Oleandro. Nerium oleander: anti-vírus e anti-câncer

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Nota: conflito de interesse declarado
Nerium Oleander was investigated on many occasions by various scientists. However, their findings have been teaching away from the subject (1-18) .
Nerium Oleander (N.O.) is mainly known in the literature for its toxicity and for the cardiac glycosides that it produces. Extreme toxicity is the main feature of the N.O. plant stated in various plant books (19) . N.O. poisoning was reported in humans (16, 20, 21) and in animals (17, 22) .
N.O. may contain as many as 50 unidentified substances, including potent glycosides (23) . During the anti-tumor screening of plant extracts which started in 1957 at the National Cancer Institute (NCI) in the U.S., approximately 35,000 plant samples were tested for anti-tumor activity. The cardiac glycosides oleandrin, adynerin, and ursolic acid, known to be present in N.O., were tested with cell lines KB, P388, and L1210. The three compounds of N.O. were among the 632 other extracts which were active against the KB tumor cells, and N.O. was ruled out when oleandrin, adynerin, and ursolic acid were found to be inactive against P388 and L1210 cell lines (5) .
According to current literature some of the compounds that N.O. plant contains include Adynerin, Alpha-amyrin, Beta-sitosterol, Betulin, Foliandrin, Folinerin, Gitoxigenin, Isoquercitrin, Lauric-acid, Linoleic-acid, Neriin, Oleandrin, Oleandrigenin, Oleanolic-acid, Oleic-acid, Quercetin, Rutin, Stigmasterol, Ursolic-acid, Uzarigenin. Most of these substances are stated in the literature to have antitumoral and/or immune stimulant and/or antiviral and/or antibacterial or other beneficiary activities
(37) . How many of these compounds co-exist in N.O. extracts could not be investigated due to lack of technologies, and is not known.

HOW HAS DR. OZEL STARTED TO WORK ON N.O.?
In 1962 the Dr. Ozel was assigned to Mugla State Hospital, in Mugla province of Turkey. Geographical distribution of cancer patients in Mugla region called his attention: most of the patients with malignant diseases (94 out of 106) lived at an altitude above 600m. Dr. Ozel studied the environment to find a correlation between the malignancy rate and environmental factors. He observed that N.O. plant was common below 600m and people had close contact with it (i.e., N.O. grew in their gardens, by their water supplies etc.) N.O. did not grow above about 600m. Also, some people were said to use N.O. plant in the treatment of so called "wild wound" ("azgin yara" in Turkish), which was a type of skin cancer. These observations led Dr. Ozel to more detailed studies on N.O. First the toxic dose of N.O. was determined using guinea pigs. An N.O. pomade was prepared and used experimentally in 1966 in the treatment of a dermic cancer. In the second case, the patient with a gastric cancer was given oral N.O. In both of these cases complete and sustained regressions were achieved.

INITIAL PUBLICATIONS IN 1973
In 1973, case reports of some patients treated with N.O. were presented at the Fourth Balkanic Medical Days (24) . More cases were later published in a Turkish medical journal (25,26) . Patients in all cases were diagnosed with cancer at various medical institutions, not related to Dr. Ozel in any manner (as are the cases presented on this site). In some cases patients had inoperable and advanced diseases, and could not be offered any treatment at the time of diagnosis. In some other cases they were given orthodox therapy, abandoned when they reached terminal stages, and this was when they presented to the author. Such patients were treated with N.O. extract, and were published when they achieved complete and sustained regressions. By his publications, Dr. Ozel hoped that interest in the effect of N.O. on malignant cells would gain impetus. However, the reaction was not all positive. Critics used one or more of the following arguments to ingore N.O. treatment:

- Late effect and success of chemotherapy/radiotherapy (if a patient had received chemotherapy and/or radiotherapy and was abondoned before starting N.O. treatment)
- Possible misdiagnosis of the patients.
- Spontaneous remission.
- Absence of such a therapy in the medical literature.
- Shortness of the follow up period of the patients who were in complete and sustained regression.
- Anecdotal.

Under the influence of this negative reaction Dr. Ozel was sued in 1976 by the Ministry of Health. After a trial of two years, he was acquitted. This court order provided legal protection for Dr. Ozel to use N.O. extracts.

1980s
Patent application for the N.O. extracts was filed in 1986 in the U.S.A.
In 1987, Swiss pharmaceutical firm Sandoz showed interest, and tested N.O.I. (injectable form of N.O. extract) *in vitro* and *in vivo* . It was found that N.O.I. was immunomodulator, not toxic, and had antitumoral activity (27) . The collaboration with this company did not continue for various reasons.
In 1988 a research team was formed at Munich University Pharmacology Institute to isolate the active components contained in the N.O. extract. Some polysaccharides, which might be responsible of some part of the immune activity, were identified. Patent application (29) was filed for these polysaccharides, and findings were presented at the BACANS symposium (Bonn, Germany on 17-22 July 1990) (28) . When some members of the research group tried to claim proprietorship of the N.O. extracts individually, the research stopped, and the team dispersed.
In 1992 patents were granted to Dr. Ozel in the U.S. (30) , Canada, Japan, Australia, and in many European countries.
In 1995 a "promise to license" agreement was signed with a U.S. venture capital company, Pharmaceutical Ventures Thrust, that later became Ozelle Pharmaceuticals, Inc. (OPI). OPI registered the name "Anvirzel" as a trademark. Outside Turkey, N.O. extracts have been known as Anvirzel.
OPI financed some research conducted at M.D. Anderson (Houston, Texas) (31-35) . The studies revealed minute amounts of oleandrin and oleandrigenin in N.O. extract. Cardiac glycosides are known to have anti-tumoral activity, and the researchers thought that N.O. extracts' activity was mainly due the presence of these two compounds.
In 2,000 phase I clinical trials were conducted at Cleveland Clinic with Anvirzel prepared by OPI (36) .
Further immunologic studies were conducted at U.C. Irvine and Drew Universities, both of them in Los Angeles, California (38)

REFERENCES

- Taylor A, McKenna GF, Burlage HM. Anticancer activity of plant extracts. Texas Reports on Biology and Medicine 1956;14:538-556.
- Tarkowska JA. Effect of water extract from leaves of Nerium Oleander L. on mitosis. Acta Societatis Botanicorum Poloniae

1971;XL(4):623-631.
- Tarkowska JA. Antimitotic action of glycosides of Nerium Oleander L. Hereditas 1971;67:205-210.
- Statz D, Coon FB. Preparation of plant extracts for anti-rumor screen. Cancer Treatment Reports 1976;60:999-1005.
- Hartwell JL. Types of anticancer agents isolated from plants. Cancer Treatment Reports 1976;60:1031-1067.
- Duke J, at all. Medicinal plants of China. Reference Publication, 1985:97-98.
- Copy of NCI SCREENING DATA SUMMARY ON NSC 251673.
- The Merck Index, 10th Ed., pub. Merck&Co., Inc., Rahway, N.J., 1983:p.355,979,1413.
- Woo WS, Lee EB, Han BH. Biological evaluation of Korean medicinal plants. Archives of Pharmaceutical Research 1979;2(2):127-131.
- Chavan SR, Nikam ST. Studies on the larvicidal properties of Nerium indicum Mill (apocynaceae) leaves. Bulletin of the Hattdine Institute 1983;11(3):68-70.
- Mansuri SM, Girdhar A, Doctor RB. Preliminary study of beta-adrenergic blocking action of Nerium odorum Linn. Indian Journal of Physiology & Allied Sciences 1980:34(I):30-31.
- Karawya MS, Baldaa SI, Khayyal SE. Isolation of oleandrin and adynerin from Nerium oleander L. growing in Egypt. Egyptian Journal of Pharmaceutical Science 1973:14(2):113-116.
- Leporatti ML, Posocco E, Pavesi A. Some new therapertic uses of several medicinal plants in the province of Terni. Journal of Ethnopharmacology 1985;14:65-68.
- Yamauchi T, Abe F, Tachibana Y, Atal CK, Sharma BM, Imre Z. Quantitative variations in the cardiac glycosides of oleander. Phytochemistry 1983;22(10):2211-2214.
- Szabuniewicz M, McCrady JD, Camp BJ. Treatment of experimentally induced oleander poisoning. Archives of Int Pharmacodynamics 1971;189:12-21.
- Haynes BE, Bessen HA, Wightman WD. Oleander tea: herbal draught of death. Annals of Emergency Medicine 1985;14(4):350-353.
- Schwartz WL, Bay WW, Dollahite JW, Storts RW, Russel LH. Toxicity of Nerium oleander in the monkey (cebus apella). Veterinary Pathology 1974;11:259-277.
- Woo SW, Shin KH, Kwon YM. Biological evaluation of Korean medicinal plants. Journal of the Pharmaceutical Society of Korea 1972;16:121-128.
- Elllis Md. Dangerous Plants, Snakes, Anthropods@Marine Life: Toxicity & Treatment. Hamilton, I11, Drug Intelligence Publ. Inc., 1978:32-33.
- Osterloh J, Herold S, Pond S. Oleander interference in digoxin radioimmunoassay in a fatal ingestion. JAMA 1982;247:1596-1597.
- Shaw D, Pearn J. Oleander Poisoning. Med J Aust 1979;2:267-269.
- Mahin L, Marzou A, Huart A. A case report of Nerium Oleander posoning in cattle. Vet Hum Toxical 1984;26(4):303-304.
- Karawya MS, Balbaa SI, Khayyal SE. Estimation of cardenolides in Nerium oleander. Planta Med 1973;23:70-73.
- Ozel HZ. Kanser tedavisinde klinik vakalar. 4. Balkan tip gunleri. 16-20 Eylul 1973, Ankara.(Clinical cases in the treatment of cancer. 4th Balkanic medical days. 16-20 September 1973, Ankara.)
- Ozel HZ. Kanser tedavisinde bir deneme (An essay in the treatment of cancer). Dirim 1974;4:172-176.
- Ozel HZ. Zakkum usaresinin malign tumorlere etkisi uzerine klinik calismalar (Clinical studies about the effect of Nerium oleander extract on malignant tumors). Dirim 1974;12:565-572.
- Report on the evaluation tests of NOI performed at Sandoz pharmaceutical company's Basel and Vienna laboratories in 1987.
- Carbik I, Baser KHC, Ozel HZ, Ergun B, Wagner H. Immunologically Active Polysaccharides from the Aqueous Extract of Nerium Oleander. Planta Med 1990;56:668 .
- Ozel HZ, Baser KHC, Carbik I, Wagner H, inventors; Polysaccharide mixture with immune stimulating and anti-proliferating effect, method of production and medicines containing the substances. Canadian patent application CA 2016948 filed on May 16, 1990.
- Ozel HZ, inventor. Extracts of Nerium species, methods of preparation, and use therefore. US patent 5,135,745. 1992 Aug 4.
- McConkey DJ, Lin Y, Nutt LK, Ozel HZ, Newman RA. Cardiac glycosides stimulate Ca2+ increases and apoptosis in androgen-independent, metastatic human prostate adenocarcinoma cells. Cancer Res 2000 Jul 15;60(14):3807-12.
- Wang X, Plomley JB, Newman RA, Cisneros A. LC/MS/MS analyses of an oleander extract for cancer treatment. Anal Chem 2000 Aug 1;72(15):3547-52.
- Pathak S, Multani AS, Narayan S, Kumar V, Newman RA. Anvirzel, an extract of Nerium oleander, induces cell death in human but not murine cancer cells. Anticancer Drugs 2000 Jul;11(6):455-63.
- Smith JA, Madden T, Vijjeswarapu M, Newman RA. Inhibition of export of fibroblast growth factor-2 (FGF-2) from the prostate cancer cell lines PC3 and DU145 by Anvirzel and its cardiac glycoside component, oleandrin. Biochem Pharmacol 2001 Aug 15;62(4):469-72.
- Ni D, Madden TL, Johansen M, Felix E, Ho DH, Newman RA. Murine pharmacokinetics and metabolism of oleandrin, a cytotoxic component of Nerium oleander. J Exp Ther Oncol 2002 Sep-Oct;2(5):278-85.
- Mekhail T, Kellackey C, Hutson T, Olencki T, Budd GT, Peereboom D, Dreicer R, Elson P, Ganapathi R, Bukowski R. Phase I study of Anvirzel in patients with advanced solid tumors. Proc Am Soc Clin Oncol 20:82b, 2001 (abstr 2077).
- Duke J. Phytochemical and Ethnobotanical Databases , U.S. Department of Agriculture, Agricultural Research Service .
- Ghoneum M, Ozel HZ, Gollapudi S. Nerium oleander leaf extract sensitizes human burkett cell lymphoma (Raji) to human cytotoxicity mediated by natural killer cells. Clinical Immunology, 2006, vol. 119, no. SUPP, pp. S188.