

In vivo evaluation of antipyretic effects of homoeopathic ultrahigh dilutions of *Typhoidinum* on baker's yeast-induced fever in comparison with *Paracetamol*

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Abstract

Introduction: Homoeopathy is a widely used, controversial alternative system of medicine. It is assumed that homoeopathic medicines are slower in action and does not work in acute conditions such as 'fever'. The study aims to estimate the effectiveness of some homoeopathic remedies in fever and to compare their effects with *Paracetamol*. **Materials and Methods:** Baker's yeast fever model of rabbits was used in the study. Rabbits were divided into four different groups ($n = 6$). Rectal temperature was measured before and after fever induction hourly. After fever induction, medicines were administered orally. *Paracetamol* and *Typhoidinum* in 200C and 1M potencies were given orally. ANOVA followed by *post hoc* test was used for statistical analysis of results. The results were considered statistically significant at $P \leq 0.05$. **Results:** Fever was induced in all the rabbits after 4 h of baker's yeast administration. The results of the study revealed the significant effectiveness of *Typhoidinum* in 200C and 1M potencies in baker's yeast-induced fever ($P = 0.05$). *Typhoidinum* in both potencies showed less significant results as compared to *Paracetamol*. However, all the medicines' effects were significant compared to the negative control. **Conclusion:** *Typhoidinum* 200C and 1M worked against baker's yeast-induced fever. However, the results were slower and less significant than *Paracetamol* that might be due to lack of similarity of remedy picture and disease picture.

Keywords: Antipyretic, Homoeopathic ultrahigh dilutions, *Typhoidinum*

INTRODUCTION

Fever is a complex physiologic process that is characterised by elevated body temperature above the normal range, associated with increased pulse, aches, chills, tissue destructions, restlessness and other symptoms. Fever can be caused by many factors including factors effecting the temperature regulating centre, bacterial diseases, any abnormality in the brain as brain tumours and many environmental conditions such as heat stroke.^[1,2] The primary manifestation of fever is an elevation of body temperature, usually by 1°C – 4°C .^[3] In fact, fever is not a disease, but it is the symptom of other pathological state and the immune response of the body that attempt to neutralise microbial infection in the body. Increased temperature led to the disturbance of the human physiology and is responsible for patient discomfort.^[4] There are various antipyretics to control fever such as *Paracetamol*. It reduces fever in multiple species including rabbits, but it has certain side effects,^[5] such

as asthma, hepatotoxicity and hypertension.^[6-8] Thus, there is need to find therapeutic alternatives for fever.

Homoeopathy is one of the most popular complementary and alternative systems of medicine.^[9]

Homoeopathy is based on similia principle 'similia similibus curantur' that means to treat with something that can produce an effect similar to the suffering.^[10] Remedy pictures are obtained by administering homoeopathic medicines in non-toxic dilutions to healthy volunteers during homoeopathic drug proving. In Homoeopathy, medicines are selected based on the similarity between remedy picture and disease-specific individual status.^[11]

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Hahnemann often said that the primary method of treatment is to remove the fundamental cause of the disease.^[12]

Typhoidinum is a nosode (homoeopathic remedy prepared from diseased products) prepared from *Salmonella typhi*. It is useful for fever with numbness all along right side, with impaired hearing in the right ear, slight nausea, vertigo and numbness that is worse from lying down and better in sitting position. General amelioration from lying down. There is no appetite and no thirst.^[13] *Typhoidinum* is proved to be antiviral medicine in one study. Homoeopathic medicines in potencies of 100C to 1M of *Typhoidinum*, *Tuberculinum*, *Hydrophobinum*, *Nux vomica* and *Malandrinum* completely inhibit chicken embryo DNA virus-induced pock-like lesions. The effects were found to be significant compared to controls.^[14]

'Baker's yeast-induced fever model' is a commonly used method of fever induction. In the experimental studies, baker's yeast (*Saccharomyces cerevisiae*) causes fever in animals in large doses (intraperitoneally or subcutaneous).^[15,16] It causes high-grade fever in a very short period. Some studies have shown that *S. cerevisiae* and constituents of its cell wall, such as mannans, cause fever that is accompanied by an increase in the plasma levels of tumour necrosis factor- α , interleukin-1 β and interferon- γ .^[17,18]

The study aimed to evaluate:

1. The effectiveness of *Typhoidinum* (ultrahigh dilutions) in baker's yeast-induced fever
2. The effectiveness of *Typhoidinum* (ultrahigh dilutions) in comparison with standard antipyretic '*Paracetamol*'.

MATERIALS AND METHODS

Medicines, reagent and apparatus

Typhoidinum 1M and 200C (Dr. Willmar Schwabe, GmbH and Co., KG, Germany), *Paracetamol* GlaxoSmithKline, Pakistan, Limited, baker yeast (Rossmoor food products, Karachi, Pakistan), Digital Thermometer (Medisign MANA and CO., Pakistan) were used.

Animals

Adult healthy rabbits of local strain were purchased from the market. The weight of rabbits ranged from 1 to 1.5 kg, and both male and female rabbits were included in the study. The study was carried in rabbits as they are not aggressive and comes under the purview of local Ethical Committee.^[19] Moreover, rabbits were selected because they develop fever more easily than rats.^[20]

All the animals stayed in the air-conditioned animal house situated in Khawaja Fareed Campus, in the Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur Figure 1. They were fed on standard diet *ad libitum*. They were acclimatised to animal house conditions 7 days before the start of the experiment. They were also habituated to handling, temperature measurement procedure and injection stress. The study was approved by the Pharmacy Research Ethics Committee, Faculty of Pharmacy and

Alternative Medicine, the Islamia University of Bahawalpur, Pakistan, through Notification number '88-2015/PREC'.

Antipyretic activity

Animals were grouped into four groups and each group contained six rabbits. The dosage of baker's yeast as well as *Paracetamol* was adjusted according to weight of each rabbit. Rectal temperature of rabbits was checked with digital thermometer. Fever-inducing agent was prepared according to method of Tomazetti *et al.*^[15] Commercially available baker's yeast (*S. cerevisiae*) was suspended in normal saline and was injected intraperitoneally at the dosage of 135 mg/kg/10 ml to induce fever. Rectal temperature was checked after 4 h of yeast injection.^[15] Temperature raise $\geq 0.5^{\circ}\text{F}$ – 1.5°F was considered as 'induced fever'. Group I was negative control and received 90% succussed alcohol (vehicle of used homoeopathic medicines). Group 2 was standard control and received *Paracetamol* 150 mg/kg orally.^[16] Groups 3 and 4 received *Typhoidinum* 1M and 200C, respectively. A few drops of homoeopathic medicines in 5 cc distilled water were administered orally to rabbits of respective groups. Minimum dose of ultrahigh dilutions was administered to avoid medicinal aggravation. Negative control group received few drops of succussed alcohol in 5 cc distilled water orally. Rectal temperature of rabbits was again checked after administration of medicines hourly.

Statistical analysis

Results obtained by this activity were analysed by Social package of Statistical sciences SPSS version 20.0 software. The test applied for analysis of data was ANOVA followed by *post hoc* test. ANOVA was used for comparison among groups. Fischer least significant difference *post hoc* test was applied only if ANOVA was significant. $P \leq 0.05$ was taken as statistically significant.

RESULTS

At the 4th h after yeast administration, temperature of more than 1°F was raised in all the rabbits. The temperature variations in different groups at different hours are as follows.



Figure 1: Rabbits in animal house of Khawaja Fareed Campus

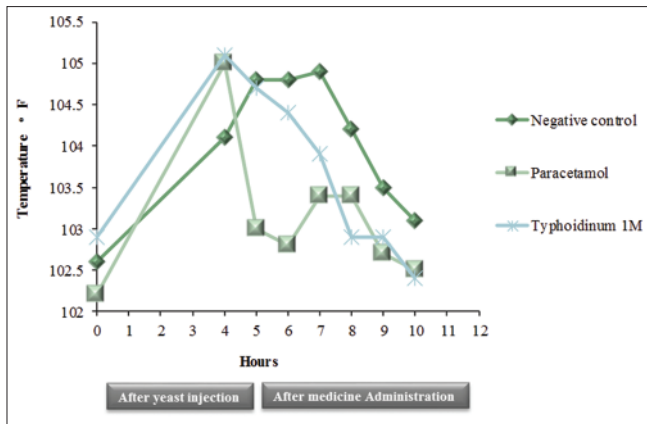


Figure 2: Antipyretic effects of *Typhoidinum* 1M, 0 h is the normal baseline temperature reading before fever induction, 4th h reading is temperature-induced reading, 5th–10th h readings are after medicine administration ($n = 6$ in each group)

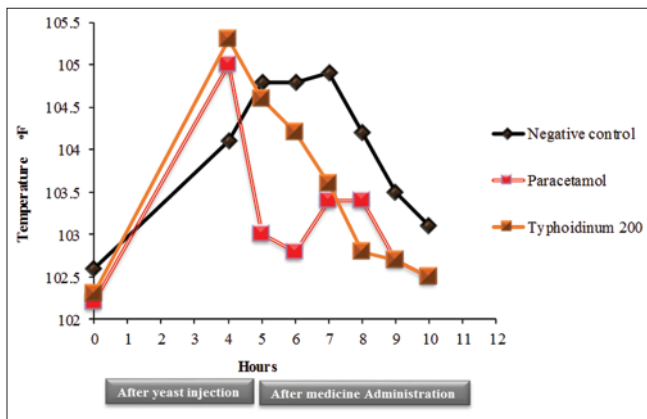


Figure 4: Antipyretic effects of *Typhoidinum* 200C, 0 h is the normal baseline temperature reading before fever induction, 4th h reading is temperature-induced reading, 5th–10th h readings are after medicine administration

Effect of vehicle on fever induced by baker's yeast

The negative control group showed a continuous increase of temperature till the 8th h from the time of yeast administration and then showed the progressive decline in temperature. At 0 h, normal mean temperature of the group was 102.6°F. Up till 8th h, a temperature raise of 2.3°F was observed that is started to decline afterward [Figure 2]. Three of the rabbits in negative control group suffered from diarrhoea (greenish watery) and later euthanised in the end of 5th h.

Effect of Paracetamol on fever induced by baker's yeast

At 4th h of yeast administration, 2.8°F temperature increase was observed. *Paracetamol* was administered orally at this time, and this group showed the decrease of 2°F temperature in the 1st h of medicine administration ($P = 0.002$). At the 2nd h of medicine administration, a further decrease of 0.2°F temperature was observed ($P < 0.001$). In the succeeding 2 h, a slight increase of temperature was seen that was going to normal temperature in the 10th h of the experiment [Figures 2-5]. All the rabbits survived in this group.

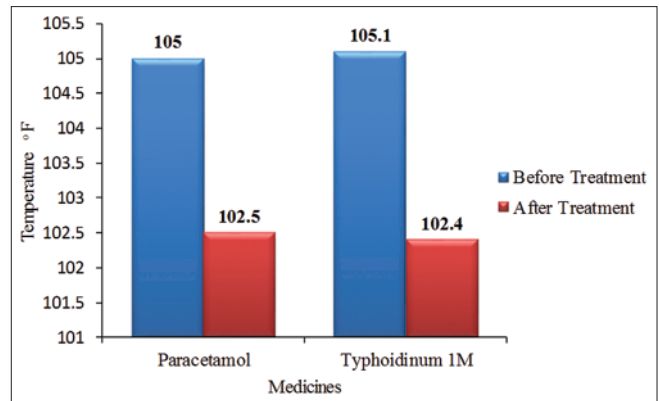


Figure 3: Comparative effectiveness of *Paracetamol* and *Typhoidinum* 1M at the end of experiment

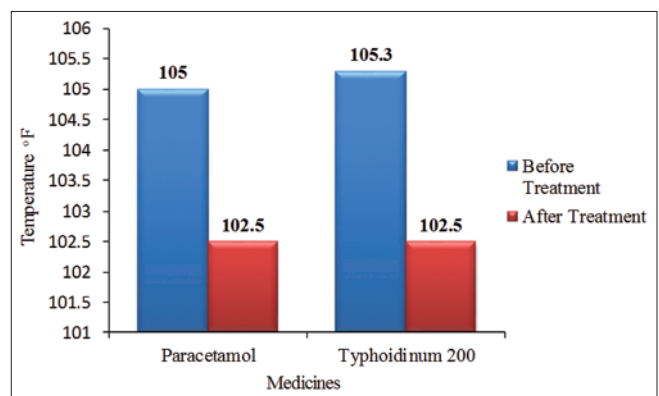


Figure 5: Comparative effectiveness of *Paracetamol* and *Typhoidinum* 200C at the end of experiment

Effect of Typhoidinum 1M on fever induced by baker's yeast

Typhoidinum 1M group showed an increase of 3°F after 4 h of yeast administration. After medicine administration, a gradual decrease of temperature was observed that became statistically significant ($P < 0.05$) in 3rd h to onward [Figure 2]. At the end of experiment, both *Paracetamol* and *Typhoidinum* 1M showed equal decrease of temperature ($P < 0.001$) [Figure 3].

Effect of Typhoidinum 200C on fever induced by baker's yeast

Typhoidinum 200C group showed an increase of 2.2°F after 4 h of yeast administration. After medicine administration, a slight non-significant decrease of temperature was observed in first 2 h. In 3rd h temperature decrease became significant ($P < 0.05$) that was continuous at the end of experiment [Figure 4]. At the end of experiment, both *Paracetamol* and *Typhoidinum* 200C showed equal decrease of temperature ($P < 0.001$) [Figure 5].

DISCUSSION

Homoeopathy is the widely used complementary and alternative system of medicine.^[9] Homoeopathy faces many criticisms, the most common condemnation is about biological activities of homoeopathic ultrahigh dilutions beyond

Avogadro's number.^[21] The present study examined the effects of *Typhoidinum* in fever in baker's yeast-induced fever model of rabbits. In the present study, administration of baker's yeast in rabbits causes a significant elevation of temperature in 4 h. Our results matched to earlier studies reporting fever induced by baker's yeast in rats and rabbits.^[15,22]

Orally administered *Paracetamol* (150 mg/kg) significantly decreased baker's yeast-induced fever in rabbits. Results are in accordance with other study results.^[16,23,24] *Typhoidinum* ultrahigh dilutions slowly decreased temperature as compared to *Paracetamol*; however, results became statistically significant in 3rd h of medicine administration. Antipyretics and non-steroidal anti-inflammatory drugs decreased fever by decreasing inflammation at the peripheral sites in tissue inflammation and within central nervous system thermoregulatory sites.^[25] However, homoeopathic medicines has supposed action on the regulation of inflammatory pathological changes as it is perceived as an expression of natural healing dynamics (commonly known as Hahnemann's 'life force').^[26] Homoeopathic medicines in ultra-high dilutions are safe and have no adverse effects.^[27] Large doses of ultrahigh dilutions ingestion showed that nothing happened, they have not the power to cause adverse effects as the conventional drugs.^[28]

In Homoeopathy, medicines are selected based on the similarity between drug-specific pathogenesis 'remedy picture' and disease-specific individual status.^[11] *Typhoidinum* is useful for low-grade fever types such as typhoid with numbness.^[13] Baker's yeast caused high-grade fever during the study. Lack of complete similarity between disease condition and remedy picture might be responsible for slow onset of decline in temperature by *Typhoidinum* ultrahigh dilutions as compared to *Paracetamol*. Another study with similar protocols reported effectiveness of *Aconitum napellus* on baker's yeast-induced fever due to similarity of high-grade fever.^[23]

The potency should be selected according to disease energy activity (intensity), intense diseases need higher and mild diseases require lower or medium potency.^[29] Experimentally induced diseases are short term and high intensity.^[15] It is evident from study results that both selected potencies (high potencies) of *Typhoidinum* have similar effect in reducing temperature.

The specific effects of homoeopathic medicines are of a non-molecular origin, yet provide powerful biological activities that are clinically effective.^[30] It has been assumed that highly diluted substances transfer biological activity to cells by electromagnetic fields. Another working hypothesis about homoeopathic ultrahigh dilutions is interactions between the radiation fields of a charged molecule. The electric dipoles of water generate permanent polarisation of water which becomes coherent. It transmits specific information to cell receptors, somewhat like a laser.^[30] However, the exact mechanism of action of homoeopathic ultrahigh dilution is not proved yet.

The effects of *Typhoidinum* ultrahigh dilutions should be evaluated on *S. typhi*-induced fever as it is the source of medicine administration. It can be hypothesised that medicine will be more effectively work in *S. typhi*-induced fever. Moreover, it can also be hypothesised that *Belladonna* and *Pyrogenium* would be effective remedies in baker's yeast-induced fever on the basis of some similarity of these medicines with baker's yeast-induced fever.

CONCLUSION

Homoeopathic medicines worked well when the criteria of similarity met entirely. If disease picture and drug picture have partial similarity, then results are slower or sometimes none. However, there is no ambiguity about the effects of homoeopathic medicines as the study showed positive results on animals. Hence, the effects of homoeopathic medicines are not mere placebos, and in fever, homoeopathic medicines worked as *Paracetamol*.

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Conflicts of interest

None declared.

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पैरासिटामोल की तुलना में बेकर यीस्ट से उत्प्रेरित बुखार पर टायफाइडिनम के होम्योपैथिक अल्ट्राहाई डायल्यूशन्स के ज्वरनाशक प्रभाव का इन विवो मूल्यांकन

सार

परिचय: होम्योपैथी व्यापक रूप से प्रयोग होने वाली विवादास्पद वैकल्पिक औषधीय प्रणाली है। ऐसा माना जाता है कि होम्योपैथिक औषधियाँ असर करने में धीमी होती हैं और ज्वर जैसी विकट स्थितियों में कार्य नहीं करती। अध्ययन का उद्देश्य बुखार पर कुछ होम्योपैथिक दवाईयों की प्रभाविकता का अनुमान लगाना और उनके प्रभावों की पैरासिटामोल से तुलना करना था।

सामग्रियाँ और विधियाँ: अध्ययन में खरगोशों का बेकरस्यूरीस्ट फीवर मॉडल प्रयोग किया गया। खरगोशों को चार विभिन्न समूहों में विभाजित कर दिया गया (एन=6)। ज्वर प्रेरण से पहले और बाद में प्रत्येक घंटे मलाशयी तापमान मापा गया। ज्वर प्रेरण के बाद, औषधियाँ मुख से दी गईं। पैरासिटामोल और 200 सी और 1 एम में टायफाइडिनम मौखिक रूप से दी गईं। परिणामों के सांख्यिकीय विश्लेषण के लिए अनोवा के बाद पोस्ट होक टेस्ट प्रयोग किया गया। परिणाम $P \leq 0.05$ सांख्यिकीय रूप से महत्वपूर्ण माने गए।

परिणाम: बेकर यीस्ट देने के 4 घंटे बाद सभी खरगोशों में ज्वर उत्प्रेरित कर दिया गया। अध्ययन के परिणामों ने बेकर यीस्ट उत्प्रेरित ज्वर ($P=0.05$) में 200सी और 1 एम पोटेन्सी की टायफाइडिनम की महत्वपूर्ण प्रभावशीलता प्रकाशित की। पैरासिटामोल की तुलना में दोनों पोटेन्सी में टायफाइडिनम ने कम महत्वपूर्ण परिणाम प्रदर्शित किए। हालांकि नकारात्मक नियंत्रण की तुलना में सभी दवाईयों का प्रभाव महत्वपूर्ण था।

निष्कर्ष: टायफाइडिनम 200सी और 1 एम ने बेकर यीस्ट द्वारा उत्प्रेरित ज्वर में प्रतिकूल कार्य किया। हालांकि, परिणाम पैरासिटामोल से धीमे व कम महत्वपूर्ण थे। ये शायद उपचार की स्थिति और रोग की स्थिति में समानता के अभाव के कारण थे।

In Vivo Bewertung Antipyretischer Wirkung Von Homoeopathischen Ul-Tra hohen Typhoidinum Verdünnungen Bei Bäckerhefeindiziertem Fieber Im Vergleich Zu Paracetamol

Abstrakt

Einführung: Homöopathie ist ein weit verbreitetes, umstrittenes Alternativsystem der Medizin. Es wird davon ausgegangen, dass homöopathische Arzneimittel langsamer und nicht in akuten Fällen, wie etwa bei Fieber wirken. Die Studie zielt darauf ab, die Wirksamkeit einiger homöopathischer Heilmittel bei Fieber einzuschätzen und ihre Wirkungen mit Paracetamol zu vergleichen.

Methode: Das Bäckerhefe-Fieber-Modell von Kaninchen wurde in der Studie verwendet. Kaninchen wurden in vier verschiedene Gruppen aufgeteilt (n = 6). Die Rektaltemperatur wurde vor und nach der Fieberinduktion stündlich gemessen. Nach Fieberinduktion wurden Medikamente oral verabreicht. Paracetamol und Typhoidinum in C 200 und 1 M wurden oral verabreicht. ANOVA gefolgt von Post-hoc-Test wurde für die statistische Analyse der Ergebnisse verwendet. Die Ergebnisse wurden bei $p \leq 0,05$ als signifikant angesehen.

Ergebnisse: Fieber wurde in allen Kaninchen vier Stunden nach der Verabreichung von Bäckerhefe induziert. Die Ergebnisse der Studie zeigten die signifikante Wirksamkeit von Typhoidin in C 200 und 1 M Potenzen beim von Bäckerhefe induziertem Fieber (P 0,05). Typhoidin in beiden Potenzen zeigte weniger signifikante Ergebnisse im Vergleich zu Paracetamol. Allerdings waren alle Arzneimittelwirkungen im Vergleich zur Negativkontrolle signifikant.

Fazit: Typhoidinum C 200 und 1 M wirken gegen von Bäckerhefe induziertes Fieber. Aber die Ergebnisse stellten sich langsamer und weniger signifikant als bei Paracetamol ein, was an einer mangelnden Ähnlichkeitsbeziehung von und Arzneimittel- und Krankheitsbild gelegen haben dürfte.

Evaluación In Vivode Los Efectos Antipiréticos De Las Ultradilusiones Homeopáticas De *Tiphoidinum* En La Fiebre Inducida Por La Levadura Del Pan, En Comparación Con El Paracetamol

Resumen

Introducción: La homeopatía, un sistema médico alternativo controvertido, se utiliza ampliamente. Se supone que los medicamentos homeopáticos tienen una acción más lenta y no funcionan en patologías agudas como la “fiebre”. El objetivo del estudio es estimar la eficacia de algunos remedios homeopáticos en la fiebre y comparar sus efectos con el paracetamol.

Métodos: En este estudio en conejos, se aplicó el modelo de fiebre por la levadura del pan. Los conejos fueron divididos en 4 grupos diferentes (n=6). La temperatura rectal se midió cada hora antes y después de la inducción de la fiebre. Tras la inducción de la fiebre, los medicamentos, paracetamol y *Typhoidinum* (potencias: 200c y 1M), se administraron por vía oral. Se utilizó ANOVA seguido de una prueba post-hoc para el análisis estadístico de los resultados. Los resultados fueron considerados significativos a $p \leq 0,05$.

Resultados: En todos los conejos se indujo fiebre cuatro horas tras la administración de la levadura del pan. Los resultados del estudio revelan una eficacia significativa de *Typhoidinuma* las potencias de 200c y 1M en la fiebre inducida por la levadura del pan (P0,05). Las dos potencias de *Typhoidinum* dieron lugar a resultados menos significativos en comparación con el paracetamol. Sin embargo, todos los efectos medicamentosos fueron significativos en comparación el control negativo.

Conclusiones: *Typhoidinum* 200c y 1M fueron eficaces en la fiebre inducida por la levadura del pan. Sin embargo, los resultados fueron más lentos y menos significativos que el paracetamol, lo que puede deberse a la falta de similitud del cuadro del medicamento con el cuadro patológico.

Une évaluation in vivo des effets antipyrétiques des dilutions homéopathiques ultra-élevées du *Typhoidinum* dans le cas de la fièvre induite par la levure de boulanger par rapport au Paracétamol

Résumé

Introduction: L'homéopathie est un système de médecine alternative largement utilisé et controversé. On suppose que les médicaments homéopathiques ont une action plus lente et ne sont pas efficaces dans des conditions aiguës comme 'la fièvre'. L'étude vise à estimer l'efficacité de certains remèdes homéopathiques dans le cas de la fièvre et à comparer leurs effets à ceux du Paracétamol. **Matériels et Méthodes:** Le modèle des lapins atteints de la fièvre induite par la levure de boulanger a été utilisé dans l'étude. Les lapins ont été répartis sur quatre groupes différents (n = 6). La température rectale a été mesurée toutes les heures avant et après l'induction de la fièvre. Après l'induction de la fièvre, les médicaments ont été administrés par voie orale. Le Paracétamol et le *Typhoidinum* dans des potences de 200c et 1M ont été administrés par voie orale. L'analyse de la variance (ANOVA) suivie d'un test post hoc a été utilisée pour faire une analyse statistique des résultats. Les résultats ont été considérés comme étant statistiquement significatifs à $P \leq 0,05$. **Résultats:** La fièvre a été induite chez tous les lapins 4 heures après l'administration de la levure de boulanger. Les résultats de l'étude ont révélé l'efficacité significative du *Typhoidinum* dans des potences de 200c et 1M dans le cas de la fièvre induite par la levure de boulanger ($P = 0,05$). Le *Typhoidinum* dans les deux potences a montré des résultats moins significatifs par rapport au Paracétamol. Cependant, les effets de tous les médicaments étaient significatifs par rapport au contrôle négatif. **Conclusion:** Le *Typhoidinum* à 200c et à 1M s'est avéré efficace contre la fièvre induite par la levure de boulanger. Cependant, les résultats ont été plus lents et moins significatifs que ceux obtenus avec le Paracétamol, ce qui pourrait être dû au manque de similitude quant à la présentation du remède et à celle de la maladie.

以貝克氏酵母菌誘導發燒以進行體內評估，比較順勢療法極度稀釋液傷寒病質藥 (*Typhoidinum*) 和撲熱息痛 (Paracetamol) 退熱的有效性

摘要

簡介：順勢療法被廣泛應用，是一個備受爭議的替代醫療系統。曾有假設順勢療法藥物作用較慢，不能應用於急性個案中，如「發燒」。這項研究的目的是評估順勢療法藥劑在治療發燒上的有效性，與撲熱息痛進行比較。

方法：在這項研究中，採用了貝克氏酵母菌發燒的兔來進行。兔子隨機分為4個不同的組別 (n=6)。每小時測量誘導發熱前後的直腸溫度。當引起發熱後，便給予口服藥物。給予的口服藥物有撲熱息痛、傷寒病質藥200c和1M。在統計分析結果上，會先使用ANOVA變異數分析，再進行事後比較檢定。當 $p \leq 0.05$ ，結果會被認為是顯著的。

結果：所有兔子在四小時後都經歷由貝克氏酵母菌誘導的發燒。研究結果顯示，傷寒病質藥 200c 和1M 在貝克氏酵母菌誘發發燒中有顯著效果 ($p=0.05$)。兩個層級的傷寒病質藥與撲熱息痛相比，結果都不及撲熱息痛顯著。然而，與陰性對照組比較，所有藥物效應都是顯著的。

結論：傷寒病質藥200c 和1M有效處理由貝克氏酵母菌誘導的發燒。但效果比撲熱息痛慢和較不顯著，這可能是由於藥劑圖像與症狀圖像不相似。