Squalene

Another in the Dr. Smith's Client Education Series

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Shark Liver Oil

When I was a kid, it was all I could do to get out of my grandmother's house in the morning before she awakened to avoid her morning dose of cod liver oil. She claimed it kept me healthy…yuck!

Historically, fish oils have a longstanding usage in "folk medicine." Today the use of fish oils as a supplement is accepted and used by many physicians, alternative practitioners and the general public.

Over the last few decades, one fish oil stands above all the rest; Shark liver oil.[1] The list of benefits has been the subject of much research, especially as an adjunct to cancer treatment.[i] So let's examine the research data, history and the benefits.

Scandinavian and Caribbean fishermen discovered that oil extracted from the liver of the deep water shark sped up skin tissue repair if applied to wounds. The fishermen filled stomach sacs of fish with the shark's liver oil and used it to alleviate respiratory tract infections. They also found through practical usage that the oil strengthened them, especially when taken after illness. In Ernest Hemingway's last book, The Old Man and the Sea, there is a scene where the old fisherman drinks the shark liver oil for his eyes.

The usage of this "folk remedy" had all but died out by the end of the 19th Century apart from a few isolated fishing communities. This valuable knowledge would have completely disappeared, had it not been for two Japanese scientists who, in 1922, discovered a lipid which differs from the usually fatty substances by the presence of a single atom of oxygen. They called these healing molecules ALKOXYGLYCEROLS or AKGs for short.

In 1906, Dr. Mitsumaru Tsujimoto made an in depth research on shark liver oil, specifically that of the deep-sea shark species; the "Squalidae Group", and discovered that an extremely great quantity of unsaturated hydrocarbons was contained in the liver oil of these deep-sea sharks. He later called the oil "Squalene". Dr. Tsujimoto's brilliant discovery was not fully established until 1931 when Prof. Calour, a Nobel Prize recipient at Zurich University, Switzerland certified that squalene shark liver oil is a lipoprotein, an unsaturated hydrocarbon with a chemical structure C30H50. This means simply that it mainly contains 30 carbon atoms and 50 hydrogen atoms. Dr. Calour in his study of the chemical behavior of this unsaturated hydrocarbon revealed that the compound is naturally lacking 12 hydrogen atoms in its original form for it to be stable (the stable compound is C30H62) and will "capture hydrogen atoms" from any source available to make it stable and saturated. The most abundant source of hydrogen is water & shyp; H20. (Our food contains much H20, body fluids and blood are mainly H20, body cells contain much water, the human body is actually 70% water). Theoretically, C30H50 (squalene) reacts with water (H20) this way: C30H50 + 6H20 & shyp; C30H62 + 302. By capturing the hydrogen molecules, 3 oxygen molecules from the water are released.

[1] Please note that Dr Smith's shark liver oil is sourced from Scandinavia, where the sharks are fished for human consumption and pet food and are not fished exclusively for its oil.

This shows that squalene, through a natural reaction with water, is capable of providing oxygen essential for healthy metabolism. This basic scientific theory shown in the above formula should provide us an insight how squalene might work when present in our bodies.

These molecules were synthesised in 1930 and then research into their versatile healing applications progressed rapidly. The technological advances of the 1940s and 1950s enabled the Swedish researchers, Hallgren and Larsson, to undertake extremely specific studies of shark liver oil in the 1960s.[2] The liver oil was found to contain extremely high concentrations of active alkoxyglycerols usually only found in mother's milk and bone marrow. Further scientific research was then undertaken over the next twenty years by other researchers especially with Squalene's effectiveness with cancer.[3]

The reason Squalene works against cancer and, in particular, the AKG content[4ii] is because Squalene has the ability to inhibit the growth of new blood vessels which cancer tumors must produce to survive, the process known as angiogenesis. While the mechanism of action is not well understood, the fact is that it does work to effectively starve cancer tumors to death.

Squalene has been clinically proven to be cytoprotective.[5] In other words, it protects cells from damage either by naturally occurring free radicals or radiation and chemo' induced damage. This is good news for those who elect to undergo the rigors of chemotherapy and/or radiation.

Additionally, two Swedish scientists made the exciting discoveries that shark liver oil, with its potent alkoxyglycerols:

- activated and enhanced the body's lymphatic immune defense system by stimulating the formation of antibodies and increasing the number of white blood cells and thrombocytes in our blood.[6]

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[2] Hallgren, B. and Larsson, S., *'The Glycerol Ethers in the Liver Oils of Elasmobranch Fish'*, Journal of Lipid Research, 1962: 3, 3238. Hallgren, B. and Larsson, S., *'The Glycerol Ethers in Man and Cow'*, Journal of Lipid Research, 1962: 3, 3943 Hallgren, B., Staelberg, G., and Boeryd, B., *'Occurrence, Synthese and Biological Effect of Methosysubstituted Glycerol Ethers'*, Progress in Chemistry of Fats and other Lipids, 1978: 16, 45.

[3] Brohult, A., *Alkoxyglycerols and their use in Radiation Treatment,* Acta Radio, 1963: Suppl. 223. Brohult, A., Brohult, J., and Brohult, S., *Biochemical Effects of Alkoxyglycerols and their Use in Cancer Therapy.* Acta. Chem. Scand., 1970: 24, 730. Brohult, A., Brohult, J., and Brohult, S., *Regression of Tumour Growth after Administration of Alkoxyglycerols.* Acta Obsten. Gynecol. Scand., 1978: 57: 1, 79.

[4] Many products on the market contain varying amounts of AKG's. The best products are from Scandinavia and contain 20% AKG's such as found in Dr. Smith's 's Squalene. See EndNotes for analysis of Squalene.

[5] *In Vitro* cytoprotective activity of squalene on a bone marrow versus neuroblastoma model of cisplatin-induced toxicity: implications in cancer chemotheraphy. B.Das, H.Yeger, H.Baruchel, M.H.Freedman, G.Koren, S.Baruchel. Published in the European Journal of Cancer, this study proves that Isshō Genki Squalene iP6 actively protects the cells against cancer chemotheraphy.

[6] Boeryd, B. et al, 'Stimulation of Immune Reactivity by Methoxy-substituted Glycerol Ether Incorporated into the feed', European Journal of Immunology, 1978: 8, 678, 680.

- diminished the harmful side-effects following radiation therapy by reducing leucopenia and thrombocytopenia (both of which invariably occur during the course of irradiation). The alkoxyglycerols neutralized and counteracted the detrimental changes in the blood cell ratio caused by radiation treatment.[7]

In the 1990's Johns Hopkins University discovered another ingredient in shark liver oil, Squalene, found to be effective against many yeast, fungus and bacterial infections, and especially offers promise to immune compromised individuals such as AIDS and cancer patients. Shark liver oil may well contain the secret of improved health and longevity for mankind.

The anti-angiogenesis effect can be of further benefit with individuals suffering from macular degeneration. Adult Macular Degeneration (AMD) occurs when the capillaries behind the retina begin to lift the retina from the back of the eye. Squalene reduces the angiogenesis and some have reported very high degrees of reversal of AMD.[8]

There are other factors at work here, as well. Squalene has been researched and used for

- Recurring infections.
- Strengthening the immune system, particularly in chronic degenerative diseases.
- Beneficial for coughs, colds and influenza.
- Important for tissue repair, delayed wound healing and acne.
- Recommended before, during and after radiation therapy.
- Promotes healing and recovery of nervous system.
- Normalizes metabolism in diabetics.
- Effective against viral hepatitis and cirrhosis of the liver.
- Has an analgesic and anaesthetizing effect to neutralize pain.
- Lowers serum cholesterol.

Dosage Recommendation:

We suggest 2 capsules per day as an adult maintenance dosage. For intensive use, we recommend 15mg per pound of body weight per day, not to exceed 5,000 mg per day.

[7] Brohult, A., Alkoxyglycerols and their use in Radiation Treatment, Acta Radio, 1963: Suppl. 223. Brohult, A., Brohult, J., and Brohult, S., Biochemical Effects of Alkoxyglycerols and their Use in Cancer Therapy. Acta. Chem. Scand., 1970: 24, 730.

[8] We also recommend Aptinol as an adjunct to AMD recommendations.

[i] **Genaera Initiates Clinical Trial for Antiangiogenesis Drug Squalamine with IND for the Treatment of Fibrodysplasia Ossificans Progressiva**

Plymouth Meeting, PA, January 16, 2002 -- Genaera Corporation. (NASDAQ: GENR) today announced the initiation of a clinical trial for squalamine, its antiangiogenic agent, in fibrodysplasia ossificans progressiva (FOP). The study will be conducted in collaboration with the University of Pennsylvania School of Medicine, under the direction of Frederick Kaplan, M.D., Isaac and Rose Nassau Professor of Orthopedic Molecular Medicine, an internationally recognized authority on FOP. An IND (investigational new drug application) has been accepted by the FDA to support the initiation of the clinical trial, as is required.

FOP is a rare genetic disorder in which there is progressive formation of new bone in the large muscles, leading to progressive immobility and disability. The disease starts in childhood, with initial painful swelling of muscles, which in days to weeks often turns to bone. The disease begins in the neck and upper spine, and progresses over a period of years to the muscles around the hips, jaw, and other major joints. The swollen muscles represent a type of growth very similar in appearance to a sarcoma cancer. Similar to cancer, these growths in the swollen muscles are nourished by a network of newly formed primitive blood vessels, as a result of active angiogenesis in the lesions.

Early research, conducted in collaboration with Dr. Judah Folkman, the world's leading angiogenesis research scientist, and Dr. Michael Zasloff, Genaera's founding scientist, has shown that angiogenic factors, including basic fibroblast growth factor, are elevated during periods of active disease in FOP. By blocking the angiogenic process, squalamine has the potential to inhibit the progression of the muscle growths seen in FOP, and prevent the muscle turning into bone.

Dr. Kaplan commented, "Our laboratory has studied squalamine and found it to possess potent antiangiogenic properties. I believe antiangiogenic therapies may have important medical benefits in debilitating conditions in which angiogenesis is an important part of the disease process, such as FOP and cancer. I am delighted to have the opportunity to conduct this initial study of squalamine in FOP during periods of active disease."

Roy C. Levitt, M.D., President and Chief Executive Officer of Genaera, commented, "To date, no current therapy is approved to treat this devastating disease. Due to the rarity and severity of FOP, substantial uncertainties exist when evaluating experimental therapies. We are delighted to further advance the clinical development of squalamine for FOP and aid in the search for a cure, and are hopeful that this approach may provide clinical benefit for this orphan indication."

This study is partially funded by the International Fibrodysplasia Ossificans Progressiva Association (IFOPA), a non-profit organization that supports education, clinical care, research, and international communication on fibrodysplasia ossificans progressiva.

Squalamine is the first clinical drug candidate in a class of naturally occurring, pharmacologically active, small molecules known as aminosterols. Squalamine is a potent anti-angiogenic molecule with a unique multi-faceted mechanism of action that blocks the action of a number of angiogenic growth factors, including vascular endothelial growth factor (VEGF). The Company currently has ongoing trials evaluating squalamine in the treatment of non-small cell lung cancer, ovarian cancer, and other adult solid tumors. Genaera anticipates the start of clinical trials in age related macular degeneration (AMD) in 2002.

Genaera Corporation is a biopharmaceutical company committed to developing medicines for serious diseases from genomics and natural products. Research and development efforts are focused on antiangiogenesis, obesity, infectious diseases and respiratory diseases.

This announcement contains forward-looking statements that are subject to risks and uncertainties. Forward-looking statements reflect management's current views and are based on certain expectations and assumptions. Such statements include, among others, statements regarding the preliminary results and future clinical development plans and prospects for squalamine (for lung cancer, ovarian cancer and in other indications), the IL-9 antibody program, the small molecule mucoregulator program, and trodulamine. You may identify some of these forward looking-statements by the use of words in the statements such as “anticipate,” “develop,” “continuing,” and “progress,” or other words of similar meaning. Genaera’s actual results and performance could differ materially from those currently anticipated and expressed in these and other forward-looking statements as a result of a number of factors, including, but not limited to, the additional data to be collected from the clinical trials, results of additional clinical development plans, results of ongoing preclinical and clinical studies in our drug development candidates, general financial, economic, regulatory and political conditions affecting the biotechnology industry and the other risks and uncertainties discussed in this announcement and in Genaera’s filings with the U.S. Securities and Exchange Commission. Genaera does not intend (and it is not obligated) to publicly update, revise or correct these forward-looking statements. This discussion is permitted by the Private Securities Litigation Reform Act of 1995.

[ii] **Analysis of HemaTek Squalene**

Analysis	Reference	Specification	Result
Alkoglycerols	Vendor	20% Min	21:2
Acid Value	AOCS Cd 3a-63	4.0 mg KOH/g Max	0.51
Peroxide Value	AOCS Cd 8-53	8.0 meg/kg Max	8
Capsule	N/A	500 mg	500 mg
		10 Oval	10 Oval
		Clear	Clear
Matrix	Shark Liver Capsule 500 mg.		
FA Profile and PO			
Analytical Methods	AOAC –28.060. 28.025		

Test	Result	Unit
C14:0 Myristic	**5.96**	%
C15:0 Pentadencenoic	**0.48**	%
C16:0 Palmitic	**17.97**	%
C16:1 Hexadecanoic (Palmitol)	**4.44**	%
C17:1 Heptadecenoic	**1.93**	%
C18:1 Oleic	**10.55**	%
C18:2 Linoleic	**4.66**	%
C18:3 *gama*-Linolenic	**1.45**	%
C18:3 Linolenic	**2.91**	%
C20:1 Icosenic	**5.65**	%
C20:5 Eicosapentenoic (EPA)	**7.84**	%
C22:1 Erucic	**0.62**	%
C22:6 Docosapenoic (DHA)	**5.79**	%
C24:0 Lignoic	**15.91***	%
Unknown Components	**13.0**	%
Peroxide Value	**2.04**	MEg/Kg