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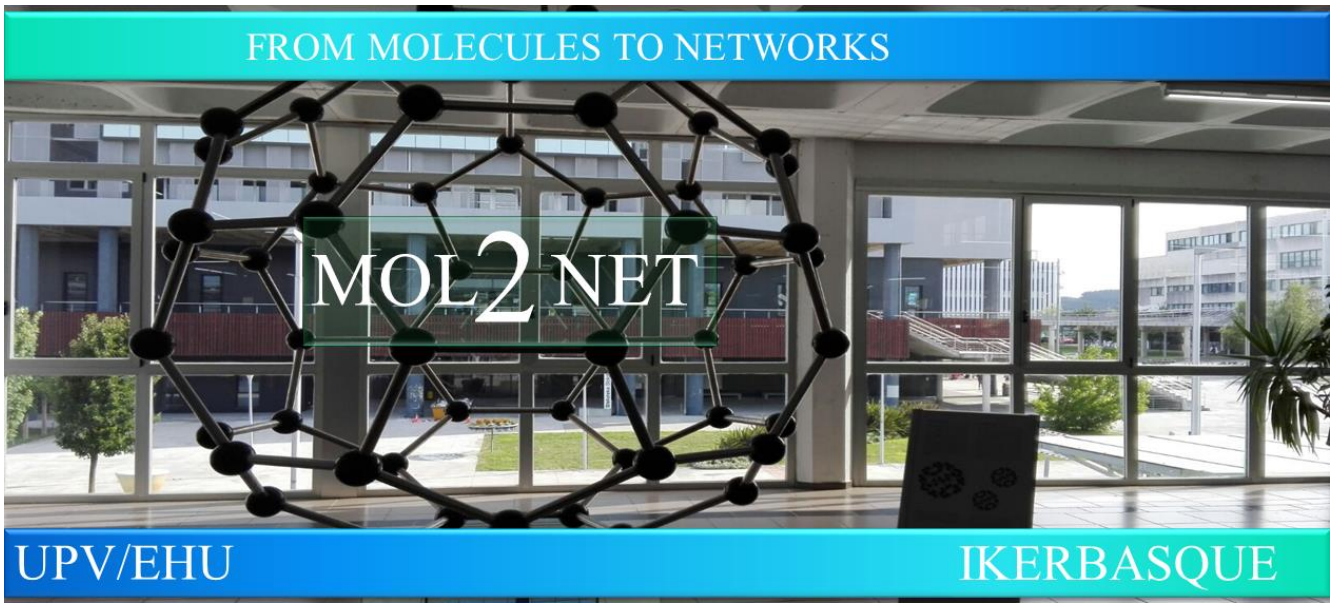

Theoretical comparison between α, β-amyrin isomers against *Staphylococcus aureus*

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Abstract: The progressive spread of antibiotic-resistant microorganisms is a public health problem, so the search for new substances with antimicrobial properties has been growing over the years, especially natural products. Triterpenes are widely distributed in the plant kingdom and have several pharmacological activities described. Studies involving the stereochemistry of drugs greatly contribute to the choice of the isomer that is more active and that promotes fewer adverse effects for humans. The α,β-amyrin isomers in their isolated form may have different or even similar pharmacological properties, but with different intensities of activity due to the change in the position of the methyl groups that influence bioactivity. From the studies previously carried out, it was seen that both have antibacterial activity against *S. aureus* when they are separated or mixed, leading to the conclusion that there is no need to separate these two, because the migration of the C-29 methyl does not influence in this type of activity.

Keywords: oleanan; ursan; antibacterial activity; stereochemistry.

Bacterial infections have been a public health problem for many years. Although the discovery of antibiotics has revolutionized medicine, preventing the death of individuals caused by infectious diseases over time, the progressive spread of microorganisms resistant to such substances is a major challenge for microbiologists (FREITAS et al., 2020).

Currently, the development of resistance mechanisms is present in almost all species of bacteria. This phenomenon occurs due to intrinsic mutations in the microorganism, such as changes in the genetic code during the reproductive process, leading to changes in biochemical systems that prevent the action of drugs, or it occurs through the transfer of genes responsible for such mechanisms that, when imported by transduction, promote bacterial resistance (TAVARES, 2000).

Among the microorganisms that have changes in antibiotic sensitivity, Staphylococcus aureus stands out, a Gram-positive pathogenic bacterium acquired in hospital involved in skin, respiratory, urogenital and gastrointestinal infections, which causes concern for health professionals due to its ability to acquire resistance to all useful antibiotics commonly used in the clinic (GIBBONS, 2004).

Looking at this problem, the search for new substances with antimicrobial properties has been growing over the years, highlighting natural products due to the great diversity of structurally distinct compounds present in plants. Different classes of secondary metabolites had cited as antibacterial, including terpenoids (GIBBONS, 2004).

Terpenes are a class of secondary metabolites found in the plant kingdom, involved in the growth, development and survival of these organisms. Structurally, they are formed from the union of isoprene units (C_5), being classified as hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesteterpenes (C_{25}), triterpenes (C_{30}), tetraterpenes (C_{40}) and polyterpenes (> C_{40}) (RIPARDO, 2021).

Triterpenes make up one of the largest classes of natural products, with more than 20,000 substances described. They are structurally diversified, formed by the union of six isoprene units, with a total of 30 atoms of carbons, and can be classified as tetracyclic or pentacyclic, and divided into groups according to their structural skeletons, for example: cucurbitan, cycloarthane, dammarane, euphane, friedelan, holostane, hopane, lanostane, lupane, oleanane, protostane, tirucalan and ursane (SILVA et al., 2020).

Pentacyclic triterpenes have been the subject of a large number of studies due to their pharmacological potential. Previous studies have reported its antitumor, anti-inflammatory, immunomodulatory, antioxidant, antiviral, antidiabetic, hepatoprotective, cardioprotective, antiobesity and antimicrobial activities (RIPARDO, 2021).

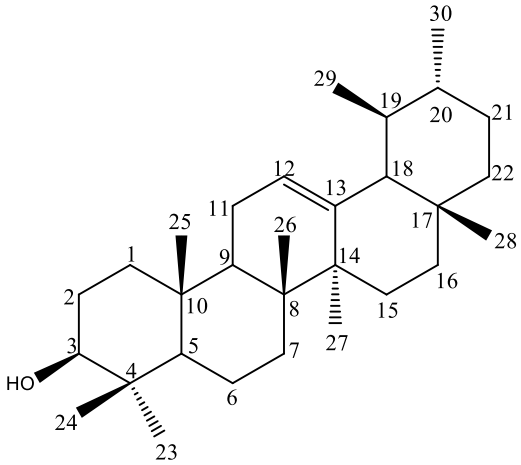
Stereochemistry is the area of chemistry that studies the spatial arrangement of atoms within molecules, enabling a better understanding of their structure-activity. Geometric changes in a drug can modify its function, suppressing its pharmacological action or making it more active, in addition to causing it to present more or less adverse effects. Therefore, work in this area has grown and contributed to the knowledge of the mechanism of action of drugs, in order to take the most beneficial advantage of the molecule, leading to the choice of the isomer that is more active and that does not promote considerable adverse effects for the human being (MAGALHÃES, 2016).

The term isomer refers to compounds that have the same molecular formulas, but different order of binding of their atoms in space, being classified, mainly, as stereoisomers and constitutional isomers, the latter being our focus in this work. Constitutional isomers have the same type and number of atoms,

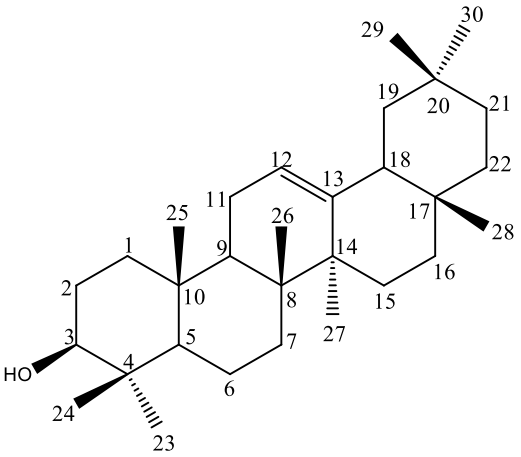
but differ in the order of bonding between them. They have the same molecular formula, but different chemical, physical and biological properties (MAGALHÃES, 2016).

The present abstract is based on the study carried out by Kemboi and collaborators in 2022, where they investigated the antibacterial potential of β-amyrin, which was isolated from the dichloromethane extract of the roots of *Euphorbia grandicornis* against a strain of *Staphylococcus aureus* (ATCC 6538) (KEMBOI *et al*., 2022).

The β-amyrin triterpenoid, belonging to the oleanane group, is widely distributed in the plant kingdom and is frequently isolated as a mixture with its isomer, α-amyrin, belonging to the ursane group. The difference between the oleanane and ursane group is based on the migration of a methyl group (C-29) from position C-20 to C-19, as shown below. Common derivatives of these two compounds are based on hydroxylation at C-3, carboxylation at C-28 and a double bond at the C-12 position to form oleanolic acid and ursolic acid (RIPARDO, 2021).



α-amyrin



β-amyrin

The mixture of these isomers has some biological activities reported in the literature, such as: antinociceptive, anti-inflammatory, gastroprotective, antihyperglycemic and hypolipidemic and hepatoprotective. However, depending on the pharmacological target, the isomers in their isolated form may have different or even similar pharmacological properties, but with different intensities of activity due to the change in the position of the methyl groups that influence the bioactivity (RIPARDO, 2021).

Kemboi et al. (2022) observed a low percentage of bacterial growth of 27.17 ± 0.07 µg/mL, with β-amyrin at a concentration of 50 µg/mL, indicating that this substance inhibits the growth of *S. aureus* (KEMBOI et al., 2022).A study developed by Abreu et al. (2011) tested the antibacterial activity of α-amyrin, where it presented a MIC (minimum inhibitory concentration) greater than 1024 µg/mL (ABREU et al., 2011). Considering that the tests performed in each article used different methodologies, it is not possible to prove which of the two isomers has greater activity against *Staphylococcus aureus* strains.

It was reported that when tested as a mixture, the α-amyrin and β-amyrin isomers showed potent antibacterial activity against S. aureus with MIC of 0.25 mg/mL, probably due to a synergistic effect (KIPLIMO, KOORBANALLY and CHENIA, 2011). Another study demonstrated the potential of this mixture to increase antibacterial activity in association with antibiotics, along with the ability to be a strong candidate for an efflux pump inhibitor (OLIVEIRA et al., 2021).

In view of the data presented, it is possible to conclude that the two isomers present good results when they are in mixture, not needing to submit them to a separation process, and in addition, it is likely that the change in position of the methyl group (C-29) of the position C-20 to C-19, does not influence antibacterial activity. This is supported by the absence of antibacterial effect when the C-3 position is acetylated instead of hydroxylated, suggesting that this portion of the molecule is involved in its interaction with the bacterial cell target (ABREU et al., 2011).

References

ABREU, V. G. C.; TAKAHASHI, J. A.; DUARTE, L. P.; PILÓ-VELOSO, D.; JUNIOR, P. A. S.; ALVES, R. O.; ROMANHA, A. J.; ALCÂNTARA, A. F. C. Evaluation of the bactericidal and trypanocidal activities of triterpenes isolated from the leaves, stems, and flowers of *Lychnophora pinaster*. **Revista Brasileira de Farmacognosia**, v. 21, n. 4, 2011.

FREITAS, P. R.; ARAÚJO, A. C. J.; BARBOSA, C. R. S.; MUNIZ, D. F.; SILVA, A. C. A.; ROCHA, J. E.; OLIVEIRA-TINTINO, C. D. M.; RIBEIRO-FILHO, J.; SILVA, L. E.; CONFORTIN, C.; AMARAL, W.; DESCHAMPS, C.; BARBOSA-FILHO, J. M.; LIMA, N. T. R.; TINTINO, S. R.; COUTINHO, H. D. M. GC-MS-FID and potentiation of the antibiotic activity of the essential oil of *Baccharis reticulata* (ruiz & pav.) pers. and α-pinene. **Industrial Crops & Products**, v. 145, p.112106, 2020.

GIBBONS, S. Anti-staphylococcal plant natural products. **Natural Prodacts Reports**, v. 21, n. 2, p. 263–277, 2004.

KEMBOI, D.; LANGAT, M. K.; SIWE-NOUNDOU, X.; KRAUSE, R.W. M.; ISAACS, M. L.; TEMBU, V. J. In vitro antibacterial and cytotoxic effects of *Euphorbia grandicornis* Blanc chemical constituents. **BMC Complementary Medicine and Therapies,** v. 22, n. 90, 2022.

KIPLIMO, J. J.; KOORBANALLY, N. A.; CHENIA, H. Triterpenoids from *Vernonia auriculifera* Hiern exhibit antimicrobial activity. **African Journal of Pharmacy and Pharmacology**, v. 5, n. 8, p. 1150-1156, 2011.

MAGALHÃES, Joana Cristina Anacleto. **Importância da quiralidade e da estereoquímica na terapia antimicrobiana**. Dissertação de Mestrado (Mestrado em Ciências Farmacêuticas) – Universidade Fernando Pessoa, Porto, Portugal, 2016.

OLIVEIRA, R. C.; BANDEIRA, P. N.; LEMOS, T. L. G.; SANTOS, H. S.; SCHERF, J. F.; ROCHA, J. E.; PEREIRA, R. L. S.; FREITAS, T. S.; FREITAS, P. R.; PEREIRA-JUNIOR, F. N.; MARINHO, M. M.; MARINHO, E. M.; MARINHO, E. S.; NOGUEIRA, C. E. S.; COUTINHO, H. D. M.; TEIXEIRA, A. M. R. *In silico* and *in vitro* evaluation of efflux pumps inhibition of α,β-amyrin. **Journal of biomolecular Structure & Dynamics**, 2021.

RIPARDO, Rose Anny Costa Silva. **Efeito dos triterpenos ácido oleanólico, ácido ursólico e alfa, beta-amirina no distúrbio metabólico induzido por olanzapina em camundongos e em células 3T3-L1**. 2021. Tese de Doutorado (Doutorado em Ciências Médicas) – Universidade Federal do Ceará, Fortaleza, 2021.

SILVA, F. C. O.; FERREIRA, M. K. A.; SILVA, A. W.; MATOS, M. G. C.; MAGALHÃES, F. E. A.; SILVA, P. T.; BANDEIRA, P. N.; MENEZES, J. E. A.; SANTOS, H. S. Bioatividade de triterpenos isolados de plantas: uma breve revisão. **Revista Virtual de Química**, v. 12, n.1, p. 234-247, 2020.

TAVARES, W. Bactérias gram-positivas problemas: resistência do estafilococo, do enterococo e do pneumococo aos antimicrobianos. **Revista da Sociedade Brasileira de Medicina Tropical**, v. 33, n. 3, p. 281-301, 2000.