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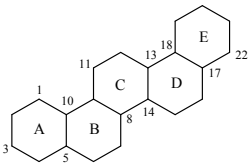
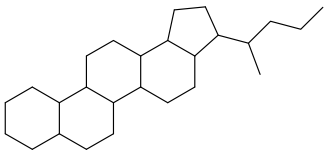
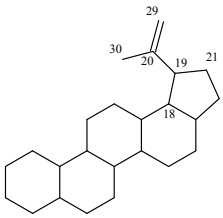
their skeleton may be substituted. As result, there are at least 4000 known PCTTs (Dzubak et al., 2006), exhibiting a large spectrum of biological activities (James & Dubery, 2009). Some classes of triterpenes present other skeleton, such as fernane- and lupane-type triterpenes.



Basic skeleton of **PCTT**



Basic skeleton of fernane-type triterpenes



Basic skeleton of 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. aeroginosa*, *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*	Chattopadhyay et al., 2001
Austroplenckia populnea	Triterpenes	*S. aureus*	-	Miranda et al., 2009
Aquilaria agallocha	Triterpenes, alkaloids, anthraquinones, and tannins	*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
Cardiospermum 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
Finlaysonia obovata	Triterpenes	*S. aureus*	*E. coli* and *P. aeruginosa*	Mishra & Sree, 2007
Galium mexicanum	Triterpenes, saponins, flavonoids, sesquiterpene lactones, and glucosides	*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. pneumoniae*	*E. coli*	Mangathayaru et al., 2005
Miconia ligustroides	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 gengivalis*	Kim et al., 1999
Phyllanthus simplex	Triterpenes, steroids, lignans, flavonoids, glycosides, and phenolic compounds	*S. aureus*	*E. coli*, *P. aeruginosa*, and *S. flexneri*	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
Tridesmostemon omphalocarpoides	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. fluorencens* (**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. pneumonae*, and *P. aeroginosa* 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. freundi*, *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 (**1**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
Olean-1,12-dien-29-oic acid, 3-oxo (**2**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
lα-Hydroxy-3-oxoolean-12-en-30-oic acid (**3**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
2-Oxo-3β-hydroxyolean-12-en-30-oic acid (**4**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
Olean-12-en-1,3-dihydroxy (**5**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
3,30-Dihydroxyl-12-oleanen-22-one (**6**)	*Cambretum imberbe*	*E. faecalis* and *S. aureus*	*E. coli*	Angeh et al., 2007; Katerere et al., 2003
Arjulonic acid (**7**)	*Syzygium guineense*	*B. subtilis*	*E. coli* and *Shigella sonnei*	Djoukeng et al., 2005
Terminolic acid (**8**)	*Syzygium guineense*	*B. subtilis*	*E. coli* and *S. sonnei*	Djoukeng et al., 2005
2α,3β,24-Trihydroxyolean-12-en-28-oic acid (**9**)	*Planchonia careya*	MRSA	*Enterococcus vancomicin-resistant* (VRE)	McRae et al., 2008
2,3,23-Trihydroxy-(2α,3β,4α) olean-11-en-28 oic acid (**10**)	*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

Compound	Vegetal species	Activity against Gram-positive bacteria	Activity against Gram-negative bacteria	Ref.
Arjungenin (**11**)	*Planchonia careya*		*Pseudomonas fluorencens*	McRae et al., 2008
Arjunic acid (**12**)	*Terminalia arjuna*		*P. fluorencens*	Sun et al., 2008
3-Acetyl aleuritolic acid (**13**)	*Spirostacheps africana*	*S. aureus*	*E. coli, Shigella 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*-[*β*-*D*-glucopyranosyl] Ester (**19**)	*Drypetes paxii*	*S. aureus*	*E. coli* and *S. typhi*	Chiozem et al., 2009
1*α*,3*β*-Dihydroxyolean-12-en-29-oic acid (**20**)	*Cambretum imberbe*	*E. faecalis* and *S. aureus*	*E. coli*	Angeh et al., 2007; Katerere et al., 2003
1*α*,3*β*-Hydroxyimberbic-acid-23-*O*-*β*-*L*-4-acetylrhamnopyranoside (**21**)	*Cambretum imberbe*	*E. faecalis* and *S. aureus*	-	Angeh et al., 2007; Katerere et al., 2003
1,3,24-Trihydroxyl-12-olean-29-oic acid (**22**)	*Cambretum imberbe*	*S. aureus*	*E. coli*	Angeh et al., 2007; Katerere et al., 2003
1*α*,23-Dihydroxy-12-oleanen-29-oic acid-3*β*-*O*-2,4-diacetyl-*L*-rhamnopyranoside (**23**)	*Cambretum imberbe*	*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
3*β*,6*R*,13*β*-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.
18*α*-Oleanane-3*β*-ol,19*β*,28-epoxy (**27**)		-	*Chlamydia pneumoniae*	Dehaen et al., 2011
9*β*,25-cyclo-3*β*-*O*-(*β*-*D*-glucopyranosyl)-echynocystic acid (**28**)	*Syniplocos panicrelata*	*B. subtilis* and *S. aureus*	*E. coli* and *P. aeruginosa*	Semwal et al., 2011
3-Oxoolean-l,12-dien-30-oic acid (**29**)	*Dellenia papuana*	*B. subtilis*	*E. coli*	Nick et al., 1994
3*R*-Hydroxyolean-12-en-27-oic acid (**30**)	*Aceriphyllum rossii*	MRSA, quinolone resistance *S. aureus* (QRSA), and *S. aureus*	-	Zheng et al., 2008
3*β*-Hydroxyolean-12-en-27-oic acid (**31**)	*Aceriphyllum rossii*	MRSA, QRSA, and *S. aureus*	-	Zheng et al., 2008
Aceriphyllic acid A (**32**)	*Aceriphyllum rossii*	MRSA, QRSA, and *S. aureus*	-	Zheng et al., 2008
Methyl ester of aceriphyllic acid A (**33**)	*Aceriphyllum rossii*	MRSA, QRSA, and *S. aureus*	-	Zheng et al., 2008
22*α*-Acetyl-16*α*,21*β*-dihydroxyoleanane-13*β*:28-olide-3-*O*-[*β*-glucopyranosyl-(1'''→6')][6''-*O*-coumaroylglucopyranosyl-(1''→2')]-*β*-glucopyranoside (**34**)	*Maesa lanceolata*	*S. aureus*	-	Manguro et al., 2011
16*α*,22*α*-Diacetyl-21*β*-angeloyloleanane-13*β*:28-olide-3*β*-*O*-[*β*-glucopyranosyl-(1''→2')][*β*-glucopyranosyl-(1'''→4')]-*β*-glucopyranoside (**35**)	*Maesa lanceolata*	*B. subtilis, E. faecalis*, *S. aureus,* and *S. pneumoniae*	*E. coli, P. aeruginosa,* and *V. cholera*	Manguro et al., 2011
16*α*,22*α*,28-Trihydroxy-21*β*-angeloylolean-12-ene-3*β*-*O*-[*α*-rhamnopyranosyl-(1'''→6'')][*β*-glucopyranosyl-(1''→2')]-*β*-xylopyranoside(**36**)	*Maesa lanceolata*	*E. faecalis* and *S. pneumoniae*	*S. typhi* and *V. cholera*	Manguro et al., 2011
16*α*,28-dihydroxy-22*α*-acetyl-21*β*-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**)	*Drypetes laciniata*	-	*E. coli* and *S. typhi*	Fannang et al., 2011
3*β*-[(*α*-*L*-Arabinopyranosyl)-oxy]olean-12-en-28-oic acid (**39**)	*Clematis ganpiniana*	*B. subtilis*	-	Ding et al., 2009
Hederagenin-3*β*-*O*-*α*-*L*-arabinopyranoside (**40**)	*Clematis ganpiniana*	*Bacillus pumilus* and *B. subtilis*	-	Ding et al., 2009
3*β*-*O*-*α*-*L*-Rhamnopyranosyl-(1→2)-*α*-*L*-arabinopyranosyl 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-3*β*-ethan-3-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. subtillis*	*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 camaldulensis*	*S. aureus* and *S. epidermidis*	*E. coli*, *K. pneumonae,* 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*	Panizzi et al., 2000
1β,2β,3β–Trihydroxy-urs-12-ene-23-oic-rhamnoside (**52**)	*Commiphora glandulosa*	*B. subtilis, C. perfringens,* and *S. aureus*	-	Montlhanka 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**)	*Carophora 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
Lantic acid (**57**)	*Lantana camara*	*B. cereus, B. subtilis, M. luteus, S. aureus,* and *S. faecalis*	*E. coli*	Saleh et al., 1999
22β-Acetoxylantic acid (**58**)	*Lantana Camara*	*S. aureus*	*E. coli*, *P. aeruginosa,* and *S. typhi*	Barre et al., 1997
Taraxast-20-ene-3β-ol (**59**)	*Saussurea petrovii*	*B. subtilis* and *S. aureus*	*E. coli*	Daí et al., 2001
Taraxast-20(30)ene-3β,21α-diol (**60**)	*Saussurea petrovii*	*B. subtilis* and *S. aureus*	*E. coli*	Daí et al., 2001
20α,21α-Epoxy-taraxastane-3β,22α-diol (**61**)	*Saussurea petrovii*	*B. subtilis* and *S. aureus*	*E. coli*	Daí et al., 2001
Taraxast-20-ene-3β-ol (**62**)	*Saussurea petrovii*	*B. subtilis* and *S. aureus*	*E. coli*	Daí et al., 2001
Taraxast-20-ene-3 β,30-diol (**63**)	*Saussurea petrovii*	*B. subtilis* and *S. aureus*	*E. coli*	Daí et al., 2001
20(29)-Lupene-3β-isoferulate (**64**)	*Euclea 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	Vegetal 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. freundi, 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-20*α*-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
3*β*-Hydroxyfriedelane-7,12,22-trione (**70**)	*Drypetes laciniata*	-	*E. coli, P. aeruginosa,* and *S. typhi*	Fannang et al., 2011
12*α*-Hydroxyfriedelane-3,15-dione (**71**)	*Drypetes paxii*	*S. aureus*		Chiozem et al., 2009
Friedelanol (**72**)	*Visnia rubescens*	*S. aureus*	*P. aeruginosa* and *S. typhi*	Angeh et al., 2007; Katerere et al., 2003
3*β*-Hydroxyfriedelan-25-al (**73**)	*Drypetes paxii*	*S. aureus*	-	Chiozem et al., 2009
3-Hydroxy-2,24-dioxo-3-friedelen-29-oic acid (**74**)	*Elaeodendron schlechteranum*	*B. cereus* and *S. aureus*	-	Maregesi et al., 2010
22*β*-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-friedelane-29-oic acid methyl ester (**76**)	*Crossopetalum gaumeri*	*B. cereus, M. luteus,* and *S. epidermidis*	-	Ankli 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-2*α*,16*α*-dihydroxy-3*β*-*O*-(*β*-*D*-glucopyranosyl)-hopan-24-oic acid (**81**)	*Syniplocos panicrelata*	*B. subtilis* and *S. aureus*	*E. coli* and *P. aeruginosa*	Semwal et al., 2011
Hopan-27-al-6*β*,11R,22-triol (**82**)	*Conoideocrella tenuis* (*fungus*)	-	*Mycobacterium tuberculosis*	Isaka et al., 2011
A'-Neogammacerane-6,11,22,27-tetrol (**83**)	*Conoideocrella 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-6*β*,7*β*,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**)	*Osyris 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* and *S.typhimurium*	Parveen et al., 2009
2-Chrysene acetic acid, 9-carboxy-1,2,3,4,4a,4b,5,6,6a,7,8,9,10,10a,12,12a-hexadecahydro-*α*,*α*,1,4a,4b,6a,9-heptamethyl-1-(2-oxoethyl),2-methyl ester (**89**)	*Dillenia papuana*	*B. subtilis* and *M. luteus*	*E. coli*	Nick et al., 1994
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
3*α*-Hydroxy-24-methylene-23-oxolanost-8-en-26-carboxylic acid (**92**)	*Fomitopsis rosea* (*fungus*)	*S. aureus*	-	Popova et al., 2009
3*α*-Carboxyacetoxyquercinic acid (**93**)	*Fomitopsis rosea* (*fungus*)	*S. aureus*	-	Popova et al., 2009
3*α*-Oxepanoquercinic 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
3*α*-(3'Butylcarboxyacetoxy)oxepanoquercinic acid C (**96**)	*Fomitopsis rosea* (*fungus*)	*S. aureus*	-	Popova et al., 2009
Helvolic acid (**97**)	*Pichia guilliermondii* (*fungus*)	*B. subtilis*, *S. aureus*, and *Staphylococcus haemolyticus*	*Agrobacterium tumifaciens*, *E. coli*, *Pseudomonas lachrymans*, *Ralstonia solanacearum*, and *Xanthomonas vesicatoria*	Zhao et al., 2010
5*α*,8*α*-Epidioxi-24(ξ)-methylcholesta-6,22-diene-3*β*-ol (**98**)	*Fomitopsis rosea* (*fungus*)	*S. aureus*		Popova et al., 2009
1,3,16*β*-yl-Phenypropylacetate-lanostan-5,11,14,16,23,25-hexen-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
3*β*-*O*-*cis*-*p*-Coumaroyltormentic acid (**101**)	*Planchonia careya*	*S. aureus*	VRE	McRae et al., 2008
3*β*-*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.)

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. aureus*, *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-[2-[(1*S*,2*R*,3*R*)-2-(3-ethoxy-3-oxopropyl)-3-(1-hydroxy-1-methylethyl)-2-methyl-6-methylenecyclohexyl]ethyl]-1,3-dimethyl-6-(1-methylethenyl) (**110**)	*Lansium domesticum*	*B. cereus*, *B. subtilis*, *M. luteus*, *S. aureus*, *S. epidermidis*, and *S. pyogenes*	-	Dong et al., 2011

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

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-Maltotriosídeo methyl oleanolate (**116**)	*S. aureus*	-	Takechi & Tanaka, 1992
Oleanolic acid acetate (**117**)	*S. aureus*	*E. coli* and *P. aeruginosa*	Hichri et al., 2003

Table 3. Bactericidal activity of triterpene derivatives

Compound	Activity against Gram-positive bacteria	Activity against Gram-negative bacteria	Ref.
3*β*-*O*-Acetate *β*-amyrin (**118**)	*S. aureus*	*E. coli* and *P. aeruginosa*	Hichri et al., 2003
2*β*,3*β*-Dihydroxy-ll-oxooleana-12,18-dien-30-oic acid (**119**)	*B. subtilis*	*Erwinia* sp.	Pitzele, 1974
2*β*,3*α*-Dihydroxy- ll -oxooleana-12,18-dien-30-oic acid (**120**)	-	*Erwinia* sp.	Pitzele, 1974
2*β*,3*α*-Dihydroxy- ll -oxo-l8*β*-olean-12-en-30-oic acid (**121**)	*B. subtilis*	-	Pitzele, 1974
2*β*,3*β*-Dihydroxy-ll-oxo-18*β*-olean-12-en-30-oic acid (**122**)	-	*Erwinia* sp.	Pitzele, 1974
2*β*,3*β*-Diacetoxy-ll-oxo-18*β*-olean-12-en-30-oic acid (**123**)	-	*Erwinia* sp.	Pitzele, 1974
3*β*-Acetyl-11-oxooleanolic acid (**124**)	*S. aureus*	*E. coli, P. aeruginosa,* and *S. typhimurium*	Hichri et al., 2003
Methyl 2*β*,3*α*-dihydroxy-18*β*-olean-12-en-30-oate (**125**)	-	*Erwinia* sp.	Pitzele, 1974
1*α*-Bromo-2,3-dioxo-18*β*-olean-12-en-30-oic acid (**126**)	-	*Erwinia sp.*	Pitzele, 1974
3*β*-*O*-Nicotinoyl-20-(4-methylpiperazin-1-yl)carbonyl-11-oxoolean-12(13)-ene (**127**)	*S. aureus*	-	Kazakovaa et al., 2010
N-3-pyridinacetyloleanolic amide (**128**)	*S. aureus*	*E. coli, P. aeruginosa,* and *S. typhimurium*	Hichri et al., 2003
3*β*-Hydroxyolean-12-en-28-carboxydiethylphosphonate (**129**)	*S. aureus*	*E. coli, P. aeruginosa,* and *S. typhimurium*	Hichri et al., 2003
3*β*-Acetoxy-12*α*-hydroxyoleanan-13*β*,28-olide (**130**)	-	*S. typhimurium*	Hichri et al., 2003
Oleanan-28-oic acid, 3*β*,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-Maltotriosídeo methyl ursolate (**133**)	*S. aureus*	-	Takechi & Tanaka, 1993
Urs-12-ene-28-carboxy-3*β*–dodecanoate (**134**)	*Bacillus sphaericus*, *B. subtilis,* and *S. aureus*	*Pseudomonas syringae*	Mallavadhani et al., 2004
Urs-12-ene-28-carboxy-3*β*–tetradecanoate (**135**)	*Bacillus sphaericus*, *B. subtilis,* and *S. aureus*	*P. syringae*	Mallavadhani et al., 2004
Urs-12-ene-28-carboxy-3*β*–hexadecanoate (**136**)	*Bacillus sphaericus*, *B. subtilis,* and *S. aureus*	*E. coli* and *P. syringae*	Mallavadhani et al., 2004
Urs-12-ene-28-carboxy-3*β*–octadecanoate (**137**)	*Bacillus sphaericus*, *B. subtilis,* and *S. aureus*	*E. coli* and *P. syringae*	Mallavadhani et al., 2004
3-Oxo-17-(4-methylpiperazin-1-yl)carbonyloursan-12(13)-ene (**138**)	*S. aureus*	-	Kazakovaa et al., 2010
2-Furfurylidenebetulonic acid (**139**)	*S. aureus*	-	Kazakovaa et al., 2010
(4-Methylpiperazin-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.)

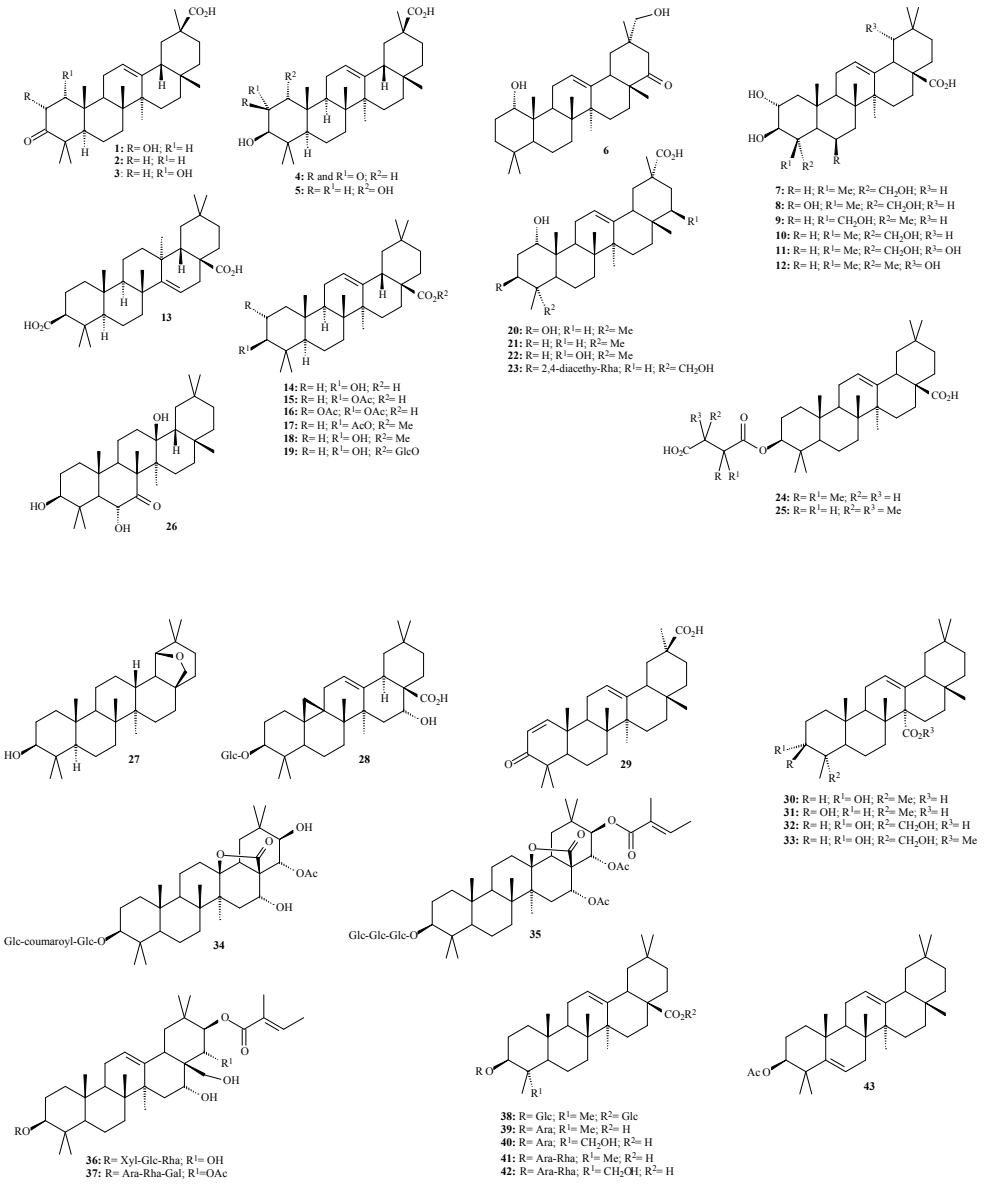


Fig. 1. Oleanane-type triterpenes with bactericidal activity isolated from vegetal species.

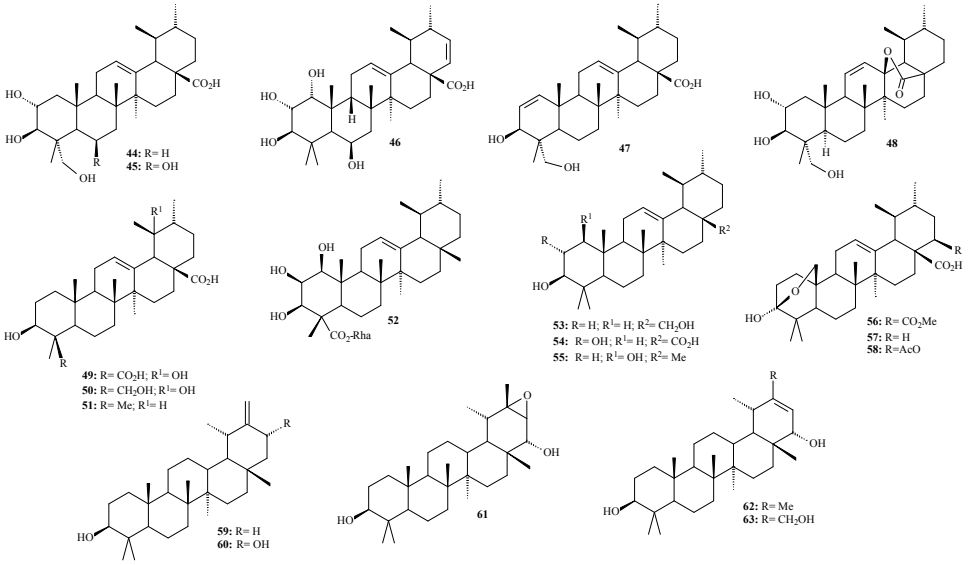


Fig. 2. Ursane-type triterpenes with bactericidal activity isolated from vegetal species.

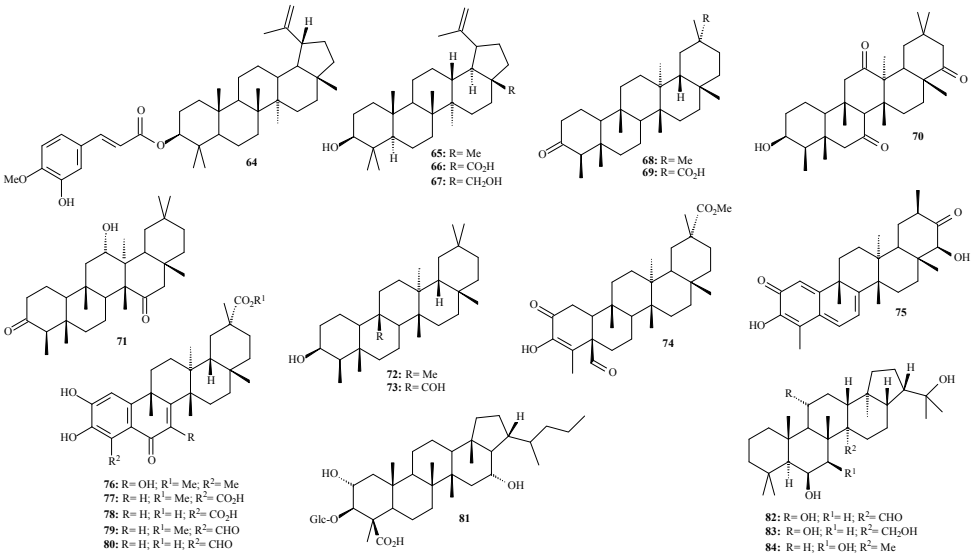


Fig. 3. Lupane-, friedelane-, and fernane-type triterpenes with bactericidal activity isolated from vegetal species.

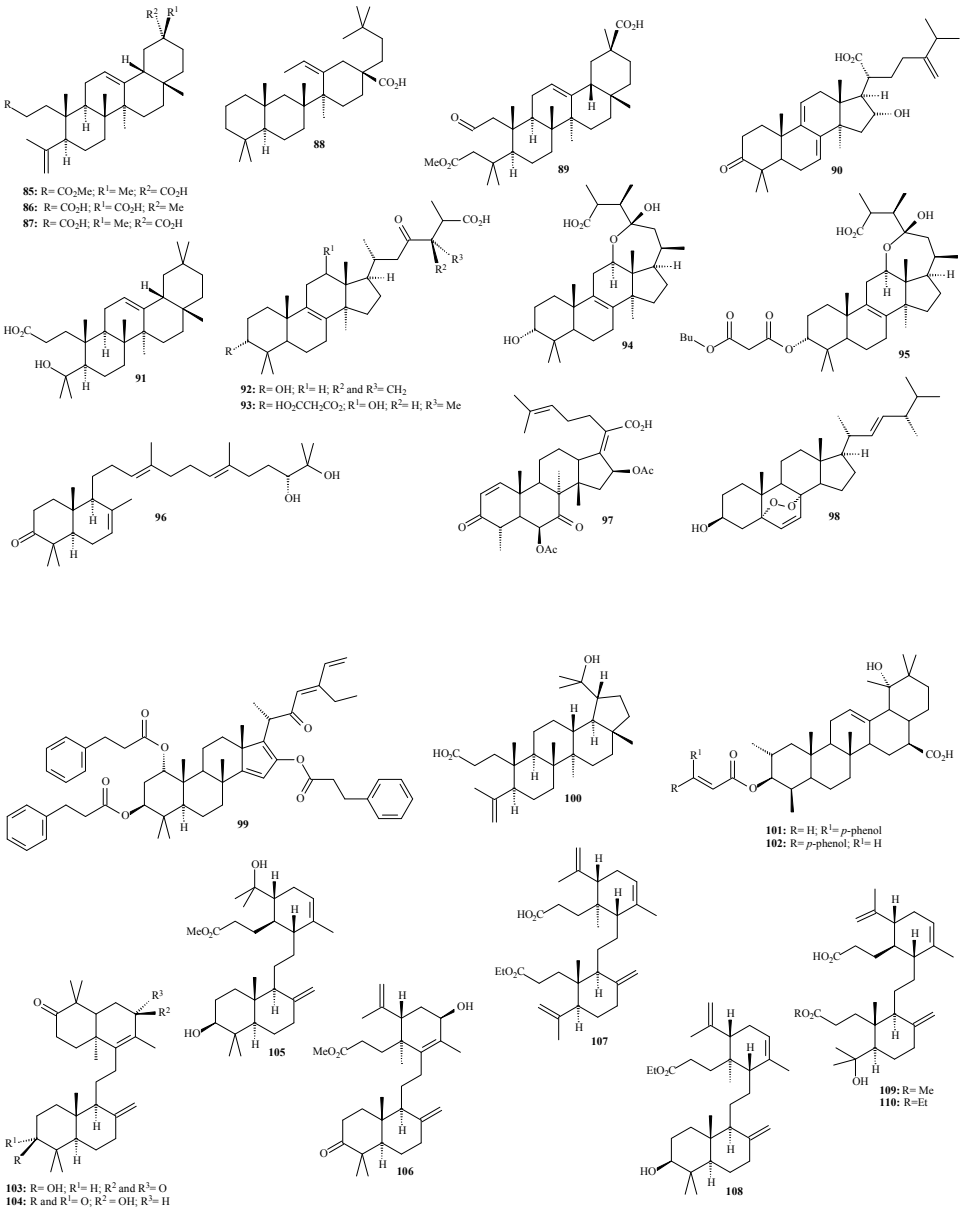


Fig. 4. Miscellaneous types of triterpenes with bactericidal activity isolated from vegetal species.

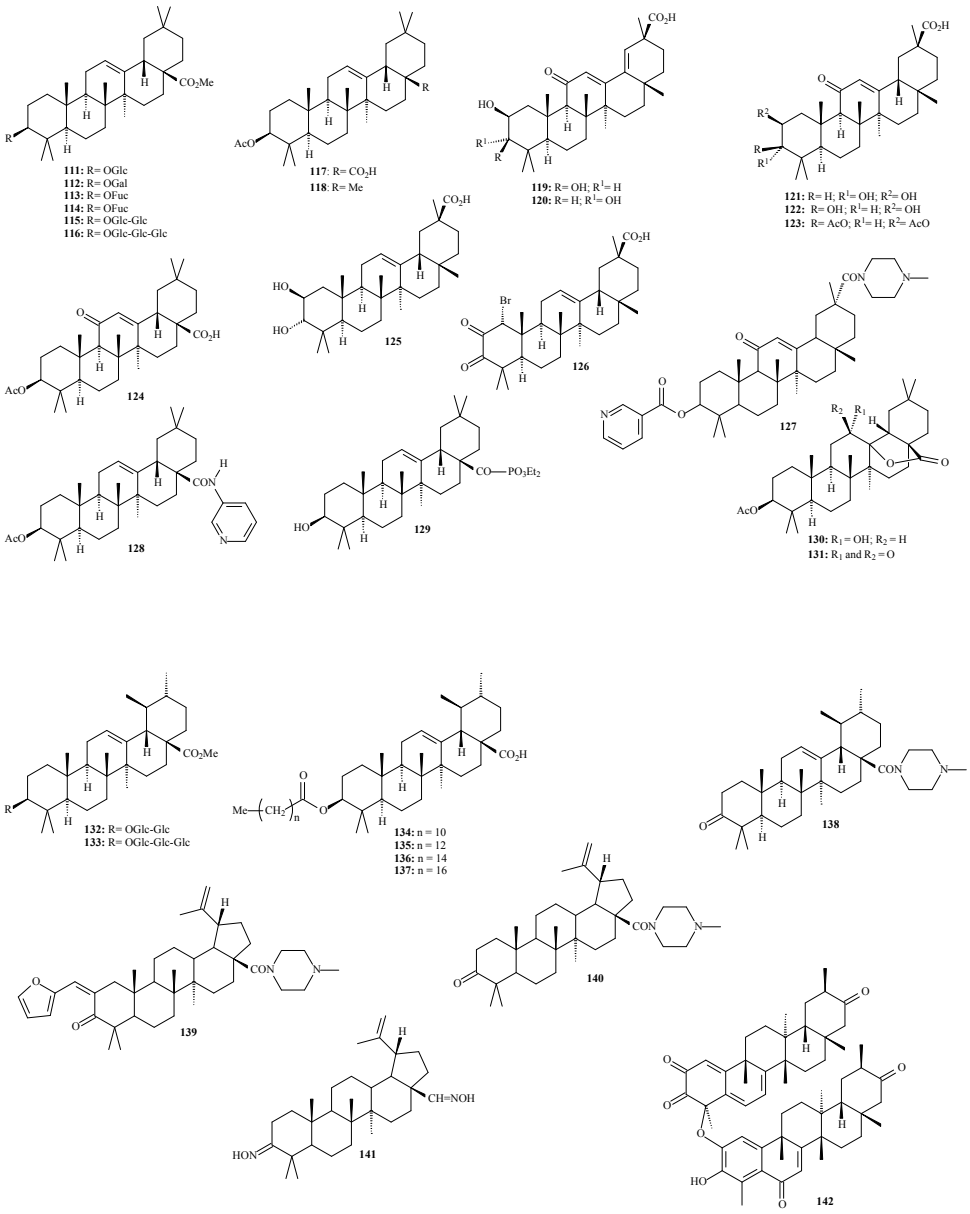


Fig. 5. Various types of triterpene derivatives obtained from synthesis with bactericidal activity.

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, glycosideo, esther (mainly acethyl), 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., $\Delta^{5,6}$ $\Delta^{9,11}$, and $\Delta^{12,13}$, respectively), few of them present $\Delta^{20,30}$ and $\Delta^{20,21}$, 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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