11. AN ASSESSMENT OF TOXINS

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INTRODUCTION

Toxin weaponry is a new category of the chemical-biological agents spectrum and is especially a challenge to future chemical-biological medical treatment. Obviously, there is a need for assessing the future threat from toxin weapons and determining its development in the future. But many questions often arise regarding the assessment of toxins. Therefore, an overlook discussion will be made in the present paper.

DIVERSITY IN TOXINS

In scientific terms, toxins are biogenic nonreplicating toxic natural substances, which cover an immense range of compounds found in plant, animal and microbial organisms. It is increasingly realized that toxins are not needless natural products of organisms. On the contrary, they are primary products or secondary metabolites with specific functions in biology. Toxins have been shown to play a critical role in the behavior and ecological interaction of different kinds of organisms; the toxins have often likely evolved for specific biological functions, such as defense, offense, digestion etc. On the other hand, the isolation of natural toxins and the study of both the chemical knowledge and the biological information about their functions and specificities have provided a foundation for new drug and agrochemical research.

Diversity is an essential character of nature and a colorful display of life; it seems that toxins also display a distinguishing feature of diversity in many aspects as biogenic sources, chemical structure, functions, and mechanisms of action.

Biogenic diversity

It is the fundamental feature of diversity in toxins; thousands of poisonous substances are produced by a variety of living organisms from various phyla. These include a great quantity of species of living organisms, such as bacteria, fungi, plants, insect, reptile, amphibious animals, and numerous genera of marine organisms. All of these can produce a huge variety of compounds with very different toxic actions.

Chemical diversity

Toxins are a distinct class of active biomolecules in the nature, which span a wide variety of chemical structure types from extremely complex biomacromolecules to very simple organic and inorganic compounds (See Table 1). Furthermore, a number of noticeable structure types in natural toxins do not appear in synthetic molecules. It is obvious that the chemical diversity of natural toxins provide a rich source of lead structure for drug design or biotechnological application.

Diversity of action

Natural toxins act in many different ways on many different life systems and processes in the body. They usually specifically target important enzymes, cell membrane structures, ion-channels, receptors, ribosomal proteins, etc., to induce a vast array of lethal and non-lethal toxic effects. This characteristic diversity is also valuable because it provides new opportunities and selectivities for new drugs and bioactive substance development.

The diversity of natural toxins is very attractive to scientists of biology, chemistry, medicine, drug research and many approaches in life science; research in natural toxins became a new interesting inter-discipline subject - toxinology - in recent decades. In the meanwhile, it implies a risk threat that rapid development in natural toxins open up new opportunities for military purposes.

TOXIN AGENT IN/OUT TOXINS

When we talk about toxins in the chemical biological defense (CBD) arena, the word "toxin" is applied as an abbreviated form of the military term "toxin warfare agents" or "toxin weapon." But, the same word "toxin" in the scientific and CBD fields may have quite different messages. It is true some natural toxins should be listed in the spectrum of toxin warfare agents; however, toxin warfare agents may consist of other meaningful military toxic substances derived from natural toxins indirectly as well. In short, we can say toxin agents are in natural toxins and out of them.

Based on potent toxicity of natural toxins, there are great possibilities and promotive forces to select some of the most poisonous toxins as toxin weapons. Several hundreds of known toxins exhibit toxicity higher than classic nerve agents. It is well known that some toxins from bacteria or marine organisms, botulinum toxin, palytoxin, maitotoxin are even 1,000,000 times more toxic than nerve agents. From one Data Bank of Poisons and Toxins, the data show that in the collection of more than 8000 toxic substances, including synthetic poisons and natural toxins with toxicity up to 10 mg/kg, all known most potent toxic substances, whose toxicity is higher than 0.1 µg/kg, can be classified as natural toxins (As shown in Table 2.) But it is also true that a series of factors other than toxicity may play a major role in developing natural toxins as toxin weapons. Not unexpectedly, up to now, only a very few natural toxins have been reported to be weaponized, stockpiled or used.

On the other hand, especially if one could look into the future, more and more opportunities for toxin weapons may result from indirect approaches to find new toxin agents by making use of the achievements in natural toxin researches. At the present time, it is an easy way to create valuable derivatives or modifiers of known toxins through chemical and biotechnological approaches to overcome their critical shortcoming. The derivative structures may be related to but different from original natural toxins. Furthermore, rapid advances in chemistry, molecular biology, biotechnology and drug design technology greatly facilitate the search for new drugs and other active substances with novel structure or scaffold. Based on the information of mechanism of action and target receptor structure of known natural toxins, it is possible to elaborate hitherto unknown types of toxic compounds by means of de novo design approach. These toxin-mimics and artificial toxins (a novel class of toxins), may have similar specific and potent actions to natural toxins, although their structural appearance may be different from the original toxins. Therefore when assessing the toxin threat, these new derivatives, modifiers, mimics and artificial toxins must be considered in addition to natural toxins.

Hence, the toxin warfare agents arise from natural toxins and toxiconological researches have inherent relationships with natural toxins, but the scope and construction will differ greatly from each other (As illustrated in Fig. 1).

ASSESSMENT FACTOR

Many assessments of toxins have discussed and organized toxins mainly on their toxicity basis. Some authors have pointed that a set of critical factors must be considered in assessment of toxins other than toxicity. And many primary factors may be contributed from chemical essence of toxins, so it is important to assess toxins from a chemical viewpoint.

In general, the primary assessment factors of toxins should consist of following set:

Toxicology Factors

This set of factors should include toxicity potency, intoxication route as inhalation, percutaneous etc., onset time and other related factors. Undoubtedly the principal route of intoxication of toxins in the case of military use is inhalation. It is important to note that although it seems unreasonable, and the mechanism is not clear, the experiment results show some toxins have higher potency by the inhalation route even than by injection. This is in large contrast with the toxicological property of known chemical warfare agents such as nerve agents (As shown in Table 3).

Application Factors

These are closely related to weaponizaton of toxins. Among the essential factors of this set are dissemination property and stability in different environmental conditions. The package technology may have an important effect on stability property.

Production Factors

Toxins can be obtained by biochemical processes, synthetic routes and biotechnological methods (i.e., fermentation, gene manipulation, etc.), but often in relatively small quantities. The key issues are degree of difficulty in technological requirements, cost and material availability of applicable methods. Meanwhile, it is noteworthy to note the dual-use property of manufacture process. In this case, it could facilitate to the last degree for production.

R&D Factors

At present, it seems no one toxin can be chosen as a "good" toxin agent. Each of the known toxins reveals some remarkable inadequacy in one or more aspects of the assessment factors mentioned above. However, our concern is not only for the present time, but also to have tools to evaluate toxins in the future. So when we consider the assessment issue of toxins as a dynamic task, then R&D factors become key in toxin assessment. In this group, we should pay more attention to the following factors:

1) Discoveries in novel structure types of toxins and related approaches in structure reconstruction.

2) Advances in new production technology as applicable technology in stereo-synthetic chemistry, new methods from biosynthesis pathway and new achievements in biotechnology.

3) Discovery of new target receptor systems of toxin, which could be used as template for novel series of chemical structures with high specificity.

ASSESSMENT OF TOXINS AT DIFFERENT LEVELS

In fact, when we talk about assessment of toxins, the question may involve some issues at different levels, and may be to get at divergent opinions or conclusions.

Firstly, at the category level, that means regarding toxin agents as a new field in chemical and biological agent spectrum. In this case, much of the information indicates an affirmative deduction, which classifies toxins as a real threat in addition to classic chemical and biological agents.

Secondly, there is a need to assess toxins according to their different types at class level. Several ways of classification can be applied to toxins. Because a series of primary assessment factors may be contributed from chemical essence of toxins, it is important to assess the toxins on chemical classification first, rather than on other basis.

According to *chemical structure type*, toxins could briefly be classified into the following classes:

1) Proteins: enzymes, bacterial toxins
2) Peptides: a variety of venoms from animals
3) High-stereo organic compounds such as palytoxin, maitotoxin etc. polyether toxins from marine organisms;
4) Organic compounds: numerous toxic substances from plants, fungi, and marine life.

To assess toxins at the class level, scientific discussion and information shows that the peptides and high-stereo organic compounds receive heavy attention for their high toxicity, have acceptable characteristic in application, and are potentially availability through chemical synthesis and genetic engineering in advance. More favorable feature may be derived from assessment of toxins on a gradual subclass basis.

Finally, to assess toxins at the individual level is helpful to chemical and biological defense work, but also it is a very complicated, even impossible task at the present time. No one toxin fits all the necessary requirements of a toxin agent; all have too many characteristics of uncertainness and immaturity relative to individual toxins; hence, even at the individual level, assessment of toxins is probably senseless or impossible. On the contrary, selecting an individual toxin as a protoype or representative substance of various toxin classes is a necessary step to make assessment of any case. Then, the discussion may lead to real conclusions and future prospective figures, which is a great necessity for chemical and biological defense work.

FUTURE TOXIN AGENT SPECTRUM

Of toxins that have been stockpiled or used, there is a small group consisting of botulinum toxin, diphtherin toxin, staphylococcal enterotoxin, ricin, saxitoxin and T-2 toxin. At most, we could also include dart poisons in this history. Their military significance and the intelligence of the information of their use can still be debated. Nevertheless, in the CBD and chemical and biological disarmament field, the scope is widened far beyond the list mentioned above. At least 400 toxins have been discussed in CWC or BWC related activities. The whole range of toxins from different sources such as bacteria, animals, fungi, plants and marine life organisms were investigated from the view of military risk assessment. Why? It is really these things that bring the attention to the future toxins spectrum. From our discussion on the assessment of toxins, there is yet no possibility to construct a clear future toxins spectrum today. Certainly, the future toxin spectrum is more complex, more variable and more unpredictable than known chemical or biological agents spectrum.

In summary, the goal of assessing toxins for chemical and biological defense requires the construction of a future toxin agent spectrum, but this is a dynamic and complex task.

KEYWORDS

Toxin, toxin agent, toxin spectrum

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FIGURES AND TABLES

Figure 1. Toxin agents in and out toxins

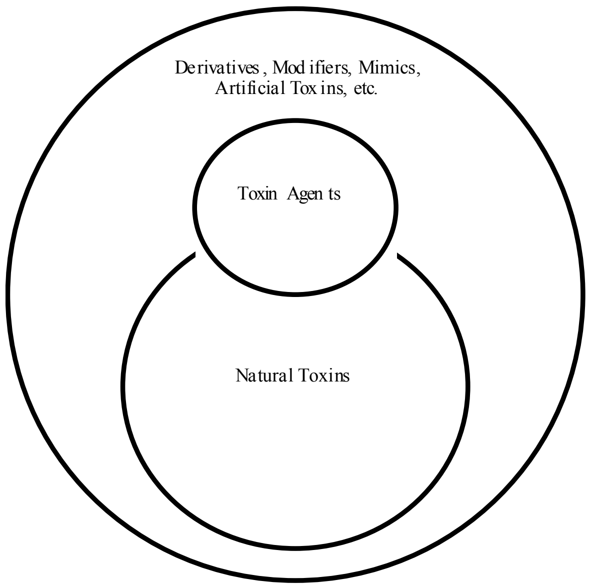
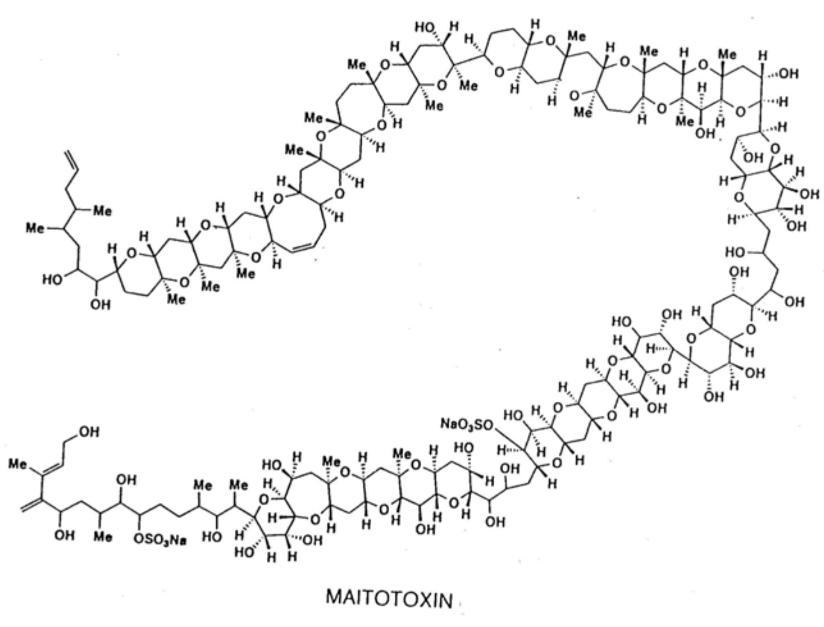


Figure 2A Maitotoxin



MAITOTOXIN

Figure 2B. Palytoxin

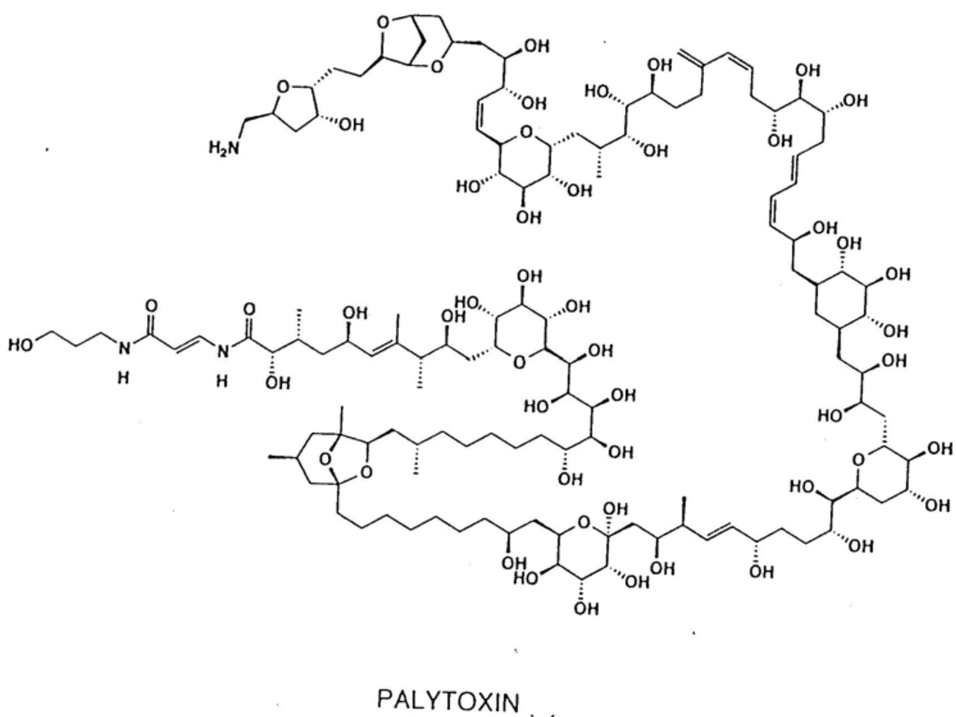


Table 1. Chemical Diversity in Toxins

Plants		**Target**	**Toxin**
proteins	40	Seeds	Ricin,abrin
cyano-glycosides	30	Fruit kernel	Amygdalin
saponin	100	Widespread	Phytolacecatoxin
sesquiterpene	200	Compositae	Picrotoxin
diterpenoids	200	Resins	Grayanotoxins
alkaloids	2000	Angiosperms	Tubocurarine, aconitine

Table 2. Ratio of Toxin Toxicity to Poison

Toxicity ug/kg	Number of Toxins A	Number of Poisons B	Ratio Toxins/Poisons A/B %
< 10,000	1589	7295	21.6
<5000	1371	5149	26.6
<1000	889	2640	33.7
<500	677	1948	34.7
<100	310	910	34.1
<50	192	610	31.5
<10	96	196	49
<1	43	52	82
<0.5	34	39	87
<0.1	20	22	90.9
<0.01	13	13	100

Table 3. Inhalation Toxicity of STX and Sarin

Agent	LD_{50} µg/kg mouse i.v	LD_{50} µg/kg mouse i.h	LC_{50} µg.min/L mouse i.h	LC_{50}µg.min/L human (calc.)
STX	8	0	3	2
Sarin	42	100	200	70-100