Discovery of Anticoagulant Warfarin

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In the 1920s there was an outbreak of an unrecognized, strange, cattle bleeding disease, in Northern United States and Canada. After investigations by veterinary pathologist, it was found to be due to ingestion of spoiled silage from sweet clover (M. Officinalis), which caused cattle deaths whereas ingestion of fresh sweet clover had no ill effects. Sweet clover flourishes in poor soil and provides a rich source of protein, enriches the soil and makes a good fodder. However, Spoilage is likely to occur in sweet clover silage since its small leaves dry quickly, leaving succulent stems that are damaged by organisms. In case of spoiled sweet clover, the harmless ingredient coumarin is converted into bis-hydroxycoumarin (dicoumarol) which is toxic due to its anticoagulant property.

The identity of anticoagulant substance in spoiled sweet clover remained a mystery until 1940. At the University of Wisconsin, the lab chemist Karl Paul Link set out to isolate and characterize this agent. After five years, Link’s student, Harold Campbell recovered 6mg. of crystalline anticoagulant. Later, another student took over the project and initiated a large scale extraction in 4 months. Through degradation experiments, they established the molecular structure of the agent and named it Dicoumarol.

Dicoumarol is a product of plant molecule Coumarin. Coumarin is harmless when ingested and is present in many plants. It produces notably sweet smell of freshly cut grass or hay and plants like sweet grass. It is present in green leafy vegetables like Amaranths. It was once used to scent tobacco and snuff, as the hay-like aroma of dried sweet woodruff intensifies and persists for years. Coumarin can be manufactured from trans-cinnamic acid, a compound isolated by Austrian chemist Joseph Loschmidt (1821-1895). Coumarin can also be produced from aldehydes such as cinnamic aldehyde which is found in the bark of cinnamon and is used in manufacture of perfumes due to its pleasant odour.

Name WARFARIN is an acronym for the patent holder-Wisconsin Alumni Research Foundation with the suffix ‘in’ from coumarin.

Although it was first developed by Link, the name Warfarin was given because of most involved in the discovery of Dicoumarol were students of the University of Wisconsin. Warfarin is a synthetic derivative of Dicoumarol. It was first registered for use as a rodenticide in US in 1948, and was immediately popular due to its self baiting. The WARF financially supported the research and assigned the patent. Warfarin acts by depleting vitamin K, and affecting its recycling in the body. Its action can be reversed by replacing vitamin K.

In 1951, a US army inductee, unsuccessfully attempted suicide with rodenticide pills of Warfarin. His survival with vitamin K led to the start of clinical trials in patients with thrombo-embolic syndromes. It was approved by FDA in 1954, and has come in wide use till today. An early recipient of warfarin was US President Eisenhower who was prescribed the drug after he suffered myocardial infarction in 1955.