Supplementary material

Myrtucommulones and Related Acylphloroglucinols from Myrtaceae as a Promising Source of Multitarget SARS-CoV-2 Cycle Inhibitors

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Figure S1. Scores (A), X-loadings weight (B) for the PLS model based on the LC-MS data obtained in the electrospray ionization in negative mode of the 15 samples of five species of Myrtaceae family, and the inhibition values of the extracts on the RBD:ACE2 interaction of SARS-CoV-2. The dashed line indicates the cutoff for contributions exceeding 0.1 (loadings weights).

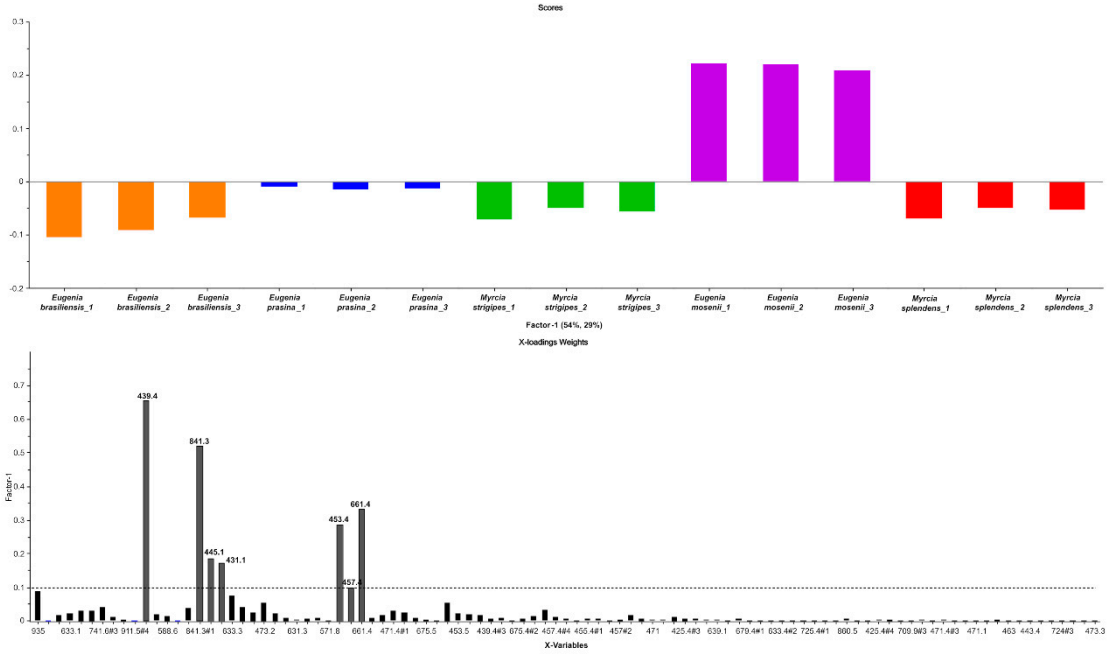


Figure S2. Scores (A), X-loadings weight (B) for the PLS model based on the LC-MS data obtained in the electrospray ionization in negative mode of the 15 samples of five species of Myrtaceae family, and the inhibition values of the extracts on the activity of the r3CLpro enzyme of SARS-CoV-2. The dashed line indicates the cutoff for contributions exceeding 0.1 (loadings weights).

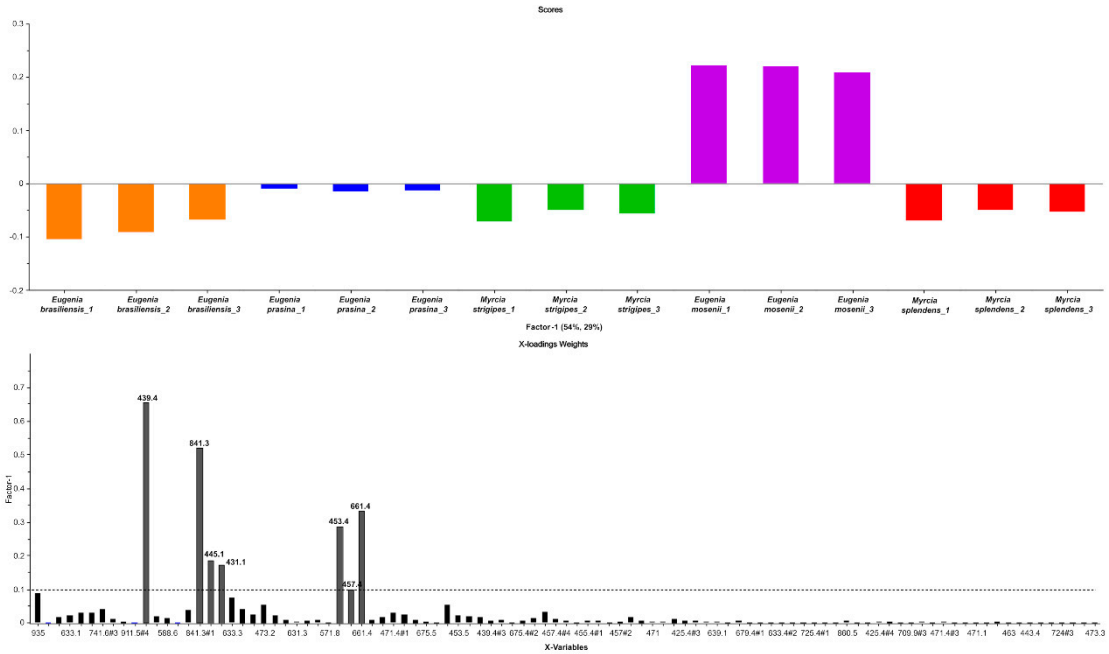


Figure S3. Scores (A), X-loadings weight (B) for the PLS model based on the LC-MS data obtained in the electrospray ionization in negative mode of the 15 samples of five species of Myrtaceae family, and the inhibition values of the extracts on the activity of the rPLpro enzyme of SARS-CoV-2. The dashed line indicates the cutoff for contributions exceeding 0.1 (loadings weights).

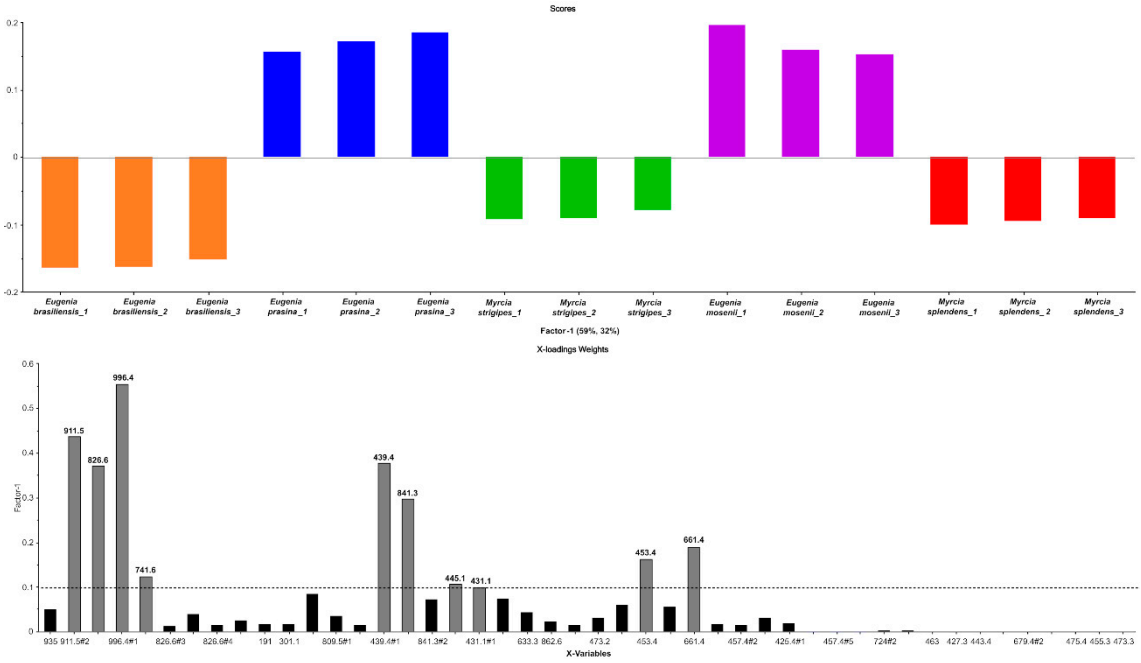


Figure S4. Feature Based Molecular Network (FBMN) of Myrtaceae extracts

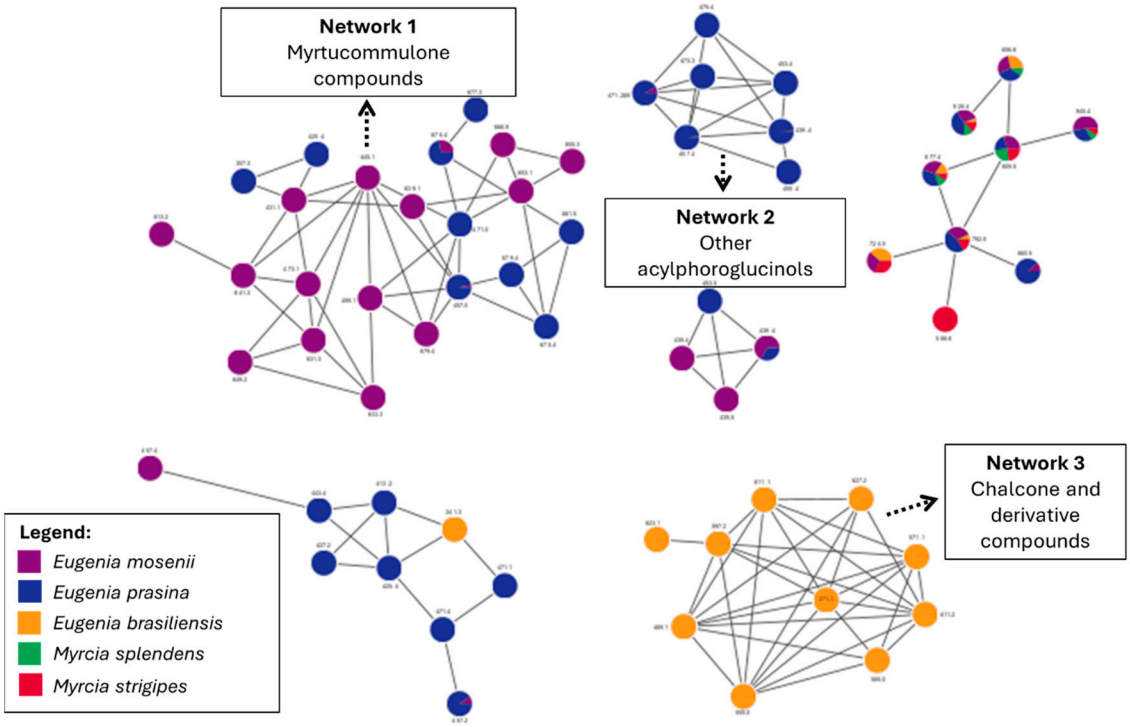


Figure S5. MS/MS spectrum of compound **1** at *m/z* 445.1 $[M-H]^-$ (semimyrtucommulone)

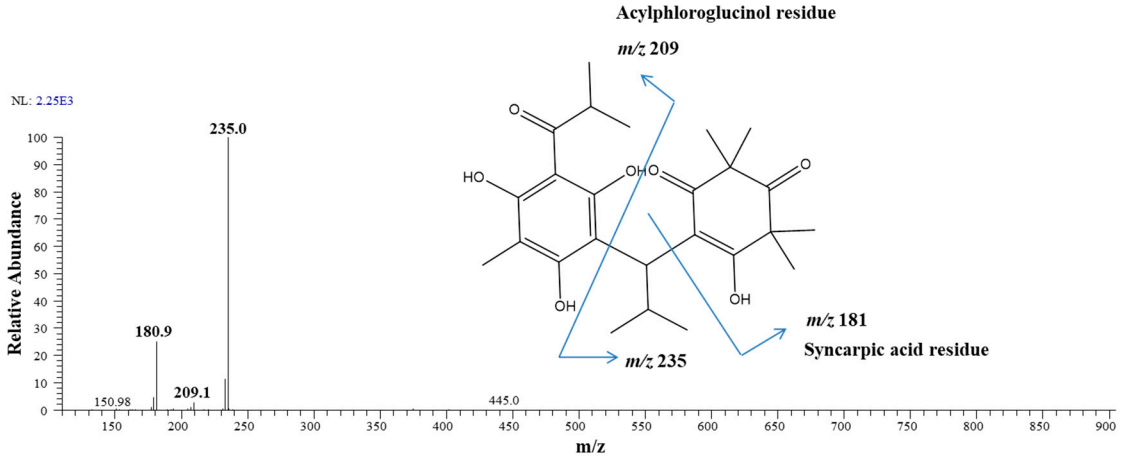


Figure S6. MS/MS spectrum of compound **2** at *m/z* 431.1 $[M-H]^-$ (*nor*-semimyrtucommulone)

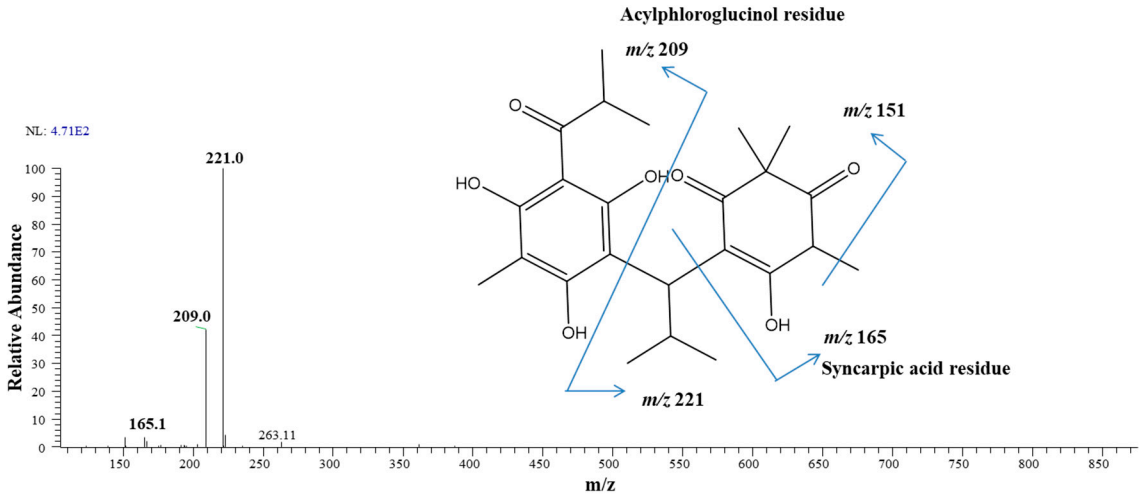


Figure S7. MS/MS spectrum of proposed compound **3** at *m/z* 473.2 $[M-H]^-$

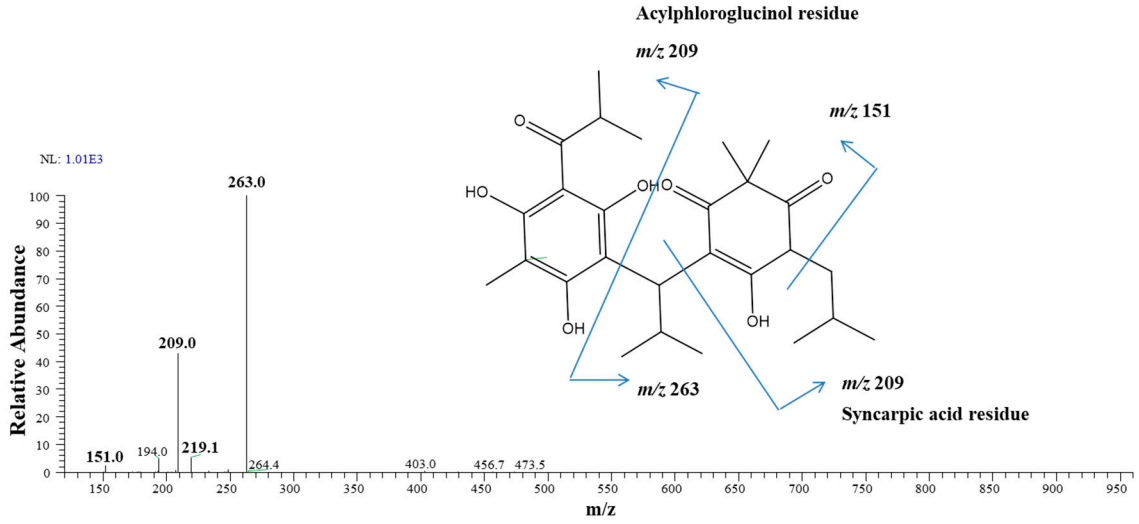


Figure S8. MS/MS spectrum of proposed compound **4** at *m/z* 633.3 $[M-H]^-$

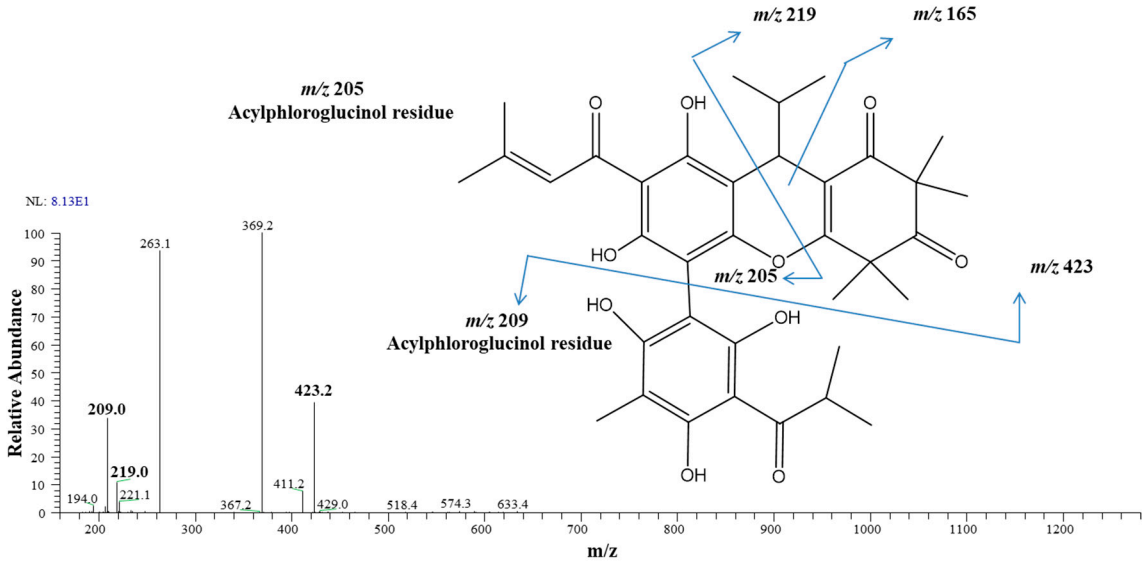


Figure S9. MS/MS spectrum of proposed compound **5** at *m/z* 841.3 $[M-H]^-$

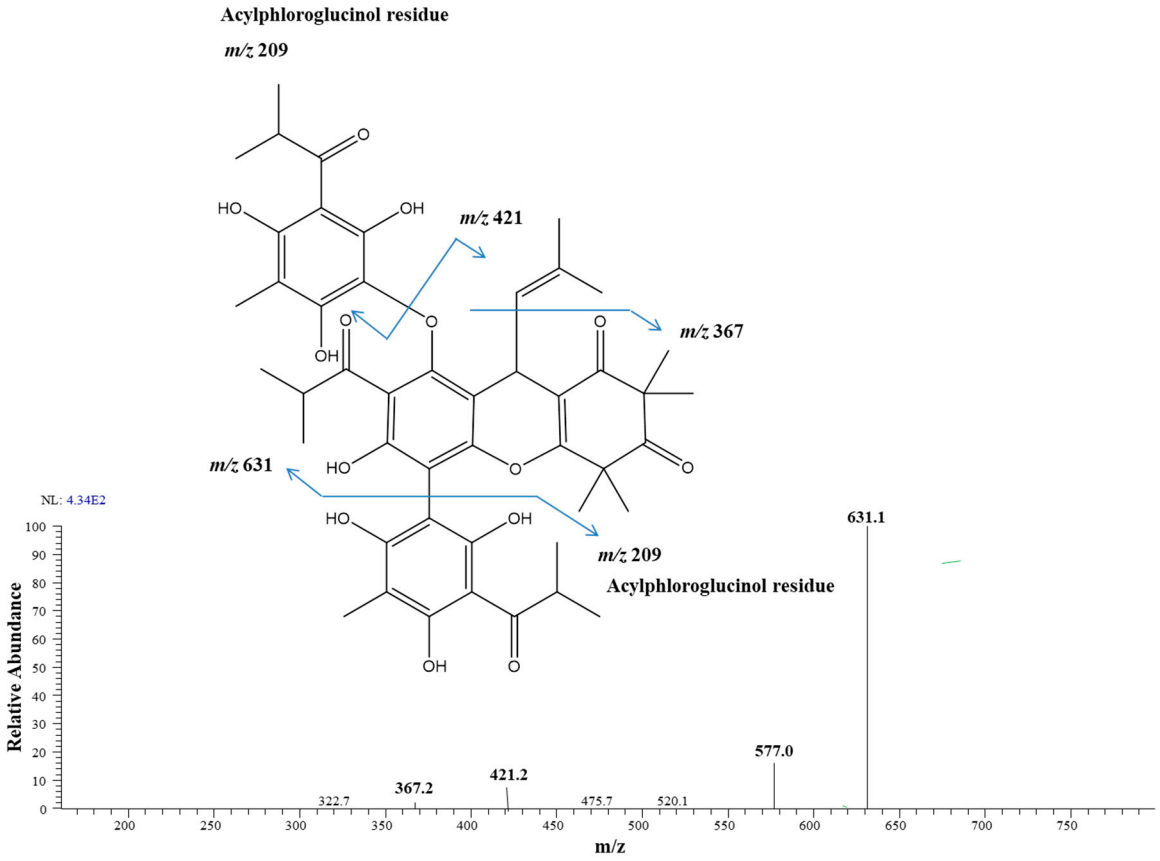


Figure S10. Molecular network of chalcone and chalcone-derivative compounds and MS/MS spectrum of *m/z* 271.1 $[M-H]^-$ (2',6'-dihydroxy-4'-methoxydihydrochalcone)

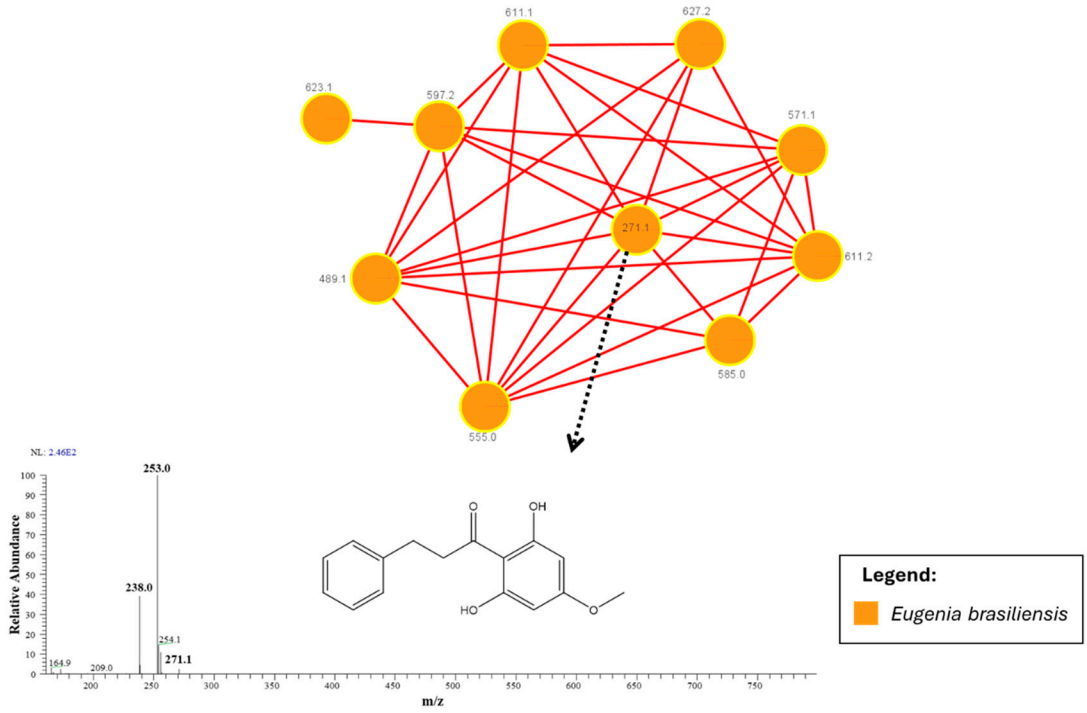
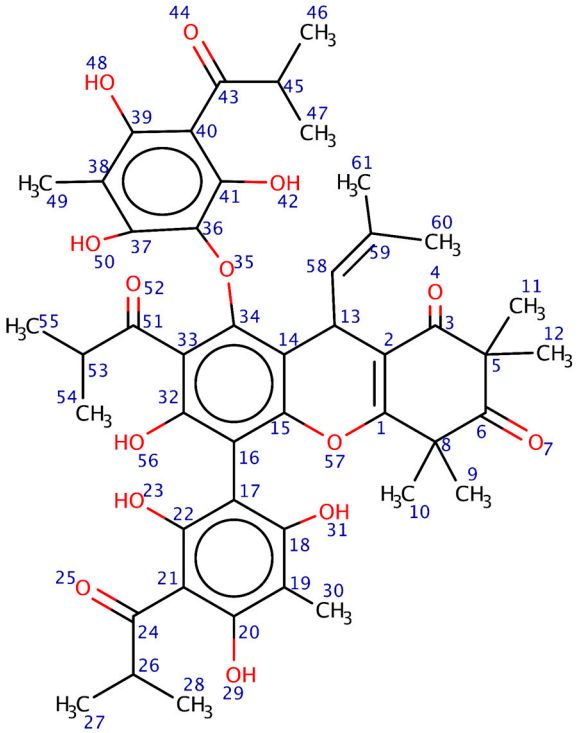


Figure S11. 2D structure of compound **5** (*m/z* 841 $[M-H]^-$) with atomic positions.



Movie S1 - Molecular dynamics results of the complex PLpro with compound 5. The protein structure is shown in gray, the BL2loop is shown in yellow and the compound 5 is shown in blue. The file is available in 10.5281/zenodo.10257486.

Movie S2 - Molecular dynamics results of the complex $3CL^{pro}$ active site with compound **5**. The protein structure is shown in gray and the compound **5** is shown in orange. The file is available in https://doi.org/10.5281/zenodo.10257448.

Movie S3 - Molecular dynamics results of the complex $3CL^{pro}$ allosteric groove with compound **5**. The protein structure is shown in gray and the compound **5** is shown in magenta. The file is available in https://doi.org/10.5281/zenodo.10257460.

Table S1 - Description of the pharmacokinetic properties of the compounds **3**, **4**, **5**, *nor*-semimyrtucommulone (**2**), and semimyrtucommulone (**1**).

	COMPOUND 3 (*m/z* 473 [M-H]-)	compound 4 (*m/z* 633 $[M-H]^-$)	compound 5 (*m/z* 841 $[M-H]^-$)	*nor*-semimyrtucommulone (2)	semimyrtucommulone (1)
CYP1A2-INH	Yes	Yes	Yes	Yes	Yes
CYP1A2-SUB	No	No	No	No	No
CYP2C19-INH	Yes	Yes	Yes	Yes	Yes
CYP2C19-SUB	No	Yes	Yes	No	No
CYP2C9-INH	Yes	No	Yes	Yes	Yes
CYP2C9-SUB	No	No	No	No	No
CYP2D6-INH	Yes	Yes	Yes	Yes	Yes
CYP2D6-SUB	Yes	Yes	Yes	Yes	Yes
CYP3A4-INH	Yes	Yes	Yes	Yes	Yes
CYP3A4-SUB	No	No	No	No	No
CACO-2	Yes	No	No	Yes	Yes
BBB	Yes	Yes	Yes	Yes	Yes
PPB	High	High	High	High	High
FU (%)	High	High	High	High	Less

CYP: Cytochrome P; Caco-2: *Cancer coli* –2; BBB: Blood–Brain Barrier; PPB: Plasma protein binding; Fu: Fraction unbound.