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

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Nota: conflito de interesse declarado

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 (12). 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 N.O. plant contains include Adynerin, Alpha-amyrin, Beta-sitosterol, Betulin, Folidin, Folinin, Gixoxigenin, Isoquercitrin, Lauric-acid, Linoleic-acid, Nerin, Oleandrin, Oleandrigenin, Oleanolic-acid, Oleic-acid, Quercetin, Rubin, 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 HAS DR. OZEL STARTED TO WORK ON N.O.?

In 1957, H. Ziya Ozel was assigned to Mугла State Hospital, in Mугла 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. 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 reported 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 abandoned 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 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) and 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 to 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

- Tarkowska JA. Effect of water extract from leaves of Nerium Oleander L. on mitosis. Acta Societas Botanicorum Poloniae