Original article

Homeopathic drugs complementary, antidotal and inimical to *Nux vomica* produce stronger anti-alcoholic effect on toads than *Nux vomica*

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ABSTRACT

Background: In homeopathy some drugs are known to act as complementary, antidotal or inimical to a particular drug. Practitioners can follow this rule when they apply one drug following another. Potentized Nux vomica can reduce acute hypnotic effect of alcohol on toads. Sulphur and Sepia are reported to be complementary to Nux-vom, while Coffea cruda and Zincum met are antidotal and inimical to Nux, respectively .The four drugs have been tested on the toad model to find out their actual therapeutic relationship with Nux vom. **Objective:** To verify the complementary effect of Sulphur and Sepia, antidotal effect of Coffea and inimical effect of Zincum in relation to Nux vom in the toad model. **Methods:** Five batches of toads, each comprising 20 individuals, were treated by partial immersion in a drug diluted with distilled water 1:500 for 20 min. The control consisted of 90% ethanol diluted with distilled water 1:500. The drugs were Nux vom 200 CH, Sulphur 200 CH, Sepia 200 CH, Coffea 200 CH and Zincum 200 CH. Toads of each batch were separately exposed to 260mM ethanol solution and tested every 10 min to see if they had lost their righting reflex (RR). For this, each toad was laid on its dorsal surface. If it failed to turn on its ventrum in a cut-off time of 60 sec it was considered to have lost its RR. Four more batches of toads were pretreated with Nux vom 200 CH and subsequently treated separately by Sulphur 200 CH, Sepia 200 CH, Coffea 200 CH and Zincum 200 CH. All the toads were then exposed to 260 mM ethanol solution to record their tolerance to ethanol anesthesia in terms of time to lose RR. **Results:** Toads treated with the five drugs took significantly longer time ($P<0.01$, one-way ANOVA) to lose RR than those treated with the control. The time taken to lose RR was significantly longer ($P<0.01$, one-way ANOVA) with Sulphur 200 CH, Sepia 200 CH, Coffea 200 CH and Zincum 200 CH than with Nux vom 200 CH alone. The situation was same when Nux treatment was followed by each of the four drugs. Of the five drugs Coffea showed the strongest anti-hypnotic effect. **Conclusion:** 1. Drugs complementary, antidotal and inimical to Nux vom showed the same anti-alcoholic effect as Nux in terms of increased tolerance to alcohol anesthesia. 2. The anti-alcoholic effect of Nux vom was markedly superseded by the above four drugs. 3. Of all the drugs tested Coffea showed the strongest anti-alcoholic effect. 4. It appears that the above four drugs produced their individual dominant effect cancelling the individual effect of Nux vom.

Keywords: Nux vom, alcohol anesthesia, righting reflex, complementary, antidote, inimical.

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Introduction

In a series of experiments we demonstrated anti-alcoholic effect of potentized *Nux vomica* on mice, rats and toads in terms of alcohol consumption, loss of righting reflex and degeneration of adrenergic nerve plexus in heart valves [1-6].

Homoeopathic Materia Medica and Repertory mention drugs which are complementary, antidotal or inimical to *Nux vomica* [7,8]. The interrelationship between homeopathic drugs was reviewed by Agarwal [9]. Drugs complementary to *Nux vom* are *Sulphur* and *Sepia*. *Coffea cruda* and *Zincum metallicum* are antidotal and inimical to *Nux vom,* respectively. The purpose of the present study is to see the actual effect of those four drugs on alcohol induced loss of righting reflex (RR) in toads *Duttaphyrnus melanostictus*. We have examined the individual anti-alcoholic effect of those four drugs and also the combined effect of each of those drugs with *Nux vomica* on toads. Toads and frogs have long been used as a suitable animal model to evaluate the efficacy of different anesthetic agents including alcohol [10-14]. Loss of righting reflex (RR) has been used as a standard criterion to assess the onset and depth of anesthesia in experimental animals [13,15,16].

The semicircular canals in the inner ear are responsible for maintaining equilibrium with respect to gravity in vertebrates. The gravireceptor comprises otoliths in the utricle. Any tilting would change the position of otoliths on hair cells of the sensory epithelium of the utricle. Neural impulses are transmitted by the vestibular nerve to the hind brain [17]. The RR maintains the normal upright posture of animals through a series of responses which are integrated mostly in the mid brain [18].

Methods

Animal Model - Toads: Male adult toads were collected from the rural areas of South 24 Parganas, West Bengal during the post monsoon period of October, 2013. Body mass of the toads varied from 71 to 81.4 g. Each group of toads, control or treatment, consisted of 20 individuals. Toads were kept in starvation for 24 hours before the experiment so that their regurgitation did not contaminate the anesthetic solution, here 260 mM ethanol. The anesthetic solution was prepared from pure absolute ethanol mixed with appropriate amount of sterile distilled water.

Drugs: Before exposure to the anesthetic solution, toads were treated with a drug or its vehicle 90% ethanol (control). All the drugs as well as the control were diluted with sterile distilled water 1:500 before treatment. The treatment protocol was as follows:

- Group I: Treated with 90% ethanol.
- Group II: Treated with *Nux vom* 200 CH
- Group III: Treated with *Sulphur* 200 CH
- Group IV: Treated with *Sepia* 200 CH
- GroupV: Treated with *Coffea cruda* 200 CH
- Group VI: Treated with *Zincum met* 200 CH
- GroupVII: Pretreated with *Nux vom* 200 CH followed by *Sulphur* 200 CH
- GroupVIII: Pretreated with *Nux vom* 200 CH followed by *Sepia* 200 CH
- Group IX: Pretreated with *Nux vom* 200 CH followed by *Coffea cruda* CH
- Group X: Pretreated with *Nux vom* 200 CH followed by *Zincum met* 200 CH

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All the drugs were obtained from the market (Dr Reckeweg, Germany) in the form of aqueous ethanol, in which the ethanol content was 90%. Toads were partly immersed in the drug or control solutions for 20 min after which they were thoroughly washed in sterile tap water. Toads were then exposed to anesthetic solution (260 mM ethanol) in plastic jugs . Each 2.5 lit jug contained only two toads partly immersed in 150 ml of anesthetic solution (Figure 1).

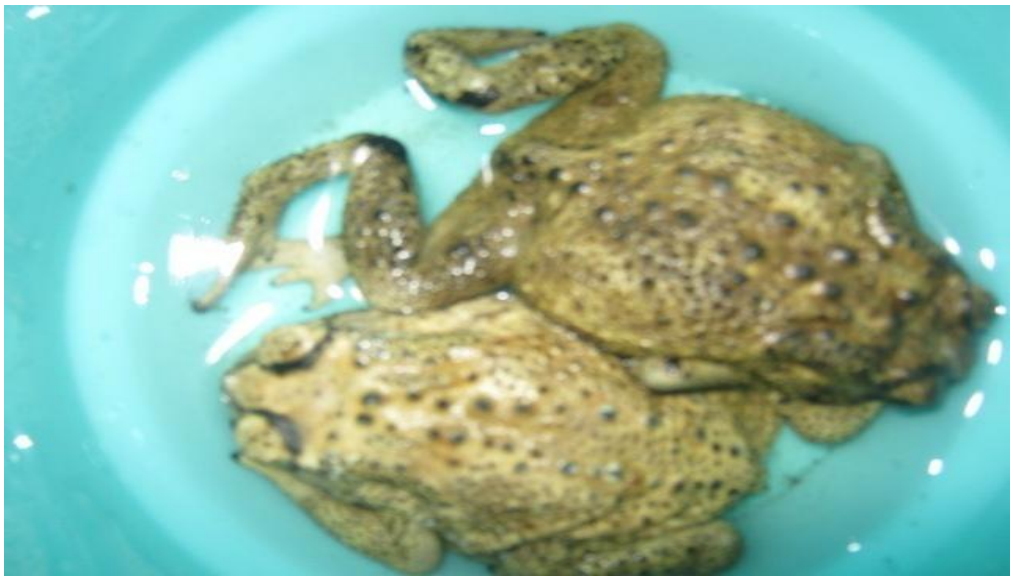

Figure 1- Two toads partly immersed in the anesthetic solution (260mM ethanol) inside a plastic jug.

Toads were examined every 10 min to see whether they had lost RR. RR was evaluated by assessing the toad's ability to assume a sitting posture on its ventrum in 60 sec when it was placed on its back (Figure 2).

Figure 2 – Toads placed on their back to test their ability to assume normal erect posture.

Data were analysed by ANOVA. Anesthesia was further confirmed by loss of corneal reflex and cessation of spontaneous abdominal respiratory movement. Only one group of toads was tested in one day. After the experiments the toads were washed in tap water and released in their natural habitat. None of them were killed. The experimental protocol was approved by the Ethical Committee of the Molecular Homoeopathy Research Unit (Dr. Bholanath Chakravarty Memorial Trust) Kolkata.

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Results

Initially toads, when exposed to anesthetic solution, showed hyper-activity for 5-7 min. This is the delirium phase of anesthesia usually observed in amphibians[19].The number of toads that lost their RR during the scheduled time intervals in the groups I to VI are shown in graphs against the time of exposure to anesthetic solution in Figures 3,4. It is evident from the figures that the percentage of toads losing RR was higher with the passage of time. However, the toads pretreated with the drugs took significantly longer time to lose RR as compared to the control (90% ethanol).

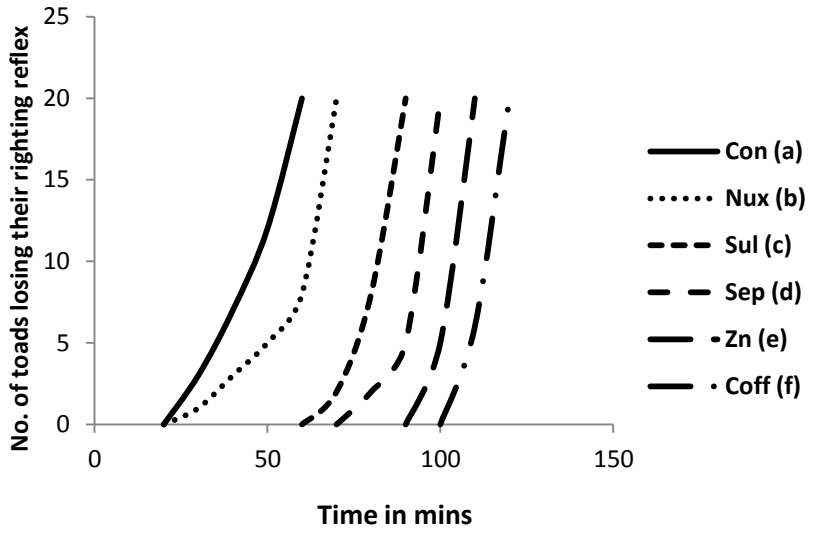

Figure 3. No. of toads losing righting reflex at different intervals of time following drug treatment. Different small letters (a-f) indicate significant difference by one way ANOVA ($p < 0.01$). F-value=80.71.

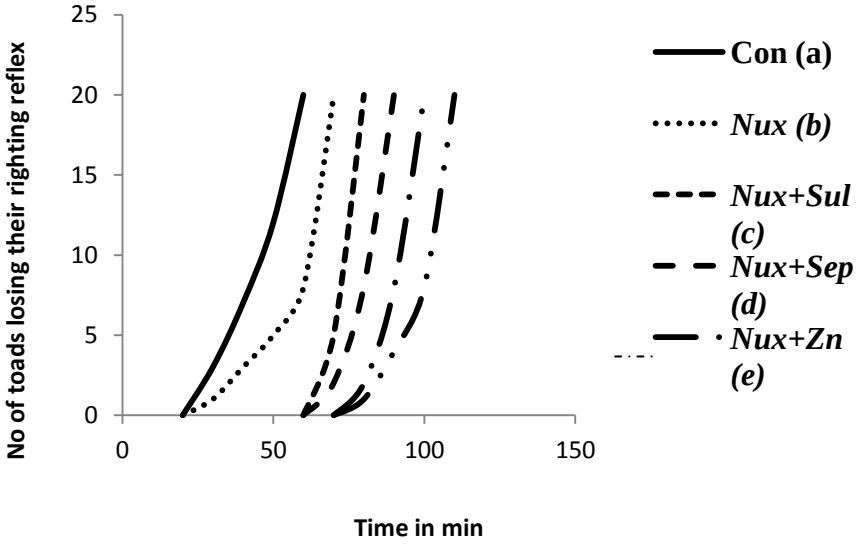

Figure 4. No. of toads losing righting reflex at different intervals of time in the control (con) and treatment with *Nux* 200 alone and *Nux* followed by *Sul* 200, *Sep* 200, *Zn* 200 and *Coff* 200. Different small letters (a-f) indicate significant difference by one way ANOVA ($p<0.01$). F-value=93.32.

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Data were analysed by one-way ANOVA. All the five drugs *Nux vom* 200 CH, *Sulphur* 200 CH, *Sepia* 200 CH, *Coffea* 200 CH and *Zincum* 200 CH significantly resisted the anesthetic effect of ethanol in terms of loss of RR(P<0.01,ANOVA) as compared to the control in the same time interval (Table 1). The resistance was evident that significantly fewer toads lost RR with the drugs than with the control within the same period. However, significantly far fewer toads lost their RR in the same time interval (P<0.01 ,ANOVA) with the combined treatment with *Nux vom* 200 CH followed by *Sulphur* 200 CH, *Sepia* 200 CH, *Coffea* 200 CH and *Zincum* 200 CH than with *Nux vom* 200 CH alone or the control (Table 1).

Table 1. Differences between drug treatments expressed in terms of Critical Difference (CD) in between different drugs by one-way Analysis of variance (ANOVA).

Treatment	Critical Difference	Minimum Critical Difference
Nux – Sul	480*	143.033
Nux - (Nux + Sul)	320*	134.856
Nux - Sep	570*	143.033
Nux - (Nux + Sep)	470*	134.856
Nux - Zn	600*	143.033
Nux - (Nux + Zn)	670*	134.856
Nux - Coff	1050*	143.033
Nux - (Nux +Coff)	840*	134.856

***** Significant difference (P<0.01) by one-way ANOVA between *Nux* and one of four other drugs, and between *Nux* and *Nux* followed by each of four other drugs. *Sul, Sep, Zn* and *Coff* show significant difference from *Nux* in ascending order.

Discussion

The drugs complementary *(Sulphur* 200 CH, *Sepia* 200 CH), antidotal (*Coffea* 200 CH) and inimical (*Zincum* 200 CH) to *Nux vom* 200 CH showed very strong anti-hypnotic effect of ethanol. These four drugs, when combined with *Nux vom*, produced the same anti-hypnotic effect. While this type of effect is anticipated with the drugs complementary to *Nux vom* , it is not so with the drugs antidotal or inimical to *Nux* at least with respect to the single symptom of loss of RR. But actual results showed otherwise. Since all the four drugs individually produced stronger anti-hypnotic effect than *Nux vom* 200 CH alone, we can say that those four drugs, when used in succession to *Nux,* might have cancelled the individual effect of *Nux*. In other words, these drugs did override the action of *Nux vom*. In this sense they are complementary, antidotal and inimical. Whatever is the nature of relationship, all the five drugs have one thing in common. All of them countered alcohol induced loss of RR. The results might have been more meaningful had the totality of symptoms been taken into account, but this is not possible with the present animal model. This is for the first time the relationship of a homeopathic drug with other remedies has been put to rigorous scientific test.

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Since amphibian skin is semi-permeable, it allows absorption of aqueous ethanol directly [20]. The binding of ethanol to plasma proteins appears to be negligible[21,22]. After absorption through the skin ethanol comes into the blood stream and is distributed into total body water. It is metabolized mostly by sequential hepatic oxidation, first to aldehyde by the enzyme alcohol dehehydrogenase (ADH) and then to acetic acid by aldehyde dehydrogenase (ALDH). Each metabolic step needs NAD+ [23]. Both the enzymes occur in amphibians. Potentized drugs used in this study might have interfered with the metabolism of ethanol in the liver thereby reducing it's hypnotic effect.

Ethanol interacts non-specifically with the phospho-lipid bilayers at the lipid water interface of cell membrane. It changes the orientation of lipid head groups and modifies the function of various proteins in the central nervous system membranes.Thus ethanol produces acute changes in different cells and organs. As a result of this non-specific interaction large numbers of ethanol molecules are required to produce intoxication vis-à-vis loss of RR [24]. Alcohol also interacts directly with integral membrane proteins [25].Thus a combination of non-specific alcohol induced changes in cell membrane and specific interaction of alcohol with membrane proteins may result in anesthesia [26].

A homoeopathic potency appears to be specifically H-bonded water structure maintained by the large non polar tail of ethanol molecules. It is presumed that the potency after absorption through the skin modifies the structured water at the lipid water interface thereby decreasing the anesthetic effect of alcohol [27].

Conclusion

Nux vom 200CH and four other drugs *Sulphur* 200CH, *Sepia* 200CH, *Coffea cruda* 200CH and *Zincum met* 200CH, related to *Nux vom* 200CH in some form or other, reduced alcohol induced loss of RR in toads. The four drugs related to *Nux* produced their individual effect overriding the individual effect of *Nux vom* on toads. Thus relationship in the form of complementary, antidotal or inimical has only one meaning here that the related drugs have dominant effect superseding the individual effect of the main drug, here *Nux Vom*.

Author's Contributions

NCS conceived, designed and guided this work and drafted the manuscript. AK, TS, IC carried out the experiments and typed the manuscript. A.S supervised the study; RC coordinated the work and helped in procuring necessary equipments and materials.

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