Available online at www.jpbms.info

Research article

ISSN NO- 2230 – 7885
CODEN JPBSCT
NLM Title: J Pharm Biomed Sci.

JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Homeopathic analgesic formulations: A critical appraisal of evidence

Sanjeev Dole[1], Amit D. Kandhare[2], Pinaki Ghosh[2], Tejas P. Gosavi[1]*, Subhash L. Bodhankar[2]

[1]Sanjeeven Homeo Clinic and Research Centre, Pune-411004, Maharashtra, India.
[2]Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune-411038, Maharashtra, India.

Abstract:

Homeopathic medicines are popular across the globe for their unique nature of administration and manufacturing process. Evolutions of various schools of thoughts have created a therapeutic nihilism among the homeopathic principles of practice. Relevant communication and procrastinating follow ups added a call for development of newer formulation other than ultra molecular dilutions. In this context the novel tool for analysing the collective evidence for support of scientific homeopathy similar to clinical trial evaluation by Jadad score as well as Downs-Black scoring enlighten the path for development of effective logical platform for homeopathic system of medicine. Critical appraisal and meta analysis inform us about true nature and inner essence of facts and figures involved in published data. Difference between quality and quantity for essential impact of clinical trials in homeopathy can be better explained by such outfits. Unprejudiced estimate of accurately classified research question can be more precisely tested with such valuable equipments. This will help to remove the pitfalls and bizarre impression about homeopathy. Pain is a global health issue and desires a special attention while managing. Almost every school of medicine claims therapeutic privileges over the last few decades. Conventional medicine undoubtedly advanced in its treat modalities. However complementary and alternative medicine has also improved to better clinical outcomes. Likewise homeopathy in such case also carried few clinical trials with formulation in spite of single medicine.

Keywords: Analgesic, Downs-Black score, Homeopathy, Jadad score, Metaanalysis, Systematic Review

Introduction:

Rising intolerance to number of marketed drugs for pain relief has attracted the attention once again towards the plant based drugs [1-3]. WHO has revealed a statement that 80% world population mostly depends on herbal medicines [4, 5]. On account of number of side effects and adverse reactions, the use of NSAIDs getting challenged day by day [6]. Alternative steroids and opiate derivatives also optimally failed to produce the safe impressions on society [7, 8].

Certain homoeopathic medicines used in their ultra molecular dilutions as well as mother tinctures for annihilation of pain from its whole extent have proved to be efficacious from years of experience [9-11]. Medicines like *Rhus tox, Arnica, Brayonia, Bellis, Diascoria, and Hypericum* have been traditionally used as great anodynes in homoeopathic clinical practice [12]. Plant kingdom remained one of the chief sources of collection of drugs for homoeopathic pharmacy form its inception.

Homoeopathic medicines are usually singly administered in their potencies in cases of algesia depending on the totality of similarly characterizing symptoms. Formulations and patents do not fit in philosophical model although the use of such combinations in increasingly becoming the fashion of prescription in homoeopathic community [13-15].

SRL gel, Neuragen-PN and TraumeelS are also such kind of homoeopathic preparations including combination of more than one drug substance. Individually the role of homoeopathic medicines in several clinical trials is reported with good quality but formulation research is seldom collectively reviewed [16-19]. Singular analysis of single effects of single medicine versus the multiple combinations of drug substances in homoeopathy is still a subject of controversy for the different school of thoughts in homoeopathic system of medicine [20]. Assessment of these combinations through randomized blinded clinical trials needs to be evaluated with proper scoring system as well as international standards.

Critical appraisal using Jadad and Downs-Black scoring are one of the judicious and precise tools for reviewing the quality of clinical trials and methodological flaws [21, 22]. This ultimately converts in collective weightage of the real efficacy of homoeopathic medicines in their formulations for eradication of pain.

Methods:

Literature review was performed in order to identify the studies relative to our objectives using clinical data bases like Pubmed, EMBASE, Google Scholar and Medscape. The following terms were used as keywords in the database search: “Homoeopathy”, “Analgesic activity”, “Clinical trials” till July 2012. Studies were scrutinized on the basis of predetermined inclusion and exclusion criteria.

Inclusion criteria:

a. Published studies where analgesic action of homoeopathic medicines was tested.
b. Published studies that have carried research on formulation of homoeopathic medicines.
c. Studies published on and after year 2000.

Exclusion criteria:

a. Publications in which investigational product(s) were not recognized as homoeopathic patents.
b. Publications in which studies were not sponsored or funded.
c. Publications available in other than english language.

Description of each publication was accessed focusing on some key features such as:

a. Sponsorship
b. Treatment duration
c. Number of patients screened
d. Number patients randomized
e. Adverse events observed
f. Particulars of interventions
g. Primary outcomes of the study
h. Secondary outcomes of the study

Data was extracted by a single reviewer and checked by the three reviewers. We chose Jadad and Downs-Black checklist to critically evaluate the included studies [21, 22]. Meta analysis was carried by including the disorders undertaken for homeopathic treatment against the formulation of homeopathic medicines. These tools were selected for complete qualitative and quantitative review and differential analysis.

Data Synthesis and analysis:

Data was analysed using RevMan v 5.0 analysis software. The data of experimental and control group was represent as Mean ± SD and 95% confidence interval. Tau², Chi², I² i.e heterogeneity value were calculated overall. The entire data was plotted and represented in the form of Forest plot depicting the mean difference with 95% confidence interval of mean difference. Mean difference and 95% confidence interval (95% CI) was calculated for the association between reduction in plantar cutaneous pain in pre treatment and post treatment. Mean difference and 95% CIs were calculated for each individual study and for all studies combined. For forest plot analysis we used Random-effects model (DerSimonian-Laird method) and for funnel plot we used fixed-effects model (Mantel-Haenszel method).

Results:

Study selection:

A total of 34 articles were identified by computerized search of databases, and, from these, 26 were excluded by examination of their titles. Excluded studies were mainly duplicates, studies on rheumatic diseases other than OA, study designs other than randomized controlled trials, studies on analgesia, studies on animals and studies published in languages other than english. Abstracts of the remaining 8 studies and those identified by the screening of references of relevant original and review articles were scrutinized by the three reviewers. From this process, a total of 3 articles were potentially eligible [23-25]. Identification of relevant studies is detailed in Fig. 1.

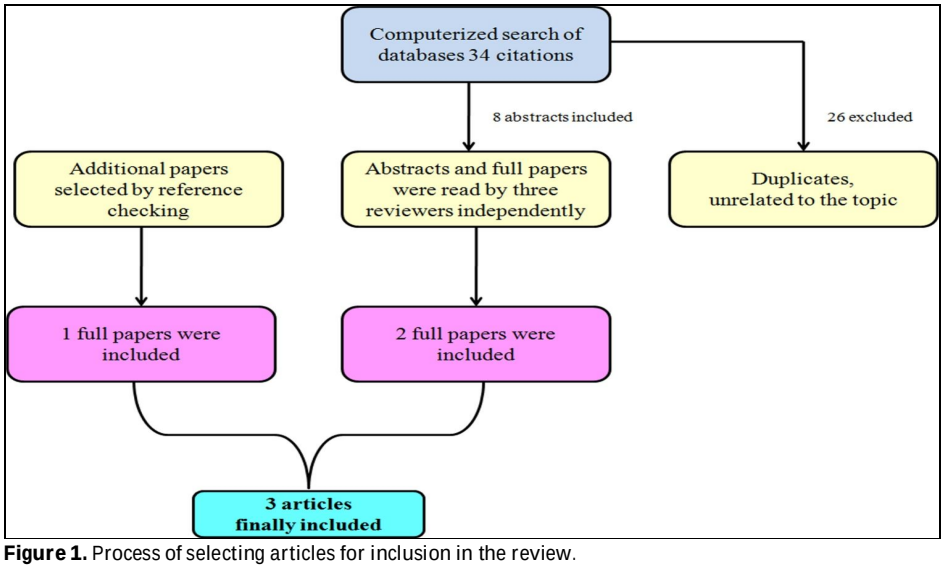

Figure 1. Process of selecting articles for inclusion in the review.

Study characteristics and results:

The three trials were fulfilled the above criteria and thus included in the study. Table 1 summarizes key data from these publications. van Haselen and Fisher (2000) [23] performed a Comparative, pragmatic, randomized, double-blind controlled trial of topical piroxicam gel with a homeopathic gel i.e. SRL® gel in osteoarthritis. SRL® gel contains the homeopathic ingredients *Symphytum officinale* (comfrey), *Rhus toxicodendron* (poison ivy) and *Ledum palustre* (marsh-tea). One hundred and eight four patients with primary knee OA were admitted into the trial with radiographically confirmed symptomatic osteoarthritis of the

knee and treated with 1 g of gel three times daily for 4 weeks. Analysis of the difference in therapeutic efficacy of primary outcome measures of subjective pain experienced during active movement, measured by standardised visual analogue scale (VAS). The pain reduction was 16.5 mm VAS in the SRL® gel ($n = 86$) and 8.1 mm in the piroxicam group ($n = 86$); the difference between treatment groups was 8.4 mm (95% confidence interval 0.8-15.9). In conclusion, the SRL® gel was at least as effective and as well tolerated as the NSAID gel. (Table 1)

Singer et al. (2010) [24] performed a randomized, double blind, placebo-controlled trial to evaluate the efficacy of the homeopathic preparation i.e. Traumeel S® in minimizing post-operative pain and analgesic consumption following surgical correction of hallux valgus. Traumeel S® is an over-the-counter homeopathic preparation composed of extracts from a combination of plants and minerals that have been highly-diluted, though not beyond Avogadro's number. One hundred and seventy two patients were admitted into the trial and eighty consecutive patients were received either treatment with Traumeel tablets or an indistinguishable placebo for 13 days following surgery. Traumeel was not found superior to placebo in minimizing pain or analgesic consumption over the 14 days of the trial, however a transient reduction in the daily maximum post-operative pain score favoring the Traumeel arm was observed on the day of surgery. In conclusion, homeopathic complex Traumeel S® was not superior to placebo in minimizing pain or analgesic consumption over the 14 days of the trial. (Table 1)

Table: 1 **Description of the study designs and patients' characteristics for trials included in the meta-analysis.**

Study name (trials)	Treatment duration	Sponsorship(s)	Country(ies)	No. of Patients Evaluated (Patients Screened) (n)	Patients randomized (n)	Study design	Jadad score	Adverse events	QoL
van Haselen and Fisher (2000)	4 Weeks	Medical Scientific department of VSM, Geneesmiddelen, The Netherlands	United Kingdom	184	184	Comparative Randomized controlled Trial	4	Mild local reactions	No QoL outcomes reported
Singer et al. (2010)	13 Days	The Heel Company, Baden-Baden, Germany	Israel	172	80	Parallel double blind randomized controlled trial	5	Wound infection, cellulitis	No QoL outcomes reported
Li (2010)	Over a 2 weeks period	Origin Biomed Inc, Reilly family foundation, Lousiana Life course and ageing centre	USA	67	60	Cross over double blind randomized control trial	5	No adverse events observed	No QoL outcomes reported

Li (2010) [25] carried out double blind, randomized, placebo controlled study to evaluate the safety and efficacy of the naturally derived topical oil i.e. Neuragen PN® for the treatment of neuropathic pain. Neuragen PN® is consist of six homeopathic substances are St. John's Wort (*Hypericum perforatum*), Wolfsbane (*Aconitum napellus*), Club Moss (*Lycopodium clavatum*), phosphorus, Poison Ivy (*Rhus toxicodendron*) and Rye ergot (*Secale cornutum*). Sixty seven patients were included into the trial, seven were exclude from the study and sixty participants with plantar cutaneous (foot sole) pain were receive one of two treatments (Neuragen PN® or placebo) per week over a 2 weeks period. Fifty six of sixty subjects (93.3%) receiving Neuragen PN® reported pain reduction within 30 minutes. This reduction within 30 minutes occurred in only twenty one of sixty (35.0%) subjects receiving the placebo. In a break out analysis of the diabetic only subgroup, 94% of subjects in the Neuragen PN® group achieved pain reduction within 30 minutes vs 11.0% of the placebo group. No adverse events were observed. In conclusion, Neuragen PN® provided significant relief from neuropathic pain in an all cause neuropathy group. (Table 1)

Various characteristic of Downs and Black score was recorded and the findings were reported. The mean of characteristic "Reporting" was found out to be "9", whereas mean of characteristic "External Validity" was found out to be "2". "5.3" was the mean of characteristic "Bias" and "4.3" was the mean of characteristic "Confounding". The mean of characteristic "power" was found out to be "0.3". (Table 2)

Table 2. Mean score obtained from Downs and Black scale

Characteristic of Downs and Black score	Mean
Reporting	9
External Validity	2
Bias	5.3
Confounding	4.3
Power	0.3

The data synthesis of the various studies fulfilling the inclusion criteria revealed the following findings: The study conducted by van Haselen and Fisher, 2010 [23] has worked over osteoarthritis in which SRL® gel treated groups has the Mean ± SD as 59.8 ± 21.8 whereas Mean ± SD for control i.e. placebo was 56.4 ± 20.7, including its weight as 7.3%. The mean difference and its 95 % of CI for this study was found out to be 3.40 (-2.74, 9.54). The study conducted by Singer *et al.*, 2010 [24] has covered three locomotor surgical disorders viz. additional osteotomy, chevron only and proximal osteotomy in which Traumeel S® treated groups has the Mean ± SD as 63.1 ± 25.6, 46.1 ± 23.4 and 51.6 ± 49 respectively whereas Mean ± SD for control i.e. placebo was 59.5 ± 55.5, 61.8 ± 34.1 and 49.2 ± 49 respectively, including their weights as 09, 1.9 and 44.6% respectively.

The mean difference and its 95 % of CI for each study were found out to be 3.60 (-15.54, 22.74), -15.70 (-28.63, -2.77) and 2.40 (-19.21, 24.01). The z value and p value were computed to be equal to 0.403 and 0.687 respectively. (Figure 2).

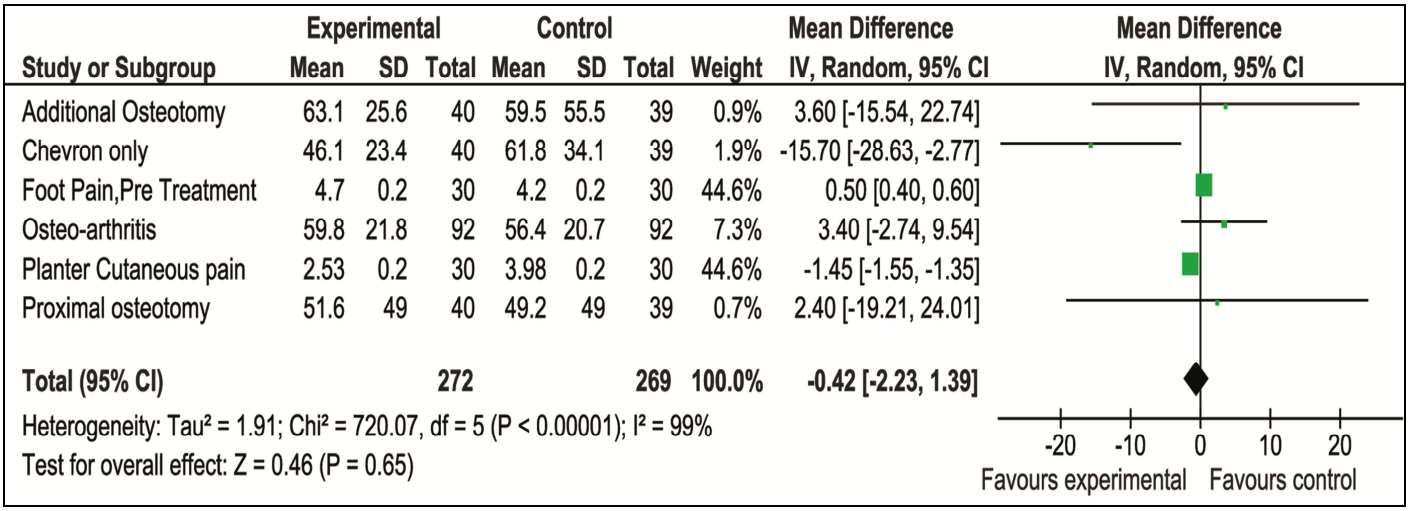

Figure 2. A forest plot depicting the meta analysis of the association between reduction in plantar cutaneous pain in pre treatment and post treatment. It shows mean difference, 95% CI (confidence interval).

Similarly Li (2010) [25] also published as trial comprising of plantar cutaneous (sole) foot pain in two schedules i.e. pre and post intervention. In this study Neuragen PN® treated groups has the Mean ± SD as 4.7 ± 0.2 and 2.53 ± 0.2 respectively whereas Mean ± SD for control i.e. placebo was 4.2 ± 0.2 and 3.98 ± 0.2 respectively, including their weights as 44.6 %. The mean difference and its 95 % of CI for each study were found out to be 0.50 (0.40, 0.60) and -1.45 (-1.55, -1.35). The total mean difference and its 95 % of CI were computed to be equal to -0.42 (-2.23, 1.39). The combined value of Tau^2 was 1.917. The overall value of Chi^2 was 720.07 and the I^2 value was 99%. The diamond represents the overall mean (Figure 2). As shown in figure 3 i.e. forest plot of metaanalysis of the association between reduction in plantar cutaneous pain in pre treatment and post treatment indicates that the study had sufficient validity and low publication bias.

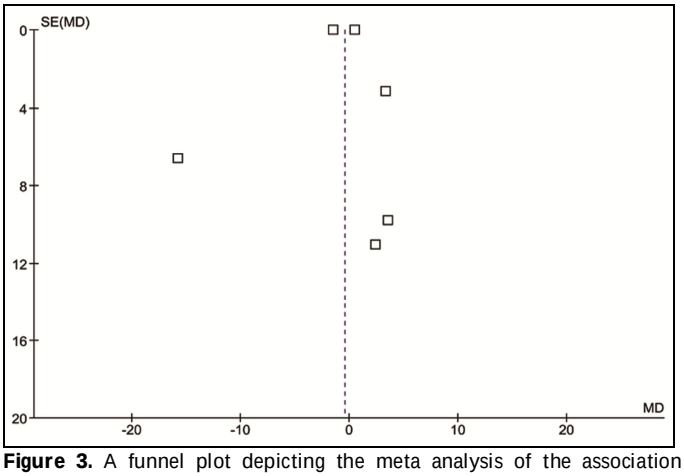

Figure 3. A funnel plot depicting the meta analysis of the association between reduction in plantar cutaneous pain in pre treatment and post treatment.

Discussion:

In the present investigation it is evidence that the studies in which subgroup consisted of foot pain pretreatment as well as post treatment of plantar cutaneous pain evaluation, the weight associated with them has a discernable impact on the overall mechanism. The heterogeneity amongst the studies was very high which shows that these studies did not bear any similar school of thought so that it is also indicative that a uniform patient population was not recruited in all the studies. These factors played an important role in the overall outcome of the meta-analysis [18, 19]. It is not clear and the evidence remains inconclusive. It is an urgent need to conduct valid clinical trial recruiting patient who bear a set of pain symptoms and capture patient reported outcome using a reproducible scale which should be uniform patient population and a reproducible scale is followed in the subsequent trial then they may provide a clear indication toward the use of homeopathic formulation for the amelioration of pain. This would also reduce heterogenesis and inter-study variants which contribute to confusion and inconclusive findings.

Philosophical evidence in homoeopathic literature support the implementation of single remedy and single dose as based on its cardinal principles. Use of poly-pharmacy and multiple prescriptions of multiple medicines was serious concept among orthodox homoeopathic schools [26, 27]. Ever increasing use of formulations and combinations of several drugs or medicines also fascinated a market in homoeopathic pharmaceutical industry and became popular among the physicians also. Mono therapy in homoeopathic clinical practice requires expert advice and consultancy where such combinations of various drug substances for different disease conditions befall the trend in over the counter prescription. Economic supervision and gossip also suggest that these medicines are widely frenzied across the world.

The classical approach for the treatment of sick desires second look in this up-to-the-minute strategy [28-32]. Studies selected in this review furthermore went through all these parameters as well as tests not only to prove their safety and efficacy but also for the distributive justice and rational art of healing.

Methodological quality of the study and quantitative outputs must encompass correlation in-between them to prove the sum and total effect of the investigational product comprise larger precision and accuracy [33]. Multiple errors or bias occurred during the study may reduce the chance of occurring event as a true outcome of the study which may affect the power [34]. Selected publications were also assessed on similar views and principles to make certain the real effect of homoeopathic formulations for pain relief.

Sheer placebo nature of the drug substance as compare to homoeopathic medicine or system is a prestigious issue for survival of ideology and essentials of the system. Taking an account of single disease entity such as pain, which is a symptomatic expression as homoeopathy believes in treating the symptoms in general and not the disease in particular. Pain can be the expression of any vital or apparent inflammation which occurs as a manifestation of thousands of diseases [35-38]. It is also most distressing as well as burning issue for clinical management. Furthermore the mechanism of most of the homoeopathic medicines which are traditionally used for the treatment of pain is still unclear. But the reassessment of the clinical trials somehow attempts to explain the path of remedy reaction and complete assay of the prospective nature of homoeopathic research.

Conclusion:

Current review explains the pain relieving accomplishment of permutation of homoeopathic medicines in different clinical conditions including post surgical trial which if not seems difficult to explain by basic strategies. The likelihood of placebo effect of homoeopathic drugs in the course of high quality randomized blinded clinical trials with fairly good Jadad score is very petite. It will be very difficult to articulate the irrefutable statement that; does homoeopathic formulations really boast the effect over such medical conditions. Because the more number of clinical trials needs to be raised en route for achieving the significant upshot and influence for overall appraisal. The trials conducted were also undersupplied in reporting and close look over quality of life during proposed visits; because the law of homeopathy believes in complete restoration of health and not simply the deletion of symptoms.

Acknowledgement:

The authors would like acknowledge Dr. S. S. Kadam, Vice-Chancellor and Dr. K. R. Mahadik, Principal, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Pune, India, for providing necessary facilities to carry out the study. The authors would like acknowledge Dr. Manohar Dole charitable trust and entire research team of Sanjeeven Homeo Clinic and research Centre, Pune.

References:

1. Zulfiker AHM, Mahbubur Rahman M, Kamal Hossain M, Hamid K, Mazumder MEH, Rana S. In vivo analgesic activity of ethanolic extracts of two medicinal plants - Scoparia dulcis L. and Ficus racemosa Linn. Biology Medicine 2010; 22: 42-8.
2. Patil MVK, Kandhare AD, Bhise SD, Bhale S. A comparative cross sectional descriptive market survey of various brands of Levofloxacin. *Asian J Pharm Biol Res* 2011; 1(2): 174-81.
3. Patil MVK, Kandhare AD, Bhise SD. Anti-arthritic and anti-inflammatory activity of Xanthium srtumarium L. ethanolic extract in Freund's complete adjuvant induced arthritis. *Biomed Aging Pathol* 2012; 2: 6-15.
4. Patil MK, Kandhare AD, Bhise SD. Pharmacological evaluation of ameliorative effect of aqueous extract of *Cucumis sativus* L. fruit formulation on wound healing in Wistar rats. Chron Young Sci 2011; 2: 207-13
5. Raygude KS, Kandhare AD, Ghosh P, Bodhankar SL. Anticonvulsant effect of fisetin by modulation of endogenous biomarkers. *Biomed Prev Nutr* 2012; In press http://dx.doi.org/10.1016/j.bionut.2012.04.005.
6. Patil MVK, Kandhare AD, Bhise SD. Anti-inflammatory effect of *Daucus carota* root on experimental colitis in rats. *Int J Pharm Pharm Sci* 2012; 4(1)337-43.
7. Ghosh P, Kandhare AD, Gauba D, Raygude KS, Bodhankar SL. Determination of efficacy, adverse drug reactions and cost effectiveness of three triple drug regimens for the treatment of *H. pylori* infected acid peptic disease patients. *Asian Pac J Trop Biomed* 2012. B62 In press.
8. Gosavi TP, Kandhare AD, Raygude KS, Ghosh P, Bodhankar SL. Evaluation of clinical outcome in arthritis with AIMS2. *Deccan J Pharmacol* 2011; 2(3): 10-30.
9. Grabia S, Ernst E. Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials. Homeopathy 2003; 92: 92-8.
10. Fisher P, Dantas F, Rampes H. The safety of homeopathic products. J R Soc Med 2002; 95: 474-5.
11. Gosavi TP, Ghosh P, Kandhare AD, Bodhankar SL. Unwrapping Homeopathic Principles in the Wake of Research: Serendipity, Placebo or True Therapeutic Milestones. *Pharmacologyonline* 2011; 1: 894-906.
12. Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. Pediatr Infect Dis J 2003; 22: 229-34.
13. Thompson T, Owen D, Swayne J. Editorial: The case for cases: publishing high-quality case reports in homeopathy. Homeopathy 2002; 91(1): 1-2.
14. Gosavi TP, Ghosh P, Kandhare AD, Bodhankar SL. Therapeutic effect of *H. pylori* nosode in healing of chronic *H. pylori* infected ulcers in laboratory animals. *Asian Pac J Trop Dis* 2012. In press. D152.
15. Gosavi TP, Kandhare AD, Ghosh P, Bodhankar SL. Anticonvulsant activity of *Argentum metallicum*, a homeopathic preparation. *Der Pharmacia Lettre* 2012; 4(2): 626-37.
16. CRD (NHS Centre for Reviews and Dissemination) Report Number 4 (2nd edn), Undertaking Systematic Reviews of Research on Effectiveness. York: CRD, 2001.
17. Gosavi TP, Kandhare AD, Raygude KS, Ghosh P, Bodhankar SL. A comparative study on the efficacy, safety

and cost effectiveness of *Viscum album* and *Rauwolfia serpentina* mother tincture in hypertensive patients. *Deccan J. Natural Products* 2011; 2(3): 29-35.
18. Raygude KS, Kandhare AD, Ghosh P, Gosavi TP, Bodhankar SL. Consumption of Alcohol and *H. pylori* infection: A Cumulative Meta-Analysis of Literature. *Asian J Biochem Pharm Res* 2011; 3(1): 338-45.
19. Ghosh P, Kandhare AD, Raygude KS, Gauba D, Gosavi TP, Bodhankar SL. Cigarette smoking and *H. pylori* infection: A meta-analysis of literature. Der Pharmacia Lettre 2012; 4(1): 128-34.
20. Van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. Homeopathy 2004; 93: 3-11.
21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. McQuay. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17(1): 1-12.
22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized studies of health care interventions. J Epidemiol Community Health1998; 52: 377-84.
23. van Haselen RA, Fisher PA. A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. Rheumatol (Oxford) 2000; 39(7): 714-9.
24. Singer SR, Amit-Kohn M, Weiss S, Rosenblum J, Maoz G, Samuels N, et al. Traumeel S for pain relief following hallux valgus surgery: a randomized controlled trial. BMC Clin Pharmacol 2010; 10: 9.
25. Li L. The effect of Neuragen PN on neuropathic pain: A randomized, double blind, placebo controlled clinical trial. BMC Complement Altern Med 2010; 10: 22.
26. Kandhare AD, Raygude KS, Ghosh P, Gosavi TP, Bodhankar SL. A comparative cross sectional descriptive study of individual pharmacy Vs mall pharmacies to evaluate customer satisfaction as well as purchasing behavior. *Der Pharmacia Lettre* 2011; 3(4): 71-83.
27. Patil MVK, Kandhare AD, Bhise SD. Evaluation of patient information leaflets on basis of consumer psychology and opinion. *Int J Phar Pharm Sci Res* 2011; 1(2): 87-92.
28. Fisher P, McCarney R, Hasford C, Vickers A. Evaluation of specific and non-specific effects in homeopathy: feasibility study for a randomized trial. Homeopathy 2006; 95: 215–22.
29. Aickin M. Participant-centered analysis in complementary and alternative medicine comparative trials. J Altern Complement Med 2003; 9: 949-57.
30. Ghosh P, Kandhare AD, V. Shiva Kumar, Rajmane AR, Mohammad Adil, Bodhankar SL. Determination of clinical outcome and pharmacoeconomics of anti-rheumatoid arthritis therapy using CDAI, EQ-5D-3L and EQ-VAS as indices of disease amelioration. *Asian Pac J Trop Dis* 2012. In press. D157.
31. Kandhare AD, Raygude KS, Ghosh P, Bodhankar SL. The ameliorative effect of fisetin, a bioflavonoid, on ethanol-induced and pylorus ligation-induced gastric ulcer in rats. *Int J Green Pharm* 2011; 5: 236-43.
32. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Gosavi TP, Badole SL, Bodhankar SL. Effect of hydroalcoholic extract of *Hibiscus rosa sinensis* Linn. leaves in experimental colitis in rats. *Asian Pac J Trop Biomed* 2012; 5: 337-44.
33. Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997; 350(9081): 834-43.
34. Chapman EH, Angelica J, Spitalny G, Strauss M. Results of a study of the homoeopathic treatment of PMS. J Am Inst Homeopath 1994; 87: 14-21.
35. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Neuroprotective effect of naringin by modulation of endogenous biomarkers in streptozotocin induced painful diabetic neuropathy. *Fitoterapia* 2012; 83: 650-9.
36. Kandhare AD, Raygude KS, Ghosh P, Ghule AE, Bodhankar SL. Therapeutic role of curcumin in prevention of biochemical and behavioral aberration induced by alcoholic neuropathy in laboratory animals. *Neurosci Lett* 2012; 511: 18-22.
37. Kandhare AD, Raygude KS, Ghosh P, Gosavi TP, Bodhankar SL. Patentability of Animal Models: India and the Globe. *Int J Pharm Biol Arc* 2011; 2(4): 1024-1032.
38. Raygude KS, Kandhare AD, Ghosh P, Ghule AE, Bodhankar SL. Evaluation of ameliorative effect of quercetin in experimental model of alcoholic neuropathy in rats. *Inflammopharmacol* 2012 DOI 10.1007/s10787-012-0122-z.

Corresponding Author:-
Dr. Tejas P. Gosavi (MD)
Research Associate,
Sanjeeven Homeo Clinic and Research Centre,
Pune-411004, Maharashtra, India
Contact No. +919689676714

Quick Response code (QR-Code) for mobile user to access JPBMS website electronically.

Website link:- www.jpbms.info

Abbreviations:
CI: Confidence Interval; NSAID: Non-Steroidal Anti-Inflammatory Drugs; OA: Osteoarthritis; QoL: Quality of life; VAS; Visual Analogue Scale.