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Bioguided isolation and feature-based identification of bioactive molecules from *Fagraea berteriana* targeting dermal papilla cells and the Wnt pathway.

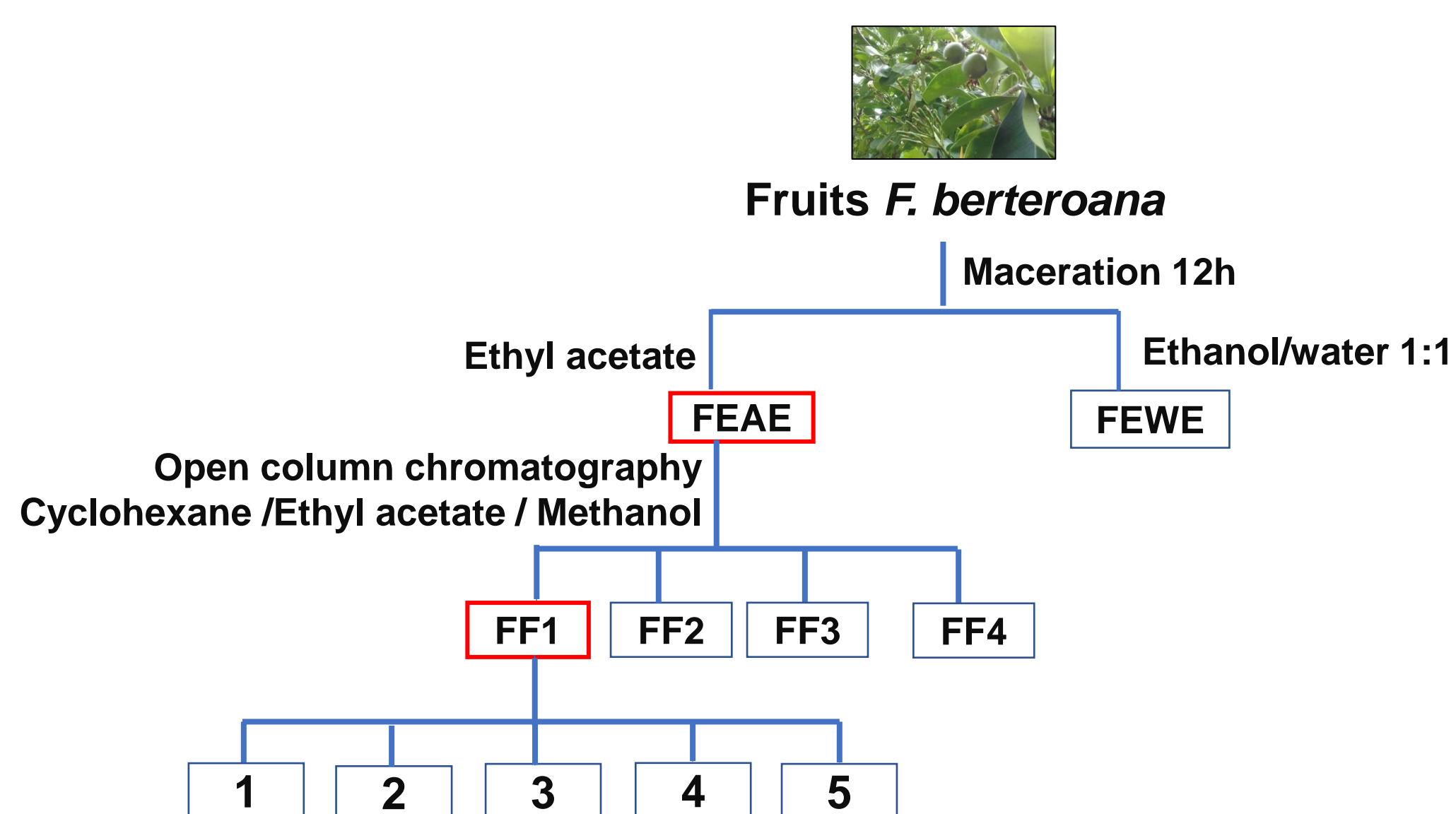
Kristelle Hughes^a, Raimana Ho^b, Stéphane Greff^c, Gaëtan Herbette^d, Edith Filaire^e, E. Ranouille^e, Jean-Yves Berthon^e and Phila Raharivelomanana^{c*}

^a Pharmacognosy Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Avenue E. Mounier 72, B1.72.03, B-1200 Brussels, Belgium; ^b SECOPOL, UMR 241, University of French Polynesia, BP 6570, 98702 Faa'a, French Polynesia; ^c IMBE, UMR 7263 CNRS, IRD, Aix Marseille, Avignon Université, rue de la Batterie des Lions, 13007 Marseille, France; ^d Aix Marseille Université, CNRS, Centrale Marseille, FSCM, Spectropole, Service 511, Campus Saint-Jérôme, 13397 Marseille, France; ^e Greentech SA, Biopôle Clermont-Limagne, 63360 Saint-Beauzire, France.

INTRODUCTION: *Fagraea berteriana* (Gentianaceae) is a small tree, whose scented flowers are used in French Polynesia as fragrance in the preparation of monoi [1]. More unconventionally, its ground fruits were used on cadavers to prevent hair loss [2]. Our aim was to identify the bioactive chemical constituents of the fruits of *F. berteriana* and their potential effect on the hair growth cycle.

METHODOLOGY

Bioguided isolation of compounds

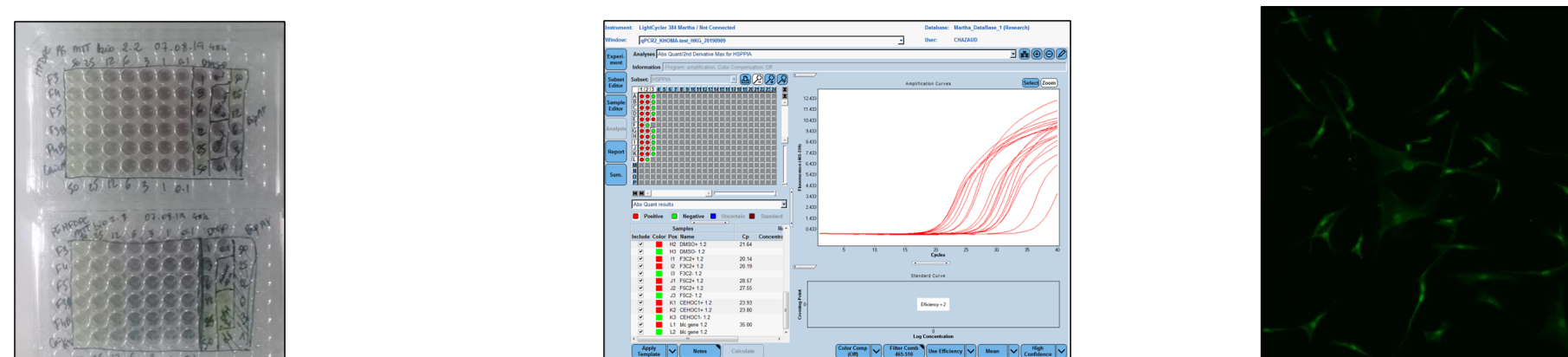


Bioassays

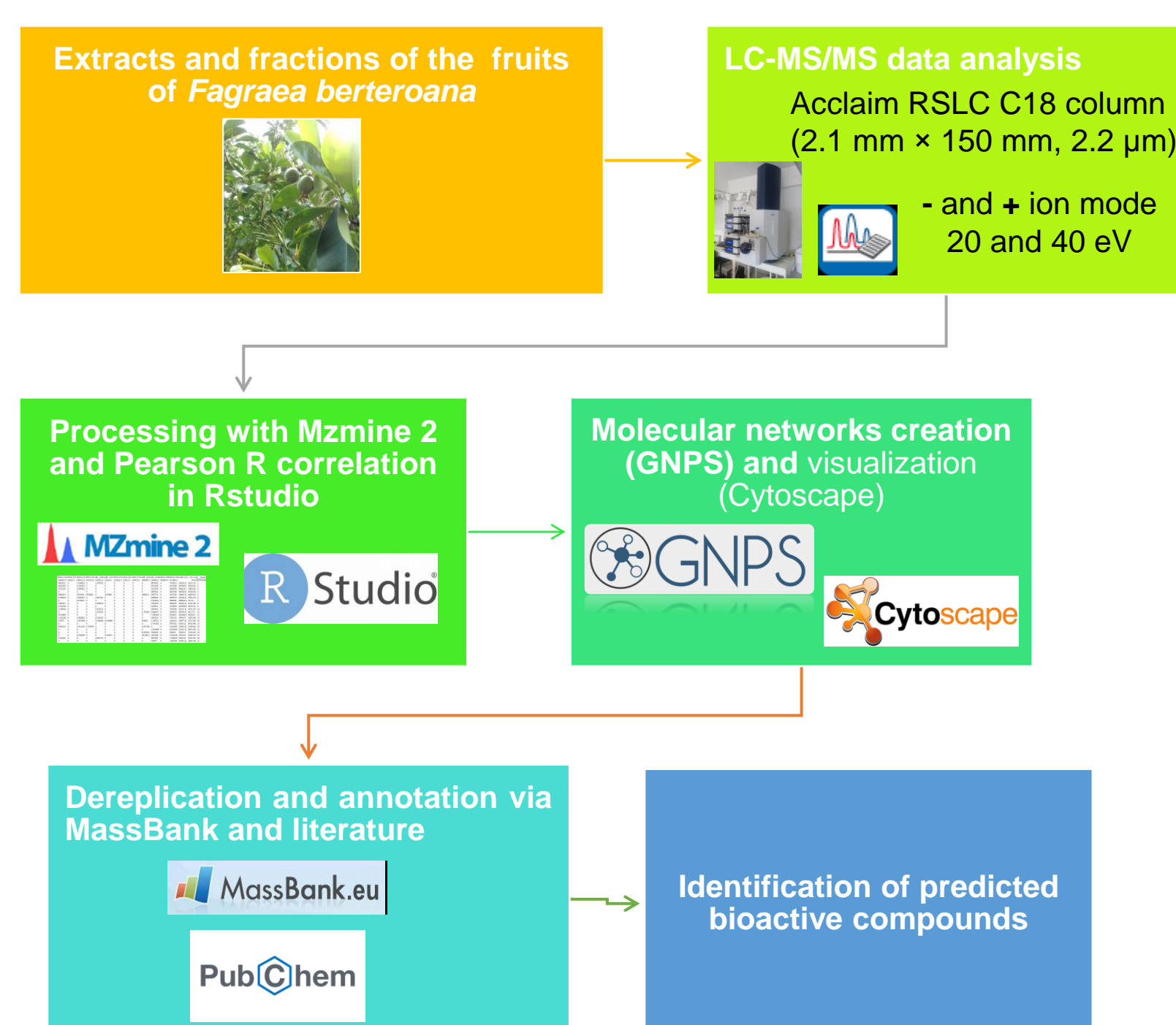
MTT assay for dermal papilla cells viability determination after 48h of treatment with samples (50 to 0.1 µg/ml)

RT-qPCR analysis of CND1, BMP2, TGFB1 after 48h of dermal papilla cells treatment with 50 µg/ml of samples

Immunofluorescence staining of nuclear β-catenin after 72h of treatment with 50µg/ml of FF1



Compound annotation and bioactivity scoring



CONCLUSION

The bioassay guided fraction of the fruits of *F. berteriana* highlighted a low polarity fraction, FF1, that appears to target the Wnt/β-catenin pathway and BMPs in dermal papilla cells, suggesting a role in the regulation of the hair follicle cycle.

The fraction was shown to possess iridoids, seco-iridoids, and pentacyclic triterpenes that could be responsible for the bioactivity observed. These results propose *Fagraea berteriana* as a promising candidate for future studies in the search for hair growth-promoting natural ingredients.

RESULTS

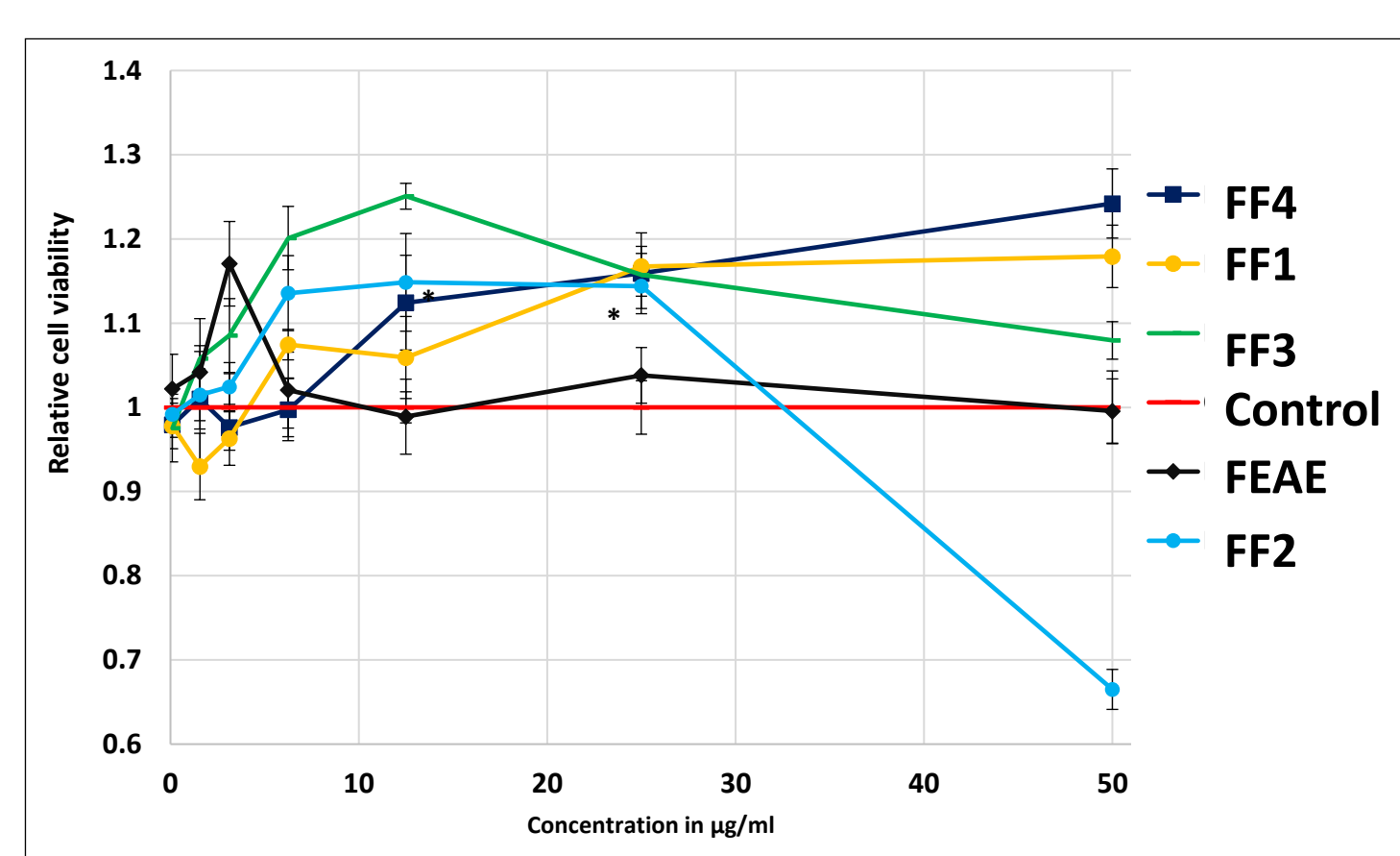


Figure 1. Cell viability profiles of dermal papilla cells after 48h of treatment with samples or DMSO.

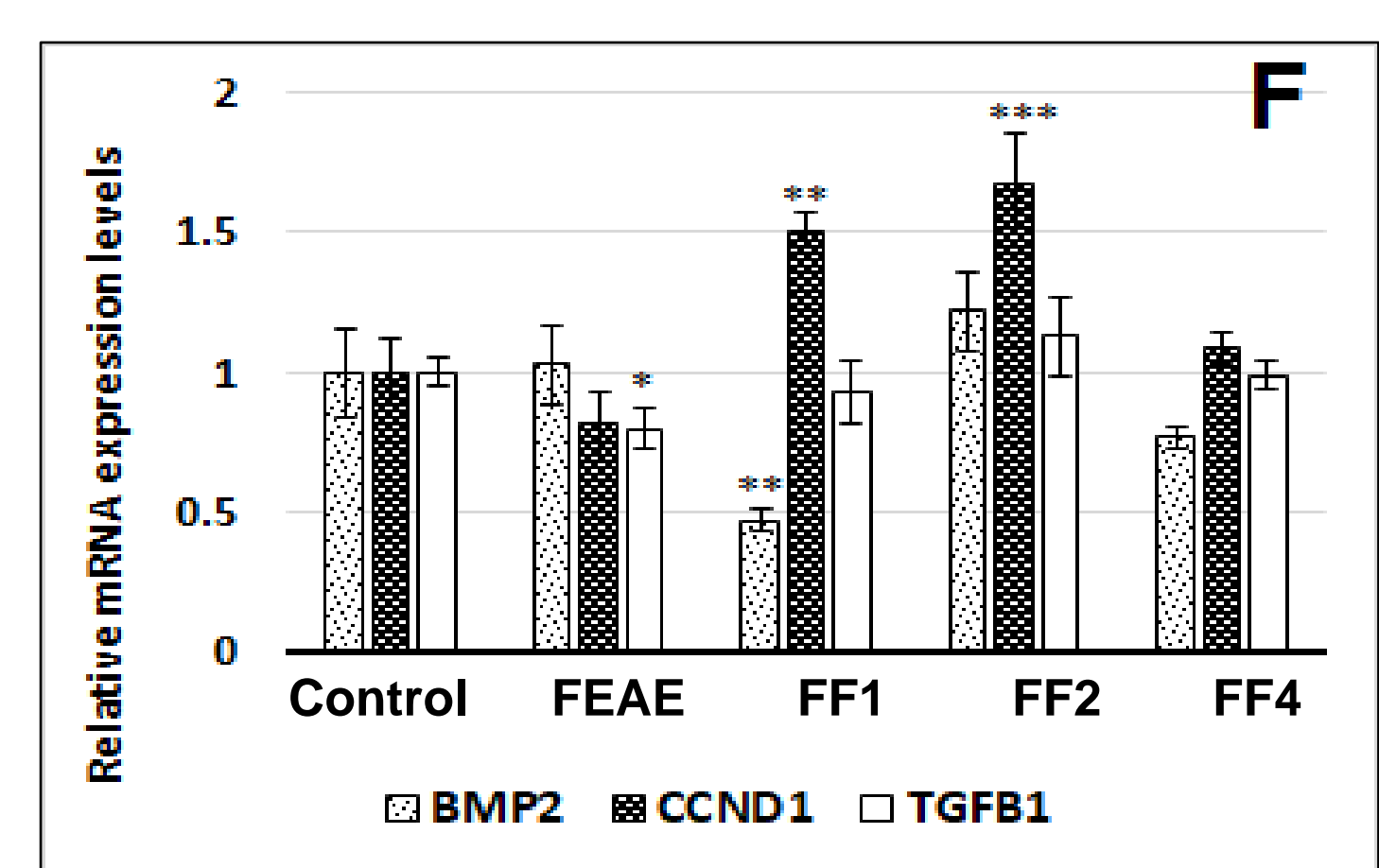


Figure 2. Regulation of relative mRNA expression of BMP2, CCND1 and TGFB1 ± S.E after 48h of treatment with samples at 25 or 50 µg/ml. Significance is determined by * p < 0.05, ** p < 0.01, *** p < 0.001 and **** p < 0.0001

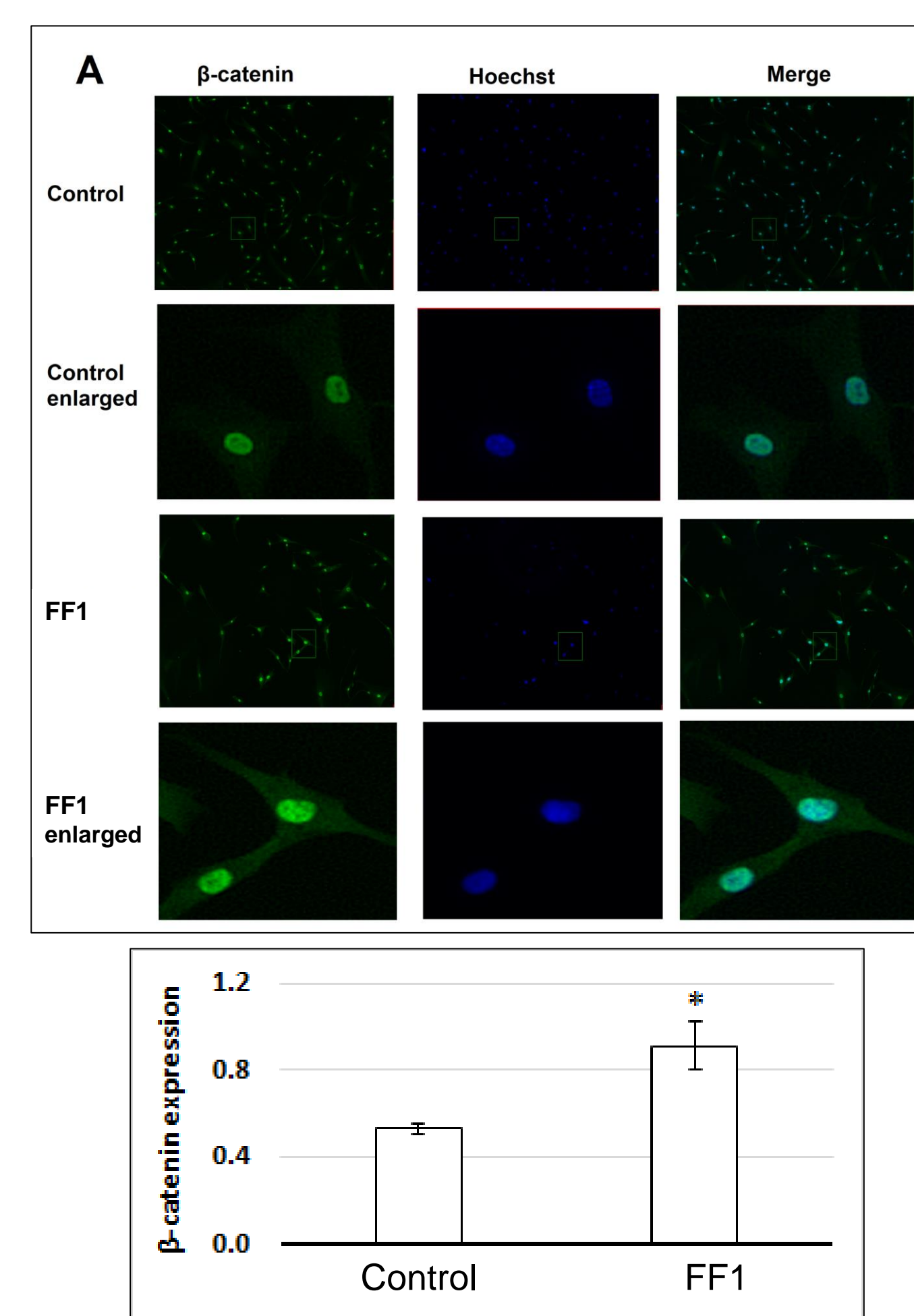


Figure 3. Nuclear β-catenin protein expression ± S.E after 72h of treatment with FF1 at 50 µg/ml. Significance is determined by * p < 0.05.

F. berteriana extract FEAE and fractions FF1, FF3 and FF4 at 50 µg/ml, induced hair follicle dermal papilla cell viability comparable or higher than DMSO-treated control (**Figure 1**).

FF1 was most active (**Figure 2**) as it showed a significant 1.5x increase in CCND1 mRNA levels with a simultaneous 2x decrease of BMP2 levels compared to DMSO treated cells. Further testing revealed that FF1 significantly increased β-catenin nuclear levels (**Figure 3**). This is indicative of an active Wnt/β-catenin pathway and a potential inhibition of BMPs which lead to preserving the anagen phase during which the hair follicle is able to grow and elongate and inhibiting the apoptotic catagen phase.

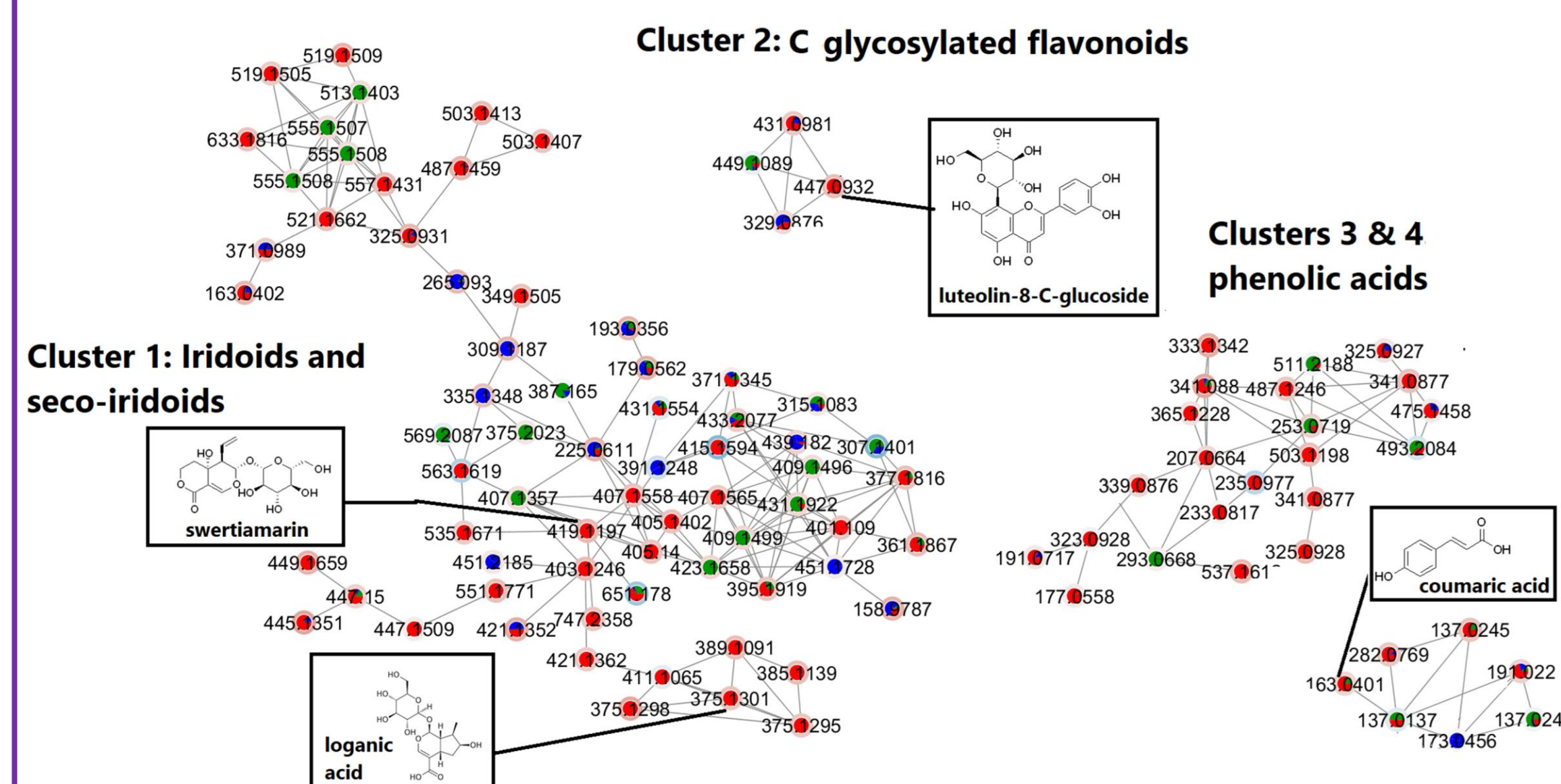


Figure 4. Several clusters of molecular network of features detected in *F. berteriana* extracts and fractions (red nodes) in negative ionization mode. Red node borders indicate correlation to proliferation of dermal papilla cells.

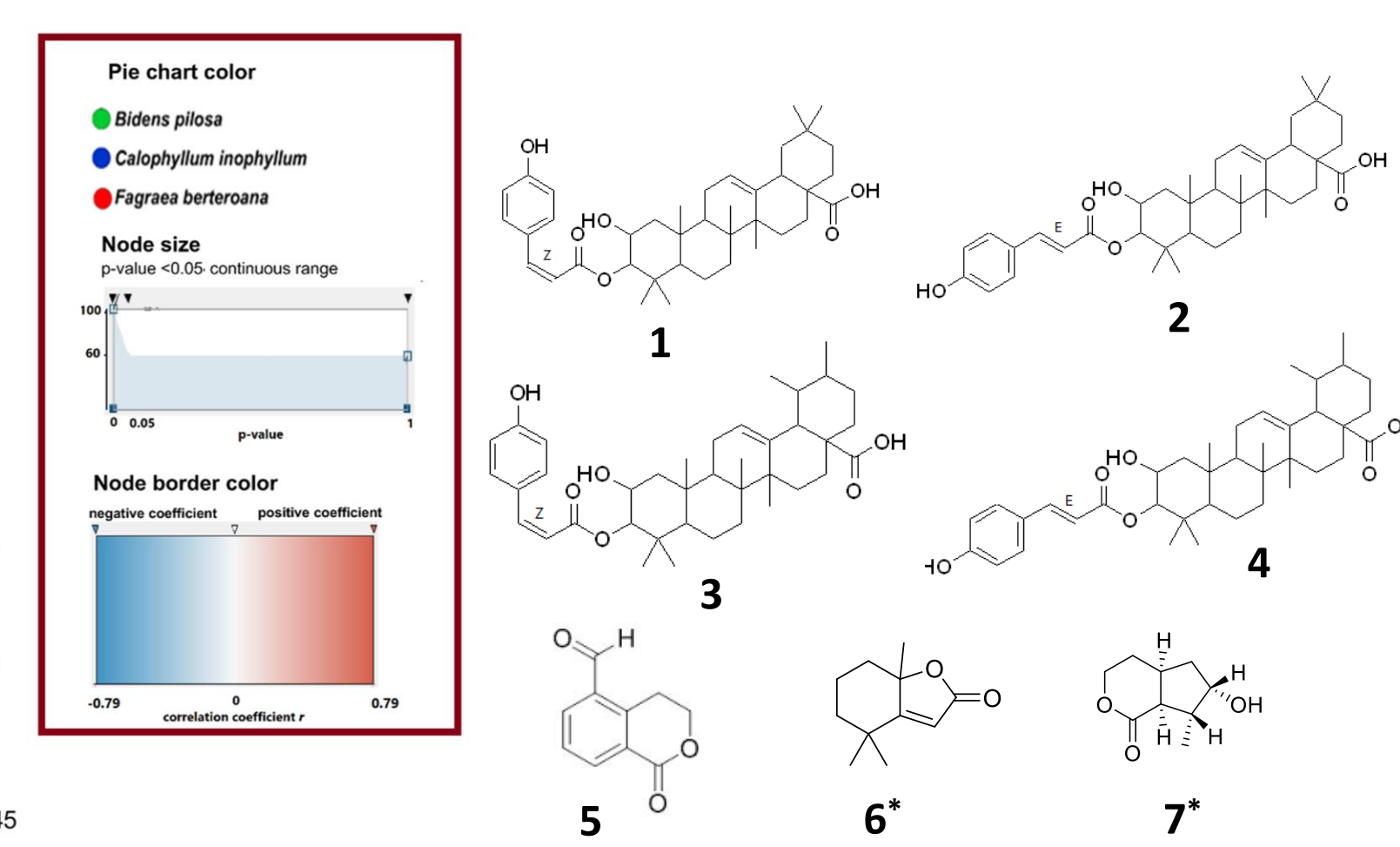


Figure 5. Metabolites isolated (1-5) from FF1 or annotated (6-7) in pos ionization LC-MS/MS analysis

According to the bioactivity scoring predictions, iridoids and secoiridoids such as swertiamarin and loganic acid were predicted to induce dermal papilla cells proliferation as well as C-glycosylated flavonoids, like luteolin-8-C-glucoside and phenolic acids such as coumaric acid (**Figure 4**).

The structures of *cis*- and *trans* *p*-coumaroylmaslinic acids (**1 & 2**) and *cis*- and *trans*-*p*- coumaroyl corosolic acids (**3 & 4**) were identified by NMR analysis after isolation from bioactive fraction FF1, as well as erythrocentaurin (**5**). Dihydroactinidiolide (**6**) and boonein (**7**) were tentatively identified by comparison of their fragmentation data with literature after LC-HRMS/MS analysis of FF1 (**Figure 5**).