinin from the bark of *Terminalia arjuna* Linn. Antiviral Research. 2002; 55(3):447-55.
[50] Goto W, Kusumoto IT, Kadota S, Namba T, Kurokawa M, Shiraki K. Suppression of hepatitis B virus surface antigen secretion by traditional plant medicines. Phytotherapy Research. 1996; 10(6):504-7.
[51] Bachaya HA, Iqbal Z, Khan MN, Jabbar A, Gilani AH, Islam UD. *In Vitro* and *In Vivo* Anthelmintic Activity of *Terminalia arjuna* Bark. International Journal of Agriculture and Biology. 2009; 11(3):273-8.
[52] Hussain A, Khan MN, Sajid MS, Iqbal Z, Khan MK, Abbas RZ et al. *In Vitro* Screening of Ziziphus Mauritiana and *Terminalia arjuna* for Their Anthelmintic Activity. Journal of Animal and Plant Sciences. 2011; 21(4):781-6.
[53] Baliga MS, Meera S, Mathai B, Rai MP, Pawar V, Palatty PL. Scientific Validation of the Ethnomedicinal Properties of the Ayurvedic Drug Triphala: A Review. Chinese Journal of Integrative Medicine. 2012; 18(12):946-54.
[54] Sagar A, Parvez S. Antibacterial Activity of *Terminalia chebula* (Retz.), *Emblica officinalis* (Gaertn.) and *Terminalia bellirica* (Gaetn.) Roxb. Journal of Pure and Applied Microbiology. 2012; 6(3):1475-80.
[55] Srikumar R, Parthasarathy NJ, Shankar EM, Manikandan S, Vijayakumar R, Thangaraj R et al. Evaluation of the growth inhibitory activities of triphala against common bacteria isolates from HIV infected patients. Phytotherapy Research. 2007; 21(5):476-80.
[56] Amanullah S, Chandramoorthy HC, Kumar A, Khatheeja S. Antimicrobial activity of Triphala against bacterial isolates from HIV infected patients. Jundishapur Journal of Microbiology. 2011; 4:S9-S17.
[57] Kumar MS, Kirubanandan S, Sripriya R, Sehgal PK. Triphala promotes healing of infected full-thickness dermal wound. Journal of Surgical Research. 2008; 144(1):94-101.
[58] Rani P, Khullar N. Antimicrobial evaluation of some medicinal plants for their anti-enteric potential against multi-drug resistant *Salmonella typhi*. Phytotherapy Research. 2004; 18(8):670-3.
[59] Limsuwan S, Chusri S, Mitsuwan W, Voravuthikunchai SP. Anti-quorum Sensing Activity of Medicinal Plants Used in Thai Traditional Medicine for Infections. Journal of Pure and Applied Microbiology. 2013; 7(3):1717-24.
[60] Aqil F, Khan MSA, Owais M, Ahmad I. Effect of certain bioactive plant extracts on clinical isolates of beta-lactamase producing methicillin resistant *Staphylococcus aureus*. Journal of Basic Microbiology. 2005; 45(2):106-14.
[61] Sharma A, Patel VK, Chaturvedi AN. Vibriocidal activity of certain medicinal plants used in Indian folklore medicine by tribals of Mahakoshal region of central India. Indian Journal of Pharmacology. 2009; 41(3):129-33.
[62] Phatthalung PN, Chusri S, Voravuthikunchai SP. Thai ethnomedicinal plants as resistant modifying agents for combating *Acinetobacter baumannii* infections. Bmc Complementary and Alternative Medicine. 2012; 12.
[63] Upadhyay A, Agrahari P, Singh DK. 2014. A Review on the Pharmacological Aspects of *Terminalia chebula.* International Journal of Pharmacology. 2014; 10: 289-98.
[64] Ahmad I, Mehmood Z, Mohammad F. Screening of some Indian medicinal plants for their antimicrobial properties. Journal of Ethnopharmacology. 1998; 62:183-93.

[65] Kannan P, Ramadevi SR, Hopper W. Antibacterial activity of *Terminalia chebula* fruit extract. African Journal of Microbiology Research. 2009; 3(4):180-4.
[66] Saleem A, Ahotupa M, Pihlaja K. Total phenolics concentration and antioxidant potential of extracts of medicinal plants of Pakistan. Zeitschrift fur Naturforschung C. 2001; 56(11-12):973-8.
[67] Malekzadeh F, Ehsanifar H, Shahamat M, Levin M, Colwell RR. Antibacterial activity of black myrobalan (*Terminalia chebula* Retz) against *Helicobacter pylori.* International Journal of Antimicrobial Agents. 2001; 18:85–8.
[68] Aneja KR, Joshi R. Evaluation of antimicrobial properties of fruit extracts of *Terminalia chebula* against dental caries pathogens. Jundishapur Journal of Microbiology. 2009; 2(3):105-11.
[69] Dutta BK, Rahman I, Das TK. Antifungal activity of Indian plant extracts. Mycoses. 1998; 41(11-12):535-6.
[70] Elmekkawy S, Meselhy MR, Kusumoto IT, Kadota S, Hattori M, Namba T. Inhibitory Effects of Egyptian Folk Medicines on Human-Immunodeficiency-Virus (Hiv) Reverse-Transcriptase. Chemical & Pharmaceutical Bulletin. 1995; 43(4):641-8.
[71] Ahn MJ, Kim CY, Lee JS, Kim TG, Kim SH, Lee CK et al. Inhibition of HIV-1 integrase by galloyl glucoses from *Terminalia chebula* and flavonol glycoside gallates from *Euphorbia pekinensis*. Planta Medica. 2002; 68(5):457-9.
[72] Ajala OS, Jukov A, Ma CM. Hepatitis C virus inhibitory hydrolysable tannins from the fruits of *Terminalia chebula.* Fitoterapia. 2014; 99:117-23.
[73] Kurokawa M, Nagasaka K, Hirabayashi T, Uyama S, Sato H, Kageyama T et al. Efficacy of Traditional Herbal Medicines in Combination with Acyclovir Against Herpes-Simplex Virus Type-1 Infection *In Vitro* and *In Vivo*. Antiviral Research. 1995; 27(1-2):19-37.
[74] Nguyen DMC, Seo DJ, Lee HB, Kim IS, Kim KY, Park RD, Jung WJ. Antifungal activity of gallic acid purified from *Terminalia nigrovenulosa* bark against *Fusarium solani*. Microbial Pathogenesis. 2013; 56:8-15.
[75] Saha, D., Ved, D., Ravikumar, K. & Haridasan, K. *Terminalia pallida*. In: The IUCN Red List of Threatened Species. Version 2015.2. [cited 2015 Jun 25]. Available from: http://www.iucnredlist.org/
[76] Gupta_M, Mazumder UK, Manikandan L, Bhattacharya S, Haldar PK, Roy S. Antibacterial activity of *Terminalia pallida.* Fitoterapia. 2002; 73:165-7.
[77] *Terminalia complanata*. In ABRS Flora of Australia Online Search Results [cited 2015 Jul 7]. Available from: http://www.anbg.gov.au/abrs/onlineresources/flora/
[78] Khan MR, Kihara M, Omoloso AD. Antimicrobial activity of *Terminalia complanata* and *Flacourtia zippelii*. Fitoterapia. 2002; 73(7-8):737-40.
[79] Collins DJ, Pilotti CA, Wallis AFA. Triterpene Acids from Some Papua-New-Guinea *Terminalia* Species. Phytochemistry. 1992; 31(3):881-4.
[80] *Terminalia muelleri*. In ABRS Flora of Australia Online Search Results [cited 2015 Jul 7]. Available from: http://www.anbg.gov.au/abrs/onlineresources/flora/
[81] Bajpai M, Pande A, Tewari SK, Prakash D. Phenolic contents and antioxidant activity of some food and medicinal plants. International Journal of Food Sciences and Nutrition. 2005; 56:287-91.
[82] Anam K., Suganda AG, Sukandar EY, dan Kardono LBS. Antimicrobial activity of *Terminalia muelleri* Benth. leaves. Indonesian Journal of Natural Products. 2009; 7:40-3.
[83] Anam K, Suganda AG, Sukandar EY, Kardono LBS. Antibacterial Effect of Component of *Terminalia muelleri* Benth against *Staphylococcus aureus*. International Journal of Pharmacology. 2010; 6(4):407-12.

