

Review

Taxines: a review of the mechanism and toxicity of yew  
(*Taxus spp.*) alkaloids

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**Abstract**

This literature review summarizes relevant information and recent progress regarding the scientific investigations of taxine alkaloids. Taxines are the active, poisonous constituents in yew plants (*Taxus spp.*) and have been implicated in animal and human poisonings. Several taxine alkaloids have been isolated and characterized through the use of high performance liquid chromatography, mass spectroscopy, and nuclear magnetic resonance. Recently, as a result of electrophysiological investigations, significant progress has been made with regard to their pharmacological and toxicological mechanisms of action. Current investigations suggest that their chief action is on cardiac myocytes resulting in heart failure and death in instances of animal and human poisoning. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Yew; *Taxus*; Taxine; Toxicity; Physiology; Review; Human; Animal

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## 1. Introduction

Yews (*Taxus spp.*, Taxaceae) are evergreen, gymnospermous shrubs commonly used for ornamental landscaping. The most common horticultural varieties are English yew (*Taxus baccata*), Pacific or Western yew (*Taxus brevifolia*), American yew (*Taxus canadensis*), and Japanese yew (*Taxus cuspidata*) (Kingsbury, 1964). These plants are toxic and have been implicated in human and animal poisonings.

The poisonous nature of the yew plant has been cited since the second century B.C. (Bryan-Brown, 1932). Julius Caesar (102–44 B.C.) documented an instance when Catuvolcus, the king of Eburones, poisoned himself with yew ‘juice’ (Fröhne and Pfänder, 1984). Celts committed ritual suicides by drinking extracts from yew foliage and used the sap to poison the tips of their arrows during the Gaelic Wars (Foster and Duke, 1990; Hartzell, 1995). Some primitive cultures even used extracts as fish and animal poisons to aid in hunting (Watt and Breyer-Brandwijk, 1962; Hartzell, 1995). During the 18th and 19th centuries, people in Europe and India used decoctions of yew leaf as an abortifacient and an emmenagogue (Bryan-Brown, 1932; Watt and Breyer-Brandwijk, 1962).

The toxicity of the yew is ascribed to taxine alkaloids that are present in all parts of the plant except the scarlet aril (berry) (Bryan-Brown, 1932). To date, several taxines and their structural analogues have been characterized. This literature review is intended to survey what is known about both the pharmacology and toxicity of taxines with emphasis on their structural characteristics.

## 2. Characterization of taxines

### 2.1. Early investigations

Investigations leading to the characterization of taxines date from 1828 when Peretti chemically analyzed the leaves of English yew (*T. baccata* L.). He discovered that the leaves contained a ‘bitter’ volatile oil, oxalic acid lime, chlorophyll, and resin; his methodology is not cited (Lucas, 1856).

Lucas (1856) was the first to phytochemically analyze yew foliage (*Taxus baccata* L.) for alkaloid content. He recovered a white, non-crystalline powder and called this ill-defined residue ‘taxine.’ Twenty years later Marmé, a French scientist, became the first to isolate a crystalline form of taxine using an extraction method similar to Lucas’s (Hilger and Brande, 1890).

Hilger and Brande (1890) derived a basic molecular formula of taxine based on elemental combustion analyses. Exploiting taxine’s solubility in acid, they crystallized a variety of taxine salts. The percent composition of carbon, hydrogen, nitrogen, and oxygen in these taxine salts was determined. From this information,

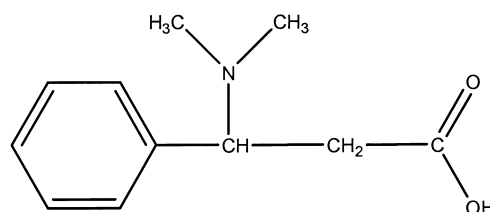


Fig. 1. Partial structural formula for taxine, proposed by Winterstein, 1921. ( $\beta$ -Dimethylamino- $\beta$ -phenylpropionic acid).

Table 1  
Physical and chemical properties of taxine alkaloids

	Taxines	Molecular formula	Melting point (°C)	Optical rotation	UV max (nm)	IR max (cm <sup>-1</sup> )
1a.	Taxine A	C <sub>35</sub> H <sub>47</sub> NO <sub>10</sub>	204–206	[α] <sub>D</sub> <sup>20</sup> = -140°	220, 255	1780, 1250
1b.	2-Deacetyltaxine A	C <sub>33</sub> H <sub>45</sub> NO <sub>9</sub>	–	[α] <sub>D</sub> <sup>20</sup> = -106°	224, 264	1734, 1691
1c.	Taxine B	C <sub>33</sub> H <sub>45</sub> NO <sub>8</sub>	115	[α] <sub>D</sub> <sup>25</sup> = +116°	210, 277	3578, 1730
1d.	Isotaxine B	C <sub>33</sub> H <sub>45</sub> NO <sub>8</sub>	–	–	282	–

they derived a crude molecular formula for taxine: C<sub>37</sub>H<sub>52</sub>NO<sub>10</sub>.

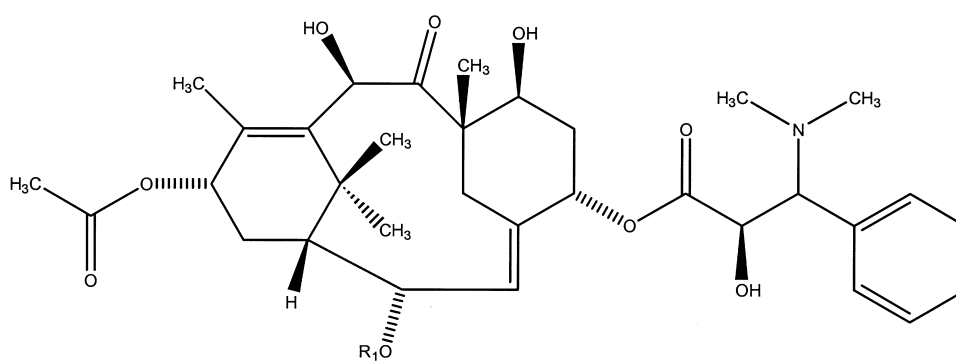
In 1921, Winterstein and colleagues investigated degradation products of amorphous taxine in order to elucidate its structural components (Graf and Boeddeker, 1956). Using acid hydrolysis, they recovered a crystalline degradation product identified as β-dimethylamino-β-phenylpropionic acid. Based on this research, they suggested that taxine was an alkaloid containing esters of this compound and deduced a partial structural formula for taxine (Fig. 1). However, many investigators questioned this derived structural formula because the homogeneity of their taxine extract was questionable.

Graf and Boeddeker (1956) discovered that taxine was a mixture of heterogeneous compounds. Proof of this alkaloid's heterogeneity began with the analysis and isolation of Winterstein's β-dimethylamino-β-phenylpropionic acid. Cleavage of this compound resulted in hydrocinnamic acid (determined spectrophotometrically) and dimethylamine (determined by alkaline hydrolysis).

Utilizing this method, Graf demonstrated that taxine is a mixture of unstable alkaloids. Further investigations relating to the distribution of total taxines determined spectrophotometrically, chromatographically, and by infrared (IR) analysis made it possible for Graf to recognize two major types of taxine alkaloids: taxine A and taxine B (Graf, 1956).

## 2.2. Taxines A

Graf examined amorphous taxines for uniformity using electrophoresis (Graf, 1956). Of the two major bands observed, the fastest moving band was taxine A, which comprised approximately 1.3% of the total alkaloid extract. Spectrophotometric analyses have since revealed the molecular formula of taxine A as well as its basic physical and chemical properties (Graf and Bertholdt, 1957; Graf et al., 1982 and Table 1a). Graf et al. (1982) elucidated the structural formula for taxine A using proton/carbon nuclear magnetic resonance (<sup>1</sup>H/<sup>13</sup>C-NMR) and X-ray diffraction (Fig. 2a).



	Taxine Alkaloids	R <sub>1</sub>
2a.	Taxine A	Ac
2b.	2-Deacetyltaxine A	H

Fig. 2. Structural formulas for taxines A.

Poupat et al. (1994) isolated an analogue of taxine A, 2-deacetyltaxine A ( $C_{33}H_{45}NO_9$ ), from the leaves of *T. baccata* (Table 1b). The structure of 2-deacetyltaxine A was established using chemical ionization mass spectroscopy (CIMS) and  $^1H/^{13}C$ -NMR (Fig. 2b).

### 2.3. Taxines B

As mentioned previously, electrophoretic examination of amorphous taxines revealed two major bands. The slower migrating band, taxine B, represented approximately 30% of the total alkaloid fraction extracted from *T. baccata* L. (Graf, 1956; Graf and Bertholdt, 1957). In further experiments, Graf used  $^{13}C$ -NMR to derive a structural formula for taxine B (Graf et al., 1986). However, Ettouati et al. (1991) scrutinized Graf's results and revised the structural formula by means of  $^1H$ -detected multiple bond heteronuclear multiple quantum coherence spectroscopy ( $^1HMBC$ ) (Table 1c and Fig. 3a).

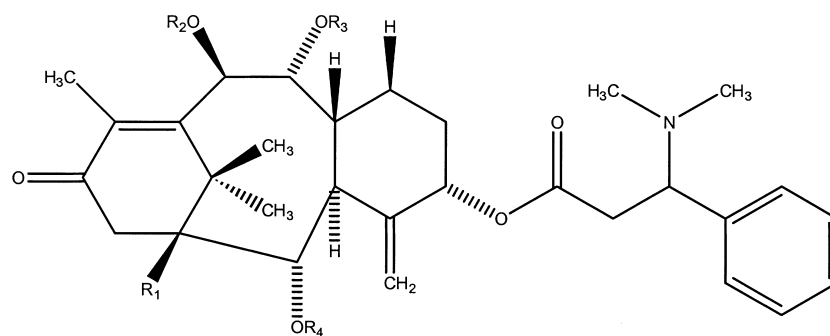
$^1H/^{13}C$ -NMR analysis of purified taxine fractions from *Taxus spp.* reveals the presence of several taxine B-related compounds. Isotaxine B ( $C_{33}H_{45}NO_8$ ), a structural isomer of taxine B, is present as a major constituent in the alkaloid fractions (Poupat et al., 1994; Jenniskens et al., 1996; Potier et al., 1997; Adeline et al., 1997; Table 1d and Fig. 3b). Present as minor constituents in *Taxus spp.* are 1-deoxytaxine B (Fig. 3c) and 1-deoxyisotaxine B (Fig. 3d) (Jenniskens et al., 1996; Potier et al., 1997). Taxine B, isotaxine B,

1-deoxytaxine B, and 1-deoxyisotaxine B are easily separated using HPLC (Jenniskens et al., 1996; Potier et al., 1997). Also present as minor constituents, at approximately 2% of the total concentration, are the taxine B pseudoalkaloids 13-deoxy-13 $\alpha$ -acetyloxy-taxine B ( $C_{35}H_{49}NO_9$ ), 13-deoxy-13 $\alpha$ -acetyloxy-1-deoxytaxine B ( $C_{35}H_{49}NO_8$ ), and 13-deoxy-13 $\alpha$ -acetyloxy-1-deoxy-nortaxine B ( $C_{34}H_{47}NO_8$ ) (Appendino et al., 1997).

In a series of publications, between 1958 and 1967, Lythgoe and colleagues investigated ester derivatives of taxines extracted from *T. baccata* L. and described two additional taxines, taxine I and taxine II (Baxter et al., 1958, 1962; Lythgoe and Harrison, 1966; Dukes et al., 1967). More recent investigations substantiated the conclusion that taxine I, often referred to as diacetyltaxine B, is synthesized by acetylation of taxine B and therefore, the natural occurrence of taxine I in yew is questionable (Graf et al., 1986; Ettouati et al., 1991; Jenniskens et al., 1996 and Fig. 4).

### 3. Chemical characteristics

Important chemical characteristics of taxines have also been recognized. For example, taxines are a mixture of alkaloids formed from nitrogen-free polyhydroxylic diterpenes (taxicins) esterified with  $\beta$ -dimethylamino- $\beta$ -phenylpropionic acid and acetic acid (Graf and Boeddeker, 1956; Baxter et al., 1962; Graf



	Taxine Alkaloids	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
3a.	Taxine B	OH	Ac	H	H
3b.	Isotaxine B	OH	H	Ac	H
3c.	1-Deoxytaxine B	H	Ac	H	H
3d.	1-Deoxyisotaxine B	H	H	Ac	H

Fig. 3. Structural formulas for taxines B.

et al., 1963). Many researchers noted that taxine extracts were particularly unstable in a neutral or alkaline environment, observing a decrease in toxicity of their crude extracts over time (Bryan-Brown, 1932; Graf and Boeddeker, 1956; Baxter et al., 1962; Jenniskens et al., 1996). In the presence of alkaline solutions, the  $\beta$ -amino ester structural group of taxines promotes elimination of dimethylamine from the parent compound leading to the formation of cinnamoyl taxanes (Baxter et al., 1962; Jenniskens et al., 1996). This instability is also characterized by acetyl group migration and photodegradation (Jenniskens et al., 1996). However, it has been shown that conversion of amorphous taxines into sulfate salts increases the stability of the compound (Tekol, 1985). Therefore, sulfate salts of taxines are stable in solid form maintaining their toxicity over time (Tekol, 1985; Jenniskens et al., 1996).

Amorphous taxines persist as granular powders (Graf and Bertholdt, 1957; Jenniskens et al., 1996). Amorphous taxines are readily soluble in dilute acids, low esters, low ketones, alcohols, chloroform, di- and trichloroethane, as well as acetic acid. However, taxines are only slightly soluble in water and practically

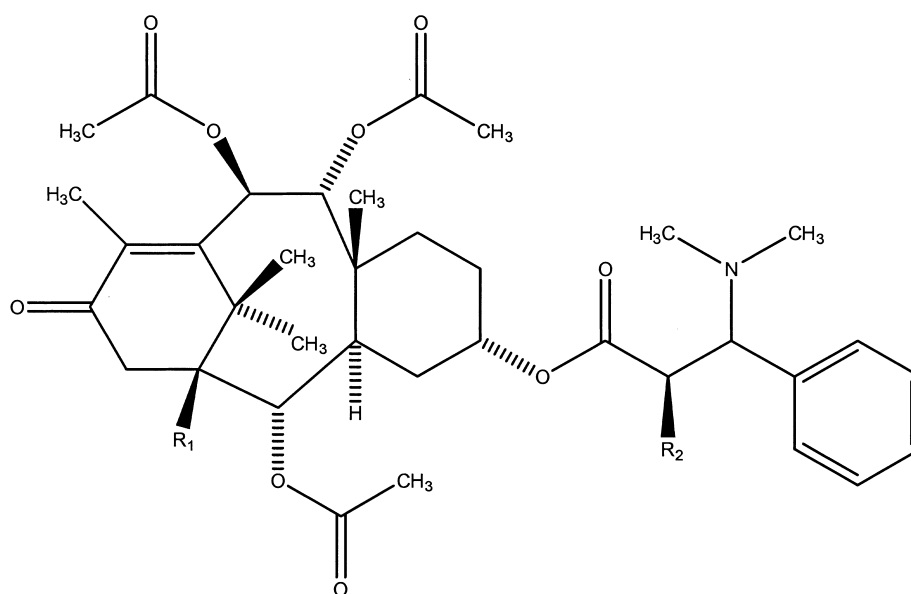
insoluble in petroleum ether (Lucas, 1856; Graf and Bertholdt, 1957). Taxine salts are lyophilic forming prisms in chloroform and resemble crude needles in methanol (Graf and Bertholdt, 1957).

#### 4. Pharmacology

##### 4.1. Early investigations

Early pharmacological investigations of taxine alkaloids revealed that their chief action is cardiovascular. In 1921, Winterstein and Iatrides injected lethal doses (0.004–0.009 g/kg body weight) of crude taxine extracts intraperitoneally and intravenously into rabbits and dogs (Bryan-Brown, 1932). Hypotension, ultimately resulting in cardiac arrest, occurred in both species at these doses. Additionally, when the initial onset of hypotension was observed, Winterstein and Iatrides noted that peristaltic contractions of the gastrointestinal tract ceased.

Bryan-Brown directed the first comprehensive pharmacological research of taxines in 1932. Electrocardiograms recorded from isolated perfused hearts of



	Taxine Alkaloids	R <sub>1</sub>	R <sub>2</sub>
4a.	Taxine I	OH	H

Fig. 4. Structural formula for taxine I.

rabbits and frogs revealed that crude taxine extracts gradually induce bradycardia resulting in diastolic cardiac arrest. Further investigations have indicated that taxines depress atrio-ventricular (A-V) conduction in a dose-dependent manner in an isolated frog heart having the greatest effect on the ventricular rate (Smythies et al., 1975; Tekol and Kameyama, 1987). This hypotensive effect could not be inhibited by atropinization, vagotomy, or ganglionic/adrenergic blockade (Bryan-Brown, 1932; Vohora, 1972). Thus, the hypotension induced by taxine extracts was not mediated via the sympathetic or parasympathetic nervous systems, but rather by a direct action on the myocardium (Vohora, 1972).

#### 4.2. Cardiovascular actions of taxines A and B

Although recent research suggests that the yew's poisonous properties are due to the combined activity of taxine alkaloids, large differences in the cardiotoxicity of taxine A and taxine B have been reported (Alloatti et al., 1996; Bauereis and Steiert, 1959). Infusions of taxine B administered in vivo and in vitro experiments reveal that taxine B is more cardiotoxic than taxine A (Alloatti et al., 1996; Bauereis and Steiert, 1959). Taxine B induces inotropic effects while causing marked changes in A-V conduction. In isolated perfused guinea pig hearts, a 5  $\mu\text{M}$  concentration of taxine B markedly increased A-V conduction time and QRS duration, while 1  $\mu\text{M}$  concentrations (lowest concentration used) were sufficient to significantly reduce heart rate (Alloatti et al., 1996). These changes ultimately resulted in II/III degree A-V conduction blocks and complete diastolic cardiac arrest. This marked increase in QRS duration has also been reported in one case of human poisoning by yew ingestion (Matthew et al., 1993). Additionally, taxine B causes a marked reduction in the maximum rate of depolarization of the action potential in isolated papillary muscle and thus, resembles the action of class I antiarrhythmic drugs (e.g., flecainide, procainamide, quinidine) (Alloatti et al., 1996; Tekol, 1985; Bauereis and Steiert, 1959). Taxine A, however, has minimal effects on A-V conduction time and QRS duration. Even at the highest concentration used (10  $\mu\text{M}$ ), taxine A induced only mild reductions in heart rate (Alloatti et al., 1996).

#### 4.3. Effects on other organ systems

Minor effects of taxines have been reported in other organ systems. In the few studies reported, crude taxine extracts have adverse effects in involuntary muscles, but have no action on voluntary muscles, (Bryan-Brown, 1932; Vohora, 1972). Contraction of the uterus in situ, relaxation of the intestines, and in

some cases contraction of the duodenum and ileum were noted in experimental animals dosed with yew extracts (Bryan-Brown, 1932; Vohora, 1972). Recently, Tekol and Gögüsten (1999) reported that taxine sulfate inhibits peristaltic movement reducing the amplitude of contractions in the jejunum (rabbit) with a median inhibitory concentration of  $1.86 \times 10^{-5}$  g/ml.

#### 4.4. Mechanism of action

Research regarding the mechanism of action of taxines has utilized crude extracts of taxines from yew, as opposed to using purified taxines A and B. However, because taxine B is present as the major alkaloid and because it is more potent than other taxine alkaloids, it is assumed that the primary effects of taxines in the following investigations are a direct result of the activity of taxine B.

Preliminary investigations of taxine extracts on cardiac myocytes and medullated axons indicated that taxines cause an increase in cytoplasmic calcium by altering both calcium and sodium ion channel conductance (Smythies et al., 1975; Tekol, 1985; Tekol and Kameyama, 1987; Tekol, 1991). Recent electrophysiological investigations have demonstrated that taxines are calcium and sodium channel antagonists (Tekol and Kameyama, 1987; Tekol and Gögüsten, 1999). Electrophysiological studies, conducted by Tekol and Kameyama (1987), investigated the effects of taxines on membrane channel currents in isolated ventricular cells from guinea pigs. Under current/voltage clamp conditions, taxines inhibited calcium ( $I_{\text{Ca}}$ ) and sodium ( $I_{\text{Na}}$ ) currents decreasing the amplitudes of each in a dose-dependent manner. They concluded that taxines have  $I_{\text{Ca}}$  and  $I_{\text{Na}}$  inhibiting properties similar to the action of antiarrhythmic drugs.

Recent investigations regarding the cardioselectivity of taxines have provided more conclusive evidence that they are calcium channel antagonists (Tekol and Gögüsten, 1999). Isolated aorta, atrium, and jejunum preparations from rabbits were used to compare the cardioselectivity of taxines to verapamil, a known calcium channel antagonist. Using patch-clamp conditions, taxines elicit a dose-dependent inhibition of calcium ( $\text{Ca}^{+2}$ )-induced contractions in the aorta at concentrations as low as  $10^{-6}$  g/ml (1.7  $\mu\text{M}$ ). Inotropic and chronotropic effects were observed in the isolated rabbit atrium at taxine concentrations equal to  $10^{-7}$  g/ml (0.17  $\mu\text{M}$ ). In isolated jejunum, taxines inhibited peristaltic movements completely at doses of  $10^{-4}$  g/ml (170  $\mu\text{M}$ ); however, at concentrations below  $10^{-4}$  g/ml, their effects on peristaltic contractions were unremarkable. In this study, investigations comparing the cardioselectivity of taxines to verapamil in tissue preparations revealed that verapamil is more potent. Inotropic effects of verapamil on the aorta and atrium

Table 2  
Oral lethal doses of yew leaves in animals

Animal	Estimated average body weights <sup>a</sup> (kg)	LD <sub>min</sub> of yew leaves (g)	LD <sub>min</sub> (g yew leaves/kg body weight)	Estimated LD <sub>min</sub> of taxines (mg/kg body weight)	Reference <sup>b</sup>
Chicken	1.82	30	16.5	82.5	C
Cow	250	500	2.0	10.0	C
Dog	13	30	2.3	11.5	C
Goat	40	480	12.0	60.0	C
Horse	500	100–200	0.2–0.4	1.0–2.0	C
Pig	102	75	0.7	3.5	C
Sheep	40	100	2.5	12.5	C
Mouse	0.025	N.R. <sup>c</sup>	N.R. <sup>c</sup>	0.5 (s.c.) <sup>d</sup>	T
Rat	0.25	N.R. <sup>c</sup>	N.R. <sup>c</sup>	5.0 (s.c.) <sup>d</sup>	T
Human	80	50–100	0.6–1.3	3.0–6.5	W
Rabbit	2.5	1.75	0.7	3.5	W

<sup>a</sup> Estimated average body weights of adult animals in Table 2 referenced in Spector, 1956.

<sup>b</sup> References: C = Clarke and Clarke (1988), T = Tekol (1991), Tekol and Gögüsten (1999), W = Watt and Breyer-Brandwijk (1962).

<sup>c</sup> N.R. = data not reported.

<sup>d</sup> (s.c.) = Rat LD<sub>min</sub> is based on subcutaneous dose.

were minimal, while the chronotropic effects of verapamil were more selective for the aorta. From these experiments, Tekol and Gögüsten concluded that taxines are more cardioselective than verapamil, their mechanism of action is primarily based on their Ca<sup>2+</sup>-channel antagonistic properties, and that taxines could potentially provide a valuable treatment for cardiac disturbances. It is likely that the toxicity of taxines in animals and humans also occurs through this same mechanism.

## 5. Toxicity

With the exception of the aril, all parts of the yew plant contain taxine alkaloids and are poisonous. Whether fresh or dried, toxic levels of taxines remain in the plant throughout the year (Alden et al., 1977), while maximal concentration occurs during the winter season (Watt and Breyer-Brandwijk, 1962). It has been reported that taxines are relatively abundant in English yew (*T. baccata*) and Japanese yew (*T. cuspidata*), yet only minimal amounts are found in Pacific yew (*T. brevifolia*) (Tyler, 1960; Suffness, 1995).

The vast majority of clinical cases of taxine poisoning occur in livestock. Poisoning is often accidental and is frequently a result of livestock being unwittingly fed clippings from yew (*Taxus spp.*) bushes. In early toxicity studies of taxines in animals, minimum lethal dose (LD<sub>min</sub>) values were assessed based on oral doses of yew leaves and branches (Watt and Breyer-Brandwijk, 1962; Clarke and Clarke, 1988). Using these values, and estimating that 1 g of yew leaves contains approximately 5 mg of taxines (Smythies et al., 1975; Tekol, 1985; Jenniskens et al., 1996; Tekol and Gögüsten, 1999), minimal toxic doses of taxines (mg/kg body weight) in animals can be estimated and are summarized in Table 2. The body weights of the animals listed are average values for adult animals only (Spector, 1956). It is evident from Table 2 that the minimal toxic dose of taxines varies between species of animals. Comparatively, horses are more sensitive (LD<sub>min</sub> of 1.0–2.0 mg/kg) and chickens are least sensitive (LD<sub>min</sub> of 82.4 mg/kg). Additionally, there has been one case report supporting the decreased sensitivity of the avian species to the toxicity of taxines. In this case report, llamas, chinchillas, macaws, and parrots were inadvertently fed clippings from yew bushes. From this incident, one llama and one chinchilla were found dead the following day. Taxine alkaloids were detected in the rumen/stomach contents of each animal. However, no adverse clinical signs were observed in the macaws or parrots that had ingested the yew clippings (unpublished clinical case, abstract presented at the World Association of Veterinary Laboratory Diagnosticians, Annual Meeting, June, 1999).

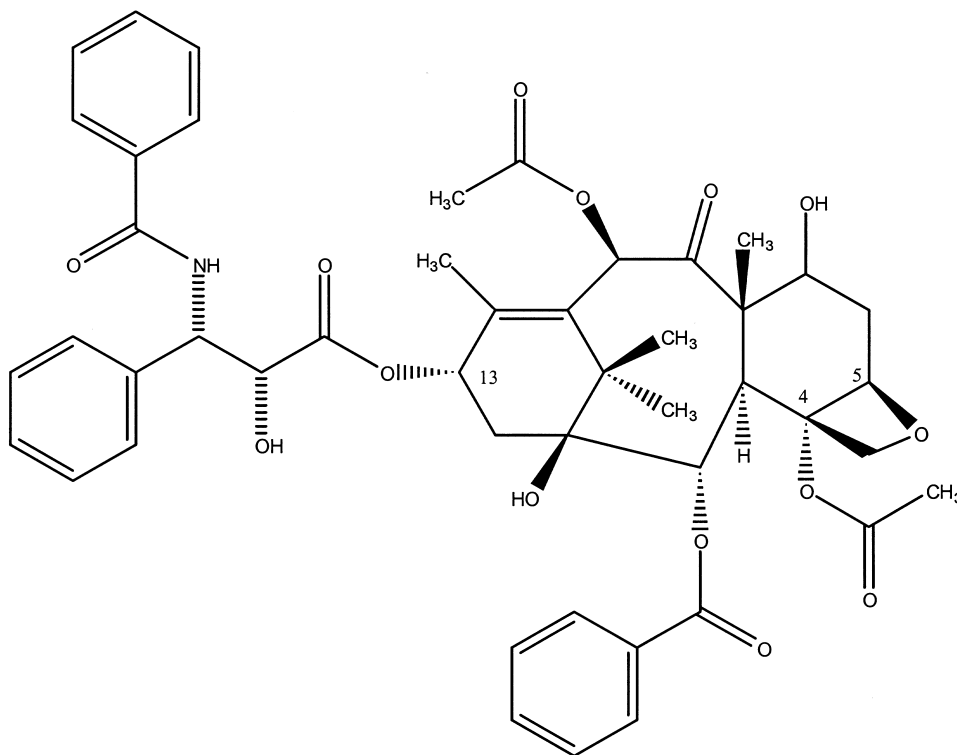


Fig. 5. Structural formula for paclitaxel.

## 6. Signs and symptoms of poisoning

Clinical signs in livestock vary depending on the degree of toxicosis. In most cases of acute poisoning, animals are often found dead. In subacute poisonings, which occur infrequently, clinical signs may include ataxia, bradycardia, dyspnea, muscle tremors, recumbency, and convulsions leading to collapse and death (Evers and Link, 1972; Casteel and Cook, 1985; Veatch et al., 1988; Evans and Cook, 1991; Tekol, 1991; Arai et al., 1992). In cases of deliberate yew poisoning in humans, signs and symptoms are similar to those reported in animals. Human ingestion of yew causes dizziness, pupil dilation, nausea, vomiting, diffuse abdominal pain, tachycardia (initially), muscle weakness, and convulsions (Blyth, 1884; Czerwek and Fischer, 1960; Fröhne and Pribilla, 1965; Schulte, 1975). These symptoms can proceed to bradycardia, bradypnea, diastolic cardiac standstill, or death (Blyth, 1884; Fröhne and Pribilla, 1965; Schulte, 1975; Sinn and Porterfield, 1991).

## 7. Diagnosis of taxine poisoning in livestock

History of exposure and identification of the yew

(*Taxus spp.*) in the digestive tract are crucial to the diagnosis of taxine poisoning in animals. In suspect cases, yew fragments are either found in the mouth, stomach content, rumen content, and/or small intestine. Sometimes exposure may be evident, yet gross identification of plant material is unconfirmed (or vice versa). Hence, diagnosis of taxine poisoning can prove to be difficult. In horses for example, complete mastication of their food can limit the ability to grossly identify yew leaves in their ingesta, often requiring a more detailed microscopic evaluation (Karns, 1983). Additionally, thin-layer chromatography (TLC) can be used to confirm the presence or absence of taxine alkaloids in extracts from stomach/rumen contents (Stahr et al., 1977). Vanillin-sulfuric acid spray has been utilized as a developing reagent for the detection of taxine alkaloids with TLC separation (Touchstone and Dobbins, 1978; personal observation, method presented at the American Association of Veterinary Laboratory Diagnosticians, Annual Meeting, October, 1997).

## 8. Pathology

Post-mortem evaluations of acute poisonings in animals are usually unremarkable. Gross visible abnorm-



alities are often absent and microscopic lesions are rarely observed (Kingsbury, 1964; Alden et al., 1977; Ogden, 1988; Rooks, 1994). In subacute poisonings, gastroenteritis may be evident; however, the inflammation is probably due to an irritant oil present in the yew and not taxine (Watt and Breyer-Brandwijk, 1962; Kingsbury, 1964; Evans and Cook, 1991). Rarely, other gross changes are observed. These changes can include moderate to severe rumenitis, superficial hemorrhages in the right ventricular myocardium and right atrium, and mild focal interstitial myocarditis (Ogden, 1988; Panter et al., 1993).

### 9. Treatment

Death is often the first indication of exposure in animals that have ingested yew leaves; therefore, no treatment is possible. However, in instances where ingestion has recently occurred, treatment involves symptomatic and supportive care primarily because there is no specific antidote for taxine poisoning. Rumenotomy, followed by replacement therapy with a mixture of mineral oil, electrolytes, activated charcoal, and alfalfa pellets has been effective in treating some cases of taxine poisoning in ruminants (Casteel and Cook, 1985). In subacute poisonings, intramuscular doses of atropine sulfate or lidocaine have been suggested to be beneficial in alleviating the cardiodepressant effect of taxine (Schulte, 1975; Osweiler, 1996). In cases of human poisoning, resulting from deliberate ingestion, treatment has involved induction of emesis or gastric lavage (Arena, 1979), followed by general detoxification measures. A variety of clinical measures such as the administration of circulatory stimulants, artificial respiration, and cardiac pacemakers have not been able to prevent death from yew intoxication (Fröhne and Pfänder, 1984).

### 10. Paclitaxel and taxine B

As previously mentioned, the cardiotoxicity of the

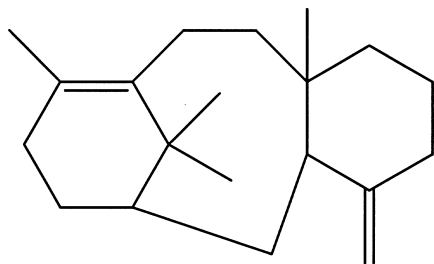


Fig. 6. Taxane ring structure for taxine B and paclitaxel.

yew is attributed to the presence of taxine B. Yews, particularly *T. brevifolia*, also contain paclitaxel, a naturally occurring mitotic spindle poison (Wani et al., 1971 and Fig. 5). Given that both taxine B and paclitaxel have different mechanisms of action, many similarities between the two have been reported. During phase I and phase II clinical trials of paclitaxel, bradycardia occurred in a high proportion of patients (Rowinsky et al., 1991). At high doses, cardiac disturbances such as atrio-ventricular blocks and ventricular tachycardia were also documented (Rowinsky et al., 1991; Gianni et al., 1995). Low concentrations of paclitaxel have no effect on the sodium/calcium permeability in cells; whereas high concentrations inhibit the calcium pump promoting an increase in cytoplasmic calcium (Thuret-Carnahan et al., 1985). This is similar to the electrophysiological mechanism of taxine B on cardiac myocytes (Tekol, 1991; Tekol et al., 1987; Tekol and Göğüsten, 1999) as it has been shown that taxine B blocks calcium and sodium ion channels in cardiac membranes causing an increase in cytoplasmic calcium levels (Tekol, 1991; Tekol et al., 1987; Tekol and Göğüsten, 1999).

The side chains of paclitaxel and taxine B have similar spatial positions; therefore, it is possible that the cardiotoxicity of paclitaxel and taxine B is due to their capability of binding the same ion channels on myocardium (Suffness, 1995). The structural features responsible for the cardiotoxicity of taxine B are not thoroughly understood. However, many similarities between paclitaxel and taxine B have been reported, including the fact that they share the same taxane ring structure (Fig. 6).

### 11. Conclusions

Significant progress has been made regarding the scientific investigations of taxine alkaloids. Through the aid of chromatography, mass spectroscopy, and  $^1\text{H}/^{13}\text{C}$ -NMR, several taxines have been isolated and characterized. Recent electrophysiological studies on taxines have defined their mechanism of action. The recent advancements in understanding their mechanism of action on cardiac myocyte ion channels could lead to the development of useful pharmacological compounds and may provide a more specific, successful treatment of cardiac disturbances caused by exposure of animals and humans to taxine alkaloids.

### References

- Adeline, M.T., Wang, X.P., Poupat, C., Ahond, A., Potier, P., 1997. Evaluation of taxoids from *Taxus spp.* Crude

- extracts by high performance liquid chromatography. *J. Liq. Chrom. Rel. Tech.* 20 (19), 3135–3145.
- Alden, C.L., Fosnaugh, C.J., Smith, J.B., Mohan, R., 1977. Japanese yew poisoning in large domestic animals in the midwest. *J. Am. Vet. Med. Assoc.* 170 (3), 314–316.
- Alloatti, G., Penna, C., Levi, R.C., Gallo, M.P., Appendino, G., Fenoglio, I., 1996. Effects of yew alkaloids and related compounds on guinea-pig isolated perfused heart and papillary muscle. *Life Sci.* 58 (10), 845–854.
- Appendino, G., Özen, H., Fenoglio, I., Gariboldi, P., Gabetta, B., Bombardelli, E., 1997. Pseudoalkaloid taxanes from *Taxus baccata*. *Phytochem.* 33 (6), 1521–1523.
- Arai, M., Stauber, E., Shropshire, C.M., 1992. Evaluation of selected plants for their toxic effects in canaries. *J. Am. Vet. Med. Assoc.* 200 (9), 1329–1331.
- Arena, J.M., 1979. Poisonous plants. In: *Poisoning. Toxicology, Symptoms, Treatments*, 4th ed. Charles C Thomas, Springfield, IL, p. 554.
- Bauereis, V.R., Steiert, W., 1959. Pharmakologische eigenschaften von taxin A und B. *Arzneim.-Forschun.* 9, 77–79.
- Baxter, J.N., Lythgoe, B., Scales, B., Scowston, R.M., Trippett, S., 1962. Taxine. Part I: Isolation studies and the functional groups of *o*-Cinnamoyltaxicin-I. *J. Chem. Soc. (C)*, 2964–2972.
- Baxter, J.N., Lythgoe, B., Scales, B., Trippett, S., 1958. Taxine-I, the major alkaloid of the yew, *T. baccata* L. *Proc. Chem. Soc.*, 9–10.
- Blyth, A.W., 1884. Taxine. In: *Poisons: Their Effects and Detection*. Charles Griffin, London, pp. 383–384.
- Bryan-Brown, T., 1932. The Pharmacological actions of taxine. *Q. J. Pharm. and Pharmacol.* 5, 205–219.
- Casteel, S.W., Cook, W.O., 1985. Japanese yew poisoning in ruminants. *Mod. Vet. Practice* 66, 875–876.
- Clarke, E.G.C., Clarke, M.L., 1988. Poisonous plants, Taxaceae. In: *Veterinary Toxicology*, 3rd ed. Baillière, Tindall & Cassell, London, pp. 276–277.
- Czerwek, H., Fischer, W., 1960. Tödlicher vergiftungsfall mit *Taxus baccata*. *Archiv Toxikol.* 18, 88–92.
- Dukes, M., Eyre, D.H., Harrison, J.W., Scowston, R.M., Lythgoe, B., 1967. Taxine. Part V: The structure of taxicin-II. *J. Chem. Soc. (C)*, 448–462.
- Ettouati, B., Ahond, A., Poupat, C., Potier, P., 1991. Révision structurale de la taxine B, alcaloïde majoritaire des feuilles de L'if D'Europe, *Taxus baccata*. *J. Nat. Prod.* 54 (5), 1455–1458.
- Evans, K.L., Cook, J.R., 1991. Japanese yew poisoning in a dog. *J. Am. Animal Hosp. Assoc.* 27, 300–302.
- Evers, R.A., Link, R.P., 1972. Yews, *Taxus* species. In: *Poisonous Plants of the Midwest and their Effects on Livestock*. College of Agriculture, University of Illinois at Urbana-Champaign, IL, pp. 81–82.
- Foster, S., Duke, J.A., 1990. American yew. In: *Eastern/Central Medicinal Plants*. Houghton Mifflin, Boston, MA, p. 226.
- Fröhne, D., Pfänder, J., 1984. Taxaceae, *Taxus baccata* L., yew. In: *A Colour Atlas of Poisonous Plants*, 2nd ed. Wolfe Publishing, London, pp. 223–225.
- Fröhne, D., Pribilla, O., 1965. Tödliche vergiftung mit *Taxus baccata*. *Arch. für Toxikologie* 21, 150–162.
- Gianni, L., Munzone, E., Capri, G., Fulfaro, F., Tarenzi, E., Villani, F., Spreafico, C., Laffranchi, A., Caraceni, A., Stefanelli, M., Valagussa, P., Bonadonna, G., 1995. Paclitaxel by 3-h infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer: high antitumor efficacy and cardiac effects in a dose-finding and sequence-finding study. *J. Clin. Oncology* 13 (11), 2688–2699.
- Graf, E., 1956. Zur chemie des taxins. *Angew. Chem.* 68, 249–250.
- Graf, E., Bertholdt, H., 1957. Das amorphe taxin und das kristallisierte taxin A. *Pharm. Zentralhalle* 96, 385–395.
- Graf, E., Boeddeker, H., 1956. Zur kenntnis der  $\beta$ -dimethylamino-hydrozimsäure. *Archiv der Pharm. und Berichte der Deutsch. Pharmaz. Ges.* 289, 364–370.
- Graf, E., Boeddeker, H., Johannsen, B., Rosha, R., 1963. Stand der Kenntnis des Taxins. *Abhand. Deutsch. Akad. Wis. Berlin, Klasse für Chem., Geol., Biol.*, 389–394.
- Graf, E., Kinkel, A., Wolff, G.J., Breitmaier, E., 1982. Die Aufklärung von taxin A aus *Taxus baccata* L. *Liebigs Ann. Chem.*, 376–381.
- Graf, E., Weinandy, S., Koch, B., Breitmaier, E., 1986. <sup>13</sup>C-NMR-Untersuchung von taxin B aus *Taxus baccata* L. *Liebigs Ann. Chem.*, 1147–1151.
- Hartzell, H., 1995. Yew and us: a brief history of the yew tree. In: Suffness, M. (Ed.), *Taxol: Science and Applications*. CRC Press, Boca Raton, FL, pp. 27–34.
- Hilger, A., Brande, F., 1890. Ueber taxin, das alkaloid des eibenbaumes (*Taxus baccata*). *Berichte Deutsch. Chem. Ges.* 23, 464–468.
- Jenniskens, L.H.D., van Rozendaal, E.L.M., van Beek, T.A., 1996. Identification of six taxine alkaloids from *Taxus baccata* needles. *J. Nat. Prod.* 59, 117–123.
- Karns, P.A., 1983. Intoxication in horses due to ingestion of japanese yew (*Taxus cuspidata*). *Equine Practice* 5 (1), 12–14.
- Kingsbury, J.M., 1964. Taxaceae. In: *Poisonous Plants of the United States and Canada*. Prentice-Hall, Englewood Cliffs, NJ, pp. 121–123.
- Lucas, H., 1856. Ueber ein in den Blätter von *Taxus baccata* L. enthaltenes Alkaloid (das Taxin). *Archiv der Pharmaz.* 135, 145–149.
- Lythgoe, B., Harrison, J.W., 1966. Taxine. Part III: A revised structure for the neutral fragment from *o*-Cinnamoyltaxicin-I. *J. Chem. Soc. (C)*, 1932–1945.
- Matthew, N., Elsner, G., Purdy, C., Zipes, D.P., 1993. Wide QRS rhythm due to taxine toxicity. *J. Cardiovascular Electrophys.* 3, 59–61.
- Ogden, L., 1988. *Taxus* (yews) — a highly toxic plant. *Vet. Human Toxic.* 30 (6), 563–564.
- Oswiler, G.D., 1996. *Toxicology*. Williams & Wilkins, Philadelphia, PA, p. 393.
- Panther, K.E., Molyneux, R.J., Smart, R.A., Mitchell, L., Hansen, S., 1993. English yew poisoning in 43 cattle. *J. Am. Vet. Med. Assoc.* 202 (9), 1476–1477.
- Potier, C.R., Poujol, H., Ahond, A., Mourabit, A.A., Chiaroni, A., Poupat, C., 1997. Taxoïdes: nouveaux analogues du 7-déshydroxydocétaxel préparés à partir des alcaloïdes de l'if. *Tetrahedron* 53 (14), 5169–5184.
- Poupat, C., Ahond, A., Potier, P., 1994. Nouveau Taxoïde Basique Isolé Des Feuilles d'if, *Taxus Baccata*: La 2-Désacétyltaxine A. *J. Nat. Prod.* 57 (10), 1468–1469.

- Rooks, J.S., 1994. Japanese yew toxicity. *Vet. Medicine* 89, 950–951.
- Rowinsky, E.K., McGuire, W.P., Guaneri, T., Fisherman, J.S., Christian, M.C., Donehauer, R.C., 1991. Cardiac disturbances during the administration of taxol. *J. Clin. Oncology* 9 (9), 1704–1712.
- Schulte, T., 1975. Tödliche Vergiftung Mit Eibennadeln (*Taxus baccata*). *Archiv. Toxikologie* 34, 153–158.
- Sinn, L.E., Porterfield, J.F., 1991. Fatal taxine poisoning from yew leaf ingestion. *J. Forensic Sci.* 36 (2), 599–601.
- Smythies, J.R., Benington, F., Morin, R.D., Al-Zahid, G., Schoepfle, G., 1975. The action of the alkaloids from yew (*Taxus baccata*) on the action potential in the xenopus medullated axon. *Experientia* 31, 337–338.
- Spector, W.S., 1956. In: *Handbook of Biological Data*. Wright-Patterson AFB, OH.
- Stahr, H.M., Hyde, W., Kiesey, J., Ross, P.F., 1977. Alkaloids; extraction and qualitative identification. In: *Analytical Methods in Toxicology*. Iowa State University Press, Ames, IA, pp. 178–183.
- Suffness, M., 1995. *Taxol: Science and Applications*. CRC Press, Boca Raton, FL, pp. 7/8–311/312.
- Tekol, Y., 1985. Negative chronotropic and atrioventricular blocking effects of taxine on isolated frog heart and its acute toxicity in mice. *Planta Med.* 5, 357–360.
- Tekol, Y., 1991. Acute toxicity of taxine in mice and rats. *Vet. Human Toxic.* 33 (4), 337–338.
- Tekol, Y., Gögüsten, B., 1999. Comparative determination of the cardioselectivity of taxine and verapamil in the isolated aorta, atrium, and jejunum preparations of rabbits. *Arzneim.-Forschung* 49 (8), 673–678.
- Tekol, Y., Kameyama, M., 1987. Elektrophysiologische Untersuchungen über den Wirkungsmechanismus des Eibentoxins Taxin auf das Herz. *Arzneim.-Forschung* 37 (4), 428–431.
- Thuret-Carnahan, J., Bossu, J.L., Feltz, A., Langley, K., Aunis, D., 1985. Effect of taxol on secretory cells: functional, morphological, and electrophysiological correlates. *J. Cell Biol.* 100, 1863–1874.
- Touchstone, J.C., Dobbins, M.F., 1978. Visualization procedures. In: *Practice of Thin-Layer Chromatography*. Wiley, New York, p. 212.
- Tyler, V.E., 1960. Note on the occurrence of taxine in *Taxus brevifolia*. *J. Am. Pharm. Assoc.*, 683–684.
- Veatch, J.K., Reid, F.M., Kennedy, G.A., 1988. Differentiating yew poisoning from other toxicoses. *Vet. Medicine* 83, 298–300.
- Vohora, S.B., 1972. Studies on *Taxus baccata*. *Planta Med.* 22 (1), 59–65.
- Watt, J.M., Breyer-Brandwijk, M.G., 1962. Taxaceae. In: *The Medicinal and Poisonous Plants of Southern and Eastern Africa*. E. & S. Livingstone, Edinburgh, pp. 1019–1022.
- Wani, M.C., Taylor, H.L., Wall, M.E., Coggon, P., McPhail, A.T., 1971. Plant antitumor agents. VI: the isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus Brevifolia*. *J. Am. Chem. Soc.* 93, 2325–2327.