In vitro activity of Brazilian medicinal plants, naturally occurring naphthoquinones and their analogues, against methicillin-resistant *Staphylococcus aureus*

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Abstract

Fourteen extracts from Brazilian traditional medicinal plants used to treat infectious diseases were used to look for potential antimicrobial activity against multiresistant bacteria of medical importance. *Staphylococcus aureus* strains were susceptible to extracts of *Punica granatum* and *Tabebuia avellanedae*. The minimum inhibitory concentrations (MICs) of the total extracts and of additional fractions of these plants were determined by employing strains of methicillin-resistant (MRSA) and -sensitive (MSSA) *S. aureus*, including isolates of the PFGE clone A, which is prevalent in Brazil and two ATCC reference strains. A mixture of ellagitannins isolated from *P. granatum* and two naphthoquinones isolated from *T. avellanedae* demonstrated antibacterial activity against all *S. aureus* strains tested. Semi-synthetic furanonaphthoquinones (FNQs) showed lower MICs than those exhibited by natural occurring naphthoquinones. The results indicate that these natural products can be effective potential candidates for the development of new strategies to treat MRSA infections.

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Keywords: Brazilian medicinal plants; *Punica granatum*; *Tabebuia avellanedae*; Quinones; Antimicrobial activity; MRSA strains

1. Introduction

The use of higher plants and preparations made from them to treat infections is an age-old practice in a large part of the world population, especially in developing countries, where there is dependence on traditional medicine for a variety of diseases [1]. Interest in plants with antimicrobial properties has revived as a consequence of current problems associated with the use of antibiotics [2,3].

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) isolates have increased greatly during the last decades in hospital [4,5] and the community [6]. The epidemic clones characterized by Pulsed Field Gel Electrophoresis (PFGE) are capable of rapid spread [7]. In Brazil, the PFGE clone A has been shown to be prevalent in several hospitals [5,8].

In vitro antimicrobial screening permits the selection of crude plant extracts with potentially useful properties to be used for further chemical and pharmacological studies. The present report is one of a series of studies aimed at the identification of Brazilian plants with antibiotic properties. The 14 botanical species selected here for antimicrobial activity testing against hospital isolates of *S. aureus*, including MRSA strains, are used in traditional medicine for the treatment of gastrointestinal, respiratory, urinary and skin infections. The quinones tested were obtained within a research program of our laboratory that studies the synthesis and evaluation of rare natural quinones from the Brazilian flora and their synthetic analogues against tropical endemic diseases [9].

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2. Materials and methods

2.1. Plant material extraction and fractionation

Fourteen different plant species and plant fractions were used as shown in Table 1. The plants were extracted by maceration in ethanol for 2 days at room temperature and the process was repeated twice. The total ethanolic extracts (te) were concentrated in a rotational evaporator under reduced pressure and the residues were then successively partitioned between water (w) and n-hexane (h), followed by chloroform (c) or dichloromethane (d), ethyl acetate (ea) and n-butanol (b). The solutions were completely evaporated to give the respective fractions.

The ethyl acetate fraction from the pericarp of *Punica granatum* fruits was applied to a XAD-16 resin (Sigma, St. Louis, USA) column and eluted with a continuous gradient of methanol in water from 5 to 100%. Further purifications over Sephadex LH-20 (Amersham Pharmacia Biotech, Uppsala, Sweden) by elution with a methanol/water gradient from 0 to 50%, yielded a mixture of ellagitannins (PG F1).

The hexane fraction of the wooden part of *Tabebuia avellanedae* was purified over a silica gel 230–400 mesh-ASTM (Merck, Darmstadt, Germany) column, eluted with solvent gradients from hexane to ethyl acetate and ethyl acetate to methanol. Fractions eluted with 20% ethyl acetate in hexane yielded the naphthoquinones lapachol, α-lapachone and α-xyloidone after further purification on preparative silica gel 60 (PF 254-366, Merck) TLC plates, eluted with 5% of ethyl acetate in hexane.

2.2. Synthesis of naphthoquinones

Compounds I–IV (Fig. 1) were semi-synthetically obtained from lapachol, which was isolated in this study by extraction of *T. avellanedae* sawdust, following the original procedure of Paternò [10]. Quinone I was conveniently synthesized according to Hooker [11]. Quinones II, III and IV were synthesized using our original procedure [12]. The last two quinones were synthesized for the first time in our laboratory [13].

2.3. Test organisms

The organisms used in this study were *S. aureus* ATCC 29213 (MSSA) and ATCC 33591 (MRSA), 16 MRSA strains, including seven isolates of the Brazilian prevalent PFGE clone A and eight MSSA strains. All bacteria were isolated from patients in two Brazilian hospitals that provided tertiary care. The isolates were identified by traditional biochemical tests [14], and susceptibility patterns were obtained by the disk diffusion method, according to National Committee for
Clinical Laboratory Standards (NCCLS) [15]. Presence of methicillin resistance (mecA gene) was evaluated by PCR [5]. The MRSA clones were identified by PFGE [5].

2.4. Disk diffusion method

The antibacterial activity of the above mentioned extracts and fractions was separately determined using the disk diffusion method [16]. Petri dishes containing 20 ml of Mueller–Hinton agar medium (Oxoid, Hampshire, England) were seeded with a 24 h culture of the bacterial strains in Trypticase Soy Broth (TSB, Oxoid). The inoculum size was adjusted to approximately 10⁸ colony-forming units (CFU)/ml. The solutions of the plant extracts and fractions were applied to sterile filter paper disks (Whatman No.1; 5 mm in diameter) to give the final concentrations of 250 and 500 µg/ml and placed on the surface of the inoculated medium. The plates were incubated at 35°C for 24 h. Antibacterial activity was determined by measuring the diameter of the inhibition zone formed around the disk.

2.5. Minimum inhibitory concentration

The Minimum Inhibitory Concentration (MIC) was determined by the agar dilution method in Mueller–Hinton agar medium (Oxoid), according to NCCLS [17]. Before gelling, 20 ml of agar medium were added to each of the Petri dishes containing either the plant extract, a specific fraction, or purified compounds and the Petri dishes were swirled carefully until the agar began to set. Concentrations ranging from 0.97 to 250 µg/ml were used for each plant sample. Subsequently, bacteria (10⁸ CFU/ml) were inoculated using a Steers replicator that placed 2 µl of each bacterial strain on the Mueller–Hinton agar surface.

3. Results

3.1. Preliminary evaluation of antibacterial activity

Among the total ethanolic extracts and fractions tested by the disk diffusion method, the P. granatum fruit-pericarp and the wooden part of T. avellanedae extracts and fractions presented antibacterial activity against all S. aureus strains tested. The highest activities were found in the ethyl acetate fraction of P. granatum (PG ea) and in the hexane (TA h) and chloroform (TA c) fractions of T. avellanedae, as well as in the naphthoquinone α-xyloidoside II. Lapachol, the major naphthoquinone present in the hexane fraction of T. avellanedae was inactive against all strains.

3.2. Minimum inhibitory concentration

The MICs for antibacterial activity were established for the different extracts and fractions of P. granatum and T. avellanedae, as well as for the unseparated mixture of ellagitannins from P. granatum (PGF₁), naphthoquinones and analogues from T. avellanedae by using the same 26 S. aureus strains tested by the disk diffusion method. The results reported in Table 2 show lower MICs for naphthoquinone analogues from T. avellanedae (III and IV), ranging from 15.6 to 31.2 mg/l. A regular pattern of growth inhibition was also obtained for α-lapachone (I) and PGF₁, exhibiting an MIC of 62.5 mg/l for all tested strains. The total ethanolic extracts and its fractions presented MICs ranging from 125 to ≥ 250 mg/l.

4. Discussion

Infections caused by methicillin-resistant S. aureus (MRSA) have increased over the last years. The percentage of MRSA isolated in hospitals and reported to the NNIS system ranged from 15 to 45% in 1991 [2]. By 1990, MRSA strains represented between 38 and 78% of all S. aureus strains isolated in tertiary hospitals in Brazil [3]. Its resistance has been related to the predominance of the single PFGE clone A of MRSA isolated from Brazilian hospitals [5,8]. The presence of this prevalent clone makes the control of MRSA nosocomial infections difficult because it spreads more easily in hospital institutions than other clones [18].

The increasing occurrence, particularly in hospitals, of S. aureus resistant not only to methicillin but to a wide range of antimicrobial agents, including vancomycin, made therapy more difficult [19,20]. Although strategies have been proposed in an attempt to control the spread [19], the search for new ways to treat MRSA infections stimulates the investigation of natural compounds as an alternative treatment of these infections.

In this study the analysis of the growth inhibition activity by the disk diffusion method showed that the principal chemical constituents with antimicrobial activity were concentrated in the polar fractions of P. granatum, whereas in T. avellanedae the major activity was detected in non-polar fractions. It is known that P. granatum is rich in hydrolyzable tannins [21] and this class of compounds has remarkable antimicrobial activity. T. avellanedae is rich in naphthoquinones [22], which also have antibacterial [23], antifungal [24], antiviral [25] and antineoplastic activity [26]. Our results also corroborate the previous antibacterial studies related to these two botanical species.

The mixture of ellagitannins (hydrolysable tannins) from P. granatum (PGF₁) showed a better result using the agar dilution method (MICs = 62.5 mg/l) compared
Table 2
MIC (mg/l) of extracts, fractions and isolated compounds of *P. granatum* and *T. avellanedae* by the agar dilution method

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*S. aureus* strains 1–16 were methicillin-resistant, and strains 17–24 were methicillin-sensitive PG, *P. granatum* fractions; TA, *T. avellanedae* fractions; te, total ethanol extract; h, hexane; c, chloroform; ea, ethyl acetate; b, butanol; w, water; PGF₁, *P. granatum* fraction rich in ellagitannins; I, α-lapachone; II, α-xyloidone; III, β-nor-lapachone; IV, β-nor-hydroxylapachone.
with the total ethanolic extract and fractions (MICs \(\geq 250 \text{ mg/l} \)) against \(S. \text{ aureus} \) (Table 2), suggesting that this class of compounds is responsible for the antimicrobial activity observed in this plant. For \(T. \text{ avellanedae} \), the inhibitory effect could be mainly attributed to the naphthoquinones \(\alpha\)-lapachone I (MICs = 62.5 mg/l) and \(\alpha\)-xyloidoine II (MICs = 125 mg/l), contained in the hexane fraction. This agreed with D’Albuquerque [23] who described the antimicrobial activity of these compounds isolated from \(T. \text{ avellanedae} \). Table 2 showed the total ethanolic extract of \(T. \text{ avellanedae} \) (TA I) to have MICs ranging from 125 to 250 mg/l, whereas the hexane (TA h) and chloroform (TA c) fractions had MICs \(\geq 250\text{mg/l} \). Therefore, we can conclude that different classes of compounds present in the total ethanolic extract may be acting synergically.

Furanonaphthoquinones (FNQs) III and IV showed lower MICs against \(S. \text{ aureus} \) (MRSA and MSSA strains) than those of natural occurring naphthoquinones (Table 2). Observing the results obtained for the quinones tested we can analyze some aspects concerning the chemical structures of these compounds: \(\alpha\)-xyloidoine II has a double bond (Fig. 1) which is a probable site of chemical attack by bacterial detoxification enzymes, and this may be responsible for its lower activity (MIC of 125 mg/l) when compared with the other quinones. Quinones I, III and IV presented better results with MICs ranging from 15.6 to 62.5 mg/l. Higher liposolubility of these compounds seems to be an important factor for the bacterial growth inhibition observed. Thus, the most active compound was IV where the ether group enhances its liposolubility. A percentage analysis of the bacterial growth inhibition by the FNQs corroborates these arguments: compound III showed at the concentration of 15.6 mg/l, inhibition of 33.3\% of MSSA and 11.8\% of MRSA, and showed growth inhibition of PFGE clone A only at 31.2 mg/l. On the other hand, at a concentration of 15.6 mg/l, compound IV showed an inhibition of 55.5\% of MSSA and 64.7\% of MRSA. For the MRSA clone A, growth inhibition was 85.7\%. Nagata et al. [27] also described the inhibitory effect of FNQ analogues against a large number of microorganisms, including MSSA and MRSA strains.

We can conclude that ellagitannins are the principal components responsible for the antimicrobial action of \(P. \text{ granatum} \) and the naphthoquinones for that of \(T. \text{ avellanedae} \). These polyphenols are known to form with proteins soluble complexes of high molecular weight. Thus, after being adsorbed, the polyphenols will react with the protein moiety of cell enzymes (oxidoreductases) in the cytoplasm and in the cell wall. They may also bind to bacterial adhesins and so, interfering with the availability of receptors on the cell surface [28].

This is the first report of the antimicrobial activity of extracts and fractions from these plants, as well as the naturally occurring naphthoquinones and their analogues, against hospital bacteria, including multiresistant ones. The results presented here indicate that the natural products analyzed seem to be a good choice for the development of new strategies to treat staphylococcal infections, including those caused by methicillin-resistant \(S. \text{ aureus} \).

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References


