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ALTERATIONS OF BACTERIAL TOXINS BY
THE CONSTITUENTS OF CHAMOMILE AND
HORSERADISH

4th Communication by Manfred Kienholz

VI. Study on the Question of the Conversion of Lethally Acting
Staphylococci Toxin into Toxoid under the Action of Chamomiles
and Horseradish Constituents

If we visualize and illustrate the structure of a toxin, we can find a way to detoxicate it. It is generally believed today that a toxin consists of a toxophore and a haptophore group. The toxophore group, as its name implies, is responsible for the toxicity, while the haptophore group is responsible for anchoring the toxin in the organisms.

The possibilities for rendering a toxin harmless would, accordingly, consist, first of all, in destroying both the toxophore and the haptophore group. Second, the toxin could be deprived of its toxicity through the destruction of the toxophore part. Its haptophore group would remain intact here and could occupy the receptors which are specific for the toxin in the cells. If we block all receptors by incorporating only the haptophore group, then the subsequently injected toxin could not become firmly established and would remain ineffective. In other words, we would, basically, be dealing here with a toxoid, that is to say, a poison or toxin, which had been deprived of its effectiveness but not of its antigenic properties. On the other hand, the effect of a toxin could be eliminated through the destruction of the haptophore group because a toxin without adherence to certain receptors in cells cannot take effect.

By means of immunization tests, we can prove in the animal experiments, whether or not the entire toxin complex or only the toxophore toxin portion has been destroyed. If we allow, for instance, formol to act upon an exotoxin for a longer period of time at 37° C and if we inject a quantity, out of this formol-toxin mixture, which earlier had corresponded to a multiple LD

into an animal, the animal will not die. If we administer to an animal, pretreated in this fashion, several LD's of active, identical toxin about six weeks after the injection of the formol-toxin mixture, then the animal will not survive. Accordingly, the effect of formol has destroyed the toxophore but not the haptophore group of the particular toxin. If an animal does not die right away after the incorporation of a substance-toxin mixture, and if it instead dies of the incorporation of the corresponding active toxin, following a few weeks after the first injection, then we must conclude that the substance destroyed the poison or toxin as a whole.

On the basis of these considerations I mixed the lethally acting toxin of the staphylococci with various quantities of chamomile and horseradish constituents which I had tested and I kept them at a temperature of 37° C. As soon as the toxin had been detoxicated, I administered it ip. to a series of mice; I injected it in quantities which, before the start of the experiment, had corresponded to 5 LD. Then I froze the toxin at a temperature of 70° C in order to protect it against the further action of the chamomile and horseradish constituents; 4 weeks after the first injection, the mice received the same dose of the detoxicated lethal toxin of staphylococci, ip. After another 4 weeks, the experimental animals were given 0.5 cm³ - 6 cm³ of active, lethally acting staphylococci toxin containing 5 LD. All animals died at the same time as the control mice.

VII. Discussion of Experimental Results

The experimental results reveal that chamomile and horseradish constituents inactivate the blood-corpuscle-dissolving toxins of streptococci and staphylococci.

Here the water-soluble azulín derivative and the pro-azulín containing petrolether extract from Flores Chamomillae are particularly important. They detoxicate, for instance, within a few minutes a six-fold quantity of the staphylolysin dose which was found in the empyema punctate of patients revealing a picture of serious staphylotoxiosis.

When it comes to action upon Streptolysin O, the allyl-mustard oil, which makes up about 6% of the horseradish oil, is not far behind the water-soluble azulín derivatives and the petrolether extracts from chamomile flowers. The other chamomile and horseradish constituents likewise are capable of rendering

(considerable doses of Streptolysin harmless although only after some time.

Since Streptolysin O is inactivated by oxidation (Neill and Mallory), it was obvious to try to find the detoxicating effect of the substances examined by us in an oxidation process figured by them. This was probable also inasmuch as all of our substances had double-combinations and because it is known that oxygen can accumulate next to double-compounds. As the result of this, the chamomile and horseradish constituents could have gained an activity such as we find it in the organic peroxides (Grab, 91).

In order to answer this question, I first of all allowed hydrogensuperoxide (Perhydrol Merck), cyclohexanon, and the ammonium salt of guajazulin sulfonic acid in equal molar concentrations to act upon Streptolysin O and upon the allyl-hemolysin of the staphylococci and I compared the detoxicating effect of these substances.

Compared to the allyl-hemolysin of the staphylococci, the azulin derivative was 24 times more detoxicating than hydrogensuperoxide and compared to Streptolysin O it was 12 times more detoxicating. Cyclohexanon had a detoxicating effect neither upon streptolysin or upon staphylolysin.

In order to determine whether the azulin derivative reveals a stronger detoxicating effect after contact with oxygen, I mixed the ammonium salt of the guajazulin sulfonic acid with hydrogensuperoxide. The deep-blue azulin derivative began to become discolored after nearly two hours following the addition of hydrogensuperoxide; it was bright violet after 12 hours and it was colorless after 24 hours; after 8, 16, 24, and 48 hours, the detoxicating effect of the azulin derivative, altered by the hydrogensuperoxide, was tested. It was found that, as the time of action of the hydrogensuperoxide upon the azulin derivative increased, the detoxicating effect of the latter decreased. After 48 hours of contact with hydrogensuperoxide, the azulin derivative had lost $1/6$ of its effect against staphylolysin and $1/4$ of its effect against streptolysin.

On the basis of these results we can conclude that the detoxication of the blood corpuscle dissolving streptococci and staphylococci toxins cannot be based on an oxidation in the sense of a giving-off of oxygen to the toxin complex.

Q According to more recent views, the dissolution of erythrocytes by streptolysin and staphylolysin and can be traced to the fermentative effect of the toxins (Schmidt, 280). In explaining the detoxication of streptolysin and staphylolysin by chamomile and horseradish constituents we must also think of the ferment-blocking or ferment-inhibiting property of the azulins and mustard oils. This is why we allowed the chamomile and horseradish constituents to act upon the fibrinolysin of streptococci (streptokinase) in identical molar concentrations and in the same quantities as upon the streptolysin. The fibrinolysin activity however was impaired neither by the azulins nor by the mustard oils. According to this result it does not seem possible to trace the detoxicating effect of azulins and mustard oils to a ferment blocking or ferment inhibition.

Q Through corresponding experiments we were able to prove that a detoxication of streptolysin and staphylolysin by chamomile and horseradish constituents could not be simulated by having the azulins and mustard oils accumulate around the erythrocytes and thus withdrawing them from the attack of the toxins or changing the erythrocytes membrane in such a way that it can no longer be destroyed by streptolysin and staphylolysin. Furthermore, we kept checking the effectiveness of the toxin without active substance addition as well as the pH value of all toxin-substance mixtures during the experiments.

Because the detoxication of streptolysin and staphylolysin can be explained neither in the light of the light of the oxidizing effect of chamomile or horseradish constituents in the sense of a giving-off of oxygen, nor on the basis of a ferment blocking or ferment inhibition brought about by these substances, it would seem that the detoxicating effect of these autoxidizable substances might perhaps be traced to the giving-off of electrons to the toxin complex. Through the accumulation of electrons, the toxin could be discharged partly or completely and could thus be inactivated.

Q The fact that precisely the antiphlogistically acting azulins have a strong detoxicating effect caused me to study the antirheumatically acting substances. This appeared justified inasmuch as they act not only antiphlogistically but also as a healing effect during an inflammation process which is always triggered by a chemical substance, such as body-alien protein, peptide, or toxin (Grab, 89, 90). Without going into any detail on the individual Antirheumatica, I would only like to point out

that they, likewise, have a detoxicating effect which is equal to that of the azulins.

In examining a series of chemically differing substances I found that celery oil has a detoxicating effect on streptolysin O and Staphylolysin. Celery oil is composed of about 60% d-limonene, about 10% selenene, 2.5-3.0% sedanolid, 0.5% sedanonic acid anhydride, 1% sesquiterpene alcohol, guajacol-like phenol derivative and palmitin acid. The study of the individual revealed that detoxicating effect of celery oil is to be ascribed to selenene alone which is isomeric with azulins -- it has the same sum formula -- although selenene is a bicyclic sesquiterpene while azulins consists of a condensed ring system with 7 and 5 C atoms.

The results which we obtained in connection with the action of vitamin A upon streptolysin and staphylolysin are interesting. For these experiments we used a vitamin A-palmitate which had been dissolved in propyleneglycol. It had a conserving (preserving) effect upon streptolysin. This effect of vitamin A upon streptolysin can be explained on the basis of its extraordinarily easy capability because the vitamin first of all picks up oxygen, before the latter gets to the streptolysin, in order to inactivate it (Grab, 91). Vitamin A had a weak detoxicating effect upon staphylolysin. In this connection I might mention that vitamin A is also capable of cancelling out the toxic effect of sodium benzoate and citral, something which has not yet been validly explained (Moore).

The question as to whether there are interrelationships between the detoxicating and the antibacterial effect could likewise be answered as a result of our investigations. The clarification of such a relationship appeared to be important inasmuch as the reduction of the number of germs can simulate a reduced toxin formation. A relationship between the detoxicating and the antibacterial effect is to be excluded here as far as chamomile constituents are concerned because of the fact that they do not have any effect on the growth of streptococci and staphylococci. The determination is more difficult in the case of essential horseradish oils because these, with the exception of diallylsulfid are more or less heavily germ-inhibiting. On the other hand, however, it is precisely the phenylpropyl mustard oil which most effectively suppresses the growth of streptococci and which has no effect whatever on the blood corpuscle dissolving toxin of these germs. Horseradish oil, for instance, is more bacteriostatically effective against streptococci and staphylococci than allyl-

Q mustard oil; the latter, however, can detoxicate the blood corpuscle dissolving functions of these viruses much faster and can do this through the effect of smaller quantities than in the case of horseradish oil. Thus it seems that, for essential horseradish oils likewise, there is no relationship between their antibacterial and their detoxicating properties.

Our experiments furthermore gave us information as to whether the detoxicating effect of one of the chamomile and horseradish constituents tested is due to the inactivation of already produced toxin or due to the insertion into the process of toxin formation. When we allowed the horseradish constituents to act upon growing streptococci and staphylococci, then -- on the basis of identical action times -- we achieved a detoxication of the toxins through considerably smaller active toxin concentrations than when they were acting upon already existing toxins. This can be explained as follows: First of all, the smaller active substance quantities might produce a detoxication because live bacteria form less toxin than when we use when we allow the substances to act upon already existing toxin. Second, it might be conceivable that the horseradish constituents penetrate into the body of the bacteria and participate in an inhibitory fashion in the process involved in the production of the toxin, which perhaps might require smaller quantities of the active substance. We were able to establish these mechanisms at least for the action of phenylpropyl mustard oil upon the hemolysin formation of living streptococci. Although the phenylpropyl mustard oil -- even in a concentration of nearly 2,000 μ /cm³ toxin -- was unable to detoxicate streptolysin, the 2 μ , in other words 1/10 of a growth-inhibiting dose, was enough to suppress the lysin formation of streptococci.

In the chamomile active substances we did not find any such tremendous difference in their detoxicating effect on already existing toxin, on the one hand, and on toxin produced by live streptococci, on the other hand. This is probably connected with the fact that the chamomile constituents have no effect whatever on the metabolic processes in the bacterium, at least not in the concentrations tested. They probably act only through the inactivation of already treated-secreted toxin. The quantities required for this are so small that a part of the effect of azulins in vivo might be ascribed to their detoxicating capability.

During the production of staphylococci toxin we noted

that the lethally acting toxin of staphylococci is not identical with the blood corpuscle dissolving toxin of these germs (viruses). We arrived at this conclusion because the maximum of toxin formation of the hemolysin and the lethally acting toxin was determined at different incubation periods and because the hemolysin capability of the germ-free culture filtrate was reduced already as of the 12th day, while the lethal effect remained constant mostly up to the 18th day. The blood corpuscle dissolving toxin was also more insensitive to the effect of azulins and mustard oils than the lethally acting one. Only the ammonium salt of guajazulen sulphonic acid brought about a more rapid detoxication of the blood corpuscle dissolving toxin. All of these differences, we believe, speak for a difference in the two staphylococci toxins.

Experiments end at the conversion of lethally acting staphylococci toxin into toxoid, under the action of chamomile and horseradish constituents, lead to the result that the toxicity and antigenicity of the toxin are equally cancelled out. This means that either only the haptophore group of the toxin is destroyed or the entire toxin complex.

Summary

Numerous observations in the treatment of infected wounds and infections with constituents of chamomile and horseradish indicate that these substances, in addition to the effect known in the past, probably have a detoxicating effect upon bacteria toxins.

This applies particularly for chamomile because its constituents have neither an antibacterial effect nor can be proved to participate in the regulation mechanisms of the body. Its strongly developed antispasmodic property likewise is not sufficient to explain all of the treatment successes achieved.

Horseradish and its constituents have an extraordinarily strong bacteriostatic and bactericidal force. In addition, when applied correspondingly, they influence the vegetative system of the body, increasing the sympatheticotonus. But there are also indications for a detoxicating effect upon bacteria toxins during treatment with horseradish or its constituents. In this connection we are dealing primarily with streptococci and staphylococci toxins; this caused us to consider the toxins of these disease viruses first of all from the viewpoint of their pathogenic significance.

With the help of investigations described in the literature and supplemented on the basis of our own experiments, we found that the blood corpuscle dissolving toxins both of the streptococci and of the staphylococci must be made solely responsible for the toxic manifestations in case of a disease brought about by these viruses.

Because of the overwhelming position which the oxygen-weak blood corpuscle dissolving toxin of the streptococci and the α -hemolysin of the staphylococci take up in the corresponding diseases, we allowed the chamomile and horseradish constituents to act upon these toxins and we studied the inactivating effect by means of various methods.

To test the detoxicating effect of a substance we were able to select only those methods which met a series of requirements.

First of all, it was important to prove a detoxicating effect as such, in combination with a simultaneous change not only in the active substance but also in the toxin concentrations. Second, it was necessary to arrange the experiment in such a way that it would roughly correspond to natural conditions. Our experiments furthermore had to enable us to reproduce the results exactly and to make the detoxification visible in vitro or in vivo.

There were two methods which met these requirements.

1. The testing of the hemolysin capability of toxins in a liquid environment. With the help of this method we were able to determine the impairment of various toxin concentrations without the presence of bacteria through differing but specific active substance quantities. This method at the same time enabled us to determine partial detoxications.

2. The investigation of the detoxicating effect of various substances during the process of toxin formation of bacteria in a solid nutrient medium environment. In using this method we were only able to vary the active substance quantity because it is impossible to influence the toxin formation of growing bacteria in the direction of an accurately graduated toxin production by changing the nutrient environment; but we hoped to be able to get some indications as to whether the active substances detoxicate only the toxin as such or whether they have a detoxicating effect by exerting an inhibitory effect in the

production process as such; we hoped to get these indications from the effect of chamomile and horseradish constituents upon growing, toxin-forming bacteria.

In both of these methods, we tested reactivity of the poison with the help of its blood corpuscle dissolving capability.

Using a method which was adapted to the first experimental arrangement, we investigated the effect of chamomile and horseradish constituents upon the lethally acting toxin of staphylococci. The activity of the lethally acting staphylococci toxin we were able to determine with the help of 20-g mice by means of ip. injections. In this connection, however, we had to accept the fact that the animals would reveal an individually differing sensitivity to this toxin. At any rate, these experiments are likewise sufficiently reproducible.

Of the chamomile, we investigated chamomile oil, chamazulin and a petrolether extract from this plant as well as guajazulin and the water-soluble sodium and ammonium salt of guajazulin sulphonic acid as to their detoxicating effect. The petrolether extract was of significance to our investigations inasmuch as it contains the preliminary stages of the azulins whose effectiveness we were particularly interested in.

Of the horseradish we tested the hitherto known essential oils contained in it because they are essentially credited with the healing effect of horseradish. In this connection we are dealing with the essential oil obtained from the horseradish root by means of water vapor distillation, as well as its components allyl-mustard oil, n-butyl mustard oil, phenyl-mustard oil, phenylpropyl mustard oil, and diallylsulfid.

In order to test the impairment of the blood corpuscle dissolving toxins, we allowed all substances, in graduated quantities ranging from nearly 2,000 γ to 2 γ upon the various toxins at a temperature of 37° C and upon streptolysin O additionally at 4° C. After certain action times we determined the activity loss of the toxins from their blood corpuscle dissolving capability, as compared to our control experiment.

Here we found that all chamomile constituents have a detoxicating effect upon the blood corpuscle dissolving toxin of the streptococci. In particular, the water soluble guajazulin derivatives and the proazulin containing petroether extract

from flores chamomile were able to enactivate several blood corpuscle dissolving streptolysin O doses within a few minutes.

In the case of the horseradish constituents, likewise, we were able to observe a toxin-inactivating effect, which, however, fell below that of the chamomile constituents. Only the allyl-mustard oil had the same effect upon highly-purified streptolysin as the chamomile constituents. Essential oil obtained from the horseradish root by means of water vapor distillation corresponded to the other chamomile constituents with respect to its detoxicating effect. All other essential oils of horseradish revealed a considerably weaker effect.

After these investigations, we were interested in the question as to whether there is any kind of relationship whatever between the antibacterial and the detoxicating effects because, when we use growth-inhibiting substances, the toxin formation is smaller as a result of the reduction in the number of germs and because this simulates a genuine detoxicating effect. On the basis of the very first experimental results we were able to say that there is no such relationship because precisely the chamomile constituents, which do not have any effect or only a minor effect upon the growth of bacteria, did develop the strongest detoxicating effect.

Results, which we achieved in connection with the action of chamomile and horseradish constituents upon growing, toxin-forming bacteria, are also very informative. First of all we would like to say that it was possible, with the help of the rabbit blood agar method, it was possible to investigate the effect of chamomile and horseradish constituents both upon the oxygen-weak (streptolysin O) and upon the oxygen-stable (streptolysin S), blood corpuscle dissolving toxin of the streptococci. Both toxins were always impaired equally.

In these experiments we had to take into consideration the growth-inhibiting effect of the horseradish constituents; this is why we were able to add only small quantities of this substance to the rapid blood agar, that is, quantities which would not influence the growth of the streptococci. In this connection we found out the following: The hemolysis of the rabbit erythrocytes could be prevented through the action of considerably smaller active substance quantities than we might have expected it on the basis of the preceding experiments connected with the action upon germ-free toxin. This was

particularly noticeable in the case of the action of phenylpropyl mustard oil. There were two explanations for this: First of all, the toxin formation of growing streptococci might be so small that even the very smallest quantities of phenylpropyl mustard oil would suffice in order to inactivate these toxin quantities. Second, we might think of an action of this active substance upon the toxin-forming production process of the bacteria -- which we were able to prove with sufficient reliability.

This mechanism appears to be applicable likewise for the other essential oils of horseradish, although not in this degree. At the same time, these results enable us to arrive at certain conclusions as to the conditions in vivo. As in the case of rapid agar, small quantities of horseradish oil will suffice in order to detoxicate the toxins which are secreted by the streptococci in small quantities in the tissues. In addition we have the fact that the horseradish oils -- because of their growth-inhibiting effect -- reduce the germ count and thus also the toxin output. Phenylpropyl mustard oil assumes a special position inasmuch as it has a detoxicating effect only through its involvement in the production process of the blood corpuscle dissolving toxin. It does not have any effect on already formed toxin.

This effect very probably does not apply to the chamomile constituents because the quantities necessary for detoxication -- regardless of whether they act upon germ-free toxin or upon toxin during its production by living streptococci -- practically do not differ.

In the case of the effect of chamomile constituents upon the blood corpuscle dissolving toxin of the staphylococci, we find that the two water soluble guajazulin derivatives and the proazulin containing petrolether extract from flores milli are distinguished by their strong detoxicating effect. Chamomile oil, chamazulin, and guajazulin, however, were able to inactivate the toxin quantities tested only after a longer period of action at a temperature of nearly 37° C. By the way, the chamomile constituents were less effective against the blood corpuscle dissolving toxin of the staphylococci than against that of the streptococci.

We were able to come up with similar findings in connection with the action of allyl mustard oil and horseradish oil upon the blood corpuscle dissolving toxin of the staphylococci because they, too, require longer periods of action for detoxication

than for the inactivation of streptolysin O. On the other hand, the remaining horseradish constituents behaved differently, with the exception of diallylsulfide. They had a stronger detoxicating effect upon the α -hemolysin of the staphylococci than upon streptolysin O -- both as regards the concentrations required for inactivation and as regards the action times.

In testing the α -hemolysin formation of staphylococci under the action of chamomile constituents in rabbit blood agar we found that only the two water soluble guajazulen derivatives were able to stop the toxic effect. This effect is probably based on the inactivation of already formed toxins because the same concentrations and action times were required for the detoxication of the already formed toxin and of the toxin produced during staphylococci growth.

We achieved different results in connection with the action of horseradish constituents upon α -hemolysin formation of growing staphylococci. In an allergy to the way the growing staphylococci influenced the lysin formation, we required considerably smaller quantities of active substance for the inactivation of the blood-corpuscle dissolving toxin formed by the growing staphylococci than for the detoxication of germ-free toxin and the test tube. We find the differences only to the extent that the detoxication of the blood-corpuscle dissolving toxin of the staphylococci was not as pronounced as of the hemolysing toxin of the streptococci. Second, we were able to prove the involvement in the production process of staphylolysin for none of the other horseradish constituents as definitely as we were able to do this for phenylpropyl mustard oil with respect to its inhibiting effect upon the production of streptolysin. At any rate, a comparison of the results -- which we had compiled in connection with the action of horseradish constituents upon already formed toxin and upon the hemolysin formation of growing staphylococci -- enabled us to assume that the horseradish constituents, with the exception of diallylsulfide, have a very minor inhibitory effect upon the process of the production of staphylolysin.

When making the lethally acting toxin of the staphylococci we already found indications that it is probably not identical to the blood corpuscle dissolving toxin of these bacteria. The assumption was confirmed by the differing detoxicating effects of chamomile and horseradish constituents upon the lethally acting and the blood corpuscle dissolving toxin. For instance,

all substances required differing action times in order to inactivate corresponding toxin quantities; the detoxication of the blood corpuscle dissolving toxin required considerably longer action times than the inactivation of the lethally acting one. Only the ammonium salt of guajazulin sulphonic acid produced a more rapid inactivation of the lethally acting toxin.

Investigations as to the question of the conversion of lethally acting staphylococci toxin into toxoid, through the action of chamomile and horseradish constituents, lead to the result that the toxicity and antigenicity of the toxin were equally reduced. It is therefore to be assumed that the chamomile and horseradish constituents destroy the entire toxin complex or the haptophore group. An inactivation of the toxophore group, coupled with the preservation of the haptophore toxin portion, we were unable to achieve with any of the active substances tested -- neither with streptolysin, nor with staphylolysin, nor, for that matter, with diphtheria and tetanus toxin.

Regardless of the methods used, there is one thing that applies to all chamomile and horseradish constituents: Their detoxicating effect depends on the quality of the toxin, the acting concentration of the active substance, the duration of the action, and the temperature during the action time.

The likewise antiphlogistically acting antirheumatica revealed a detoxicating effect upon streptolysin and staphylolysin which was roughly as strong as that of the azulins. Vitamin A had a preserving effect upon streptolysin O which could easily be inactivated by oxygen.

It was now obvious to think that the toxin inactivation through chamomile and horseradish constituents could be explained in the light of an oxidation involving the giving-off of oxygen; but this could not be confirmed through corresponding control experiments with hydrogen superoxide, cyclohexanon, and azulin after the action of hydrogen superoxide.

The ineffectiveness of chamomile and horseradish constituents against the fibrinolysin produced by the streptococci (streptokinase) made it very improbable that we are dealing with a ferment blocking or ferment inhibition in connection with this toxin inactivation.

Perhaps the substances we tested had a detoxicating effect

because they gave off electrons to the toxin complex and discharged the lacquer either partly or completely.

In conclusion we might say that on the basis of these investigations, the chamomile and horseradish constituents tested, ~~by us~~, in addition to their hitherto known effects, very probably also have a detoxicating effect upon bacteria toxins.

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