A REVIEW ON RESEARCH EVIDENCES IN HOMOEOPATHY FOR URINARY TRACT INFECTIONS

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ABSTRACT
Urinary tract infections (UTI) are very common morbidities encountered nowadays in clinical practice. The majority of UTIs are caused by the Escherichia coli (E. coli) bacteria. The objective of this study was to review the existing research evidences in support of the effectiveness of homoeopathy in urinary tract infections. Fourteen articles related to the objective of the study were identified, out of which 4 clinical studies on humans (2 case series, 2 case reports), 2 in vitro studies and one animal experimentation; thus total 7 studies were finally selected for assessment. Out of 12 chronic UTI cases in 4 clinical studies, 9 were cured and 3 were improved with homoeopathic individualized, constitutional medicines, whereas one lesser known remedy was found effective only in an acute case. Staphysagria was found to be most frequently prescribed medicine. In in vitro studies, Merc. sol. 12 CH and homoeopathic preparation E. coli 6X were effective in inhibition of growth of E. coli. In animal experimentation, the immunemodulatory effects of Cantharis 6 CH were observed. Although positive effects of homoeopathic medicines on UTI cases or on E. coli, in in vitro or animal models were observed, yet the number and grade of evidences...
were poor, as no randomized control trial could be identified. Randomized control trials on homoeopathic treatment of UTI in humans, rigorous in vitro studies and animal experimentations are suggested to ascertain the effects of homoeopathic medicines on E. coli.

KEYWORDS: Urinary tract infections, Homoeopathy, Evidence-based research, Clinical research on E. coli, In vitro studies, Animal experimentation.

INTRODUCTION
The urinary tract is comprised of the kidneys, ureters, bladder and urethra. The presence of pathogens in the urinary tract is known as urinary tract infection (UTI).[1] Urinary tract infections (UTI) are the third most common infections experienced by humans after respiratory and gastrointestinal infections.[2] These are the frequent causes of morbidity and mortality.[1] UTIs can occur in any age but symptomatic urinary tract infections occur most commonly in women of child-bearing age.[2] One out of two women used to suffer from urinary tract infection (UTI) at least once during their life. [3] UTIs are classified as Lower UTIs and Upper UTIs. Lower UTIs include cystitis and urethritis while Upper UTI includes pyelonephritis.[1] UTIs are generally diagnosed by urine culture.[4] The urinary tract can become infected due to various bacteria, but the most common is E. coli derived from the gastrointestinal tract; other common organisms which cause UTI are: Klebsiella spp, Staphylococcus saprophyticus, Enterococcus spp and Pseudomonas aeruginosa. Studies clearly demonstrate the increasing antibiotic resistance to uropathogens causing both community and nosocomially acquired UTIs. [5,6,7] UTIs are one of the major causes of antibiotic usage and antibiotic resistance.[1] High recurrence rates and increasing antimicrobial resistance threaten to increase the economic burden of these infections.[8] Therefore, it has been necessitated to explore the role of alternative/complementary therapies including Homoeopathy in the management of UTIs.

Homoeopathy can be defined as a system of therapeutics basing upon the law of similia, which states that a drug, capable of producing in a healthy person a diseases state exactly similar to that observed in a diseased person, acts as a curative agent if the disease is in a curable state.[9] It is an important system of alternative therapeutics and popular medicine in the world, especially in the Indian subcontinent. Approximately 200 million people take homoeopathic medicines on a daily basis across the world and almost 10% of the population in India use Homoeopathy.[10,11] Homoeopathic treatment has been found to be very efficacious and cost-effective.[12]
Several studies have already established the efficacy of Homoeopathy in different urological disorders such as benign hypertrophy of prostate (BHP),\textsuperscript{[13,14,15,16,17]} renal calculi,\textsuperscript{[18,19,20]} and UTIs\textsuperscript{[21,22,23]} etc. There are many medicines mentioned in the homoeopathic materia medica whose symptoms match with those of UTIs.\textsuperscript{[24]} Homoeopathy can play an important role in the treatment of UTIs especially combating the recurrent infections.

The objective of this study was to review the existing research evidences from a range of sources such as clinical, \textit{in vitro} and animal experimentations to evaluate the effectiveness of homoeopathic medicines in the treatment of UTIs or on its main causative organism \textit{E. coli}. A comprehensive online and manual search of the research studies on the effectiveness of homoeopathy in urinary tract infections, both \textit{in vitro} and \textit{in vivo} models, was conducted. Literature from international databases, peer-reviewed journals, the library of Dr Abhin Chandra Homoeopathic Medical College & Hospital, Bhubaneswar, Odisha, and the library of Drug Proving Unit, Bhubaneswar, a part of Central Council for Research in Homoeopathy, Govt. of India were collected. All types of studies related to the homoeopathic treatment of UTIs in humans, animal experimentations as well as actions of homoeopathic formulations on \textit{E. coli}, published from the year 2000 to January 2018 and available, were considered for the review. The research studies were categorized as per the study designs and their clinical or experimental outcomes.

**MATERIALS AND METHODS**

A comprehensive search for clinical research on human beings, \textit{in vitro} studies and animal experimentation on the effectiveness of homoeopathy in UTIs, was carried out on the following aspects.

**Types of studies**

This review included the studies where the homoeopathic interventions aimed at treating symptoms related to urinary tract infections in human beings. Any homoeopathic prescribing strategy was included in this review. This review also included \textit{in vitro} studies and animal experimentation in a laboratory model, related to the effect of homoeopathic medicines on \textit{E. coli}, the most common causative organism of UTI. The clinical studies related to the veterinary system of treatment, exclusively allopathic and other complementary therapies (Ayurveda, Unani, Siddha, Yoga and Naturopathy) were excluded from this review.
Search methods for identification of studies

Electronic search
A systematic literature search was conducted in the main international search databases such as PubMed, Embase, Medscape, Science direct, Toxnet, Thiame and Cochrane for all clinical studies on human beings, in vitro studies, animal experiments and review articles published during the period from 2000 to January 2018. Individual websites of peer-reviewed journals, publishing homoeopathic articles, were also directly searched.

Manual searches
A manual search was done at the central library of Dr A. C. Homoeopathic Medical College & Hospital, Bhubaneswar, Odisha, which has a collection of a large numbers of books and periodicals. A manual search was also made in the library of Drug Proving Unit, Bhubaneswar, Odisha, for different publications of Central Council for Research in Homoeopathy (CCRH), the apex body for homoeopathy research, under the Government of India.

Search terms
For this search all keywords related to UTI such as Cystitis, Urethritis, Pyelonephritis, Lower urinary tract infections, Upper urinary tract infections, Urinary diseases, Urinary infections, Dysuria, Burning urination and Homoeopathy/ Homeopathy were used.

Data Collection and Analysis
The relevant articles were retrieved manually as well as electronically, and details of the study were added manually. The authors cross-checked the data and other information of the studies and re-examined the entries made.

RESULTS
The summaries of three types of the included studies are given in the Table 1, 2 and 3.

Number of articles
A total of 14 studies (n=14) related to the effectiveness of homoeopathic treatment in UTIs in humans, animals and its common organism E. coli were identified. These included two case series,[21,22] two case reports,[25,26] five in vitro studies,[27,28,29,30,31] one animal experiment,[32] one study protocol,[33] one veterinary clinical study,[34] one homoeopathic pathogenetic trial[35] and one survey.[23] No randomized placebo-controlled trial could be identified. Data
collection studies, newspaper reports, short communications, and telephonic surveys were not considered for inclusion.

Out of these 14 studies, seven studies (n=7) (four clinical studies, two in vitro studies, one animal experiment) were finally included in this review. The homoeopathic pathogenetic trial, treatment survey, study protocol, veterinary clinical study and three in vitro experiments\[^{29,30,31}\] on artificially stressed E. coli were further filtered out and excluded from this review (Fig.1).

- **Clinical Observational Studies**
  
  **Number of participants**
  In the human clinical studies, there were two case series, consisting of 8 and 3 cases respectively, and two case reports of single case each.

  **Duration of treatment**
  The duration of treatment in one acute case (n=1) was from 5 to 7 days.\[^{25}\] Whereas in the chronic cases(n=8) after spinal cord injury(SCI), the duration of treatment varied from 8 months to 2 years.\[^{22}\] In the rest of chronic cases (n=4), it was from 2 months to 10 months.\[^{26,21}\]

  **Homoeopathic treatment approach**
  Homoeopathic treatment was provided as an add-on therapy along with antibiotics, in nine chronic cases of two studies,\[^{22}\] while in the remaining 4 cases of two studies,\[^{25,21}\] only homoeopathic medicines were prescribed. Short-acting, specific medicine was prescribed in one acute case.\[^{25}\] In the chronic cases (n=12), mostly individualized constitutional medicines were prescribed initially, but afterwards specific symptomatic medicines (in potencies and mother tinctures) were added.\[^{22,21}\]

  **Medicines prescribed**
  The medicines prescribed in these studies were Sulphur (n=1), Nux vom. (n=3), Lycopodium (n=3), Benz.acid(n=1), Staphysagria (n=5), Terebinth.(n=1), Sarsaparilla (n=1), Berb. vulg.(n=1), Phosphorus (n=2), Platina (n=2), Uva ursi (n=1), Colibacillinum (n=1), Causticum (n=1), Cantharis (n=1) and Eupatorium perf. (n=1).\[^{26,22,21,25}\] The medicines in both centesimal and fifty millesimal potencies were used in these studies: fifty millesimal
potencies ranging from LM1 to LM6\cite{22} and 200 potency in centesimal scale.\cite{26,25} However, in one study, no mention is made regarding potency.\cite{21}

**Outcome assessment parameters**

Frequency of UTI attacks,\cite{22} symptomatic assessment, routine and microscopic urine examination\cite{25} and urine culture\cite{22,21,26} were the outcome parameters used in these studies.

**Treatment outcomes**

In the study done with eight patients by Pannek et al, 2014,\cite{22} after homoeopathic treatment, five patients remained free of UTI attacks, whereas UTI frequency was reduced in three patients. In the remaining three clinical studies,\cite{21,26,25} total 5 cases have also shown a positive outcome and can be considered as cured. Thus, out of total 13 cases (n=13) in these 4 studies, ten cases (n=10) can be considered as cured and remaining three cases (n=3) as improved.

- **In vitro Studies**

Two (n = 2) in vitro studies were included in this review; both were non-randomized, controlled studies whereas only one study\cite{27} was blinded. Uropathogenic *Escherichia coli* (UPEC) isolated from a snow leopard, which had died of septicemia secondary to necro-hemorrhagic cystitis was incubated with homoeopathic remedies in one study,\cite{27} whereas both non-inflamed and inflamed T24 human bladder cancer epithelial cells were administered with the homoeopathic formulation in another.\cite{28}

**Interventions used**

Homoeopathic medicines like *Cantharis 12CH*, *Merc.sol. 12 CH* and *E. coli 12 CH* were used in one study\cite{27} and homoeopathic preparation of *E. coli 6X* potency in another.\cite{28}

**Outcomes**

Both the studies have shown positive response as in poor-nutrient medium, *Merc. sol. 12CH* exerted a significant inhibitory effect on the growth of bacteria *E. coli* in one study\cite{27} and homoeopathic *E. coli 6X* has shown an immune-modulation effect in another.\cite{28}

- **Animal experimentation:** In the single animal experiment\cite{32} included in this study, *E. coli* induced cystitis was treated with homoeopathic medicine *Cantharis 6CH* in the Female
BALB/c mice in a blinded, controlled and randomized model and results were found to be positive.

Types of publications
Out of 7 studies included in this study, 5 articles were published in peer-reviewed journals, whereas remaining two were published in non-peer reviewed journals.

Level of evidences
The level of evidence of the human clinical studies can be attributed as grade ‘C’ as per the WHO guidelines. The in vitro studies, when assessed with modified version of the Score for Assessment of Physical Experiments on Homoeopathy (MSAPEH) for presentation, methodology and standardization, can be scored 7 for the first study and 5 for the second study. The animal experiment (blinded, controlled and randomized) done on the mice model exhibited a good level of evidence.
Table 1: Clinical studies on Homoeopathic management of Urinary Tract Infections.

| Study | Study design | Number of Participants/ Samples (n) | Inclusion Criteria | Intervention | Type of Homoeopathy | Medicine used with potency | Outcome measures | Summary of results | Duration of treatment | Evidence grade |
|-------|--------------|-------------------------------------|--------------------|--------------|---------------------|---------------------------|------------------------|--------------------|----------------------|-----------------|----------------|
| Pannek, et al., [22] | Case series | n=8 | Recurrent UTI cases (>3UTI/year) due to a neurogenic bladder dysfunction after spinal cord injury/lesions (SCI) | Adjunctive Homeopathic treatment with Standard urologic antibiotic treatment | Constitutional treatment with required intercurrent homoeopathic medication. | Single medicine at a time, in centesimal/ 50 millesimal potencies<br>Case-1<br>Sulph. LM1, Nux vom.LM1<br>Case-2<br>Lyco. LM1<br>Benz. acid (potency not mentioned) Staphy. LM1<br>Terebinth. (Potency not mentioned) Sarsap. LM1<br>Lyc. LM4<br>Staphy. LM1<br>Case-3<br>Staphy. LM1<br>Staphy. LM2<br>Nux vom. LM1<br>Case-4<br>Lyco. LM1<br>Lyc. LM 2 & 3<br>Nax vom. LM1<br>Berb. vulg. Q and LM1<br>Case-5<br>Staphy.LM3<br>Phosph.LM1<br>Case-6<br>Lyc. LM<br>Staphy.JM<br>Case-7<br>Nax vom.10M, Nax vom.LM1<br>Case-8<br>Staphy. LM3<br>Staphy. LM6 | Frequency of UTI attacks. Urine culture Symptomatic improvement. | Five patients remained free of attacks of UTI, whereas UTI frequency was reduced in three patients. | 8 months to 2 years | C |
| Dehmeri [26] | Case report | n=1 | A 54 year old married woman, presenting with urinary problems, as chief complaint, for 2-3 years | Homoeopathy as an add-on with standard treatment | Constitutional medicine | Platina 200 one dose, followed by Placebo | Symptomatic improvement | Platina helped her not only to get rid of urinary symptoms but also helped at an emotional level as well | Two and half months | C |
| Varghese [25] | Case report | n=1 | A 31 year male comp-lained of reddish colored urine for two days. Lab report was suggestive | Homeopathy | Short acting specific medicine | Uva ursi 200, 3 globules thrice daily, for one week before food. | Symptom-atic improvement and routine | No sign and symptom; urine report normal after 5 days. | 5 days | C |
of the presence of bacterial infection in the urinary tract.

Nwabudioke[29] Case series n=3 Three cases of recurrent UTI Homeopathy Individualized remedy in all cases, additional symptomatic medicines in Case no.2 and 3 Case-1 Phosphorus Case-2 Platinum metallicum as well as homeopathic preparation of Candida albicans, and Coli bacillinnum (homeopathic Eschericha Coli) Case-3 Causticum with Cantharis and Eup. perf. (Potencies not mentioned) Urine culture; Symptom-atic improve-ment Case study comprises 3 patients with recurrent UTI. All females of different age groups benefitted from classical homeo-pathic treatment 3 months to 10 months Evidence grade C

Table 2: *In vitro* Studies evaluating the efficacy of Homoeopathic medicines on *E. coli*.

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Blinding</th>
<th>Control</th>
<th>Randomization</th>
<th>Experiment standardization</th>
<th>Intervention/ Medicine used with potency</th>
<th>Statistical analysis and presentation</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kawakami et al[27]</td>
<td>Incubation of a strain of uropathogenic <em>Escherichia coli</em> (UPEC) isolated from a snow leopard - which had died of septicaemia secondary to necro-hemorrhagic cystitis - with homeopathic remedies.</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Samples were inoculated in LB broth and incubated for 2 hours at 37°C; then, standardized for tube 4 in Mac Farland's scale and immediately diluted in scale 1:106 in normal saline.</td>
<td>Cantharis 12 CH, Merc. sol. 12 CH, E. coli 12 CH</td>
<td>Yes</td>
<td>In poor-nutrient medium, Merc. sol. 12CH exerted significant inhibitory effect.</td>
</tr>
<tr>
<td>Sonntag[28]</td>
<td>Effects of <em>E. coli 6X</em> on the cytokine release in vitro, on both, non-inflamed, immunologically inactive, and on inflamed, immunologically active T24 human bladder cancer epithelial cells.</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>The non-inflamed T24 cells are without lipopolysaccharide (LPS) inflamed cells, in contrast, were cultivated in the presence of LPS. Cells were treated with different concentrations of the test substances for 24 hours, followed by an MTT assay.</td>
<td>Homeopathic <em>E. coli 6X</em></td>
<td>Yes</td>
<td><em>E. coli 6X</em> had an immunomodulating effect on <em>E. coli</em> strains. Where immuno-logical defence was not active, <em>E. coli 6X</em> stimulated the immune system by cytokine production.</td>
</tr>
</tbody>
</table>

Table 3: Animal experimentations on the action of Homoeopathic medicines on *E. coli*.

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Species</th>
<th>Intervention/ Medicine used with potency</th>
<th>Variables measured</th>
<th>Blinding</th>
<th>Control</th>
<th>Randomization</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Paula [32]</td>
<td><em>E. coli</em> induced cystitis</td>
<td>Female BALB/c mice</td>
<td>Homoeopathy, Cantharis 6 CH</td>
<td>The cytokines present in the urinary bladder washing fluid were measured using a LUMINEX-Magpix KIT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>The inverted balance of inflammatory cells and cytokines in urinary bladder and pelvis mucosa shows specific local immune modulation induced by Cantharis 6CH</td>
</tr>
</tbody>
</table>

Along with Cantharis, other common, specific homeopathic medicines for cystitis or UTI may have included.
DISCUSSION

A significant number of studies on the efficacy of homoeopathy on UTIs or the action of homoeopathic medicines on *E. coli* could not be retrieved, which reflects that research in homoeopathy on UTIs is not adequately ventured. Publications on researches done with homoeopathic interventions, have either not been done or widely scattered; often not entered into databases, and thus difficult to find.\[^{37}\] Also, as most of the studies with positive results have been published, the chance of bias cannot be ruled out. RCTs on the homoeopathic treatment of UTI could not be found and in clinical studies, only 2 case series and 2 case reports were considered for assessment and analysis in this review. One of the case series contains 8 cases of UTI occurring after spinal cord injury/lesion (SCI) and the other five cases are primary. In most of the cases, the causative organism was *E. coli*, whereas only in one case *Klebsiella* was found. Individualized and constitutional prescribing was found useful in most of the chronic UTI cases. Occasionally, intercurrent or specific non-polychrest remedies were given during the acute exacerbations in some cases. So, in recurrent and chronic cases of UTI, the totality of symptoms should be built up consisting of characteristic mental symptoms, physical generalities and particular symptoms of the patients and remedies are to be selected accordingly, adhering to the homoeopathic principles, to obtain better results.

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**Fig. 1: Flow diagram for selection of articles for review.**

- **Identification**: Records identified through database searching (n=12)
- **Screening**: Records screened (n=14)
- **Eligibility**: Articles assessed for eligibility (n=14)
- **Included**: Studies included in review (n=7)
- **Articles excluded, with reasons (n=07)**: Veterinary clinical study (n=01), Study protocol (n=01), Survey (n=01), Drug Proving (n=01), Studies on artificially stressed *E. coli* (n=3)
In one acute case, significant improvement was observed after the administration of short-acting non-polychrest drug *Uva ursi*, which provides a clue that we may consider the use of such type of lesser-known medicines especially in acute cases of UTI or during acute exacerbation of chronic UTIs. *Staphysagria* was prescribed in the highest number of cases (n=5) followed by *Lycopodium* (n=3) and *Nuxvom.* (n=3), *Platina* (n=2), * Sulphur* (n=1), *Benz. acid*(n=1), *Terebinth.*(n=1), *Sarsaparilla* (n=1), *Berb. vulg.* (n=1), *Phosphorus* (n=2), *Uva ursi*(n=1), *Colibacillinum* (n=1), *Causticum* (n=1), *Cantharis* (n=1) and *Eupatorium perf.* (n=1), which indicate that the medicines from any kingdom/source can be a remedy for UTI.

All the studies did not have strong and clear outcome assessment parameters with required investigations and urine culture reports. Only in one case, single medicine with single dose was prescribed; so more adherence to the principles of classical homoeopathy, in other cases, was expected.

In most of the chronic cases of UTI, the treatment period was more than 6 months. The medicines were prescribed both in fifty millesimal and centesimal potencies. But in one study, there is no mention about the potency prescribed. Only in two *in vitro* studies, the effects of homoeopathic medicines on *E. coli* are mentioned. Both the studies were of good quality with MSAPEH score 7 and 5, respectively. These two studies showed the positive effects of homoeopathic medicines like *Cantharis 12 CH, Merc. sol. 12CH, E. coli 12CH* and *E. coli 6X* on the main causative organism of UTI, i.e. *E. coli*. The lone animal experimentation showed the significant positive effect of *Cantharis 6 CH* on the *E. coli* induced cystitis in mice model. Although the clinical evidence of Homoeopathy in the treatment of UTI is definitely positive, as evident from the review, yet, the quantity and quality of evidences are insufficient as RCTs or rigorous observational studies with a good number of participants are absent. The outcomes of in-vitro studies and animal experimentation are the good evidences in favour of the effectiveness of homoeopathic formulations on *E. coli*; more such experimentations with other of drugs and potencies are needed.

The common causative organisms for UTIs are *E. coli, Staphylococci, Klebsiella, Candida, Proteus* and *Enterococci*. The UTI infections lead to predisposing causes for other conditions including female sexual disorders, enlarged prostate, neuropathic bladder, urinary tract calculi, polycystic kidney disease, diabetes mellitus, vesico-ureteric reflex and bladder
catheterisation. It is observed that the most frequently prescribed homoeopathic medicines are Cantharis, Nux vomica, Sarsaparilla followed by Apis mellifica, Belladonna, Berberis vulgaris, Chimaphila umbellata, Equisetum, Lycopodium, Sepia, Staphysagria. Among the above, Cantharis, Apis.mel, Staphysagria, Sarsaparilla are considered as the top homoeopathic medicines to treat UTIs. The symptoms basing upon which the most frequently prescribed medicines were: Cantharis – for intolerable urging with burning, scalding urination; Apis mellifica – for stinging pain worse from heat; Staphysagria – for UTI resulting from sexual intercourse; Sarsaparilla – for burning pain after urination.

CONCLUSION
Our previous studies give a strong evidence that Homoeopathy can be used as an effective treatment for a series of diseases.[15,16,17,39,40,41,42,43,44] In this article, we tried to congregate evidence-based information on the use of homoeopathic remedies for the treatment of urinary tract infections. A comprehensive search for all types of studies on the role of Homoeopathy in UTIs demonstrates the effectiveness of this therapy in vivo and in vitro models. But, all the prescriptions should have been made in accordance with the homoeopathic principles. The case series and case reports documented in this review provide an indication that a range of remedies can be employed in patients with UTI. But it is difficult to reach at a definite conclusion due to lack of adequate good quality clinical trials and a small number of laboratory experiments, the other reason being preferential reporting of unusual, special or only successful cases. However, these studies definitely provided useful qualitative data concerning homoeopathic strategies for treatment of UTIs. A larger number of well-designed controlled clinical trials and laboratory experimentations with sufficient number of participants/subjects on strong evidence-based parameters are required to build a concrete research evidence base of Homoeopathy in the treatment of urinary tract infections or for combating the main causative organism E. coli.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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