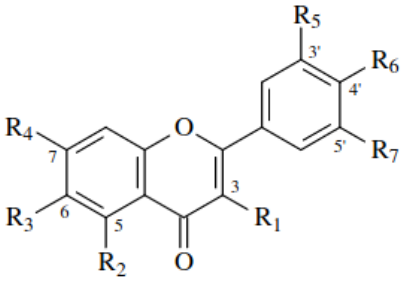
Traitement de mélanomes par flavonoïdes

Basé sur le travail de Raimundo Gonçalves de Oliveira-Júnior et al. : « Polymethoxyflavones from Gardenia oudiepe (Rubiaceae) induce cytoskeleton disruption-mediated apoptosis and sensitize BRAF-mutated melanoma cells to chemotherapy », Chemico-Biological Interactions, Volume 325, 2020, https://doi.org/10.1016/j.cbi.2020.109109.

Une série de 10 flavonoïdes sont obtenus à partir de la Rubiacée *Gardenia oudiepe*, une plante endémique de Nouvelle Calédonie. Ces molécules ont une activité cytotoxique que l'on cherche à exploiter pour traiter les mélanomes. On teste ici leur efficacité respective.

Un commentaire organisé des figures et tableaux est attendu. Des questions supplémentaires sont spécifiées sous les documents
N'hésitez pas à demander de l'aide si des problèmes de vocabulaire se posent.

Table 1. Chemical structures and antiproliferative activity of compounds **1-10**.

Substitution pattern	Compound (PMF)	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Antiproliferative activity (%)
	**1**	OMe	OH	OMe	OH	H	OH	H	18.55 ± 5.16
	2	OMe	OH	OMe	OH	H	OMe	H	66.53 ± 5.71
	3	OMe	OH	OMe	OH	OMe	OMe	OH	42.86 ± 8.27
	4	OMe	OH	OMe	OH	OMe	OMe	OMe	5.68 ± 5.00
	5	OMe	OH	H	OH	H	OH	H	22.29 ± 6.69
	6	OMe	OH	H	OH	OMe	OMe	OH	20.80 ± 6.50
	7	OMe	OH	H	OMe	OMe	OMe	OH	29.48 ± 4.95
	8	OMe	OH	H	OMe	H	OMe	H	29.79 ± 9.77
	9	OAc	OH	H	OAc	H	OAc	H	7.04 ± 7.39
	10	OAc	OAc	H	OAc	H	OAc	H	10.13 ± 5.27

Mean ± SEM of at least 3 determinations. PMF: polymethoxyflavone. All compounds were tested at 10 µM.

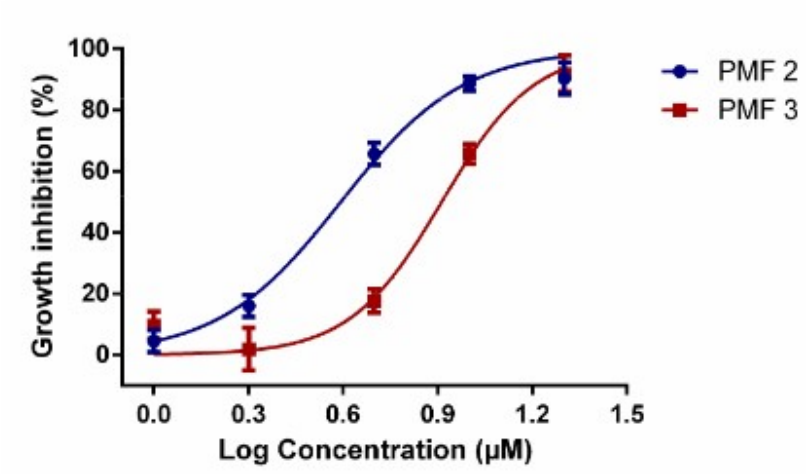


Figure 1. Effect of PMFs **2** and **3** on A2058 melanoma cells viability. Cells were cultured in the presence of increasing concentrations of molecules (1 – 20 µM) for 72h and then cell viability was determined by the MTT assay. Results are expressed as mean ± SEM of at least three independent measurements.

Wikipedia : The MTT assay is a colorimetric assay for assessing cell metabolic activity.

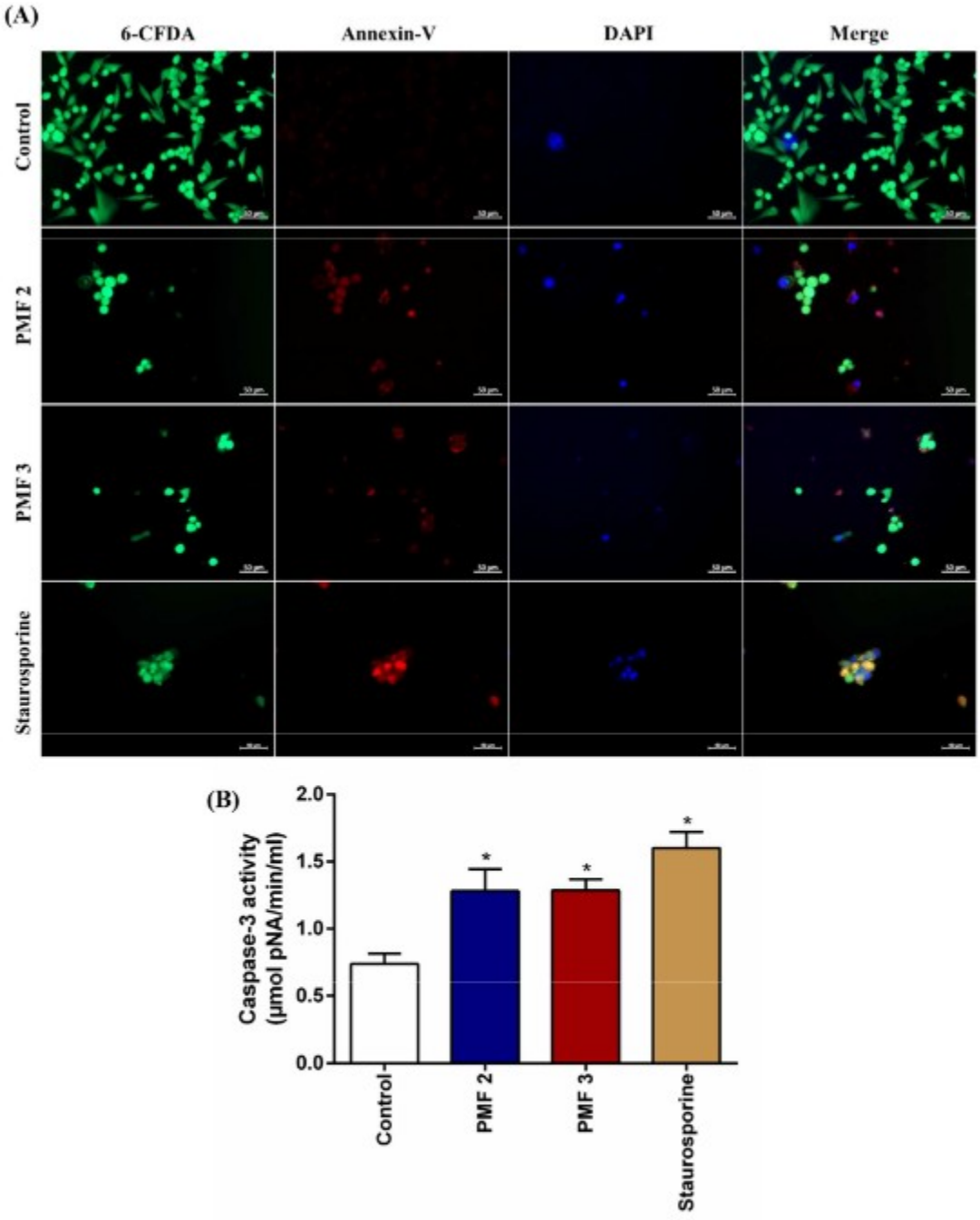


Figure 2. Pro-apoptotic effect of PMFs **2** (4 µM, ~IC_{50}) and **3** (8 µM, ~IC_{50}) on A2058 melanoma cells. (A) Photomicrographs were obtained after 72h of treatment using Annexin-V/6-CFDA double staining + DAPI for DNA staining of permeable cells. (B) Caspase-3 activity was determined by colorimetric assay. Staurosporine (2 µM, 4h) was used as positive control. Data are expressed as mean ± SEM, *p< 0.05 (*vs.* control group), according to ANOVA one-way followed by Tukey's post-test (n=3).

DAPI colore l'ADN des cellules perméables, l'Annexin-V se lie à la phosphatidylsérine présente à dans l'hémimebrane externe des celulles et le 6-CFDA induit une fluorescence des cellules vivantes.
Comment ces colorations permettent-elles la mise en évidence d'une apoptose induite ?

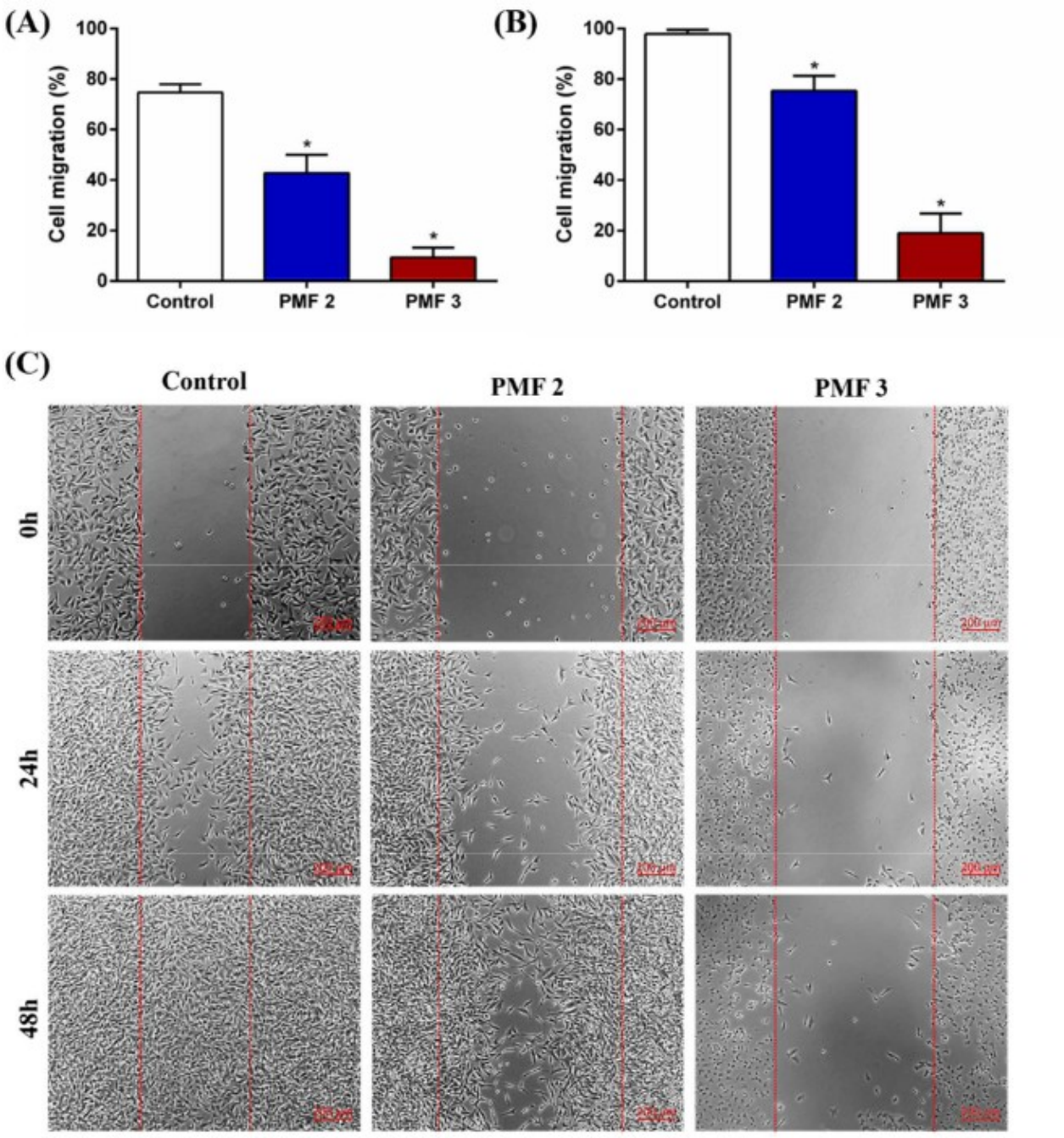


Figure 4. Effect of compounds **2** (2 µM, ~½IC_{50}) and **3** (4 µM, ~½IC_{50}) on cell mobility after 24h (A) and 48h (B) of treatment. Photomicrographs illustrate cell migration into the zone free of cells according to the treatment (C). Data are expressed as mean ± SEM, *p<0.05 (ANOVA one-way followed by Tukey's post-test), from at least three independent measurements.

Proposez des hypothèses sur le mécanisme d'inhibition de la motilité.
Pourquoi la motilité des cellules est-elle un paramètre important dans le traitement du cancer ?

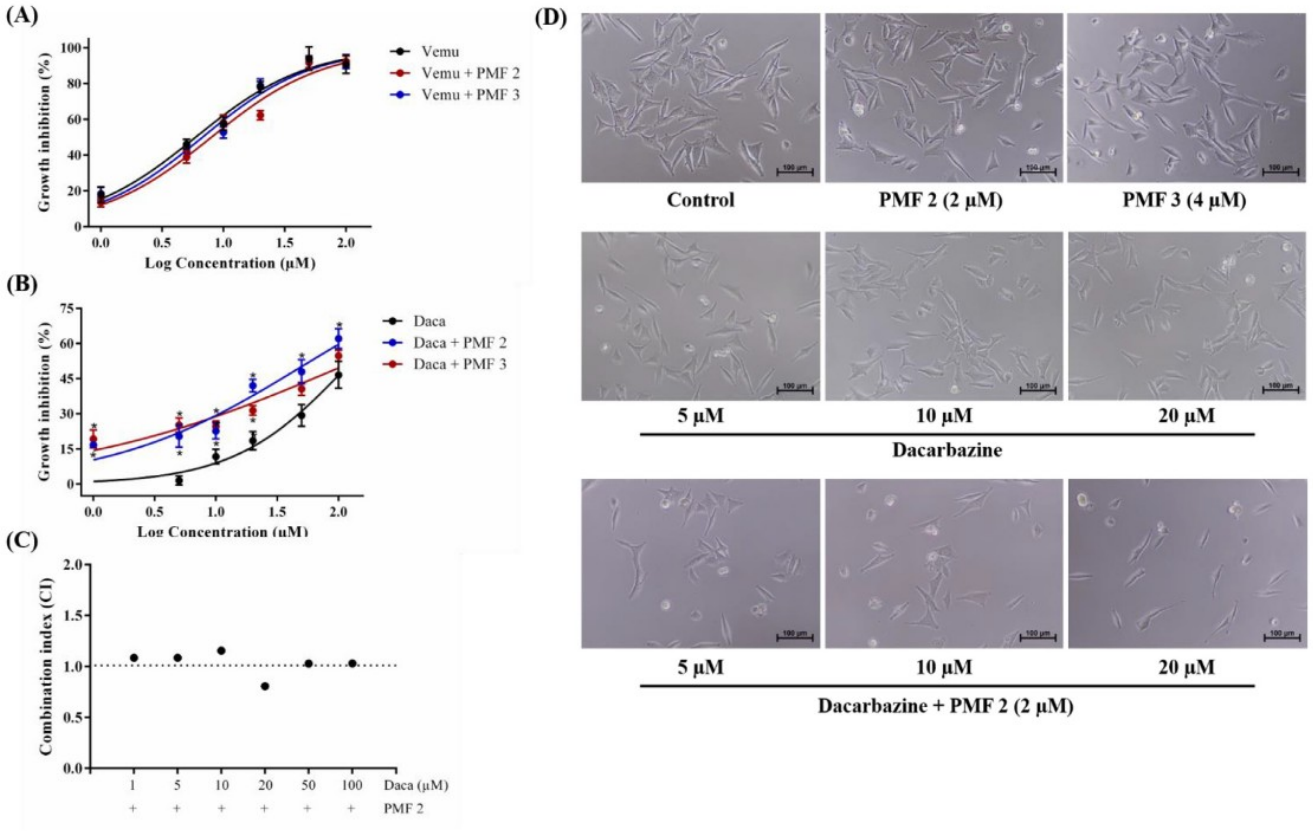


Fig. 11. Chemosensitizing effect of PMFs **2** and **3** on A2058 cells. (A): antiproliferative effect of vemurafenib (Vemu, 1–100 μM) alone or in the presence of compounds **2** and **3** (~½IC_{50}). (B): antiproliferative effect of dacarbazine (Daca, 1–100 μM) alone or in the presence of compounds **2** and **3** (~½IC_{50}). (C): combination index for the association of dacarbazine with PMF **2**. (D) photomicrographs show reduction of cell density promoted by combined therapy, compared to monotherapies and control group. Results are expressed as mean ± SEM, $^*p < 0.05$ according to unpaired Student's *t*-test, from at least three independent measurements.

Étude de l'effet combiné des molécules d'intérêts avec d'autres médicaments connus.

Proposez une analyse critique du document. (On ne s'intéressera pas à la figure C).