SUPPLEMENTARY MATERIAL

Human Lung Cancer (A549) Cell Line Cytotoxicity and Anti-*Leishmania major* Activity of *Carissa macrocarpa* Leaves: A Study Supported by UPLC-ESI-MS/MS Metabolites Profiling and Molecular Docking

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Identification of the different metabolites of *C. macrocarpa*

Phenolic acids/derivatives

Compounds **6**, **7**, **9**, **39**, **64**, and **74** that showed a molecular ion at *m/z* 353 $[M-H]^-$ were detected at retention times 1.87, 2.03, 2.16, 15.06, and 16.52, respectively. Compounds **6** and **9** produced MS^2 fragments at *m/z* 191 [quinic acid−H]$^-$, *m/z* 179 [caffeic acid−H]$^-$, *m/z* 161 [caffeic acid−H_2O−H]$^-$, hence, assigned as 3-*O*-caffeoylquinic acid and 5-*O*-caffeoylquinic acid, respectively. Where 4-*O*-caffeoylquinic acid (**7**) showed characteristic MS^2 fragments at *m/z* 191, 173 [191−H_2O] and 161 [1]. Another caffeoylquinic acid derivative, diacetoxy-5-methoxyphenylacroyl-*O*-*p*-coumaroyl-*O*-caffeoylquinic acid (**39**) was identified with the aid of MS, MS^2 data (Table 3, main manuscript), and reported literature [2].
Additionally, 4-*O*-caffeoyl shikimic and 3-*O*-caffeoyl shikimic acids have been proposed for **64** and **74** depending upon MS^2 fragments *m/z* 179 [caffeic acid−H]$^-$, *m/z* 161 [caffeic acid−H_2O−H]$^-$, the comparison with the published data [3]. Other hydroxycinnamate derivatives such as 5-*O*-*p*-coumaroylshikimic and 4-*O*-*p*-coumaroylshikimic acids have been suggested for compounds **12** and **15**. MS^2 fragmentation exhibited a base peak at *m/z* 163 due to [*p*-coumaric acid−H_2O], as well as other characteristic fragments [2]. Moreover, compound **29**, which was detected at retention time 6.58 showed a deprotonated molecular ion at *m/z* 515 and distinctive fragments at *m/z* 353 $[M-162]^-$ and 179 that are matched with the reported literature of dicaffeoylquinic acid (**29**). Feruloyl-*O*-sinapoylquinic acid (**37**) was designated for peak detected at *m/z* 573 $[M-H]^-$, based on MS^2 fragments *m/z* 397 [M−ferulic acid−H]$^-$, 223 [sinapic acid−H]$^-$, 173 [quinic acid−H_2O−H]$^-$ as compared with the literature [3]. Besides, compounds, dimethoxycinnamoyl-*O*-caffeoylquinic acid (**54**) and its isomer (**70**) were observed at different retention times 13.30 and 15.66 but exhibited similar deprotonated molecular ions at *m/z* 543 $[M-H]^-$ and characteristic fragment ions at *m/z* 353 [M−dimethoxycinnamoyl−H_2O]$^-$ and 173 that attributed to dimethoxycinnamoyl moiety. The compounds **59**, **60**, and **63** were detected at *m/z* 599 and generated MS^2 ions at *m/z* 397 and 223, hence assigned as 3-*O*-caffeoyl-4-*O*-sinapoylquinic acid (**59**) and its isomers 3-*O*-Sinapoyl-4-*O*-caffeoylquinic acid (**60**) and 1-*O*-caffeoyl-3-*O*-sinapoylquinic acid (**63**) upon comparison with the published data [3]. In addition, two dimethoxycinnamoylquinic acids isomers were suggested for compound **75** (*m/z* 383 $[M-H]^+$) and compound **78** (*m/z* 381 $[M-H]^-$) [3]. The hydroxycinnamate glycosides **8**, **13**, **76, 93**, and **94**, were detected in the current study at retention times 2,13, 2.87, 16.59, 22.78, and 22.90, respectively. Where, compounds **8** and **76** were suggested to be coumaric acid hexoside, due to their similar molecular ions at *m/z* 325 $[M-H]^-$ which generated fragment ions at *m/z* 187, 163, and 145 in accordance with the literature [4]. Also, caffeic acid hexoside was assigned for compound **13** depending upon its molecular ion at *m/z* 343 $[M+H]^+$ with distinctive fragments at *m/z* 326, 311, and 285, which agree with the reported data [5]. The protonated molecular ions of caffeoyl cyclohexanediol hexoside (**93)** *m/z* 441 $[M+H]^+$ and *p*-coumaroyl cyclohexanediol hexoside (**94**) *m/z* 443 $[M+H]^+$ produced fragmentation patterns perfectly matching the published data [6]. Compound **77** with *m/z* 337 $[M-H]^-$ was characterized as *p*-coumaroylquinic acid, based on comparing its fragmentation patterns (*m/z* 202, 190, and 163) with that in the literature [1]. Finally, compound **83** was identified as caffeoyl-2-hydroxyethane-1,1,2-tricarboxylic acid according to a comparison (Table 3, main manuscript) with the reported data [2] . Quinic acid (**2**) and galloylquinic acid (**44**), gallic acid monohydrate (**31**), hydroxycinnamic acid derivatives [ferulic acid (**32**), caffeic acid (**34**), and syringic acid (**35**)], together with hydroxybenzoic acid (**30**) and ascorbic acid (**47**), were detected at different retention times as shown in (Table 3, main manuscript).

Flavonoids/derivatives

Flavonoids are one of the major polyphenolics detected in the polar butanol and MeOH fractions. Compounds **18** and **19** provided the same deprotonated molecular ion at *m/z* 755 $[M-H]^-$ with different MS^2 fragments; 593 $[M-162\ (hexoside)]^-$ and 285 $[M-308\ (rutinoside)]^-$ for kaempferol-7-*O*-hexoside-3-*O*-rutinoside (**18)** [1]. Quercetin-7-*O*-deoxyhexoside-3-*O*-deoxyhexosyl-hexoside (**19**) generated fragment ions at *m/z* 609 [M−146 (deoxyhexosyl unit)] and *m/z* 301 $[M-146-308\ (deoxyhexosyl\ and\ rutinoside\ units)]^-$ [1]. Other kaempferol derivatives were kaempferol-*O*-deoxyhexoside-*O*-deoxyhexosyl-hexoside isomers, which were designated for compounds **21** and **22**, respectively. Both compounds provided the same molecular ions *m/z* 739 $[M-H]^-$ and MS^2 fragmentation patterns *m/z* 593 and 285 [1]. The compounds **23** and **24** were tentatively identified as quercetin-*O*-deoxyhexosyl-hexoside isomers based on their molecular ion at *m/z* 609 $[M-H]^-$ and MS^2 fragment at *m/z* 301 due to loss of rutinoside unit (−308 amu). Also, the other isomer exhibited fragment ion at *m/z* 465 in positive ionization mode due to loss of deoxyhexosyl unit (−146 amu) [1].

The compounds **98–100** are belonging to quercetin derivatives and have been identified as rhamnosyl hexosyl-methyl-quercetin, quercetin-3-*O*-galactoside, and quercetin-3-*O*-glucoside, respectively as depicted from their MS, MS^2 data and comparison with literature [7]. Compound **98** showed a molecular ion at 613 $[M+H]^+$ and MS^2 fragments at *m/z* 595, 521, 491, 449, 327, and 287. While compounds **99** and **100** provided the same molecular ion at *m/z* 465 $[M+H]^+$ and MS^2 fragments at *m/z* 301, 300, 257, 255, 229, 179, and 151.

Kaempferol derivatives were detected upon characterization of MS and MS^2 of compounds **79**, **88**, and **89** that are assigned as kaempferol galloylglucoside, kaempferol deoxyhexosyl-hexoside (**88**), and kaempferol-3-rutinoside (**89**), respectively. Kaempferol galloylglucoside (**79**) displayed molecular ion at *m/z* 601 $[M+H]^+$ and MS^2 fragments at *m/z* 447, 313, 285, 284, 169, 151, and 125 [8]. The two other compounds (**88** and **89**) exhibited the same molecular ion at *m/z* 593 $[M-H]^-$, MS^2 fragment at *m/z* 285 [1].

The compounds **26** and **58** are belonging to flavonoid glycosides [2] that were tentatively identified as myricetin pentoside [9] and vitexin [10] based on their molecular ions at *m/z* 449 $[M-H]^-$ and 431 $[M-H]^-$, respectively. Myricetin pentoside showed characteristic MS^2 fragment at 317 $[M-132]^-$, while 341 $[M-90]^-$ and 311 $[M-120]^-$ were the main fragment ions of mono-*C*-8-hexosylated flavones such as vitexin [10].

Finally, flavonoid aglycones such as quercetin (**27**) [2], tetramethoxyflavone (**42**), eriodictyol (**48**) [11], myricetin (**95**), and methyldihydroquercetin (**97**) [12] have been proposed for peaks **27**, **42**, **48**, **95**, and **97**, respectively.

Flavan-3-ols/derivatives

C. macrocarpa is an important source of falvan-3-ol bioactive metabolites responsible for many pharmacological actions of the plant [1,12]. From these interesting molecules, compound **17** has been identified as (epi) catechin based on a molecular ion at *m/z* 289 $[M-H]^-$, MS^2 fragmentation *m/z* 245, 205, 203, 187, 179, and 161, and the comparison with the literature [1]. Furthermore, the compounds **10**, **11**, **25**, and **53** are belonging to (epi)catechin derivatives of B-type; thus, (epi)catechin dimer was assigned for compounds **10**, **25**, and **53** based on deprotonated molecular ion at *m/z* 577 $[M-H]^-$, MS^2 fragmentation *m/z* 425, 289 and comparison with the literature [1]. However, compound **11** showed pseudo-molecular ion at *m/z* 865 $[M-H]^-$, and fragmentation patterns at *m/z* 451, 425, 407, and 289 were tentatively identified as (epi)catechin trimer [1]. Compounds **14**, **16**, and **20** provided the same deprotonated molecular ion at *m/z* 451 $[M-H]^-$ and different MS^2 fragments at *m/z* 408, 393, 351, 337, 301, 273, and 245 for compound **14** that was suggested to be catechin-3-*O*-glucoside. However, epicatechin 3-*O*-glucoside and its isomer were designated for compounds **16** and **20** with MS^2 fragments at *m/z* 391, 343, 301, 287, 273, and 247 [13]. The compounds **28** and **33** were detected at the same molecular ion at *m/z* 593 $[M-H]^-$ and showed MS^2 fragments at *m/z* 557, 467, 441, 425, 407, and 289, hence proposed to be (epi)gallocatechin-(epi)catechin [9].

Also, compounds **45** and **49** that were detected at retention times 11.40 and 12.78, respectively, have been identified as (epi)gallocatechin (**45**) [9] and Epigallocatechin-3-*O*-cinnamate (**49**) [14] depending upon MS and MS^2 fragments at *m/z* 305 $[M-H]^-$, 261, 219, 221, 179, 165, and 125 (**45**) and *m/z* 437 $[M+H]^+$, *m/z* 307 and 181 (**49**), respectively. Additionally, three compounds (**50**, **56**, and **61**) which were detected at different retention times displayed the same $[M-H]^-$ at *m/z* 471 and were suggested to be methyl-3-*O*-gallocatechin gallate (**50**) (MS^2, *m/z* 441, 407, 313, 303, 287, 269, 257, 243, and 161), methyl-3-*O*-epigallocatechin gallate (**56**) (MS^2, *m/z* 441, 407, 303, 288, 257, 243, 201, 169, and 161), and methyl-3-*O*-epigallocatechin gallate isomer (**61**) (MS^2, *m/z* 441, 407, 297, 269, 241, 213, 199, 168, and 161), respectively [13]. Compounds **57** that detected at retention time 14.37 exhibited $[M-H]^-$ at *m/z* 633 and MS^2 fragments at *m/z* 481 and 305 due to the loss of galloyl (−152 amu) and glucuronide moieties (−176 amu), hence has been identified as (epi)gallocatechin-*O*-gallate-*O*-glucuronide (**57**). The compounds **65** and **71** that provided the same molecular ions *m/z* 617 $[M-H]^-$ and MS^2 fragments at *m/z* (599 $[M-H_2O]^-$, 465 $[M-152]^-$, 289 $[M-152-176]^-$) were suggested to be (epi)catechin-*O*-gallate-*O*-glucuronide and its isomer upon comparison with the published data [15]. Furthermore, gallocatechin derivatives were tentatively assigned for compounds **69** and **72** based on the protonated molecular ion at *m/z* 455, and MS^2 fragments *m/z* 307, 179, and 137 as reported [16]. Dimethyl (epi)catechin was designated for peak **87** that displayed deprotonated molecular ion at *m/z* 317 and MS^2 fragment ions at 299, 289, 273, and 245 [16].

Fatty acids/derivatives

Compound **5** was proposed to be 3′-(4″-methoxyphenyl)-3′-oxo-propionyl hexadecanoate as previously reported [10]. Several octadecanoic acid derivatives (**36**, **38**, **40**, **43**, **46**, **55**, **66**, **90**, and **91**) were detected mainly in the ethyl acetate fraction of *C. macrocarpa* at different retention times and different molecular ions with characteristic MS^2 fragmentation, which may be due to loss of H_2O, COOH, and H_2O+COOH leading to $[M-18]^-$, $[M-45]^-$, and $[M-63]^-$, respectively, and successive loss of CH_2 (−14 amu) [17] . In addition, linoleic (**86**) and palmitic acids (**92**) were identified based on their molecular ions, and fragmentation patterns (Table 3, main manuscript) referenced to published literature [18].

Sterols and triterpenes/derivatives

β-Sitosterol (**52**) and stigmasterol (**96**) were identified in the ethyl acetate soluble fraction by their molecular ions *m/z* 411 $[M-H]^-$ and *m/z* 413 $[M+H]^+$ [19,20]. Furthermore, the current study detected several triterpenoid aglycones at different retention times, such as compounds **62**, **80**, **81**, and **82**. Whereas, hydroxybetulinic acid (**62**) had molecular ion at *m/z* 471 $[M-H]^-$ with characteristic MS^2 fragments at *m/z* 453, 435, 407, and 389 [21]. Additionally, compounds **80**, **81**, and **82** provided the same molecular ion at *m/z* 455 $[M-H]^-$, MS^2 fragment ions (*m/z* 439, 419, 411, 410, 407, and 397) and designated as ursolic acid, carissic acid, and oleanolic acid upon comparison with the literature [18,22]. Moreover, 3*β*-hydroxyolean-11-en-28,13*β*-olide (**51**) and methyl oleanolate (**67**) exhibited protonated molecular ions at *m/z* 455 and 471, respectively [18,21]. Other pentacyclic triterpenoids that detected at retention time 15.46 (**68**) and 15.92 (**73**) are 3,27-dihydroxy-12-ursen-28-oic acids (3*β*-form), and 27-(4-Hydroxy-3-methoxycinnamoyl) (*E*-form), and its isomer, where they provided the same deprotonated molecular ion at *m/z* 647 with MS^2 fragments at *m/z* 485, 470, 455, and 440 [18].

Miscellaneous

Lignans such as carinol (**1**) *m/z* 377 $[M-H]^-$ and MS^2 at 333, 271, 257, 163, and 119 and carissanol (**84**) *m/z* 375 $[M-H]^-$ and MS^2 at *m/z* 361, 347, 294, and 123 were assigned for (**1**) and (**84**) depending on a comparison

of their data with that previously reported [10]. Secoiridoid, which is also known as oleuropein aglycone (**41**), exhibited deprotonated molecular ion at *m/z* 377 with MS^2 fragments at *m/z* 345 $[M-CH_3OH]^-$, 327 $[M-CH_3OH-H_2O]^-$ [10]. Furthermore, sesquiterpenes such as dehydrocarissone which is known as 11-hydroxy-1,4-eudesmadien-3-one (**3**), cryptomeridiol (**4**), germacrenone (**85**) were identified based on MS, MS^2 and referenced to the published data [10,21]. Compound **101** with *m/z* 621 $[M-H]^-$ and distinctive fragment ion at 501 was assigned as 2(R)-26-([(2*E*)-3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yloxy)-2,3-dihydroxypropylester [23]. Finally, compound **102** that detected at retention time at 31.25 gave a molecular ion at *m/z* 429 $[M-H]^-$ and 431 $[M+H]^+$ with characteristic MS^2 fragments at *m/z* 205, 191, 177, 149, 121, hence assigned as α-tocopherol [24].

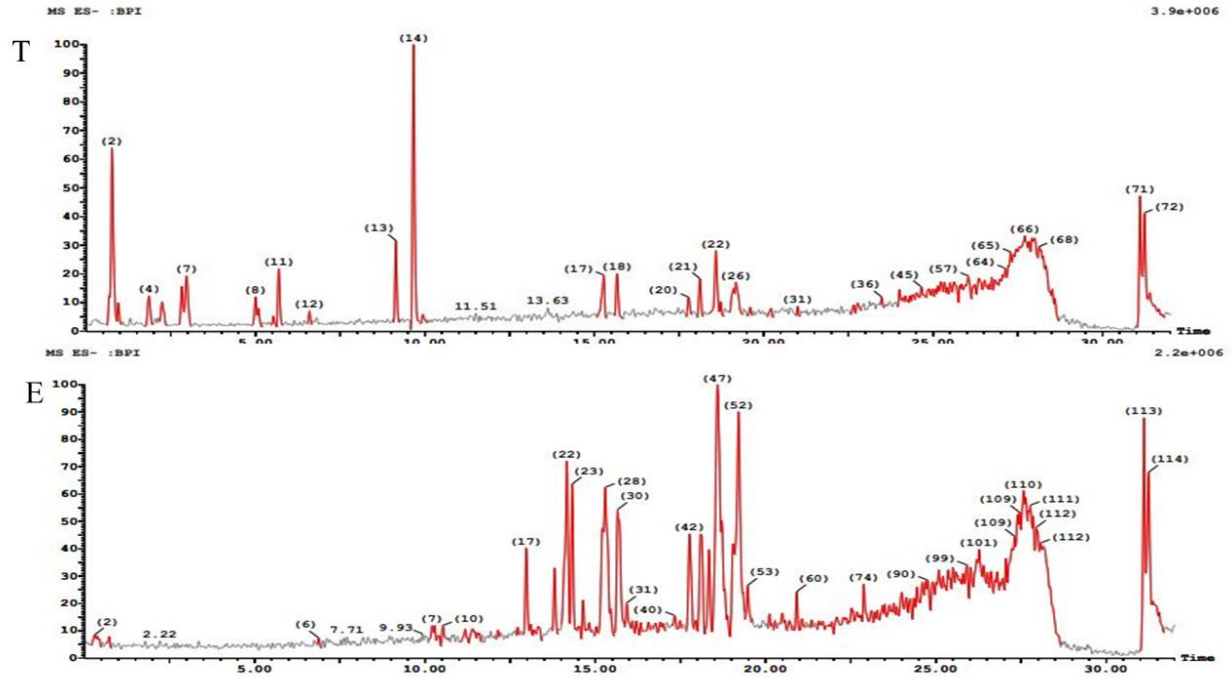

Figure S1. TIC of *Carissa macrocarpa* leaves total hydro-methanolic extract (**T**) and its ethyl acetate fraction (**E**) using UPLC-ESI-MS/MS in negative ionization mode.

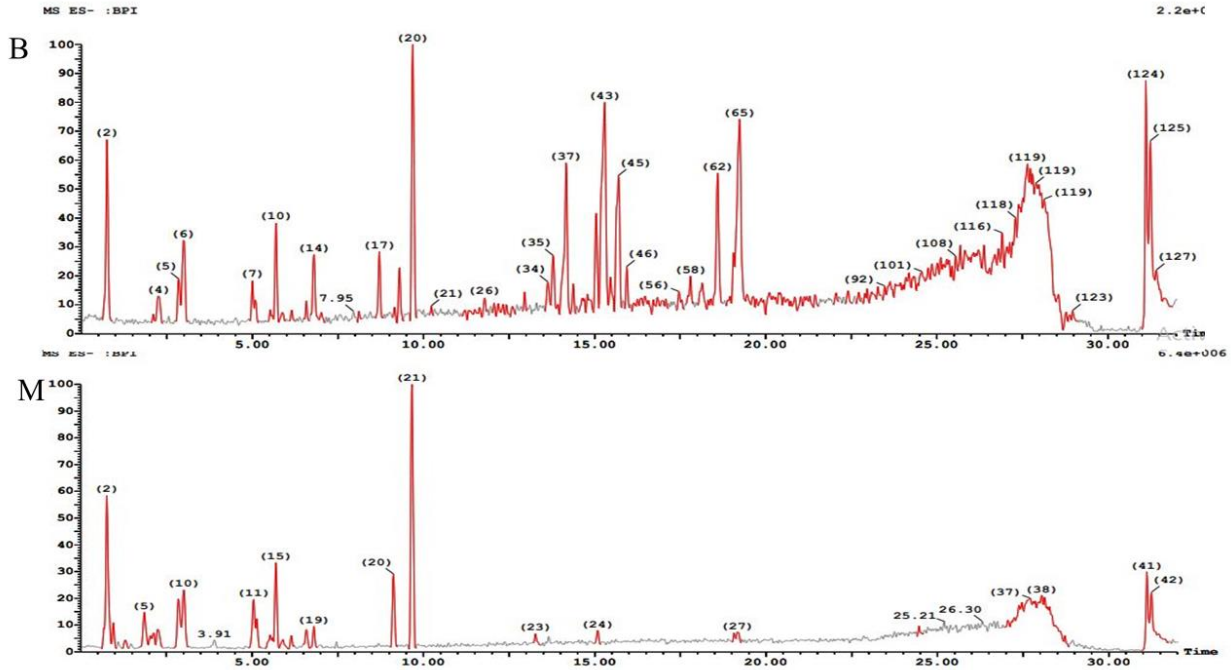

Figure S2. TIC of *Carissa macrocarpa* butanol (**B**), and methanol (**M**) fractions, using UPLC-ESI-MS/MS in negative ionization mode.

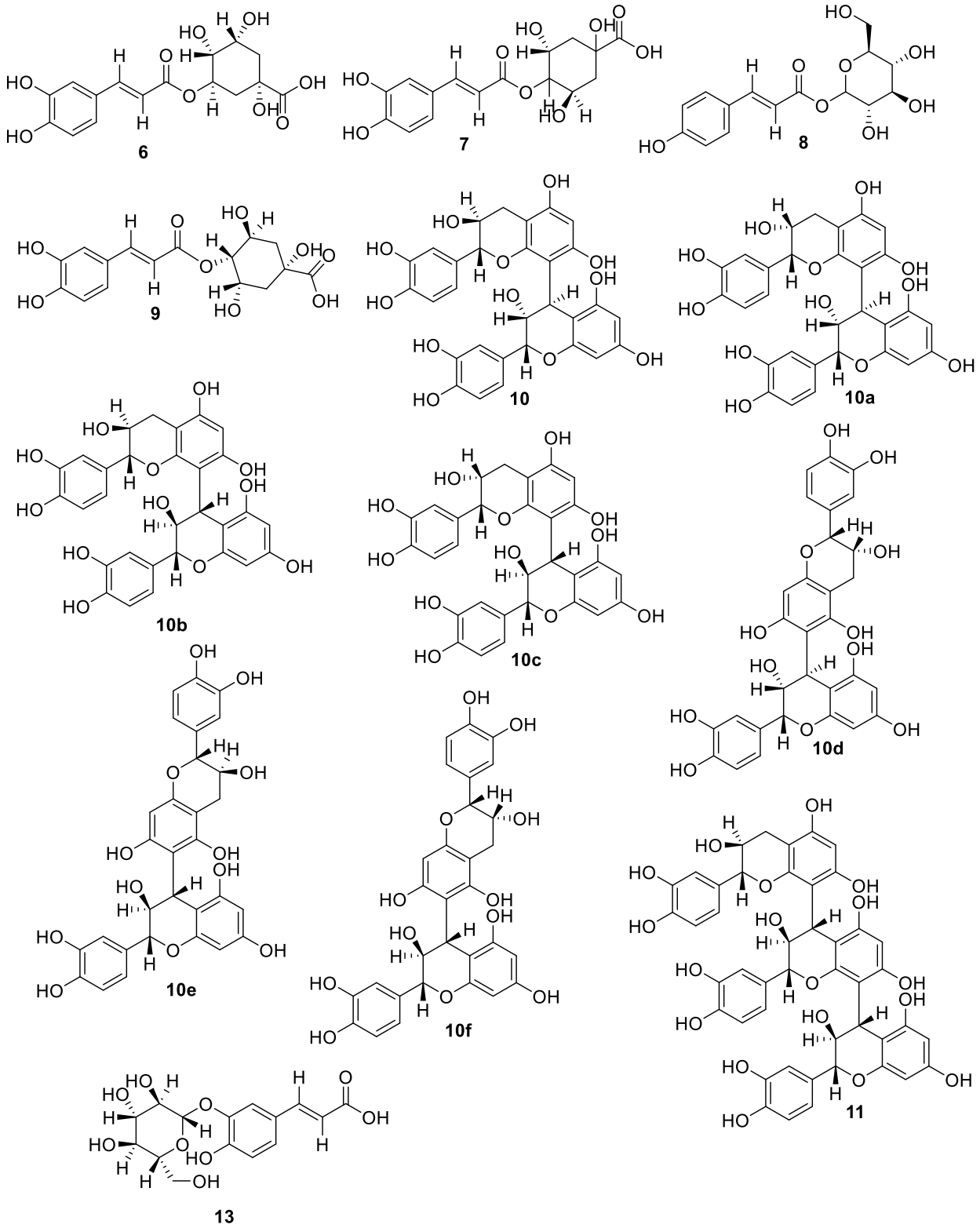

Figure S3. Structures of identified compounds and their isomers evaluated by molecular docking simulation.

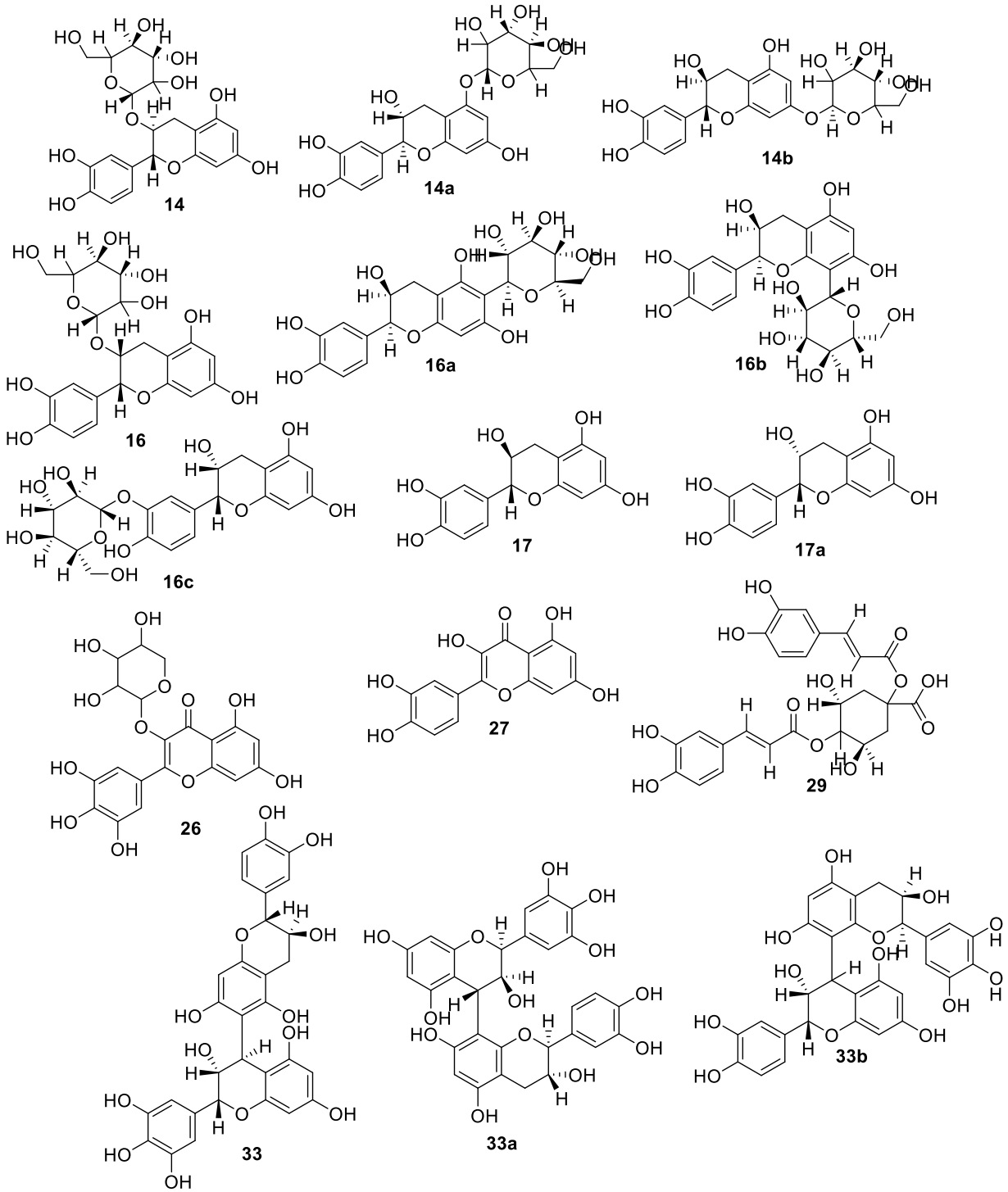

Figure S4. Continue structures of identified compounds and their isomers evaluated by molecular docking simulation.

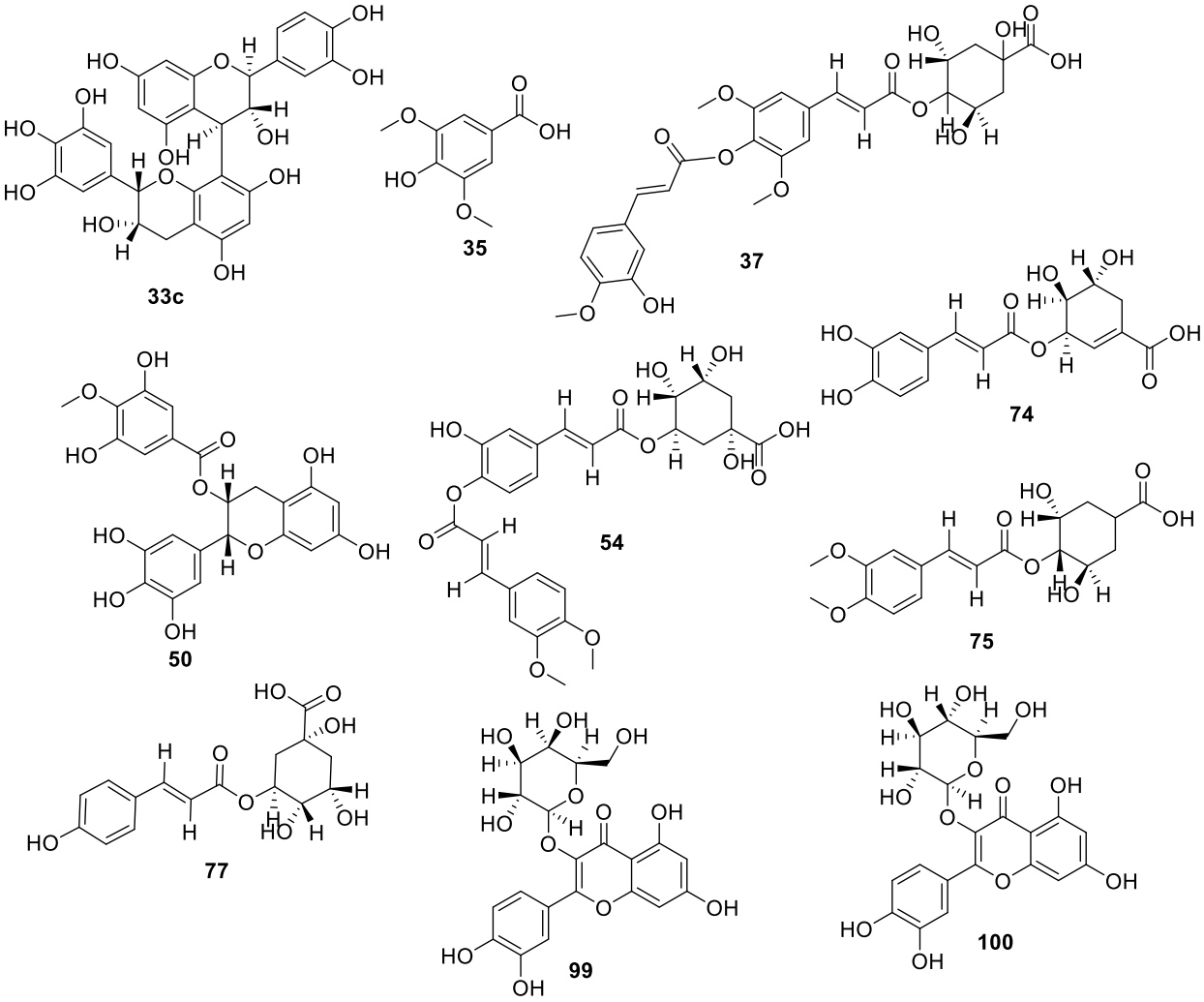

Figure S5. Continue structures of identified compounds and their isomers evaluated by molecular docking simulation.

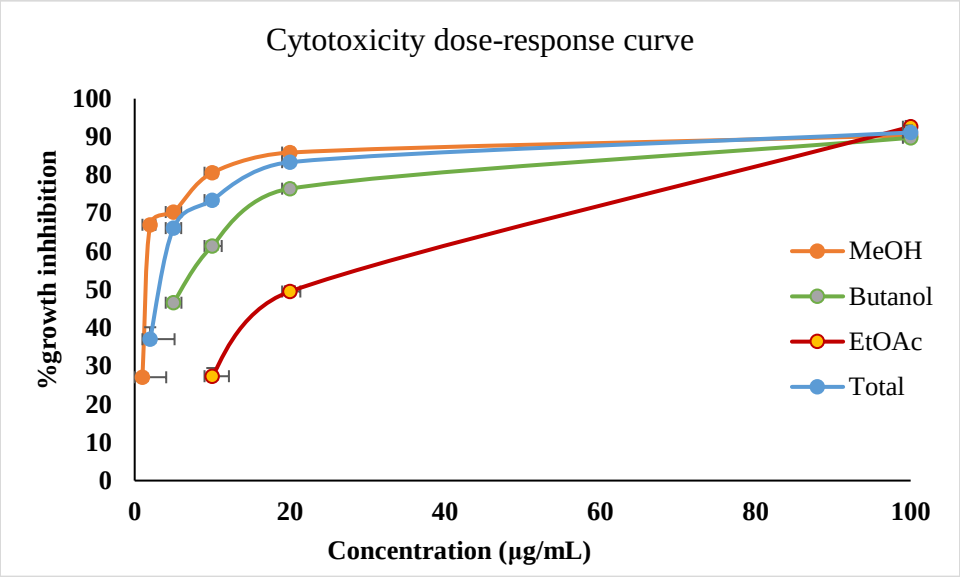

Figure S6: Dose-response curves of total extract and fractions of *C. macrocarpa* against A549 cell line.

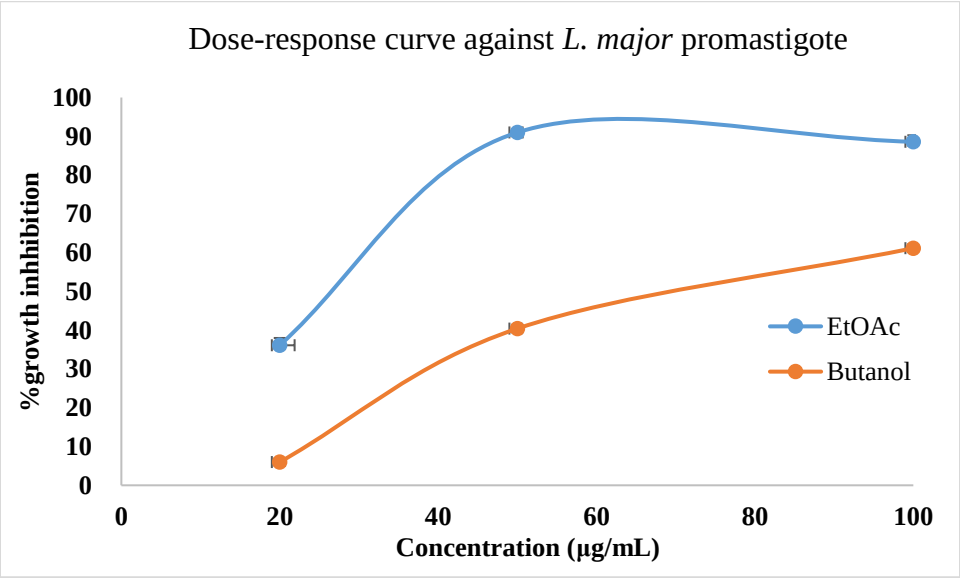

Figure S7: Dose-response curves of total extract and EtOAc and butanol fractions of *C. macrocarpa* against *L. major* promastigote.

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