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Perspective paper

Recent developments in the field of arrow and dart poisons

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Abstract

Arrow and dart poisons, considered as conventional natural sources for future drug discovery, have already provided numerous biologically active molecules used as drugs in therapeutic applications or in pharmacological research. Plants containing alkaloids or cardiotonic glycosides have generally been the main ingredients responsible for the efficacy of these poisons, although some animals, such as frogs, have also been employed. This paper, without being exhaustive, reports the greater strides made during the past 15 years in the understanding of the chemical nature and biological properties of arrow and dart poison constituents. Examples both of promising biological properties shown by these molecules and of crucial discoveries achieved by their use as pharmacological tools are given. Further studies of these toxic principles are likely to enable scientists to find new valuable lead compounds, useful in many fields of research, like oncology, inflammation and infectious diseases.
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1. Introduction

During the course of their evolution, many plant species have survived through their ability to synthesize and accumulate toxic compounds that protect them against microorganisms, insects, herbivores or even other plants. Some of these toxins have found a role in the subsistence activities of traditional societies, providing a source of arrow and fish poisons. In nearly all parts of the world, hunting poisons prepared from extracts of poisonous plants have been used as auxiliary weapons in the procurement of food and clothes. Indeed, various peoples made their hunting trips more effective by applying poisonous materials to their arrows, darts, spears or javelins. These poisons have also been employed in preventing the depredations of wild animals, or for martial purpose. Frequently, the same poisons were used in ordeals. This involved the administering of a plant poison to the suspect and the subsequent determining of guilt or innocence depending on the poison's effects (e.g. vomiting, urination, . . .). Such products continue to be utilized locally, although to an extent difficult to determine.

Even if monovalent poisons are described, more often they consist of a mixture of materials. Plant extracts containing alkaloids, diterpenoids or triterpenoids, including especially the cardiotonic glycosides, are generally the main toxic compounds responsible for the efficacy of arrow and dart poisons. However, a large number of adjuvants are also added for a variety of reasons: to thicken the extract and enable it to adhere better to the arrow, to augment the effectiveness of the poison, for magical purpose or to hide the real composition of the poison. Besides the use of plant extracts, a few ingredients are obtained from animals.

In subsistence communities, some of these poisons have also been employed as ingredients in or sources of traditional remedies. During the last century, the chemical and pharmacological study of their active principles led to the discovery of famous medicines still used in western countries, the most convincing example of which being the different types of curare (Bisset, 1992a). Arrow and ordeal poisons are still considered today as conventional natural sources for future drug discovery (Tulp and Bohlin, 2004). Moreover, they have been and still are an important source of pharmacological tools, as well as a valuable source of original chemical structures for the development of new drugs.

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In his excellent review written in 1989, Bisset reported the history of arrow and dart poisons and the geographical distribution of their use. He also considered their chemical composition, the pharmacological properties of their active principles and their applications as medicinal agents or pharmacological tools (Bisset, 1989). In this paper, we would like to mention the main discoveries in the field of arrow and dart poisons that have occurred since the publication of this outstanding document.

2. Plant sources

Among the different plant genera listed as ingredients of dart and arrow poisons, the most active are known to contain biodynamically active alkaloids or cardiotonic glycosides, and it seems that members of the other genera function mostly as additives. The latter will not be discussed here.

2.1. Alkaloids

Because of their toxicity, many *Strychnos* species have been used as arrow poisons or in ordeals. Two completely different types of toxic mechanisms are associated with the *Strychnos* species: a tetanising activity caused by strychnine (**1**) and some of its monomeric derivatives and a paralysing action due to a series of quaternary alkaloids included in curare poisons. They are also among the most renowned plants of traditional pharmacopeias.

During the last few decades, different pharmacological properties have been described for *Strychnos* alkaloids (Fig. 1) or extracts (Philippe et al., 2004). For example, recent in vitro screenings of *Strychnos* species for antiplasmodial activity have led, after bioguided purifications, to the isolation of new bisindole alkaloids with promising in vitro activities against chloroquino-resistant strains of *Plasmodium falciparum* (Frédérich et al., 2002). In particular, antiplasmodial sungucine (**2**)-type alkaloids have been isolated from the distinctively red-coloured roots of *Strychnos icaja* Baillon, widely used in ordeal and arrow poisons in West and Central Africa and traditionally employed to treat malaria. The most active alkaloid of this type to date has been strychnogucine B (**3**) (Frédérich et al., 2001). Usambarine-type alkaloids, such as isostrychnopentamine (**4**), have also been isolated from *Strychnos usambarensis* Gilg, the main ingredient of an African curarising arrow poison. The in

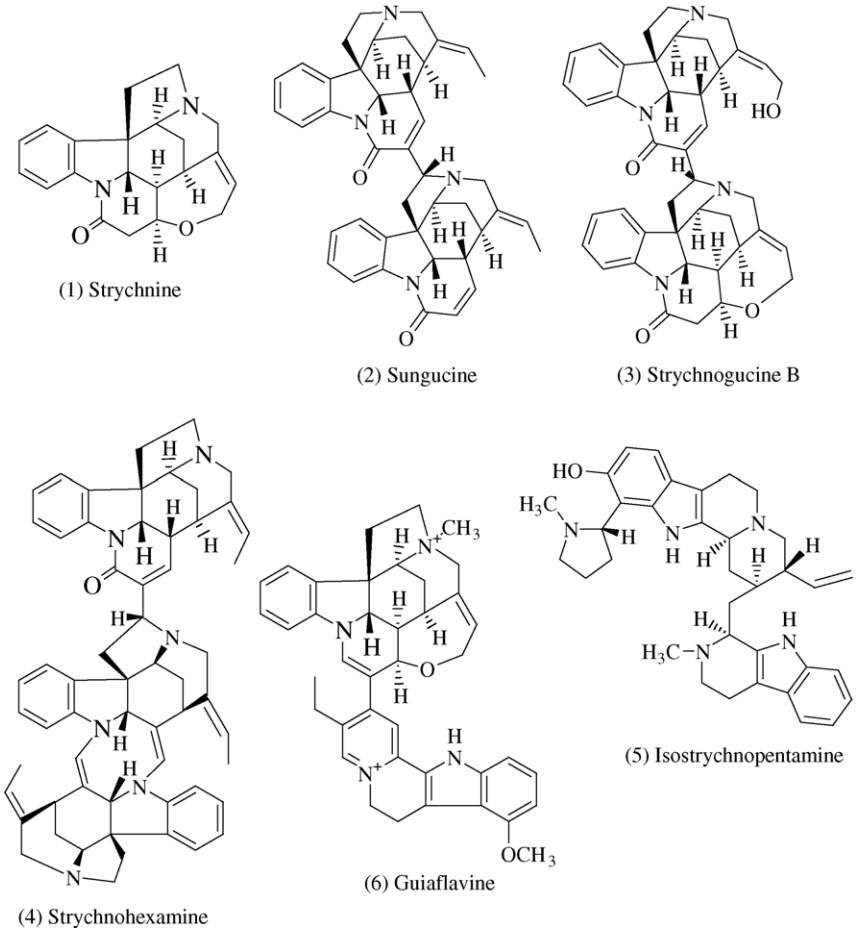


Fig. 1. Structures of alkaloids from *Strychnos* species: strychnine; sungucine and its most antiplasmodial derivative, strychnogucine B; strychnohexamine; isostrychnopentamine; guiaflavine.

vitro and in vivo antimalarial properties of isostrychnopentamine (**4**) have been demonstrated (Frédérich et al., 2004). Its proapoptotic properties have also been shown at a concentration 50–100 times higher than its antiplasmodial properties (Frédérich et al., 2003). In addition, some years ago, the first naturally occurring "trimeric" indolomonoterpenic alkaloid, called strychnohexamine (**5**), possessing mild antimalarial properties, was also isolated from *Strychnos icaja* (Philippe et al., 2002).

Surprisingly, the antinociceptive effects of crude alkaloid fractions of processed and unprocessed strychnine-containing *Strychnos nux vomica* L. seeds in different analgesic tests in mice have been studied: the extracts seemed to be about 1000 times more potent than morphine (Cai et al., 1996). Strychnine (**1**), one of the most famous poisons, is now a frequently used tool in neuropharmacological science (Rajendra et al., 1997): this alkaloid labels specifically the glycine receptor, which is often called "strychnine-sensitive glycine receptor", to avoid confusion with other receptors that glycine modulates.

Many scientists have been fascinated by curare (Bisset, 1992b). Recently, *Strychnos guianensis* (Aubl.) Mart., the first botanically identified plant of South American curares, and one of the most common ingredients of curares, has been reinvestigated. This work has led to the isolation of several bisindole quaternary alkaloids, guiachrysine, guiaflavine (**6**) and their 5′-6′-dehydrogenated derivatives (Penelle et al., 2001). These asymmetrical alkaloids were previously unidentifiable. Indeed, their structure determination was achieved by recent advances in NMR techniques (Phillipson, 1995). In vitro, these alkaloids, and especially guiachrysine, were shown to be very effective antagonists of the human nicotinic acetylcholine receptor (n-AChR), only 2–5 times less potent than *d*-tubocurarine, with a similar mechanism of action (Wins et al., 2003).

Recently, quinolizidine alkaloids have been found in the bark of *Clathrotropis glaucophylla* Cowan, of the Fabaceae family, used as admixture of curare arrow poison in Venezuela. This was the first time quinolizidine alkaloids have been isolated from an arrow poison ingredient and it was also the first report on *Clathrotropis* species being used for preparation of arrow poison (Sagen et al., 2002).

2.2. Cardiotonic glycosides

Even though their therapeutic properties have remained unknown for a long time, the cardiotoxicity of numerous plants containing cardiotonic glycosides has been used in arrow poisons from the earliest times. In patients with heart failure, cardiac glycoside treatment improves symptoms and reduces the need for hospitalization without affecting mortality. In 1997, Jens Christian Skou was awarded the Nobel Prize in chemistry for his discovery of the Na, K-adenosine triphosphatase (Na, K-ATPase or Na, K-pump), which is specifically inhibited by cardiac glycosides. While there is no doubt that cardiac glycosides are safe and effective in heart failure, the underlying mechanisms are still debated (Schwinger et al., 2003).

Besides their cardiotonic properties, the biological properties of cardenolides, and not only those of digitalis (not used in arrow poisons), could be very useful in other medical fields, such as in the treatment of inflammation or cancer. Ouabain (**7**), the rapidly active glycoside found in African *Strophanthus*-based poisons, is frequently used in research (Fig. 2). Its use is not only as a cardiotonic drug, but also as a pharmacological tool, especially in the study of the role of Na/K-ATPase (which seems to be involved in many biological processes) or the role of endogenous cardiotonic steroids (ECS), the putative ligands of the inhibitory binding site of this membrane sodium pump (Bereta et al., 1995; Xie, 2001; Dmitrieva and Doris, 2002, 2003; Masocha et al., 2003; Akimova et al., 2005).

Cardiac glycosides are now considered as potential anticancer drugs. It has been shown that digitoxin in clinically relevant concentrations induces apoptosis in different human malignant cell lines in vitro. This apoptosis-inducing capability seems to be explained by complex dose-dependent mechanisms of action involving many signalling systems, and not only Na, K-ATPase inhibition (Haux, 1999, 2002). In a digitoxin user population, there is a relationship between

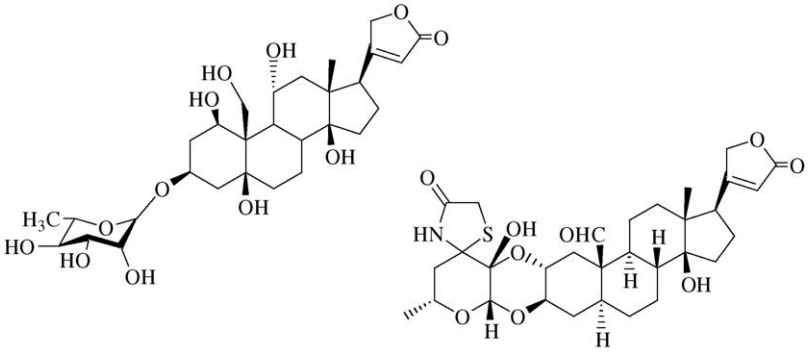


Fig. 2. Structures of ouabain and 2″-oxovoruscharin, two cardiotonic glycosides.

a high plasma concentration of digitoxin and a lower risk of leukaemia/lymphoma and of cancer of the kidney/urinary tract (Haux et al., 2001). The potential value of cardiac glycosides for the treatment of some types of human cancer is supported by recent studies: for example, interest in ouabain (**7**) is demonstrated in androgen-independent prostate cancer (Huang et al., 2004) and interest in ouabain (**7**), digoxin and digitoxin is shown in the area of breast cancer (Kometiani et al., 2005).

The targeting by cardiac glycosides of different pro-inflammatory mediators also represents an attractive approach for the development of new therapeutic strategies to control inflammation. It has been observed that ouabain, when bound to Na/K-ATPase, converts the enzyme into a signal transducer and initiates multiple gene regulatory pathways (Xie, 2001). Although ouabain (**7**) induces activation of the nuclear transcriptor factor-kappa (NF-kappa B) and stimulates VCAM-1 and iNOS expression (Bereta et al., 1995), other cardiotonic glycosides seem promising for the treatment of inflammatory diseases. By suppressing activation of NF-kappa B, oleandrin can suppress inflammation and perhaps tumorigenesis (Manna et al., 2000). Digitoxin also deserves consideration as a candidate drug for the treatment of inflammatory diseases, such as cystic fibrosis (because of its ability to suppress IL-8-dependent lung inflammation) (Srivastava et al., 2004).

Once again, chemists have been inspired by nature and are now trying to synthesize modified cardenolides with better therapeutic indices or with specific properties (for instance, inhibition of human cytochrome P450 (17alpha)) (Schneider and Wolfling, 2004). Moreover, considering that cardiac glycosides are often present in arrow and dart poisons and that numerous plant species involved in arrow poisons have not yet been investigated or only partially so, many molecules with probably original structures could still be isolated from these hunting poisons.

Most of the cardiac glycoside arrow-poison plants (*Strophanthus*, *Acokanthera*, . . .) belong to the Apocynaceae but other families are also important sources of cardenolide-based poisons (Bisset, 1989; Neuwinger, 1996). *Calotropis procera* (Ait.) R.Br., a member of the Asclepiadaceae, is a laticiferous shrub. In African countries, its latex is used in arrow poison. *Calotropis procera* is also a herbal drug used in Ayurvedic medicine. The cytotoxicity of extracts of its root, leaves and flowers has been shown (Smit et al., 1995), as well as the anti-inflammatory activity of its latex (Kumar and Basu, 1994). Different teams of scientists have identified numerous cardenolides, including uscharin and voruscharin, first isolated by Hesse and collaborators in 1939 and 1957 respectively (Brüschweiler et al., 1969; Cheung et al., 1983), and 2″-oxovoruscharin (Fig. 2) (**8**) (van Quaquebeke et al., 2005). Among these, two are protected by patents: uscharin (Anand et al., 2002) and 2″-oxovoruscharin (**8**) (and analogues thereof) (van Quaquebeke et al., 2004). Briefly, both the inventions relate to the use of these molecules as medicaments for treating cancer. In particular, novel cardenolides semisynthetically derived from 2″-oxovoruscharin (**8**) display potent in vitro anti-tumour activity and a high level of in vivo tolerance (van Quaquebeke et al., 2005). The anti-inflammatory compounds of the latex seem to be of a proteinaceous nature (Alencar et al., 2004). Using mice models, a recent study has concluded that the protein fraction derived from the whole latex of *Calotropis procera* possesses antinociceptive activity, which is independent of the opioid system (Soares et al., 2005).

The highly toxic latex from *Antiaris toxicaria* (Pers.) Lesch., belonging to the plant family Moraceae, is well known as one of the major ingredients of arrow and dart poisons made in different parts of Asia. Its toxicity is due to a complex mixture of cardenolide glycosides, which continues to be investigated. An investigation of nine Malaysian dart poisons has confirmed that their main active components are cardenolides from *Antiaris toxicaria* and alkaloids probably from different forms of *Strychnos ignatii* Berg. Two new cardiac glycosides have been isolated and their structures determined (Kopp et al., 1991). Recent bioassay-guided fractionation of the extract of a dart poison from Indonesian Borneo, derived from *Antiaris toxicaria*, has led to the isolation of three new cardenolides, toxicarioside A (Carter et al., 1997a), and its isomers, toxicarioside B and toxicarioside C (Carter et al., 1997b). Other less studied genera of the same botanical family were also investigated a few years ago, which allowed the structural determination of two new glycosides (Shrestha et al., 1992). The latex from *Maquira* Aublet and *Naucleopsis* Miq. species has been used in South America (in Colombia, Ecuador and north-west Brazil) as a source of dart poison. The principal cardiac glycosides present in *Maquira* species are strophanthidin-based and the main ones occurring in *Naucleopsis* species are antiarigenin- as well as strophanthidin-based.

3. Animal poisons

Animals (such as arthropoda, amphibians, snakes, . . .) have been the source of extremely potent toxins used in dart and arrow poisons. These generally act at single or multiple sites of the neuromuscular apparatus (Senanayake and Roman, 1992). Their study has led to the isolation and determination of valuable lead candidates for novel drugs. The specific actions of these toxins are being widely exploited in the study of neuromuscular physiology and pathology. In some countries, arrowheads have been dipped in decomposing animal or human flesh but, in those cases, the toxicity is rather microbial in origin and will not be discussed here.

In South America, three frogs of the family Dendrobatidae, *Phyllobates bicolor*, *Phyllobates aurotaenia* and *Phyllobates terribilis*, secrete toxins ranking among the most powerful animal poisons known: batrachotoxin (**9**) and homobatrachotoxin (Fig. 3). These steroidal alkaloids, already mentioned by Bisset (Bisset, 1989), are potent modulators of voltage-gated sodium channels, leading to

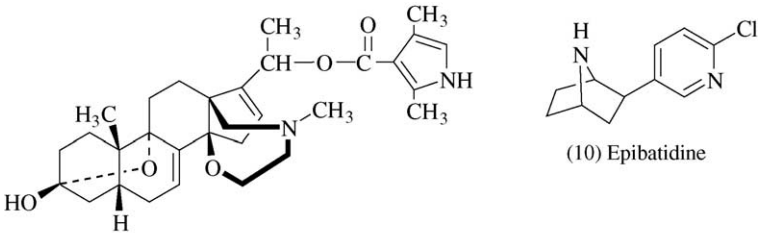


Fig. 3. Structures of poisonous frog alkaloids, batrachotoxin and epibatidine.

irreversible depolarisation of nerves and muscles, fibrillation, arrythmias and eventually cardiac failure. In particular, batrachotoxin (**9**) profoundly modulates the voltage-gated sodium channel $Na_v1.8$, which is considered to be a key player in nociception (Bosmans et al., 2004).

The isolation of batrachotoxin (**9**) and its derivatives has opened the way for the study of poisonous frogs as sources of novel useful chemical structures. Hundreds of alkaloids have been identified in extracts from frog skins, including batrachotoxins, pumiliotoxins (displaying myotonic and cardiotonic activities), histrionicotoxins (non competitive blockers of nicotinic receptor channels and potassium channels), gephyrotoxin (blocking nicotinic acetylcholine receptor-ion channel complex) and epibatidine (Fig. 3) (**10**) (Daly, 1998; Patocka et al., 2000). One of the greatest discoveries over the past 15 years has been the isolation of epibatidine from the skin of Ecuadorian poison frog, *Epipedobates tricolor* (Spande et al., 1992). An increasing number of studies are devoted to the powerful non-opioid analgesic properties of this extremely potent and selective nicotinic agonist (Qian et al., 1993; Gerzanich et al., 1995), which have led to major interest in the use of α_7 agonists in pain (Li et al., 2005). Epibatidine (**10**) is the most powerful natural nicotinic agonist known. Different ways of total synthesis have been described and interestingly, both the (+)- and (−)-isomers of synthetic epibatidine possess similar biological activity. This alkaloid of a new class has become an established source of new drugs and has served as the lead in the design of new ligands selective for distinct nicotinic receptor subtypes (for example: Wei et al., 2004; Baraznenok et al., 2005). Moreover, this alkaloid shows high binding affinity to nicotinic acetylcholine receptors and is, when radioactively labelled, an important neuropharmacological tool for the study of the distribution and characterization of nicotinic receptors (Gotti and Clementi, 2004).

Batrachotoxin alkaloids have also been found in passerine bird species endemic to New Guinea (Dumbacher et al., 1992). The presence of high levels of batrachotoxins in a group of beetles, genus Choresine (family Melyridae), found in the stomach contents of the birds suggests that they sequester these alkaloids from dietary sources. The cosmopolitan family, Melyridae, could be the source of the batrachotoxins found in the highly toxic *Phyllobates* frogs (Dumbacher et al., 2004). In the same way, the presence of pumiliotoxins has been demonstrated in two genera of formicine ants, *Brachymyrmex* and *Paratrechina*, as well as the presence of these ants in the stomach contents of the pumiliotoxin-containing dendrobatid frog, *Dendrobates pumilio* (Smith and Jones, 2004). Evidence now indicates that poison frogs have an efficient system that accumulates alkaloids from dietary alkaloid-containing arthropods. This explains the fact that frogs have been found to completely lack skin alkaloids when raised in captivity (Daly et al., 1994).

4. Conclusion

Indigenous tribes all over the world have discovered numerous plants and also animals with highly toxic properties, useful for hunting and protection from wild animals or enemies. The study of these arrow and dart poisons has led to the discovery of valuable drugs still used today (such as curare), because toxicity generally reflects high biological activity, the secret of an important remedy resting in the applied dose! Arrow and dart poisons nowadays provide chemists and pharmacologists with original chemical structures available for pharmacological screening and/or for semisynthesis. Many are important drugs or tools in hot fields of research, like oncology, inflammation, neuroscience or infectious diseases. Chemical substances derived from natural products have always been a major source of lead compounds for the pharmaceutical industry (Newman et al., 2003). Furthermore, crucial breakthroughs in separation and structure-determination technologies (Koehn and Carter, 2005) are now leading more easily to the isolation and identification of complex molecules that the chemist is not always able to synthesize. Nevertheless, it is important that ethnopharmacologists survey indigenous tribes widely before they completely lose their traditional culture. We hope that these examples of promising natural molecules emphasize how it is essential, for the provision of future effective drugs, to preserve the ecological systems.

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