

**Summary of nonclinical studies using *Nerium oleander* extracts (containing oleandrin)**

Study type	Dose	Comparison to 4 Servings/day oleandrin 6.25 ug/serving x 4 servings/day = 25 ug/day	Cell type or species	Reference
Anti-viral activity	10, 50, and 100 ug oleandrin	Greater than one serving	Human PMBCs	Hutchison <i>et al.</i> (2019) <a href="https://pubmed.ncbi.nlm.nih.gov/31824586/">https://pubmed.ncbi.nlm.nih.gov/31824586/</a>
	100 ng/mL of oleandrin	Less than one serving	Human PMBCs	Singh <i>et al.</i> (2013) <a href="https://www.sciencedirect.com/science/article/abs/pii/S0367326X12002936?via%3DIuhub">https://www.sciencedirect.com/science/article/abs/pii/S0367326X12002936?via%3DIuhub</a>
	Conc. Range 0.005 to 1.0 ug/mL for 24 and 48 hrs	Less than one serving	Vero (African Green monkey kidney) cells in culture	Newman (2020) <a href="https://www.biorxiv.org/content/10.1101/2020.07.15.203489v1.full">https://www.biorxiv.org/content/10.1101/2020.07.15.203489v1.full</a>
Tumor cell cytotoxicity	1.0 ng/ml, 10.0 ng/ml, 0.1 ug/mL and 1.0 ug/mL for 24 hrs	Less than one serving	Human prostate, mouse and canine melanoma cells in culture	Pathak <i>et al.</i> (2000) <a href="https://pubmed.ncbi.nlm.nih.gov/11001386/">https://pubmed.ncbi.nlm.nih.gov/11001386/</a>
	10 nM and 33 nM exposure ranging from 1-120 hrs		Human melanoma cells in culture	Newman <i>et al.</i> (2006) <a href="https://www.researchgate.net/profile/Edward_Felix/publication/7249455_Oleandrin-mediated_oxidative_stress_in_human_melanoma_cells/links/00b49526ec31df0fc600000/Oleandrin-mediated-oxidative-stress-in-human-melanoma-cells.pdf">https://www.researchgate.net/profile/Edward_Felix/publication/7249455_Oleandrin-mediated_oxidative_stress_in_human_melanoma_cells/links/00b49526ec31df0fc600000/Oleandrin-mediated-oxidative-stress-in-human-melanoma-cells.pdf</a>
	Conc. Range 2-1000 nM for 48 hrs		Human and mouse melanoma cells in culture	Lin <i>et al.</i> (2008) <a href="https://pubmed.ncbi.nlm.nih.gov/19066128/">https://pubmed.ncbi.nlm.nih.gov/19066128/</a>
	Conc. Range 2.5-160 ng/mL for 48 hrs	Less than one serving	Human lung cancer cell line in culture	Frese <i>et al.</i> (2006) <a href="https://pubmed.ncbi.nlm.nih.gov/16740726/">https://pubmed.ncbi.nlm.nih.gov/16740726/</a>
	0.05 µg/mL for 24 hrs	Less than one serving	Human prostate cancer cells in culture	Nasu <i>et al.</i> (2002) <a href="https://pubmed.ncbi.nlm.nih.gov/12169388/">https://pubmed.ncbi.nlm.nih.gov/12169388/</a>
	50 nM for 24 and 48 hrs		Human prostate cancer cells in culture	McConkey <i>et al.</i> (2000) <a href="https://journals.lww.com/anti-cancerdrugs/Citation/2001/08000/Oleander_extract_induces_cell_death_in_human_but.13.aspx">https://journals.lww.com/anti-cancerdrugs/Citation/2001/08000/Oleander_extract_induces_cell_death_in_human_but.13.aspx</a>
	0.05 and 0.1 ng/mL for up to 72 hrs	Less than one serving	Human prostate cancer cells in culture	Smith <i>et al.</i> (2001) <a href="https://pubmed.ncbi.nlm.nih.gov/11448457/">https://pubmed.ncbi.nlm.nih.gov/11448457/</a>
	Conc. Range 0.01– 10 µg/mL for 1 hr	Range less than to greater than one serving	Human and mouse cancer cells in culture	Manna <i>et al.</i> (2000) <a href="https://pubmed.ncbi.nlm.nih.gov/10919658/">https://pubmed.ncbi.nlm.nih.gov/10919658/</a>
	Conc. Range 0.2 -1.0 µg/mL for 4 or 6 hrs	Less than one serving	Human, monkey and mouse cells in culture	Sreenivasan <i>et al.</i> (2003) <a href="https://pubmed.ncbi.nlm.nih.gov/14609747/">https://pubmed.ncbi.nlm.nih.gov/14609747/</a>
	5, 10, and 25 nM (approx. 0.1, 0.2, and 0.5 nM oleandrin content)	Less than one serving	Human pancreatic tumor cells in culture	Clinical Trial IND 73624
10, 20, and 40 mg/kg (approx. 0.2, 0.4, 0.8 mg/kg oleandrin content)	Greater than one serving	Human pancreatic cancer Panc-1 and Capan-II cells in Mouse	Pan <i>et al.</i> (2015) <a href="https://pubmed.ncbi.nlm.nih.gov/25476893/">https://pubmed.ncbi.nlm.nih.gov/25476893/</a>	
Pharmacokinetic studies	i.v. dose (40 ug/kg) or oral dose (80 ug/kg) oleandrin	Less than one serving	Mouse	Ni <i>et al.</i> (2002) <a href="https://pubmed.ncbi.nlm.nih.gov/12416031/">https://pubmed.ncbi.nlm.nih.gov/12416031/</a>

Pharm/tox	116 mg/kg/day for 7 days and 21 days, orally (approx. 2.32 mg/kg/day oleandrin content)	Less than one serving	Rat	Clinical Trial IND 73624 <a href="https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1</a>
	0.1, 0.3, or 1.0/0.6 mg/kg for 28 days (approx. 0.002, 0.006, or 0.02/0.012 mg/kg oleandrin content)	Greater than one serving	Dog	Clinical Trial IND 73624 <a href="https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1</a>
Dose-range finding	19, 39, 77, and 116 mg/kg as oral gavage for 7 days (approx. 0.38, 0.78, 1.54, 2.32 mg/kg oleandrin content)	Less than one serving	Rat	Clinical Trial IND 73624 <a href="https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1</a>
Multiple-dose toxicity	19, 58, and 116 mg/kg as oral gavage for 14 days (approx. 0.38, 1.16, 2.32 mg/kg oleandrin content)	Less than one serving		
Dose-range finding	5, 10, and 20 mg/kg for 3-day oral dose escalation (approx. 0.1, 0.2, 0.4 mg/kg oleandrin content)	Greater than one serving	Dog	Clinical Trial IND 73624 <a href="https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04486144?term=oleander&amp;draw=2&amp;rank=1</a>

#### Summary of clinical studies using *Nerium oleander* extracts (oleandrin)

Study type	Comparison to 4 Servings/day of NDI oleandrin 6.25 ug/serving x 4 servings/day = 25 ug/day	ROA	Disease	Reference
Ph1 trial of Anvirzel™	Not an oral product	Injection	Advanced malignancies	Mekhail <i>et al.</i> (2006) <a href="https://pubmed.ncbi.nlm.nih.gov/16763787/">https://pubmed.ncbi.nlm.nih.gov/16763787/</a>
Ph1 trial of PBI-05204	equal to 4 servings/day	Oral	Advanced malignancies	Hong <i>et al.</i> (2014) <a href="https://pubmed.ncbi.nlm.nih.gov/24919855/">https://pubmed.ncbi.nlm.nih.gov/24919855/</a>
Ph2 trial of PBI-05204	10X greater than 4 servings/day	Oral	Metastatic pancreatic cancer	Roth <i>et al.</i> (2020) <a href="https://pubmed.ncbi.nlm.nih.gov/32452588/">https://pubmed.ncbi.nlm.nih.gov/32452588/</a>  Pan <i>et al.</i> (2015) <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387257/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4387257/</a>