Supplementary Table 3: Anticancer activity of phenolic compounds identified in tested ferns.

Compound	Inhibition of viability (IC_{50} in µM or % of dead cells) after 48 or 72h												References
	HeLa	HepG2	SMMC-7221	SW480	HCT116	HT29	SW 1116	C6	MCF7	K562	HL60	Positive control*	Non-cancerous	
Caffeic acid				161 µg/mL								242.6 (5-FU)		Villota et al., 2021
					10% at 20 µg/mL									Jayaprakasam et al. 2006
				40% at 50µM		28% at 50µM			27% at 50µM			20-40% at 30µM (G)		Hudson et al., 2000
	n.a. ≤ 50 µg/mL											17.5 µg/mL (5-FU)		Sun et al., 2006
	547											20.8 (5-FU)		Hemaiswarya & Doble, 2013
	155 µg/mL					158 µg/mL			270 µg/mL				163 (Vero)	Sevimli-Gur & Yesil-Celiktas, 2019
				3470										Castrillón et al., 2019
Chlorogenic acid				≥ 200										Cattivelli et al., 2023
				598 µg/mL								242.6 (5-FU)		Villota et al., 2021
	678											20.8 (5-FU)		Hemaiswarya & Doble, 2013
	n.a. ≤ 10													Frei et al., 2024)
	25.5	23.6												Nawaz et al., 2024
Ferulic acid	403					412		314				400-471 (Cis)	473 (Vero)	Erenler et al., 2017
	167 µg/mL					147 µg/mL			117 µg/mL				163 (Vero)	Sevimli-Gur & Yesil-Celiktas, 2019
	880								3970				2800 (Vero)	Saenglee et al., 2016
	323											20.8 (5-FU)		Hemaiswarya & Doble, 2013
					14% at 20 µg/mL				8% at 20 µg/mL					Jayaprakasam et al., 2006
				n.a. ≤ 50		n.a. ≤ 50			11% at 50µg/mL			20-40% at 30µM (G)		Hudson et al., 2000
p-Coumaric acid		≥ 200	55.0	≥ 200			43.5			40.2	≥ 200	0.51 - 8.19 (A)		Yao et al., 2011
	11 µg/mL					25 µg/mL			228 µg/mL				163 (Vero)	Sevimli-Gur & Yesil-Celiktas, 2019
	39.5	82.2			27.5				95.0			7.7-9.3 (Dox)		El Molla et al., 2016)
	≥1250	≥1250							1153			0.91-3.22 (El)		Heleno et al., 2014
	940								4470				2890 (Vero)	Saenglee et al., 2016

	729										20.8 (5-FU)		Hemaiswarya & Doble, 2013
				n.a. ≤ 50		13% at 50µM		n.a. ≤ 50			20-40% at 30µM (G)		Hudson et al., 2000
Proto-catechuic acid				n.a. ≤ 50		n.a. ≤ 50		n.a. ≤ 50			20-40% at 30µM (G)		Hudson et al., 2000
	n.a. ≤ 50 µg/mL										17.5 µg/mL (5-FU)		Sun et al., 2006
	40.6 µg/mL					97.5 µg/mL		19.7 µg/mL			0.07 (MCF7; Tax)		Elansary et al., 2020
Rosmarinic a.	233					262	251				400-471 (Cis)	279 (Vero)	Erenler et al., 2017
Kaempferol				cca 80									Wang et al., 2004
		n.a. ≥ 100								39.6	5.4 (Dox)		Bai et al., 2010
		46.2						27.8			3.07-4.51 (A)		Ahmed et al., 2016)
		38.6									0.17 (Dox)		Yang et al., 2018
				≥ 100	56.2						34.7 (Dec)		Choi et al., 2018
	10.5										1.4 (5-FU)	707 (HFF)	Kashafi et al., 2017
	50												Afroze et al., 2022
Luteolin				cca 100									Wang et al., 2004
		52.4	10.8	14.4			30.3		27.5	5.4	0.51 - 8.19 (A)		Yao et al., 2011
		n.a. ≥ 100								82	5.4 (Dox)		Bai et al., 2010
		10						37.9			12.5 (Dox)		Samra et al., 2021
		22	21.3	15.8	27.4	42		50					Xie et al., 2012
		49.3									61.2 (Bes)		Wu et al., 2017)
Luteolin-7-glucoside		n.a. ≥ 100			15.6% at 100µM			36.1% at 100µM			100% (Dox)		Mohammed et al., 2014
				306		368					400-471 (Cis)		Erenler et al., 2022
Quercetin				58.2									Cattivelli et al., 2023
	13.0	13.2											Nawaz et al., 2024
		12.5									0.17 (Dox)		Yang et al., 2018
		4.88						0.87			3.07-4.51 (A)		Ahmed et al., 2016
		92.7		75.3				85.6			0.5 (El)		Nguyen et al., 2024
	45.6	37.3			67.4			42.0			7.7-9.3 (Dox)		El Molla et al., 2016
				cca 80									Wang et al., 2004
Rutin					≥ 100			≥ 100					Khelifi et al., 2020
								45.6					Semwal et al., 2021

		81.5	94.2				86.2		0.5 (El)		Nguyen et al., 2024
	189	≥ 300	125					≥ 300	2.9-8.7 (Cis)	≥ 300 (HaCat)	Alonso-Castro et al., 2013
Taxifolin				≥ 100			≥ 100				Khelifi et al., 2020
				43.5	43.5				26.2 (FH535)		Razak et al., 2018
	63									≥ 100 (NHEK)	Gomes et al., 2022
		21.3					15.9		3.07-4.51 (A)		Ahmed et al., 2016
Vitexin	35.6				32.5	41.6			400-471 (Cis)	46.7 (Vero)	Erenler et al., 2017
	48.6	44.3		35.7	55.7						Bhardwaj et al., 2018
				203					55.7 (FP)		Zhao et al., 2024
		30.6% ≥ 100µM		51.2% at 100µM			73.5% at 100µM		100% (Dox)		Mohammed et al., 2014
	cca 40 µg/mL										Girish et al., 2016

* 5-FU: 5-Fluorouracil; A: Adriamycin; Bes: Bestatin; Cis: Cisplatin; Dec: Decursin; Dox: Doxorubicin; El: Ellipticine; FP: Flavopiridol; G: Genistein; Tax: Taxol

References

Afroze, N., Pramodh, S., Almutary, A., Rizvi, T., Rais, N., Raina, R., . . . Hussain, A. (2022). Kaempferol Regresses Carcinogenesis through a Molecular Cross Talk Involved in Proliferation, Apoptosis and Inflammation on Human Cervical Cancer Cells, HeLa. *APPLIED SCIENCES-BASEL, 12*. doi:10.3390/app12063155

Ahmed, H., Moawad, A., Owis, A., AbouZid, S., & Ahmed, O. (2016). Flavonoids of Calligonum polygonoides and their cytotoxicity. *PHARMACEUTICAL BIOLOGY, 54*, 2119-2126. doi:10.3109/13880209.2016.1146778

Alonso-Castro, A., Domínguez, F., & García-Carrancá, A. (2013). Rutin Exerts Antitumor Effects on Nude Mice Bearing SW480 Tumor. *ARCHIVES OF MEDICAL RESEARCH, 44*, 346-351. doi:10.1016/j.arcmed.2013.06.002

Bai, N., He, K., Roller, M., Lai, C., Shao, X., Pan, M., & Ho, C. (2010). Flavonoids and Phenolic Compounds from Rosmarinus officinalis. *JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 58*, 5363-5367. doi:10.1021/jf100332w

Bhardwaj, M., Cho, H., Paul, S., Jakhar, R., Khan, I., Lee, S., . . . Kang, S. (2018). Vitexin induces apoptosis by suppressing autophagy in multi-drug resistant colorectal cancer cells. *ONCOTARGET, 9*, 3278-3291. doi:10.18632/oncotarget.22890

Castrillón, W., Herrera, A., Prieto, L., Conesa-Milián, L., Carda, M., Naranjo, T., . . . Cardona, W. (2019). Synthesis and in-vitro Evaluation of S-allyl Cysteine Ester - Caffeic Acid Amide Hybrids as Potential Anticancer Agents. *IRANIAN JOURNAL OF PHARMACEUTICAL RESEARCH, 18*, 1770-1789. doi:10.22037/ijpr.2019.15184.12921

Cattivelli, A., Conte, A., & Tagliazucchi, D. (2023). Quercetins, Chlorogenic Acids and Their Colon Metabolites Inhibit Colon Cancer Cell Proliferation at Physiologically Relevant Concentrations. *INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, 24*. doi:10.3390/ijms241512265

Choi, J., Kim, J., Lee, H., Pak, J., Shim, B., & Kim, S. (2018). Reactive Oxygen Species and p53 Mediated Activation of p38 and Caspases is Critically Involved in Kaempferol Induced Apoptosis in Colorectal Cancer Cells. *JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 66*, 9960-9967. doi:10.1021/acs.jafc.8b02656

El Molla, S., Motaal, A., El Hefnawy, H., & El Fishawy, A. (2016). Cytotoxic activity of phenolic constituents from Echinochloa crus-galli against four human cancer cell lines. *REVISTA BRASILEIRA DE FARMACOGNOSIA-BRAZILIAN JOURNAL OF PHARMACOGNOSY, 26*, 62-67. doi:10.1016/j.bjp.2015.07.026

Elansary, H., Szopa, A., Kubica, P., El-Ansary, D., Ekiert, H., & Al-Mana, F. (2020). Malus baccata var. gracilis and Malus toringoides Bark Polyphenol Studies and Antioxidant, Antimicrobial and Anticancer Activities. *PROCESSES, 8*. doi:10.3390/pr8030283

Erenler, R., Meral, B., Sen, O., Elmastas, M., Aydin, A., Eminagaoglu, O., & Topcu, G. (2017). Bioassay-guided isolation, identification of compounds from Origanum rotundifolium and investigation of their antiproliferative and antioxidant activities. *PHARMACEUTICAL BIOLOGY, 55*, 1646-1653. doi:10.1080/13880209.2017.1310906

Erenler, R., Yildiz, I., Aydin, A., & Genc, N. (2022). Antiproliferative and cytotoxic effects of bioactive compounds isolated from Onosma bourgaei. *MEDICAL ONCOLOGY, 39*. doi:10.1007/s12032-022-01705-z

Frei, P., Nadegger, C., Vollmar, A., Müller, T., & Moser, S. (2024). Structural Characterization, and Antioxidative and Anti-inflammatory Activities of Phylloxanthobilins in Tropaeolum majus , a Plant with Relevance in Phytomedicine. *PLANTA MEDICA, 90*, 641-650. doi:10.1055/a-2225-8314

Girish, T., Kumar, K., & Rao, U. (2016). C-Glycosylated flavonoids from black gram husk: Protection against DNA and erythrocytes from oxidative damage and their cytotoxic effect on HeLa cells. *TOXICOLOGY REPORTS, 3*, 652-663. doi:10.1016/j.toxrep.2016.08.006

Gomes, D., Yaduvanshi, S., Silvestre, S., Duarte, A., Santos, A., Soares, C., . . . Sousa, A. (2022). Taxifolin and Lucidin as Potential E6 Protein Inhibitors: p53 Function Re-Establishment and Apoptosis Induction in Cervical Cancer Cells. *CANCERS, 14*. doi:10.3390/cancers14122834

Heleno, S., Ferreira, I., Calhelha, R., Esteves, A., Martins, A., & Queiroz, M. (2014). Cytotoxicity of Coprinopsis atramentaria extract, organic acids and their synthesized methylated and glucuronate derivatives. *FOOD RESEARCH INTERNATIONAL, 55*, 170-175. doi:10.1016/j.foodres.2013.11.012

Hemaiswarya, S., & Doble, M. (2013). Combination of phenylpropanoids with 5-fluorouracil as anti-cancer agents against human cervical cancer (HeLa) cell line. *PHYTOMEDICINE, 20*, 151-158. doi:10.1016/j.phymed.2012.10.009

Hudson, E., Dinh, P., Kokubun, T., Simmonds, M., & Gescher, A. (2000). Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. *CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION, 9*, 1163-1170.

Jayaprakasam, B., Vanisree, M., Zhang, Y., Dewitt, D., & Nair, M. (2006). Impact of alkyl esters of caffeic and ferulic acids on tumor cell proliferation, cyclooxygenase enzyme, and lipid peroxidation. *JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 54*, 5375-5381. doi:10.1021/jf060899p

Kashafi, E., Moradzadeh, M., Mohamadkhani, A., & Erfanian, S. (2017). Kaempferol increases apoptosis in human cervical cancer HeLa cells via PI3K/AKT and telomerase pathways. *BIOMEDICINE & PHARMACOTHERAPY, 89*, 573-577. doi:10.1016/j.biopha.2017.02.061

Khelifi, I., Hayouni, E., Cazaux, S., Ksouri, R., & Bouajila, J. (2020). Evaluation of in vitro biological activities: antioxidant; anti-inflammatory; anti-cholinesterase; anti-xanthine oxidase, anti-superoxyde dismutase, anti-α-glucosidase and cytotoxic of 19 bioflavonoids. *CELLULAR AND MOLECULAR BIOLOGY, 66*, 9-19. doi:10.14715/cmb/2019.66.1.2

Mohammed, R., Abou Zeid, A., El Hawary, S., Sleem, A., & Ashour, W. (2014). Flavonoid constituents, cytotoxic and antioxidant activities of Gleditsia triacanthos L. leaves. *SAUDI JOURNAL OF BIOLOGICAL SCIENCES, 21*, 547-553. doi:10.1016/j.sjbs.2014.02.002

Nawaz, A., Jamal, A., Arif, A., Kiran, S., Shahid, M., Arshad, S., & Shamim, Z. (2024). Bioactive compounds isolated from Solanum nigrum remarkably inhibit cancerous activity in cancer cell lines. *SOUTH AFRICAN JOURNAL OF BOTANY, 168*, 488-496. doi:10.1016/j.sajb.2024.03.048

Nguyen, T., Nguyen, K., Le, T., Nguyen, C., Nguyen, N., Kuo, P., . . . Nguyen, N. (2024). Research on chemical constituents, anti-bacterial and anti- cancer effects of components isolated from Zingiber officinale Roscoe from Vietnam. *PLANT SCIENCE TODAY, 11*, 156-165. doi:10.14719/pst.2410

Razak, S., Afsar, T., Ullah, A., Almajwal, A., Alkholief, M., Alshamsan, A., & Jahan, S. (2018). Taxifolin, a natural flavonoid interacts with cell cycle regulators causes cell cycle arrest and causes tumor regression by activating Wnt/β-catenin signaling pathway. *BMC CANCER, 18*. doi:10.1186/s12885-018-4959-4

Saenglee, S., Jogloy, S., Patanothai, A., Leid, M., & Senawong, T. (2016). Cytotoxic effects of peanut phenolics possessing histone deacetylase inhibitory activity in breast and cervical cancer cell lines. *PHARMACOLOGICAL REPORTS, 68*, 1102-1110. doi:10.1016/j.pharep.2016.06.017

Samra, R., Soliman, A., Zaki, A., Ashour, A., Al-Karmalawy, A., Hassan, M., & Zaghloul, A. (2021). Bioassay-guided isolation of a new cytotoxic ceramide from Cyperus rotundus L. *SOUTH AFRICAN JOURNAL OF BOTANY, 139*, 210-216. doi:10.1016/j.sajb.2021.02.007

Semwal, R., Joshi, S., Semwal, R., & Semwal, D. (2021). Health benefits and limitations of rutin-A natural flavonoid with high nutraceutical value. *PHYTOCHEMISTRY LETTERS, 46*, 119-128. doi:10.1016/j.phytol.2021.10.006

Sevimli-Gur, C., & Yesil-Celiktas, O. (2019). Cytotoxicity screening of supercritical fluid extracted seaweeds and phenylpropanoids. *MOLECULAR BIOLOGY REPORTS, 46*, 3691-3699. doi:10.1007/s11033-019-04812-9

Sun, L., Fu, W., Ren, J., Xu, L., Bi, K., & Wang, M. (2006). Cytotoxic constituents from Solanum lyratum. *ARCHIVES OF PHARMACAL RESEARCH, 29*, 135-139.

Villota, H., Moreno-Ceballos, M., Santa-González, G., Uribe, D., Castañeda, I., Preciado, L., & Pedroza-Díaz, J. (2021). Biological Impact of Phenolic Compounds from Coffee on Colorectal Cancer. *PHARMACEUTICALS, 14*. doi:10.3390/ph14080761

Wang, W., VanAlstyne, P., Irons, K., Chen, S., Stewart, J., & Birt, D. (2004). Individual and interactive effects of apigenin analogs on G2/M cell-cycle arrest in human colon carcinoma cell lines. *NUTRITION AND CANCER-AN INTERNATIONAL JOURNAL, 48*, 106-114.

Wu, X., Li, G., Yang, Y., Liu, H., & Long, E. (2017). Luteolin inhibit the cell growth by influencing aminopeptidase N in HepG2. *INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE, 10*, 2084-2090.

Xie, F., Lang, Q., Zhou, M., Zhang, H., Zhang, Z., Zhang, Y., . . . Yu, L. (2012). The dietary flavonoid luteolin inhibits Aurora B kinase activity and blocks proliferation of cancer cells. *EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, 46*, 388-396. doi:10.1016/j.ejps.2012.03.002

Yang, M., Liang, Y., Chen, H., Huang, Y., Gong, H., Zhang, T., & Ito, Y. (2018). Isolation of Flavonoids From Wild Aquilaria sinensis Leaves by an Improved Preparative High-Speed Counter-Current Chromatography Apparatus. *JOURNAL OF CHROMATOGRAPHIC SCIENCE, 56*, 18-24. doi:10.1093/chromsci/bmx076

Yao, H., Li, S., Hu, J., Chen, Y., Huang, L., Lin, J., . . . Lin, X. (2011). Chromatographic Fingerprint and Quantitative Analysis of Seven Bioactive Compounds of Scutellaria barbata. *PLANTA MEDICA, 77*, 388-393. doi:10.1055/s-0030-1250353

Zhao, C., He, Y., Shi, H., Han, C., Zhu, X., Wang, C., . . . Hua, D. (2024). Investigating the molecular mechanism of vitexin targeting CDK1 to inhibit colon cancer cell proliferation via GEO chip data mining, computer simulation, and biological activity verification. *NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY*. doi:10.1007/s00210-024-03341-y