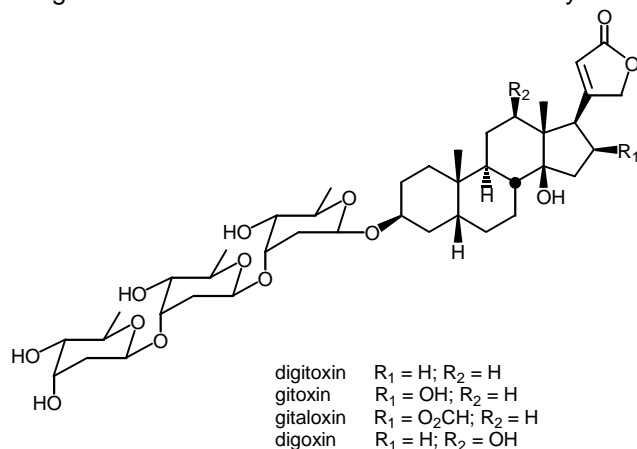


Digitalis

The cardiac glycosides also represent an important class of useful, albeit somewhat dangerous, steroids. These compounds are characterized by the steroidal cardenolide aglycone bonded at the C-3 position to a sugar moiety which can range from a monosaccharide to a trisaccharide. The most well-known use of these compounds is in the preparation digitalis. This drug, which is used to treat congestive heart failure, supraventricular tachycardia, and several other heart conditions, is a cardiotoxic agent which increases the tone of the heart muscle causing more effective emptying of the heart chambers. It has been known and used since at least 1640. Digitalis is prepared by gentle drying of the first year leaves of *Digitalis purpurea*, a biennial herb known as foxglove, at temperatures below 60°C and powdering of the dried leaves. These leaves contain over 30 different cardiac glycosides of which the most important are digitoxin, gitoxin, and gitaloxin. The cardiac glycoside content of the leaves is 0.15-0.40%. Digitoxin was once the most widely used of these cardiac glycosides, as a treatment for congestive heart failure and some cardiac arrhythmias.



Digitalis lanata, is another variety of foxglove, widely grown in America. It generally has a higher cardiac glycoside content, ca., 1%, than *D. purpurea*, so is more useful for large scale harvesting of the active compounds. Among the most important of the cardenolides isolated from *D. lanata* is digoxin, which is probably more widely used than digitoxin. Digoxin acts more rapidly than digitoxin, and is excreted through the kidneys more rapidly than is digitoxin, which is primarily metabolized in the liver. Digoxin is also used to treat congestive heart failure and atrial fibrillation.

Individual cardiac glycosides are used more frequently, particularly in the United States, than

the ground leaf mixture (Digitalis) because the dose can be better controlled and each has specific toxicity and properties. Toxicity is a major concern with the use of these compounds, and is potentially cumulative. One reason that digoxin is the preferred drug is that a specific antibody is available to treat accidental overdoses.

Other plants, such as *Strophanthus* spp., *Convallaria* spp. (Lily of the Valley), *Urginea* spp. (Squill), *Asclepias* spp. (Milkweed), and *Apocynum* spp., also produce cardiac glycosides. An interesting sidelight is that Monarch butterflies have an interdependence with milkweed. The butterflies lay their eggs on milkweed, and as the insects hatch and grow, they feed on the milkweed. As they feed the developing butterflies ingest and sequester the cardiac glycosides from the milkweed. As for humans, cardiac glycosides are toxic to birds, and the sequestered cardiac glycosides make the butterflies toxic to birds. Thus, the butterflies use the cardiac glycosides to avoid predation.

One of the side effects of the use of digitalis in some patients is yellow vision (xanthopsia). The artist van Gogh is known for his use of yellow in many paintings. Some writers have speculated that van Gogh suffered from xanthopsia brought on by heavy use of the now banned liqueur absinthe, which is derived from wormwood (*Artemisia absinthum*) which contains santonin. Santonin can also cause xanthopsia, but it now appears unlikely (*Chemical & Engineering News*, November 9, 1992) that absinthe contains sufficient quantities of santonin to have caused this problem in van Gogh. Other writers have speculated that van Gogh used digitalis to treat epilepsy and that this caused his xanthopsia. It is unlikely that this issue will be resolved to art scholars' satisfaction, but it is another interesting sidelight to the study of natural products.