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Relationships Between Chemical Structure and Activity of Triterpenes Against Gram-Positive and Gram-Negative Bacteria

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1. Introduction

Bacteria are non-chlorophyllated unicellular organisms that reproduce by fission and do not present nuclear envelope. Gram’s stain is a staining technique used to classify bacteria based on the different characteristic of their cell walls. Gram-positive or Gram-negative bacteria are determined by the amount and location of peptidoglycan in the cell wall, exhibiting different chemical compositions and structures, cell-wall permeabilities, physiologies, metabolisms, and pathogenicities.

Microbial diseases present a significant clinical interest because some species of bacteria are more virulent than other ones and show alteration in sensibility to the conventional antimicrobial drugs, mainly species of the genera *Staphylococcus*, *Pseudomonas*, *Enterococcus*, and *Pneumococcus*. The extensive use of the penicillin since the Second World War promoted the appearance of the first strains of penicillin-resistant Gram-positive bacteria (Silveira et al., 2006). Vancomycin and methicillin showed a large spectrum of bactericidal actions against many Gram-positive bacteria. However, some strains also presented resistance to these compounds, as observed to the drugs vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively. As a consequence, the resistance that pathogenic microorganisms build against antibiotics has stimulated the search of new antimicrobial drugs (Al-Fatimi et al., 2007; Rahman et al., 2002).

In the last few decades, the ethnobotanical search has been the subject of very intense pharmacological studies about drug discovery as potential sources of new compounds of therapeutic value in the treatment of bacterial diseases (Matu & Staden, 2003). The importance of secondary metabolites for the antimicrobial activity has been observed to triterpenoid compounds (Geyid et al., 2005). The triterpenes are widely distributed in the plant and animal kingdoms and occur in either a free state or in a combined form, mainly in the form of esters and glycosides (Ikan, 1991). Triterpenes present a carbon skeleton based on six isoprene units, being biosynthetically derived from the squalene, which may usually yield the pentacyclic triterpenes with six-membered rings. These pentacyclic triterpenes (PCTTs) present a basic skeleton which provides a large amount of derivative structures because different positions on

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their skeleton may be substituted. As a result, there are at least 4000 known PCTTs (Dzubak et al., 2006), exhibiting a large spectrum of biological activities (James & Dubery, 2009). Some classes of triterpenes present other skeleton, such as fernane- and lupane-type triterpenes.

The literature describes the isolation of triterpenes from the vegetal species which exhibit bactericidal activity (Katerere et al., 2003; Sunitha et al., 2001; Ryu et al., 2000; Yun et al., 1999). Table 1 shows the most recent studies relating plant that exhibit bactericidal activity and contain triterpenes. The activity against Gram-negative bacteria has been few studied in relation to Gram-positive ones. The Gram-positive bacteria more studied are *S. aureus, B. subtilis, B. cereus,* and *S. faecalis* (24, 11, 7, and 6 occurrences, respectively). On the other hand, the Gram-negative bacteria more studied are *P. aeruginosa, E. coli, K. pneumoniae,* and *S. typhi* (15, 13, 9, and 6 occurrences, respectively).

| Species                          | Isolated compound          | Activity against Gram-positive bacteria                                                                 | Activity against Gram-negative bacteria                                                                 | Ref.                  |
|---------------------------------|----------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------|
| *Abies sachalinensis*           | Triterpenes                | *Bacillus subtilis* and *Staphylococcus aureus*                                                        | -                                                                                                         | Gao et al., 2008      |
| *Acacia mellifera*              | Triterpenes                | *S. aureus*                                                                                              | -                                                                                                         | Mutai et al., 2009    |
| *Alstonia macrophylla*          | Triterpenes and steroids   | *S. aureus, Staphylococcus saprophyticus,* and *Streptococcus faecalis*                                | *Escherichia coli* and *Proteus mirabilis*                                                            | Chattopadhy y et al., 2001|
| *Austroplenckia populnea*        | Triterpenes                | *S. aureus*                                                                                              | -                                                                                                         | Miranda et al., 2009  |
| *Aquilaria agallocha*           | Triterpenes, alkaloids, and fatty acids                                                                 | *Bacillus brevis* and *B. subtilis*                                                                     | *Pseudomonas aeruginosa* and *Shigella flexneri*                                                        | Dash et al., 2008     |
| *Azadirachta indica*            | Triterpenes, glycosides, and fatty acids                                                                 | *Micrococcus luteus* and *S. aureus*                                                                   | *P. aeruginosa* and *Proteus vulgaris*                                                                  | Khan et al., 2010     |
| *Azima tetracantha*             | Triterpenes, steroids, and tannins                                                                         | *S. aureus* and *B. subtilis*                                                                          | *E. coli, Klebsiella pneumoniae,* and *P. aeruginosa*                                                    | Ekbote et al., 2010   |
| *Calophyllum inophyllum*         | Triterpenes                | *S. aureus*                                                                                              | -                                                                                                         | Yimdjo et al., 2004   |
| *Cardospermum helicacabum*       | Triterpenes, steroids, sugars, alkaloids, phenols, saponins, aminoacids, and tannins                    | *B. subtilis*                                                                                           | *P. aeruginosa* and *Salmonella typhi*                                                                   | Viji et al., 2010     |
| *Cedrus deodara*                | Triterpenes, alkaloids, steroids, flavonoids, tannins, phenolic compounds, and                          | *Bacillus cereus, E. faecalis,* and *S. aureus*                                                         | *E. coli, K. pneumoniae,* and *P. aeruginosa*                                                           | Devmurari, 2010       |

Table 1. Vegetal species that exhibit bactericidal activity and contain triterpenes
| Species                                | Isolated compound                  | Activity against Gram-positive bacteria                                                                 | Activity against Gram-negative bacteria | Ref.                        |
|----------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------|----------------------------|
| Commiphora glandulosa                  | Triterpenes                        | B. subtilis, Clostridium perfringens, and S. aureus                                                    | -                                      | Motlhanka et al., 2010     |
| Dendrophthoe falcata                   | Triterpenes, steroids, tannins, and glycosides    | B. cereus, B. subtilis, M. luteus, S. aureus, Staphylococcus epidermidis, and Streptococcus pneumoniae   | Enterobacter aerogenes, E. coli, K. pneumoniae, P. aeruginosa, Serratia marcescens, and S. typhi | Pattanayak et al., 2008   |
| Dichrostachys cinerea                  | Triterpenes and steroids            | B. subtilis and S. aureus                                                                             | E. coli and P. aeruginosa              | Eisa et al., 2000          |
| Drynaria quercifolia                   | Triterpenes, coumarins, flavones, lignans, saponins, and steroids | B. subtilis and S. aureus                                                                             | E. coli, K. pneumoniae, P. aeruginosa, and S. typhi | Ramesh et al., 2001 |
| Elaeodendron schlechteranum           | Triterpenes                        | B. cereus, B. subtilis, and S. aureus                                                                  | -                                      | Maregesi et al., 2010     |
| Ficus ovata                           | Triterpenes                        | B. cereus, S. aureus, and S. faecalis                                                                  | Citrobacter freundii, E. coli, K. pneumoniae, P. aeruginosa, and S. typhi | Kuete et al., 2009 |
| Fitalgaonia obovata                    | Triterpenes                        | S. aureus                                                                                                | E. coli and P. aeruginosa              | Mishra & Sree, 2007       |
| Gallium mexicanum                     | Triterpenes, saponins, flavonoids, sesquiterpene lactones, and glycosides | S. aureus methicillin-resistant (MRSA)                                                                  | -                                      | Bolivar et al., 2011      |
| Garcinia gummicutta                    | Triterpenes, alkaloids, steroids, oils, catechins, and phenolics | B. subtilis and S. aureus                                                                             | Aeromonas hydrophila, K. pneumoniae, P. aeruginosa, and S. typhi | Maridass et al., 2010   |
| Leucas aspera                         | Triterpenes                        | S. pneumonia                                                                                           | E. coli                                | Mangathay aru et al., 2005|
| Miconia liguistroides                 | Triterpenes                        | B. cereus                                                                                                | -                                      | Cunha et al., 2010       |
| Mirabilis jalapa                      | Terpenes and flavonoids            | B. cereus, E. faecalis, and M. luteus                                                                  | E. coli, K. pneumoniae, and P. aeruginosa | Hajji et al., 2010       |
| Moringa oleifera                     | Triterpenes, alkaloids, flavonoids, sesquiterpenes, lactones, diterpenes, and naphtoquinones | E. faecalis and S. aureus                                                                             | Aeromonas caviae and Vibrio arahaemolyticus | Peixoto et al., 2011 |
| Mussaenda macrophylla                 | Triterpenes                        | -                                                                                                       | Porphyromonas gingivalis               | Kim et al., 1999         |
| Phyllanthus simplex                   | Triterpenes, steroids, lignans, flavonoids, glycosides, and phenolic compounds | S. aureus                                                                                                | E. coli, P. aeruginosa, and S. flexner | Chouhan & Singh, 2010    |
| Psidium guajava                       | Triterpenes, tannins, and flavonoids | B. subtilis and S. aureus                                                                             | E. coli and P. aeruginosa              | Sanches et al., 2005    |
| Pulicaria dysenterica                 | Triterpenes and steroids            | B. cereus and S. aureus                                                                               | Vibrio cholera                         | Nickavar & Mojab, 2003   |
| Tridensnomen omphalocarpoidei        | Triterpenes                        | S. aureus and S. faecalis                                                                             | E. coli, K. pneumoniae, P. vulgaris, Shigella dysenteriae, and S. typhi | Kuete et al., 2006      |
| Triumfetta rhomboidea                 | Triterpenes, Steroids, flavonoids, tannin, and phenolic compounds | B. cereus, E. faecalis, and S. aureus                                                                 | E. coli, K. pneumoniae, and P. aeruginosa | Devmurari et al., 2010   |
| Vochysia divergens                    | Triterpenes                        | S. aureus                                                                                                | -                                      | Hess et al., 1995        |

Table 1. Vegetal species that exhibit bactericidal activity and contain triterpenes (contd.)
Some plants exhibit a broad spectrum of activity against both Gram-positive and Gram-negative bacteria and contain other chemical classes, such as coumarins, flavonoids, phenolic compounds, and alkaloids. However, there is an expressive quantity of vegetal species that only triterpenes were isolated, suggesting an intrinsic relationship between this chemical class and the bactericidal activity of these plants. Thus, the present work provides an extensive search in original and review articles addressing the bactericidal activity of triterpenes, which may inspire new biomedical applications, considering atom economy, the synthesis of environmentally benign products without producing toxic by-products, the use of renewable sources of raw materials, and the search for processes with maximal efficiency of energy. To systematization of the results, it was considered that the biological activities are related to the presence of functionalized sites on the chemical structure of each triterpene. Obviously the obtained data do not make them possible the comparison of the intensity of bactericidal activities among the active triterpenes. Moreover, many triterpenes were tested against few species of bacteria, and as a consequence this work only records biological positive test.

Table 2 shows the bactericidal activity of oleanane-type triterpenes isolated from vegetal species and fungi (Compounds 1 to 43 shown in Figure 1). In the case of Gram-positive bacteria, oleananes with different functionalizations exhibit activity against S. aureus and a relationship between chemical structure and bactericidal activity could not established. The oleananes 6, 20, 21, 35, and 36 exhibit activity against E. faecalis. All these compounds present functional groups on the alpha side of the triterpene skeleton (hydroxyl group at C-1 and oxygenated group at C-20 or C-16). Compounds 1 to 5, and 42 exhibit activity against M. luteus and present carboxyl group at C-17 or C-20 and oxygenated group at C-3. The presence of a functional group at C-17 is an important criterion to the activity against B. subtilis, except compounds 29 and 43, which are carboxyl group funcionalized at other positions (i.e. C-3 and C-20, respectively). The activity against S. mutans is exhibited by the compounds 14, 15, 17, 18, and 24, which present oxygenated group at C-3 and carboxyl group at C-17. Few oleanane-type triterpenes were tested against S. pneumoniae and B. pumilus, and as a consequence, relationships between chemical structure and activity against these Gram-positive bacteria were not possible.

Considering the Gram-negative bacteria, Table 2 shows many oleananes active against E. coli. These compounds present different functional groups at the oleanane skeleton, but all them present oxygenated group at C-3. Compounds 13-16, 19, 26, 28-38, and 43 exhibit activities against S. typhi and only present oxygenated group at C-3 in common. The activity against S. sonnei is registered for the compounds 7, 8, 10, and 13, which present carboxyl group at C-17 and oxygenated group at C-3. Similarly, the activity against P. gingivalis is registered for the compounds 14, 15, 18, 24, and 25, which present carboxyl group at C-17 and oxygenated group at C-3. Only two compounds exhibited activity against P. fluorescens (11 and 12) and both the oleananes present hydroxyl group at C-19 on the alpha-side of the skeleton. Few oleananes were tested against V. cholera, S. dysenteriae, S. flexneri, S. boydii, P. aeruginosa, and C. pneumoniae and relationships between chemical structure and activity against these Gram-negative bacteria were not possible.

Figure 2 shows the ursane-type triterpenes with bactericidal activity isolated from vegetal species. For the Gram-positive bacteria, the ursanes active against S. aureus and B. subtilis present oxygenated group at C-3 in common. Few compounds exhibited positive tests against S. epidermidis, A. viscosus, M. luteus, S. mutans, C. perfrigens, S. faecalis, and B. cereus.
In the case of Gram-negative bacteria, the ursanes active against *E. coli* present an oxygenated group at C-3 in common. The ursanes active against *S. sonnei*, *S. flexneri*, *B. typhi*, *K. pneumonia*, and *P. aeruginosa* concomitantly present oxygenated groups at C-3 and C-17.

Figure 3 shows the lupane-, friedelane-, and fernane-type triterpenes with bactericidal activity isolated from vegetal species. Friedelin (compound 68) exhibits the largest spectrum of activities against Gram-positive bacteria (*Bacillus megaterium*, *Bacillus stearothermophilus*, *S. aureus*, and *S. faecalis*) and Gram-negative bacteria (*C. freundii*, *E. aerogenes*, *Enterococcus cloacae*, *K. pneumoniae*, *Morganella morganii*, *P. aeruginosa*, *P. mirabilis*, *P. vulgaris*, *S. dysenterie*, *S. flexneri*, and *S. typhi*, *Salmonella typhimurium*). This compound only presents functionalization at C-3 (carbonyl group at position C-3 on the triterpene skeleton). As a consequence, the position C-3 could be considered as a strategic position to bactericidal activity of all triterpenes above-mentioned. However, the fernanes 82-84 do not present functional groups at C-3, but exhibit activity against *M. tuberculosis*.

The compounds shown in the Figures 4 and 5 are miscellaneous-types of triterpenes isolated from vegetal species or obtained from hemi-synthesis which exhibit bactericidal activity. The variety of their chemical structures does not permit to establish relationships with the bactericidal activities showed in the Tables 2 and 3. However, among the triterpenes shown in the Figures 1 to 5 and Tables 2 and 3, 90% of them exhibit activity against Gram-positive bacteria and 60% of them exhibit activity against Gram-negative bacteria. These results indicate higher resistance of Gram-negative Bacteria to the triterpenes.

| Compound | Vegetal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref. |
|----------|----------------|----------------------------------------|----------------------------------------|------|
| 2α-Hydroxy-3-oxoolean-12-en-30-oic acid | *Dillenia papuana* | *B. subtilis* and *M. luteus* | *E. coli* | Nick et al., 1994 |
| Olean-1,12-dien-29-oic acid, 3-oxo | *Dillenia papuana* | *B. subtilis* and *M. luteus* | *E. coli* | Nick et al., 1994 |
| 1α-Hydroxy-3-oxoolean-12-en-30-oic acid | *Dillenia papuana* | *B. subtilis* and *M. luteus* | *E. coli* | Nick et al., 1994 |
| 2-Oxo-3β-hydroxyolean-12-en-30-oic acid | *Dillenia papuana* | *B. subtilis* and *M. luteus* | *E. coli* | Nick et al., 1994 |
| Olean-12-en-1,3-dihydroxy | *Dillenia papuana* | *B. subtilis* and *M. luteus* | *E. coli* | Nick et al., 1994 |
| 3,30-Dihydroxy-12-oleanen-22-one | *Cambretum imberbe* | *E. faecalis* and *S. aureus* | *E. coli* | Angeh et al., 2007; Katerere et al., 2003 |
| Arjulonic acid | *Syzygium guineense* | *B. subtilis* and *Shigella sonnei* | *E. coli* | Djoukeng et al., 2005 |
| Terminolic acid | *Syzygium guineense* | *B. subtilis* and *S. sonnei* | *E. coli* and *S. sonnei* | Djoukeng et al., 2005 |
| 2α,3β,24-Trihydroxyolean-12-en-28-oic acid | *Planchonia careya* | MRSA | *Enterococcus vancomycin-resistant* (VRE) | McRae et al., 2008 |
| 2,3,23-Trihydroxy-(2α,3β,4α) olean-11-en-28-oic acid | *Syzygium guineense* | *B. subtilis* and *S. sonnei* | *E. coli* and *S. sonnei* | Djoukeng et al., 2005 |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi.
| Compound | Vegetal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref. |
|----------|----------------|-----------------------------------------|----------------------------------------|------|
| Arjungenin (11) | Planchonia careya | | Pseudomonas fluorescens | McRae et al., 2008 |
| Arjunic acid (12) | Terminalia arjuna | | P. fluorescens | Sun et al., 2008 |
| 3-Acetyl aleuritolic acid (13) | Spirostachys africana | S. aureus | E. coli, Staphylococcus boydii, S. dysenteriae, S. flexneri, S. sonnei, S. typhi, and V. cholera | Mathabe et al., 2008 |
| Oleanolic acid (14) | Periplaca laevigata | Spretococcus mutans and S. aureus | E. coli, P. gingivalis, and S. typhi | Hichri et al., 2003 |
| Oleanolic acid acetate (15) | Periplaca laevigata | S. mutans and S. aureus | E. coli, P. aeruginosa, P. gingivalis, and S. typhi | Hichri et al., 2003 |
| Maslinic acid acetate (16) | Periplaca laevigata | S. aureus | E. coli, P. aeruginosa, and S. typhi | Hichri et al., 2003 |
| Methyl 3-acetyloleanolic acid (17) | Vitis vinifera | S. mutans | | Rivero-Cruz et al., 2008 |
| Methyl oleanolic acid (18) | Vitis vinifera | S. mutans | P. gingivalis | Rivero-Cruz et al., 2008 |
| Oleanolic acid 28-O-[ß-D-glucopyranosyl] Ester (19) | Drypetes paxii | S. aureus | E. coli and S. typhi | Chiozem et al., 2009 |
| 1α,3β-Dihydroxyolean-12-en-29-oic acid (20) | Camabretum imbibe | E. faecalis and S. aureus | E. coli | Angeh et al., 2007; Katerere et al., 2003 |
| 1α,3β-Hydroxyimberbic-acid-23-O-ß-L-4-acetylhrhamnopyranoside (21) | Camabretum imbibe | E. faecalis and S. aureus | - | Angeh et al., 2007; Katerere et al., 2003 |
| 1,3,24-Trihydroxyl-12-olean-29-oic acid (22) | Camabretum imbibe | S. aureus | E. coli | Angeh et al., 2007; Katerere et al., 2003 |
| 1α,23-Dihydroxy-12-oleanen-29-oic acid-3β-O-2,4-diacetyl-L-rhamnopyranoside (23) | Camabretum imbibe | S. aureus | E. coli | Angeh et al., 2007; Katerere et al., 2003 |
| 3-O-(30,30-dimethylsuccinyl)-oleanolic acid (24) | Vitis vinifera | S. mutans | P. gingivalis | Rivero-Cruz et al., 2008 |
| 3-O-(20,20-dimethylsuccinyl)oleanolic acids (25) | Vitis vinifera | - | P. gingivalis | Rivero-Cruz et al., 2008 |
| 3β,6α,13β-Trihydroxyolean-7-one (26) | Camellia sinensis | S. aureus | E. coli, S. dysenteriae, and S. typhi | Ling et al., 2010 |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)
| Compound | Vegetal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref. |
|-----------|----------------|--------------------------------------|---------------------------------------|-----|
| 18α-Oleanane-3β,19β,28-epoxy (27) | - | Chlamydia pneumoniae | Dehaen et al., 2011 |
| 9β,25-cyclo-3β-O-β-D-glucopyranosyl-echinocystic acid (28) | Syringococcus paniculata | B. subtilis and S. aureus | E. coli and P. aeruginosa | Semwal et al., 2011 |
| 3-Oxoolean-12-dien-30-oic acid (29) | Dellenia papyracea | B. subtilis | E. coli | Nick et al., 1994 |
| 3β-Hydroxyolean-12-en-27-oic acid (30) | Aceriphylum pueruliss | MRSA, quinolone resistance S. aureus (QRSA), and S. aureus | - | Zheng et al., 2008 |
| Acericphyllic acid A (32) | Aceriphylum pueruliss | MRSA, QRSA, and S. aureus | - | Zheng et al., 2008 |
| Methyl ester of acericphyllic acid A (33) | Aceriphylum pueruliss | MRSA, QRSA, and S. aureus | - | Zheng et al., 2008 |
| 22α-Acetyl-16α,21β-dihydroxyolean-13β,28-olide-3-O-β-glucopyranosyl-(1''→6'')][6-O-coumaroylglycosyranosyl-(1''→2')]-β-glycopolpyranoside (34) | Maesa lanceolata | S. aureus | - | Manguro et al., 2011 |
| 16α,22α-Diacetyl-21β-angeloylolean-13β,28-olide-3-O-β-glucopyranosyl-(1''→6'')][β-glycopolpyranosyl-(1''→4')]-β-glycopolpyranoside (35) | Maesa lanceolata | B. subtilis, E. faecalis, S. aureus, and S. pneumoniae | E. coli, P. aeruginosa, and V. cholera | Manguro et al., 2011 |
| 16α,22α,28-Trihydroxy-21β-angeloylolean-12-ene-3β-O-[α-rhamnopyranosyl-(1''→6'')][β-glycopolpyranosyl-(1''→2')]-β-xylopolpyranoside (36) | Maesa lanceolata | E. faecalis and S. pneumoniae | S. typhi and V. cholera | Manguro et al., 2011 |
| 16α,28-dihydroxy-22α-acetyl-21β-angeloylolean-12-ene-3-O-[β-galactopyranosyl-(1''→2')][α-rhamnopyranosyl-(1''→4')]-α-arabinopyranoside (37) | Maesa lanceolata | B. subtilis | S. typhi and V. cholera | Manguro et al., 2011 |
| Chikusetsusaponin IVa methyl Ester (38) | Dryptes laciniata | - | E. coli and S. typhi | Fannang et al., 2011 |
| 3β-[α-L-Arabinoopyranosyl]-oxylolean-12-en-28-oic acid (39) | Clematis ganpiniana | B. subtilis | - | Ding et al., 2009 |
| Hederagenin-3β-O-α-L-arabinopyranoside (40) | Clematis ganpiniana | Bacillus pumilus and B. subtilis | - | Ding et al., 2009 |
| 3β-O-α-L-Rhamnopyranosyl-(1''→2')-α-L-arabinopyranoside oleanolic acid (41) | Clematis ganpiniana | B. pumilus and B. subtilis | E. coli | Ding et al., 2009 |
| α-Hederin (42) | Clematis ganpiniana | B. pumilus, B. subtilis, M. luteus, and S. aureus | E. coli and S. dysenteriae | Ding et al., 2009 |
| 5,6(11)-Oleanadien-3β-ethan-5-oate (43) | Rhododendron campanulatum | B. subtilis and S. aureus | E. coli, K. pneumoniae, and S. typhi | Tantry et al., 2011 |
| Asiatic acid (44) | Syzygium guineense | B. subtilis | E. coli and S. sonnei | Djoukeng et al., 2005 |
| Hydroxyasiatic acid (45) | Syzygium guineense | B. subtilis | E. coli and S. sonnei | Djoukeng et al., 2005 |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)
| Compound | Vegetal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref. |
|----------|----------------|-----------------------------------------|-----------------------------------------|------|
| Eleganene-A (46) | Myricana elegans | B. subtilis and S. aureus | S. flexneri and S. typhi | Ahmad et al., 2008 |
| Eleganene-B (47) | Myricana elegans | B. subtilis and S. aureus | E. coli, P. aeruginosa, S. flexneri, and S. typhi | Ahmad et al., 2008 |
| (2α,3β)-2,3,23-Trihydroxy-13,28-epoxyurs-11-en-28-one (48) | Eucalyptus canadalensis | S. aureus and S. epidermidis | E. coli, K. pneumoniae, and P. aeruginosa | Tsiri et al., 2008 |
| Ilexgenin A (49) | Ilex hainanensis | Actinomyces viscosus and S. mutans | - | Chen et al., 2011 |
| Rotundic acid (50) | Ilex integra | B. subtilis, M. luteus, and S. aureus | P. aeruginosa | Haraguchi et al., 1999 |
| Ursolic acid (51) | Geum rivale | S. aureus | E. coli and P. aeruginosa | Panizzii et al., 2000 |
| 1β,2β,3β-Trihydroxy-urs-12-ene-23-oic-rhamnose (52) | Commiphora glandulosa | B. subtilis, C. perfringens, and S. aureus | - | Montthanka et al., 2010 |
| Erythrodiol (53) | Myricana elegans | B. subtilis | P. aeruginosa and S. flexneri | Ahmad et al., 2008 |
| Corosolic acid (54) | Myricana elegans | B. subtilis | P. aeruginosa and S. flexneri | Ahmad et al., 2008 |
| 1β,3β-Dihydroxyurs-12-en-27-oic acid (55) | Caraphora coronata | B. subtilis and MRSA | - | Khera et al., 2003 |
| 22β-Acetyl lantoic acid (56) | Lantana camara | S. aureus | E. coli, P. aeruginosa, and S. typhi | Barre et al., 1997 |
| Lactic acid (57) | Lantana camara | B. cereus, B. subtilis, M. luteus, S. aureus, and S. faecalis | E. coli | Saleh et al., 1999 |
| 22β-Acetoxylactic acid (58) | Lantana Camara | S. aureus | E. coli, P. aeruginosa, and S. typhi | Barre et al., 1997 |
| Taraxast-20-ene-3β-ol (59) | Saussurea petrooii | B. subtilis and S. aureus | E. coli | Dai et al., 2001 |
| Taraxast-20(30)ene-3β,21α-diol (60) | Saussurea petrooii | B. subtilis and S. aureus | E. coli | Dai et al., 2001 |
| 20α,21α-Epoxy-taraxastane-3β,22α-diol (61) | Saussurea petrooii | B. subtilis and S. aureus | E. coli | Dai et al., 2001 |
| Taraxast-20-ene-3β-ol (62) | Saussurea petrooii | B. subtilis and S. aureus | E. coli | Dai et al., 2001 |
| Taraxast-20-ene-3β,30-diol (63) | Saussurea petrooii | B. subtilis and S. aureus | E. coli | Dai et al., 2001 |
| 20(29)-Lupene-3β-isosterulate (64) | Eucla natalensis | B. pumilus | - | Weigenand et al., 2004 |
| Lupeol (65) | Curtisia dentata | B. subtilis and S. aureus | E. coli and P. aeruginosa | Shai et al., 2008 |
| Betulinic acid (66) | Curtisia dentata | B. subtilis and S. aureus | E. coli and P. aeruginosa | Shai et al., 2008 |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)
| Compound | Vegeal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref. |
|----------|----------------|----------------------------------------|----------------------------------------|------|
| Betulin (67) | *Myricana elegans* | - | *C. pneumoniae* | Dehaen et al., 2011; Ahmad et al., 2008 |
| Friedelin (68) | *Visnia rubescens* | *Bacillus megaterium, Bacillus stearothermophilus, S aureus, and S. faecalis* | *C. freundii, E. aerogenes, Enterococcus cloacae, K. pneumoniae, Morganella morganii, P. aeruginosa, P. mirabilis, P. vulgaris, S. dysenterie, S. flexneri, and S. typhi, Salmonella typhimurium* | Tamokou et al., 2009; Kuete et al., 2009, 2007, 2006 |
| 3-Oxo-friedelan-20α-oic acid (69) | *Maytenus sinegalensis* | *B. subtilis and S. aureus* | *E. coli, K. pneumoniae, and S. flexneri* | Lindsey et al., 2003; Lindsey et al., 2006 |
| 3β-Hydroxyfriedelan-7,12,12-trione (70) | *Drypetes laciniata* | - | *E. coli, P. aeruginosa, and S. typhi* | Fannang et al., 2011 |
| 12α-Hydroxyfriedelan-3,15-dione (71) | *Drypetes paxii* | *S. aureus* | | Chiozem et al., 2009 |
| Friedelanol (72) | *Visnia rubescens* | *S. aureus* | *P. aeruginosa and S. typhi* | Anghe et al., 2007; Katerere et al., 2003 |
| 3β-Hydroxyfriedelan-25-al (73) | *Drypetes paxii* | *S. aureus* | - | Chiozem et al., 2009 |
| 3-Hydroxy-2,24-dioxo-3-friedelen-29-oic acid methyl ester (74) | *Elaeodendron schlechteranum* | *B. cereus and S. aureus* | - | Maregesi et al., 2010 |
| 22β-Hydroxytingenone (75) | *Elaeodendron schlechteranum* | *B. cereus and S. aureus* | - | Maregesi et al., 2010 |
| 2,3,7-Trihydroxy-6-oxo-1,3,5(10),7-tetraene-24-nor-friedelan-29-oic acid methyl ester (76) | *Crossopetalum gaumeri* | *B. cereus, M. luteus, and S. epidermidis* | - | Ankl et al., 2000 |
| Zeylasterone (77) | *Maytenus blepharodes* | *S. aureus* | - | Léon et al., 2010 |
| Dimethylzeylasterone (78) | *Maytenus blepharodes* | *S. aureus* | - | Léon et al., 2010 |
| Zeylasteral (79) | *Maytenus blepharodes* | *S. aureus* | - | Léon et al., 2010 |
| Dimethylzeylasteral (80) | *Maytenus blepharodes* | *S. aureus* | - | Léon et al., 2010 |
| 30-Ethyl-2α,16α-dihydroxy-3β-O-(β-D-glucopyranosyl)-hopan-24-oic acid (81) | *Syniplocos paniculata* | *B. subtilis and S. aureus* | *E. coli and P. aeruginosa* | Semwal et al., 2011 |
| Hopan-27α-6β,11R,22-triol (82) | *Conoidocrella tenuis (fungus)* | - | *Mycobacterium tuberculosis* | Isaka et al., 2011 |
| A’-Neogammacerane-6,11,22,27-tetrol (83) | *Conoidocrella tenuis (fungus)* | - | *M. tuberculosis* | Isaka et al., 2011 |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)
| Compound                                                                 | Vegetal species                      | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref.                  |
|-------------------------------------------------------------------------|--------------------------------------|------------------------------------------|-----------------------------------------|-----------------------|
| Hopane-6β,7β,22-triol (84)                                               | Conoideocrella tenuis (fungus)       | -                                        | M. tuberculosis                        | Isaka et al., 2011    |
| Dysoxyhainic acid G (85)                                                 | Dysoxylum hainanense                 | B. subtilis, M. luteus, and S. epidermidis | -                                       | He et al., 2011       |
| 20-Epikoetjapic acid (86)                                                | Orygris lanceolata                   | B. subtilis and S. aureus                | E. coli and P. aeruginosa              | Yeboah et al., 2010   |
| Dysoxyhainic acid J (87)                                                 | Dysoxylum hainanense                 | B. subtilis and S. epidermidis           | -                                       | He et al., 2011       |
| (9,11),(18,19)-Disecoolean-12-en-28-oic acid (88)                       | Ficus benjamina                      | B. subtilis and S. aureus                | E. coli                                | Nick et al., 1994     |
| 2-Chrysene acetic acid, 9-carboxy-1,2,3,4,4a,5,6,6a,7,8,9,10,12a,13,2a,  | Dillenia papuana                     | B. subtilis and M. luteus                | E. coli                                | Nick et al., 1994     |
| 12a-hexadecahydro-α,α,1,4a,4b,6a,9-heptamethyl-1-(2-oxoethyl),2-methyl  ester (89) |                                        |                                         |                                         |                       |
| Polyporenic acid C (90)                                                  | Fomitopsis rosea (fungus)            | S. aureus                                | -                                       | Popova et al., 2009   |
| Dysoxyhainic acid I (91)                                                 | Dysoxylum hainanense                 | B. subtilis and S. epidermidis           | -                                       | He et al., 2011       |
| 3α-Hydroxy-24-methylene-23-oxanost-8-en-26-carboxylic acid (92)          | Fomitopsis rosea (fungus)            | S. aureus                                | -                                       | Popova et al., 2009   |
| 3α-Carboxyacetoxyquerinic acid (93)                                      | Fomitopsis rosea (fungus)            | S. aureus                                | -                                       | Popova et al., 2009   |
| 3α-Oxepanoquerinic acid C (94)                                           | Fomitopsis rosea (fungus)            | S. aureus                                | -                                       | Popova et al., 2009   |
| Lamesticumin F (95)                                                      | Lansium domesticum                  | B. cereus and B. subtilis                | -                                       | Dong et al., 2011     |
| 3α-(3′Butylcarboxyacetoxy)oxepanoquerinic acid C (96)                    | Fomitopsis rosea (fungus)            | S. aureus                                | -                                       | Popova et al., 2009   |
| Helvolic acid (97)                                                       | Pichia guilliermondi (fungus)        | B. subtilis, S. aureus, and Staphylococcus haemolyticus | Agrobacterium tumifaciens, E. coli, Pseudomonas lachrymans,Ralstonia solanacearum, and Xanthomonas vesicatoria | Zhao et al., 2010     |
| 5α,8α-Epidoxi-24(Ω)-methylcholesta-6,22-diene-3β-ol (98)                 | Fomitopsis rosea (fungus)            | S. aureus                                |                                        | Popova et al., 2009   |
| 1,3,16β-yl-Phenyloxyacetlate-lanostan-5,11,14,16,23,25-hexan-22-one (99) | Stachyterphita jamaicensis           | S. aureus and S. faecalis               | E. coli and P. aeruginosa              | Maregesi et al., 2010 |
| Dysoxyhainic acid H (100)                                                | Dysoxylum hainanense                 | B. subtilis and M. luteus                | -                                       | He et al., 2011       |
| 3β-O-cis-p-Coumaroyltormentic acid (101)                                 | Planchonia careya                    | S. aureus                                | VRE                                    | McRae et al., 2008    |
| 3β-O-trans-p-Coumaroyltormentic acid (102)                               | Planchonia careya                    | S. aureus                                | VRE                                    | McRae et al., 2008    |

Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)
### Table 2. Bactericidal activity of triterpenes isolated from vegetal species and fungi (contd.)

| Compound                          | Vegetal species | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref.        |
|-----------------------------------|-----------------|-----------------------------------------|-----------------------------------------|-------------|
| Lamesticumin C (103)              | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. epidermidis, S. aureus, and Streptococcus pyogenes | -                                       | Dong et al., 2011 |
| Lamesticumin D (104)              | Lansium domesticum | B. cereus and B. subtilis               | -                                       | Dong et al., 2011 |
| Lamesticumin B (105)              | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. epidermidis, and S. pyogenes | -                                       | Dong et al., 2011 |
| Lamesticumin E (106)              | Lansium domesticum | B. cereus and B. subtilis               | -                                       | Dong et al., 2011 |
| Lansic acid 3-ethyl Ester (107)   | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. aureus, S. epidermidis, and S. pyogenes | -                                       | Dong et al., 2011 |
| Ethyl lansiolate (108)            | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. aureus, S. epidermidis, and S. pyogenes | -                                       | Dong et al., 2011 |
| Lamesticumin A (109)              | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. aureus, S. epidermidis, and S. pyogenes | -                                       | Dong et al., 2011 |
| 3-Cyclohexene-1-propanoic acid,2-[(1S,2R,3R)-2-(3-ethoxy-3-oxopropyl)-3-(1-hydroxy-1-methylethyl)-2-methyl-6-methylenecyclohexyl]ethyl]-1,3-dimethyl-6-[1-methylhexenyl] (110) | Lansium domesticum | B. cereus, B. subtilis, M. luteus, S. aureus, S. epidermidis, and S. pyogenes | -                                       | Dong et al., 2011 |

### Table 3. Bactericidal activity of triterpene derivatives

| Compound                          | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref.        |
|-----------------------------------|-----------------------------------------|-----------------------------------------|-------------|
| β-D-Galactosideo methyl oleanolate (111) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| β-D-Xilosideo methyl oleanolate (112) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| β-D-Fucosideo methyl oleanolate (113) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| β-L-Fucosideo methyl oleanolate (114) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| β-Maltosideo methyl oleanolate (115) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| β-Maltotriosideo methyl oleanolate (116) | S. aureus                              | -                                       | Takechi & Tanaka, 1992 |
| Oleanolic acid acetate (117)       | S. aureus                              | E. coli and P. aeruginosa               | Hichri et al., 2003 |
| Compound                                                                 | Activity against Gram-positive bacteria | Activity against Gram-negative bacteria | Ref.            |
|-------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------|-----------------|
| 3β-O-Acetate β-amyrin (118)                                             | S. aureus                               | E. coli and P. aeruginosa               | Hichri et al., 2003 |
| 2β,3β-Dihydroxy-ll-oxooleana-12,18-dien-30-oic acid (119)               | B. subtilis                             | Erwinia sp.                             | Pitzele, 1974    |
| 2β,3α-Dihydroxy- ll-oxooleana-12,18-dien-30-oic acid (120)              | -                                       | Erwinia sp.                             | Pitzele, 1974    |
| 2β,3β-Dihydroxy-ll-oxo-18β-olean-12-en-30-oic acid (121)                | B. subtilis                             | -                                       | Pitzele, 1974    |
| 2β,3β-Dihydroxy-ll-oxo-18β-olean-12-en-30-oic acid (122)                | -                                       | Erwinia sp.                             | Pitzele, 1974    |
| 2β,3β-Diaceotoxy-ll-oxo-18β-olean-12-en-30-oic acid (123)                | -                                       | Erwinia sp.                             | Pitzele, 1974    |
| 3β-Acetyl-11-oxooleanolic acid (124)                                     | S. aureus                               | E. coli, P. aeruginosa, and S. typhimurium | Hichri et al., 2003 |
| Methyl 2β,3α-dihydroxy-18β-olean-12-en-30-oate (125)                    | -                                       | Erwinia sp.                             | Pitzele, 1974    |
| 1α-Bromo-2,3-dioxo-18β-olean-12-en-30-oic acid (126)                    | -                                       | Erwinia sp.                             | Pitzele, 1974    |
| 3β-O-Nicotinoyl-20-(4-methylpiperezin-1-yl)carbonyl-11-oxoolean-12(13)-ene (127) | S. aureus                               | -                                       | Kazakova et al., 2010 |
| N-3-pyridinacetyloxooleanolic amide (128)                                | S. aureus                               | E. coli, P. aeruginosa, and S. typhimurium | Hichri et al., 2003 |
| 3β-Hydroxyolean-12-en-28-carboxydiethylphosphonate (129)                | S. aureus                               | E. coli, P. aeruginosa, and S. typhimurium | Hichri et al., 2003 |
| 3β-Acetoxy-12α-hydroxyoleanan-13β,28-olide (130)                        | -                                       | S. typhimurium                          | Hichri et al., 2003 |
| Oleanan-28-oic acid, 3β,13-dihydroxy-12-oxo-, γ-lactone, acetate (131) | S. aureus                               | E. coli, P. aeruginosa, and S. typhimurium | Hichri et al., 2003 |
| β-Gentiobiosideo methyl ursolate (132)                                   | S. aureus                               | -                                       | Takechi & Tanaka, 1993 |
| β-Maltotriosideo methyl ursolate (133)                                   | S. aureus                               | -                                       | Takechi & Tanaka, 1993 |
| Urs-12-ene-28-carboxy-3β-dodecanoate (134)                               | Bacillus sphaericus, B. subtilis, and S. aureus | Pseudomonas syringae                   | Mallavadhani et al., 2004 |
| Urs-12-ene-28-carboxy-3β-tetradecanoate (135)                            | Bacillus sphaericus, B. subtilis, and S. aureus | P. syringae                            | Mallavadhani et al., 2004 |
| Urs-12-ene-28-carboxy-3β-hexadecanoate (136)                             | Bacillus sphaericus, B. subtilis, and S. aureus | E. coli and P. syringae                | Mallavadhani et al., 2004 |
| Urs-12-ene-28-carboxy-3β-octadecanoate (137)                             | Bacillus sphaericus, B. subtilis, and S. aureus | E. coli and P. syringae                | Mallavadhani et al., 2004 |
| 3-Oxo-17-(4-methylpiperezin-1-yl)carbonyloursan-12(13)-ene (138)         | S. aureus                               | -                                       | Kazakova et al., 2010 |
| 2-Furfurylidenebetulonic acid (139)                                      | S. aureus                               | -                                       | Kazakova et al., 2010 |
| (4-Methylpiperezin-1-yl)amide betulonic (140)                            | S. aureus                               | -                                       | Kloos & Zein, 1993 |
| Betulin dioxime (141)                                                    | -                                       | C. pneumoniae                          | Kloos & Zein, 1993 |
| Umbellatin α (142)                                                      | B. cereus and B. subtilis               | -                                       | Gonzalez et al., 1992 |

Table 3. Bactericidal activity of triterpene derivatives (contd.)
Fig. 1. Oleanane-type triterpenes with bactericidal activity isolated from vegetal species.
Fig. 2. Ursane-type triterpenes with bactericidal activity isolated from vegetal species.

Fig. 3. Lupane-, friedelane-, and fernane-type triterpenes with bactericidal activity isolated from vegetal species.
Fig. 4. Miscellaneous types of triterpenes with bactericidal activity isolated from vegetal species.
Fig. 5. Various types of triterpene derivatives obtained from synthesis with bactericidal activity.
In conclusion, the general analysis of the relationships between chemical structure and activity of triterpenes against Gram-positive and Gram-negative bacteria indicates that the antibacterial activity of the triterpene may be related to the presence of an oxygenated group at C-3, since 95% of the bactericidal triterpenes present this functionality. This site is represented by hydroxyl, carbonyl, glycoside, ester (mainly acetyl), or hydroxylimine (compound 141). The bactericidal activity is also influenced by the chemical structure of the substituent group. Glycoside derivatives usually exhibit higher activity, mainly for 1→6 type bonding in relation to 1→4 type one (Takechi & Tanaka, 1993). The activity is increased for the triterpenes containing free hydroxyl group at C-3, mainly on the beta-side. In fact, the activity usually decreased when the position C-3 is an ester derivative (Abreu et al., 2011). The conversion of the carboxyl group at C-17 on the beta-side to a lactone at C-13 and C-17 increases the bactericidal activity (Hichri et al., 2003).

Moreover, the bactericidal activity attributed to the C-3 site is not influenced by the steric effects, because very active compounds contain groups that present large volumes at C-3, such as compounds 23-25, 28, 36-42, 64, 81, 99, 101, 102, 111-116, 127, and 134-137. A carboxyl group at C-17 on the beta side is also important — 78% and 81% of the triterpenes active against Gram-positive and Gram-negative bacteria, respectively, present this functional group. The same analysis can be made for the compounds containing functionality at C-20 on the alpha- or beta-side.

The majority of the active triterpenes presents π-bonding at positions C-5, C-6, C-9, C-11, C-12, and C-13 (i.e., Δ^5,6 Δ^9,11, and Δ^12,13, respectively), few of them present Δ^20,30 and Δ^20,21, and π-bondings are absent in few active triterpenes. The bactericidal activities are mainly related to functional groups at the rings A and E of the triterpene skeleton. Considering a great quantity of active triterpenes containing π-bonding at the ring C, it may be proposed that this functionalization is also important to the bactericidal activity.

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