



*Mistletoe growing on the oak tree. An illustration from Compleat History of Druggs (London, 1712), by Pierre Pomet.
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The Everlasting Mistletoe and the Cardiovascular System

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Mistletoe, with its light green, leathery leaves and translucent berries, is affectionately linked with the holiday season. Writing in 1820, the American author Washington Irving described the tradition of stealing a kiss under this intriguing plant: “. . . the mistletoe, with its white berries,” he said, is “hung up, to the imminent peril of all the pretty housemaids.” At Christmas, the young men had the privilege of kissing ladies under mistletoe, “plucking each time a berry from the bush.” Once all the berries had been plucked, no more kissing was allowed.¹

For centuries, mistletoe has provided not only a good excuse to steal a kiss at Christmas time, but also a cure for a variety of ailments. First described by the Greek naturalist Theophrastus in the 3rd century BC, mistletoe became embedded in European rituals, folklore, and folk medicine. It was the sacred plant of the Celtic peoples who dominated Europe in the first millennium BC. The Gauls had a perfect name for it: “all-healer.” The word for mistletoe in Celtic languages also implied “cure-all.”²

By the time of Pliny the Elder (AD 23-79), mistletoe was already in use as a fertility drug, an antidote, and a medication for skin problems such as sores and abscesses. During the Renaissance, it gained popularity as a cure for epilepsy and other “cephalic and nervine” diseases, including vertigo, palsy, and apoplexy.* In the 17th century, Sir Thomas Browne wrote that mistletoe was used “to provoke the after-birth,” and its oxytocic properties would be explored to a great extent by 19th-century physicians, especially in the United States.^{3,4} There also have been reports of mistletoe’s use as an abortifacient.⁵

Mistletoe belongs to the botanical family *Loranthaceae* (Mistletoe family) consisting of about 20 genera of evergreen shrubs that live on trees. It is propagated by birds that eat the berries and then excrete the seeds, or smear them on branches by wiping the sticky pulp off their beaks. Under proper conditions, the seeds germinate and the roots penetrate the branch of the host tree. Mistletoe is considered a semiparasitic plant: it synthesizes its own chlorophyll but depends on the host for its supply of water and minerals.^{6,7} For centuries, mistletoe was attributed magical powers, partly because it retains its leaves and because the berries mature in winter, when the host looks barren.

In literature, one finds references to European and American mistletoe. The best known genus of the Mistletoe family is *Viscum album* L., which grows in Europe. This sacred plant of the Druids (priestly class of the Celts) grew on oak trees (hence the French name “le gui de chêne”). Today, European mistletoe grows chiefly on apple, poplar, and plum trees. American mistletoe belongs to the genus *Phoradendron* (derived from the Greek word for tree thief) and grows mostly in the southern United States. The mistletoe that is commercially available during Christmas season in the United States is *Phoradendron serotinum*, a species also referred to as *P. flavescens* in early medical literature.

European and American mistletoe contain toxic proteins of similar chemical composition. Designated viscotoxin when obtained from *Viscum album* and phoratoxin when isolated from *Phoradendron* species, these substances were reported to have experimentally produced hypotension and bradycardia.⁸ More recent studies⁹ indicate, however, that the compounds responsible for the

* Although apoplexy is now regarded as a cardiovascular disorder, I am omitting it in this study because of its past association with diseases of the nervous system.

Key words: History of medicine, 19th cent.; history of medicine, 20th cent.; hypertension; plants, medicinal; viscum

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cardiovascular activity of mistletoe are not yet known, although a large number of constituents have been isolated. It has been further reported¹⁰ that certain Australian species of mistletoe acquire toxic substances such as alkaloids and glycosides from the host plants; hence it becomes very important to identify the host in any scientific or clinical study of mistletoe.

If the formulation of mistletoe preparations remains a problem today, it was an even more serious problem for physicians and other healers of the past. Most of the time, mistletoe was administered in the form of a decoction prepared from the leaves and twigs, using wine or some other alcoholic or aqueous solution as a base. One cannot be sure, however, that such a decoction did not include the berries. For the cure of epilepsy, at least, dried and powdered mistletoe berries, leaves, and twigs were used.¹¹ Any historical study of mistletoe as a therapeutic substance cannot then avoid the uncertainty arising both from the varied nature of this parasitic plant and from the lack of sufficient documentation of medicinal preparations.

Application to Cardiovascular Disease

Early Reports. The first recorded evidence of mistletoe's use in the treatment of heart diseases is found in a short communiqué published in 1881. Dr. R. Park of Glasgow described finding a large bottle labeled "Tincture of Mistletoe" among the drugs of a late Dr. Wigglesworth, whose practice he had taken over in June of 1870:

I had never heard of this tincture before; so my curiosity was aroused, and I carefully explored all the late doctor's books, with a view to finding a clue to its strength, mode of preparation, and therapeutics. My exploration was without results, however, so I spoke to Mrs. Wigglesworth, the widow, about the strange tincture, desiring to know if she could tell me for what purpose her husband had used it. She replied, quite frankly, that she knew the doctor had used a lot of it for treating diseases of the heart, but she knew nothing about it.¹²

Upon further investigation, Dr. Park discovered that Dr. Wigglesworth had a large number of heart cases among his patients, many of whom worked in the mines and suffered from "displacements . . . some hypertrophy, some asthenia and palpitation."¹² Although Dr. Park was unable to find any information about the composition of the tincture, he did prescribe it for "incompetency and tumultuous distressing cardiac" cases, obtaining "the very best results." He concluded that mistletoe would be a good substitute for digitalis.¹³

Also in 1881, there appeared a study¹⁴ on the physiological properties of mistletoe. Experimenting with frogs, rabbits, and a dog, Dr. R. Lee Payne of North

Carolina reported that mistletoe had opposite effects on the cold- and warm-blooded animals: while the injection of a fluid extract of mistletoe (prepared by himself, presumably from American species) slowed down the action of the heart in frogs, it increased cardiac action in the rabbits and dog. Since Dr. Payne was focusing his investigations on the oxytotoxic property of mistletoe, he did not elaborate on its use as a cardiac medicine. He did, however, suggest its possible application to cardiovascular problems: "Its action on the heart indicates its usefulness in all diseases of this organ characterized by weak action and low arterial tension."¹⁵

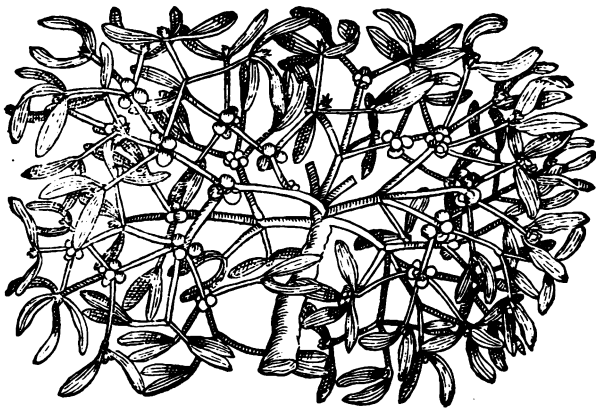
While these two 1881 reports from opposite sides of the Atlantic may now be historically important in a study of mistletoe as a cardiac medicine, they were largely ignored by members of the medical profession. Mistletoe would never be accepted as an alternative to digitalis. A short note that appeared in *Lancet* in 1904 maintained that *Viscum album* was in fact injurious to the heart.¹⁶ In reviewing the medical uses of American mistletoe, Crawford argued in 1911 that Payne's failure to use a standardized extract in his experiments invalidated his conclusions.¹⁷ There is no indication that physicians commonly employed mistletoe in the treatment of heart problems, but the extract persisted as a folk remedy in certain regions of England.¹⁸ Many doubted that predictable therapeutic results could be obtained with the use of mistletoe.¹⁹

Antihypertensive Applications. Mistletoe has had better success in surviving as an antihypertensive medication than as a possible substitute for digitalis. It has been used for lowering blood pressure since the turn of the century. Martindale's *Extra Pharmacopoeia* still lists mistletoe as a vasodilator (as well as an antineoplastic agent), and 5 different drugs* containing mistletoe are still available in Europe.²⁰ The work of French physician René Gaultier, published in 1907,^{21,22} was primarily responsible for the acceptance of mistletoe as an antihypertensive agent.

Writing in 1928,²³ Gaultier recalled how he had encountered, nearly 30 years earlier, a case of pulmonary hemorrhage caused by tuberculosis. Various treatments had been ineffective in stopping the hemoptysis, and finally a woman healer was called in. The patient responded immediately to her administration of a medication containing mistletoe. Encouraged by this observation, Gaultier undertook a series of experiments.^{21,22}

Using an extract prepared from dry and fresh mistletoe leaves and sodium chloride solution, he showed

*The best known mistletoe preparation is Iscador, manufactured by Weleda in Germany, France, and the United Kingdom. Its effectiveness as an antineoplastic agent, however, has been controversial. Helixor, Mistel, Plenosol, and Viscysat (sic) are produced in Germany.



Mistletoe. A woodcut from *De medica materia* (Venice, 1554) by Pietro Andrea Mattioli.

(Courtesy of the Blocker History of Medicine Collections, Moody Medical Library.)

that dogs responded with a rapid lowering of blood pressure. The extract, injected intravenously, first caused an increase in heart beat, which returned to normal while the blood pressure remained low during a period lasting from 45 minutes to 2-1/2 hours. Gaultier's investigations stimulated a great deal of interest in mistletoe, and in the following decades numerous studies appeared in the European medical literature.²⁴ In 1908, Gaultier received a special prize from the Académie de Médecine in Paris for his research on mistletoe.

Gaultier's recommendation of mistletoe extract, however, was not universally accepted. A study published in 1911 by Felix Dossin,²⁵ a physician from the University of Liège (Belgium), showed that mistletoe was not clinically useful. Inspired by the then-recent interest in hypertension, Dossin tested several substances, including mistletoe. Using two different extracts of mistletoe (one prepared according to Gaultier's method and the other produced by Parke-Davis pharmaceutical company), he confirmed its hypotensive action. However, the lowering of blood pressure was first preceded by a rise in pressure, frequently accompanied by convulsions.

In Dossin's opinion, the use of mistletoe was too dangerous, and better results could be obtained with other medications. It is not clear how European physicians responded to Dossin's 1911 condemnation of mistletoe as a therapeutic drug. However, his research was reported more widely in the United States *Dispensatory*²⁶—a fact that may explain, at least in part, why American physicians never embraced mistletoe to the extent their European colleagues did.

By the 1920s, preparations of *Viscum album* (or gui) had gained considerable popularity in Europe as a vasodilator. American physicians, aware of the attention mistletoe was receiving, did indeed try it.

James P. O'Hare, an authority on hypertension, and his colleague Lyman H. Hoyt reported, however, that the reduction in blood pressure was "neither striking nor uniform." Whatever preparation they used (possibly Viscysate, commercially produced by Ernst Bischoff in New York) was not effective. In fact, they concluded that "the changes observed are, by and large, well within the limits of the usual fluctuations found in the average hypertensive patient under no treatment."²⁷

Upon the suggestion of the eminent Pasteur Vallery-Radot, O'Hare and Hoyt tried another mistletoe preparation, "Intrait de Gui," imported from Paris. The results were more encouraging: of the 78 patients participating in the clinical trial at the Peter Bent Brigham Hospital in Boston, 75% found relief from headache associated with hypertension. As for the reduction in peripheral blood pressure, only 25% of the patients showed any improvement that the Boston physicians thought worthy of consideration. They concluded that mistletoe, given in the form of "Intrait de Gui" was a useful drug in the treatment of cerebral symptoms of hypertension.²⁸ Several years later, reviewing the various drugs used in hypertension, O'Hare reiterated that the French extract of mistletoe was effective in alleviating hypertensive headache and dizziness.²⁹

Viscysate, the mistletoe preparation commercially available in the United States, did not become a popular drug. C.S. Danzer, a practitioner in Brooklyn, confirmed its ineffectiveness in lowering blood pressure.³⁰ It was, nevertheless, useful in the symptomatic management of patients with hypertension and arteriosclerosis. "The outstanding effects from the drug," Dr. Danzer maintained, "are the relief of symptoms and the sense of well-being." His clinical experience indicated that *Viscum album* deserved wider application than it had received. In the following years, the pharmaceutical literature continued to list Viscysate as a vasodilator and sedative, but it appears that the drug went out of existence in the United States in the 1950s.³¹

Conclusion

For over 2 millennia, mistletoe has been employed in the treatment of a variety of diseases, ranging from skin afflictions and nervous disorders to sterility and cancer. Although the first use of mistletoe in cardiovascular disorders cannot be determined accurately, it surfaced as a folk remedy in the late 19th century. Extracts of mistletoe of unknown composition were administered to treat cardiac cases and even to stop hemorrhages. Reluctant to adopt such folk practices, the medical profession nevertheless accepted mistletoe as an antihypertensive agent, due mostly to the experimental work of René Gaultier. It has been used

as a vasodilator since the turn of the century. American physicians appear to have been more suspicious of mistletoe than their colleagues in Europe—the ancient land of the Celts, where the semiparasitic plant has indeed established deeper roots.

In recent years, there has been a great deal of interest in mistletoe as an antineoplastic drug,* and in the so-called Misteltherapie.³² While advocates of alternative medicine (mostly in Germany) endeavor to show the antitumor activity of mistletoe, members of the regular profession continue to question the findings.³³ Given the ability of mistletoe to survive through the ages as a medication for one ailment or another, though, I wonder whether it yet will have therapeutic application to some disease or condition in the century to come.

*The database MEDLINE® alone lists over 60 articles published on mistletoe research in the last five years.

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