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Investigation of therapeutically active constituents of homeopathy medicine from *Justicia adhatoda* L. and its clinical verification

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Abstract

In homeopathy system of medicine, *Justicia adhatoda* has been used in the treatment of cold, cough, pneumonia, fever, jaundice, whooping cough and asthma. We have tested the mother tincture, 6c and 30c potency of homeopathy drugs prepared from *Justicia adhatoda* using UV-vis spectrophotometer, FT-IR, LC-MS and ¹H-NMR and detect signature of therapeutically active compounds on it. We carried out 5 years of clinical observational study to test efficacy of *Justicia adhatoda*. Our results shows even if, in much diluted condition of 6c and 30c potency of *Justicia adhatoda*, there are some signature of active compounds as evident by UV-Vis, IR and LC-MS studies. Our clinical observational studies show in 45% of the cases, the 1st prescription of *Justicia adh* the patients are relieved in all the age groups. Presence of bioactive compounds in nano scale in 6c and 30c potency of homeopathy drug *Justicia adhatoda* and this scientific evidence and clinical observations shows it is a promising homeopathy drugs for respiratory disorders.

Keywords: *Justicia adhatoda*, homeopathy, IR, LC-MS, NMR, clinical observational study

Introduction

From primeval time, plants are used for many potential and powerful drugs worldwide [1]. About 80% of worlds population depends on the traditional medicine for their primary health care needs and most of these remedies involved the use of plant extract or their active compounds [2]. The extract and tincture of *Justicia adhatoda* were used as an Antispasmodic, Expectorant and febrifuge in England and very much beneficial in intermittent, typhus fever and Diphtheria [3]. Leaves of *Justicia adhatoda* are used as an expectorant and spasmolytic agent in Germany [4]. In recent years, pharmaceutical companies are taking interest in developing natural products extracted from plants, to produce more cost effective remedies that are affordable to the population [5]. *Justicia adhatoda* commonly known in English as Malabar nut (local name Vasaka) is a perennial shrub native to Asia with highly branched and lance-shaped leaves (10-15 cm in length by four wide), smooth -edged and borne on short petioles. It has opposite ascending branches with white, pink or purple flowers. The phytochemical analysis shows that phenols, tannins, alkaloids, anthraquinone, saponins, flavonoids and reducing sugars were found in the leaves of *J. adhatoda* [6]. Quinazoline alkaloid, vasicine (1, 2, 3, 9-tetrahydropyrrole [2, 1-b] quinoxalin-3-ol, C₁₁H₁₂N₂O) is the most studied chemical component in *J. adhatoda* present in the leaves, roots and flowers. The leaves contain several other alkaloids such as (Vasicinone, Vasicinol, Adhatodine, Adhatonine, Adhvasinone, Anisotine and Hydroxypeganine), betaine, steroids and alkanes [7, 8]. The importance of *J. adhatoda* plant can be understood from the ancient Indian saying, "No man suffering from phthisis need despair as long as the Vasaka plant exists" and a valuable plant in the treatment of respiratory disorders [9].

Homeopathy is an alternative method of treatment using ultra low doses of natural substances based on the principle of "like cures like". Despite of all controversy for its scientific validity and mode of action, homeopathy continues around the world as an alternative medicine. Research on homeopathy using modern tools is continuing for understanding its mechanism of action. In Homeopathy, *Justicia adhatoda* has been used in the treatment of cold, cough, pneumonia, fever, jaundice, whooping cough and asthma [10]. In the indigenous system of medicine, the source of the drug 'Vasaka' is well known, particularly in bronchitis [11]. The leaf juice is stated to cure diarrhea, dysentery and glandular tumor [12]. The plant is a well-known in Ayurvedic and Unani medicines too [13].

In spite of the various controversies on Homeopathy and frequent challenges by the scientific community regarding its efficacy, this mode of treatment has stood the test of time. Homeopathy is used in many countries for treatment of various chronic conditions, and

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medicines is prepared from a variety of herbal, animal, metal and other mineral sources^[14]. The major challenge is lack of evidence of physical existence of bioactive molecule of the original drug material (mother tincture). The foremost intricacy in arriving at a cogent clarification from that homeopathic medicines are prepared in extreme dilutions, including dilution factors beyond Avogadro's number by a number of orders of magnitude, in which any measurable remnant of the starting material to be present. In clinical practice, homeopathic potencies of 30c and 200c having dilution factors of 1060 and 10400 respectively, far beyond Avogadro's number of 6.023×10^{23} molecules in one mole, are routinely used^[14, 15]. Many hypotheses have been postulated to justify and elucidate their mechanisms of action. While some hypotheses such as the theory of water memory^[16-18] formation of clathrates, 6^[19] and epitaxy^{7 [20]} are conjectural in nature, others such as those based on the quantum physical aspects of the solutions^[21-22] have not been sufficiently tested, either due to complexity in validating the hypothesis or due to non-reproducible results. Following a dearth of credible and testable hypotheses to identify any physical entity responsible for medicinal activity, most modern scientists continue to believe that homeopathy at best provides a placebo effect. Recently Chikramane *et al.* 2010^[15] demonstrated homeopathy metal-derived medicines drugs do have presence of physical entities in these extreme dilutions, in the form of nanoparticles of the starting metals and their aggregates. Using Transmission Electron Microscopy (TEM), electron diffraction and chemical analysis by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES), they study presence of physical entities in these extreme dilutions in market samples of reputed manufacturers. However, the presence of physical entities in plant based homeopathy drugs are not evaluated or known. Therefore, we have tested for the presence of the active compound present in the mother tincture and 6c and 30c potency of homeopathy drug derived from *Justicia*. Clinical observational study has demonstrated positive health changes in routine homeopathic practice for a wide range of conditions. Clinical observational study offers an important strand of evidence in favor of the effectiveness of homeopathy in the management of a wide range of diseases. We have carried out systematic clinical observational study for 5 years to validate effectiveness of *Justicia* in homeopathic treatments.

2. Materials and Methods

2.1 Sample collection, preparation of mother tincture and 6c, 30c potency

In order to analyze the bioactive compounds, present in leaves of *Justicia adhatoda*, the plant samples were collected from different localities of Bankura, and surrounding hilly areas. After collection of the fresh leaves of *Justicia adhatoda* were washed in water. Then various solvent systems were used to first standardize maximum extraction of compounds to prepare mother tincture. Equal amount of fresh weight (50 mg) from the fresh leaves were extracted in 99% ethanol (v/v), 75% ethanol and 50% ethanol for active compound analysis and the absorption spectra were measured in a Shimadzu UV-1800 UV-visible double beam spectrophotometer in the wavelength range from 250 to 700 nm using quartz cuvettes. The 6c and 30c remedies were prepared via the Hahnemann process in washed and rinsed vials using distilled deionized water at each dilution, starting from a standard mother tincture (MT).

2.2 Detection of Active compound

We carried out different sophisticated analytical tools like Infrared spectroscopy (IR), Mass spectrometry (MS) and ¹H-NMR to detect signature of bioactive compounds present in the homeopathy preparations of *Justicia adhatoda* i.e. in Mother Tincture (MT) and 6c and 30c potency. For IR analysis, the IR spectra were measured in a PerkinElmer spectrum 100 FTIR spectrometer with range 650 to 4000 cm⁻¹. The generated IR spectra were matched with the standard Infrared spectroscopy correlation table to know the functional groups present. LC-MS analysis was carried out in a bruker microtof mass spectrometer. For NMR analysis, a borosilicate glass NMR tube rated for 400 MHz Bruker NMR, was primed with 50 to 90 µL of locking agent (either D₂O or DMSO-d₆) and 20 µL of a dilute water solution containing a known concentration of a marker molecule. The remedy or control sample (5 µM concentration) was then added to fill the tube to the 700 µL mark, followed by gentle tilting and turning to mix.

2.3 Clinical data analysis

We have collected data on repertory rubrics, homeopathic medicines prescribed, and clinical outcomes, for 5 years. The data were analyzed using classical statistical methods and likelihood ratios method. Clinical data was systematically collected at each consultation: the answer to the question: "What happened after the prescribed treatment?" and rated scale of 1 to 5. 5 = Very spectacular improvement in the total picture; symptoms have disappeared and the general state of health is completely improved; there is no need for further treatments. 4 = Spectacular disappearance of symptoms with improved general state of health, 3 = Disappearance of some symptoms, start of a general improvement, 2 = Good effect during the treatment but I am not convinced, it will improve the patient completely, other therapies are still needed, 1 = Some effect during the treatment which could be due to other factors (like placebo), 0 = No effect of the treatment. -1 = Deterioration or aggravation during or after treatment. Data are also collected for different age groups and the clinical efficacy was studied.

3. Result

The mother tincture prepared from *Justicia adhatoda* is brownish in color and analysis in the UV-Vis spectrophotometer shows a prominent peak at 280 nm, 475 nm and 665 nm. However, in 6c and 30c potency only the 280 nm peak was observed (Fig. 1). This shows even if, in much diluted condition of 6c and 30c potency, there are some signature of active compounds still existed. The FT-IR spectra of mother tincture prepared from *Justicia adhatoda* shows $\tilde{\nu}_{\max}$ 3348.98, 2776.34, 2898.22, 1647.28, 1382.48, 1327.14, 1086.60, 878.59 cm⁻¹ which is due to H-C=O:C-H stretch (aldehydes), C-H stretch of alkanes, -C=C- stretch, N-O (Nitro) group, N-O symmetric stretch (nitro compounds), C-N stretch (aliphatic amines), N-H wag (primary, secondary amines); C-H "oop" (aromatics) (Fig. 2a). The 6c potency shows N-H stretch (primary, secondary amines, amides), C-H stretch (alkanes), -C=C- stretch of alkenes (N-H bend), N-O (Nitro), C-N stretch (aliphatic amines) and N-H wag (primary, secondary amines); C-H "oop" (aromatics) (Fig. 2b). We have also detected functional groups in much diluted 30c potency and N-H stretch (primary, secondary amines, amides; -C (triple bond) C-H: C-H stretch (alkynes (terminal)), C-H stretch (alkanes), N-O (Nitro), C-N stretch (aliphatic amines) and N-H wag (primary, secondary amines);

C–H "oop" (aromatics) (Fig. 2b). The result indicates even in the diluted 6c and 30c potency there are existences of some biomolecules and that's why this homeopathy medicines work very nicely.

We have also detected mass of the major compounds in bruker microtof mass spectrometer. Analysis of the mass spectrometry data shows the mother tincture is having mixture of compounds having mass (m/z) 701.5, 423.2 and various other minor metabolites (Fig. 3a). However in the dilutions of 6c and 30c potency these major metabolites, which detected in mother tincture was not detected and two other prominent metabolites with (m/z) 683.4, 345.2 was detected in LC-MS analysis (Fig. 3b-c). To characterize the metabolites further we have also analyses the samples with 400 MHz ^1H NMR (Fig.4). However the metabolites are not detected in the sample and characteristic peaks of ethanol and DMSO was detected. In case of mother tincture there are few metabolites but the concentrations are very low to detect by 400 MHz NMR and need high sensitive NMR to detect and characterize the biomolecules.

We have analyzed the clinical data, collected for 5 years (2013-2017) and prescription of various dilutions of *Justicia adhatoda* for health complications like Cough, Corhyza (fluent), Sneezing, Expectoration, Anosmia, Headache, Over sensitiveness, Fever, Constipation, Dryness of throat, Flatulancy, and Hypertension. The profile of patients with respiratory related problems treated with *Justicia adh.* Is given in Table-1. Out of these patients 16 patients has been

diagnosed with acute corhyza, 24 with bronchitis, 5 with broncho pneumonia, 6 with bronchial asthma, 9 for violent cough on pathological basis. The duration of the suffering varies from 3 days to 35 days among the patients. These patients have been prescribed with different dilutions of *Justicia adh* and the recovery rate is quite high. The improvement from the diseased condition varies from just 1 day to 7 days of taking the homeopathy drugs in some severe cases. In 45% of the cases, the 1st prescription of *Justicia adh* the patients are cured in all the age groups and it works like wonders (Fig 5). The curing rate in case of children, young man and women is almost 50%. However, in case of old aged patients, besides *Justicia adh.* they need other follow up medicines. The homeopathic medicines, potencies prescribed and feedback of treatment received from the patients is given in Table-2. After taking the case history and depending on the severity of complications *Justicia adh.* (MT) has been prescribed to 20 patients and it give good result within 3-4 days 7 patients completely cure and they required no further treatment. In 8 patients, disappearance of symptoms with improved to general state of health and with rest 5 patients follow up medications prescribed and within 10-15 days maximum of them relived from the diseased conditions. The follow up medications like *Nux Vom*, *Nat. Sulph*, *Phosp.*, *Nat. mur*, *Bacill.*, *Cup. Met* prescribed to those patients who did not get relive in *Justicia adh.* MT or 6c potency but majority of the patients get relived with *Justicia adh.*

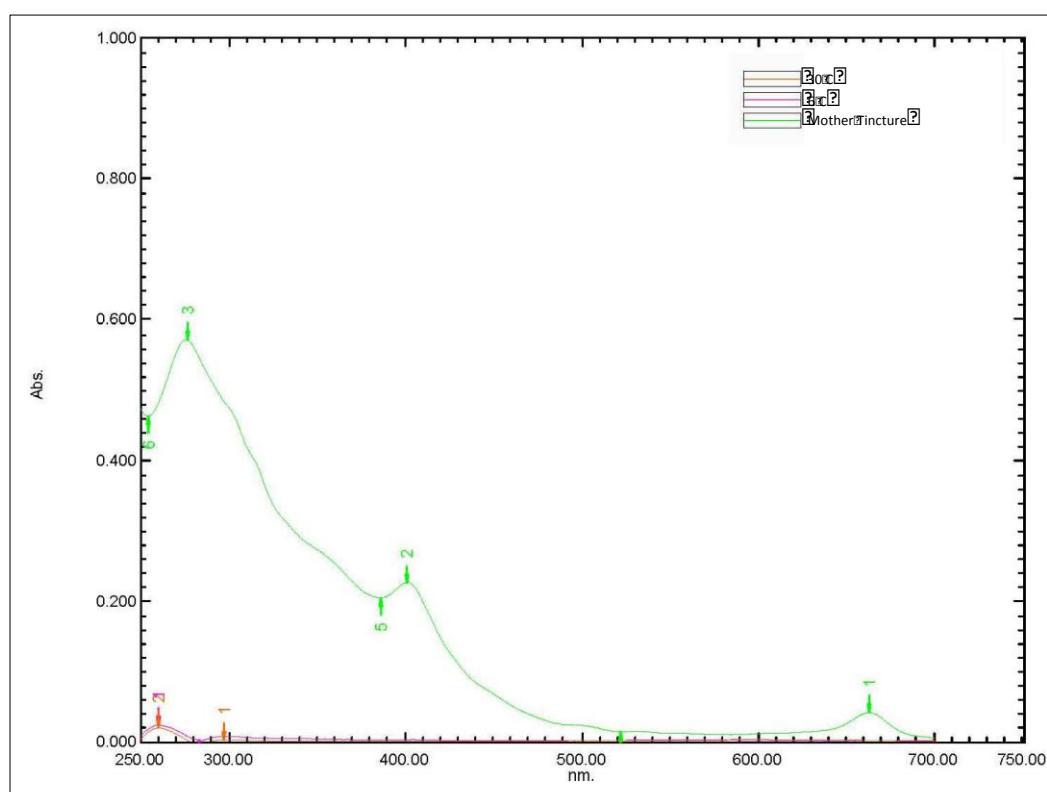


Fig 1: UV-Vis absorption spectra of homeopathic drug (mother tincture, 6c and 30c potency) prepared from *Justicia adhatoda*

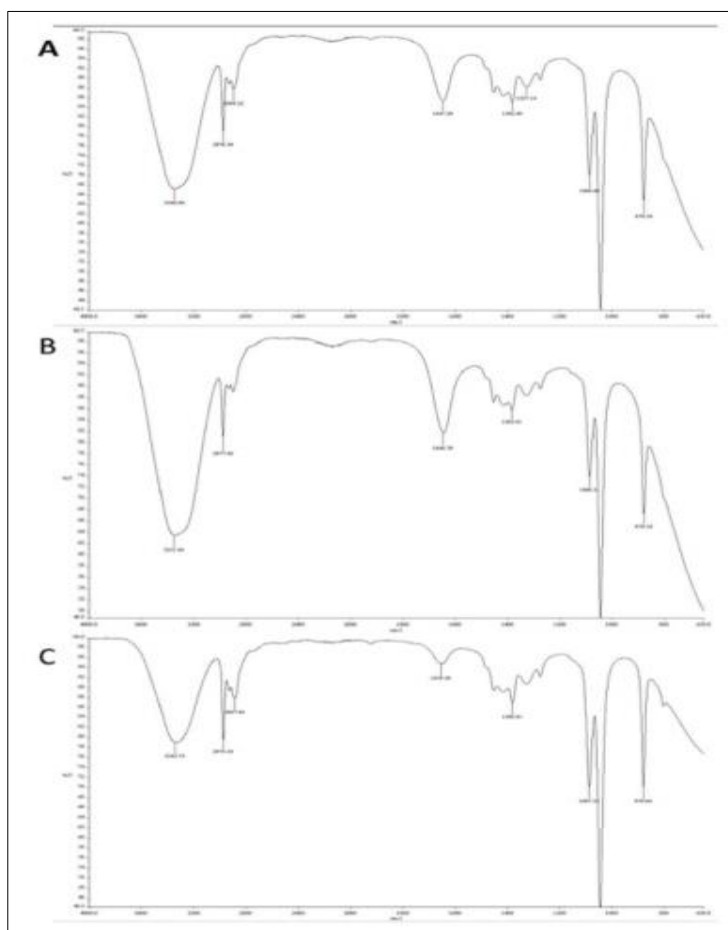


Fig 2: FT-IR spectra of homeopathic drug prepared from *Justicia adhatoda*. A. mother tincture, B. 6c potency and C. 30c potency

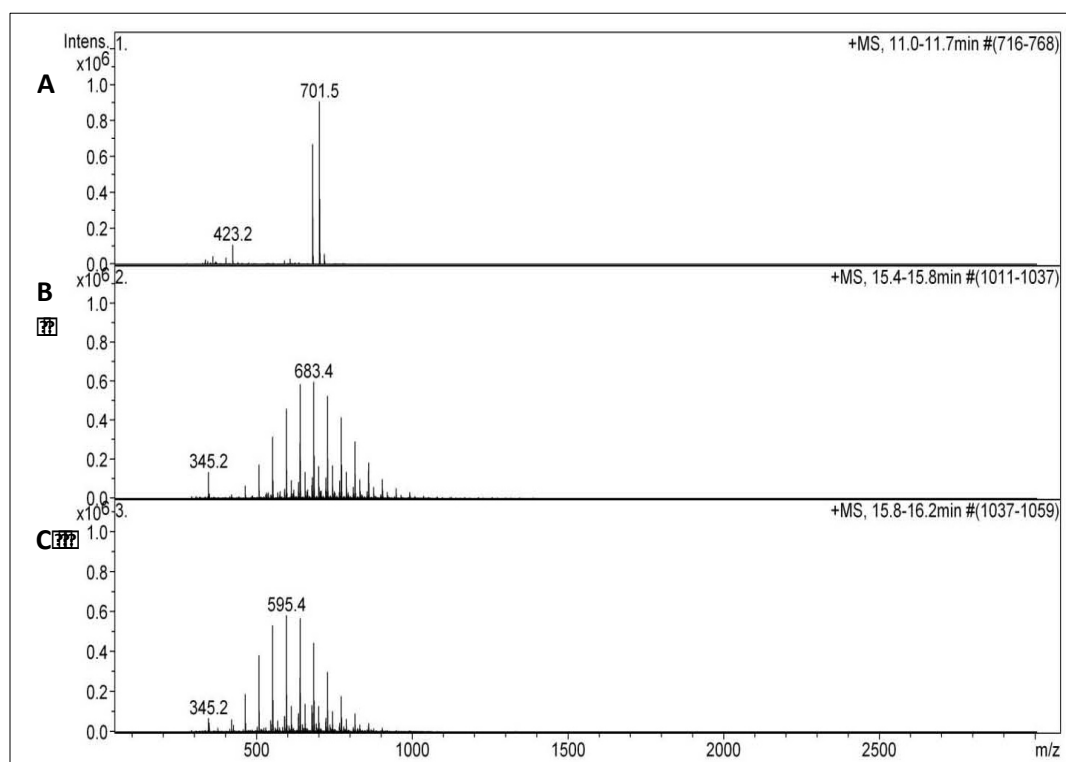


Fig 3: LC-MS micro mass of homeopathic drug prepared from *Justicia adhatoda*. A. mother tincture, B. 6c potency and C. 30c potency

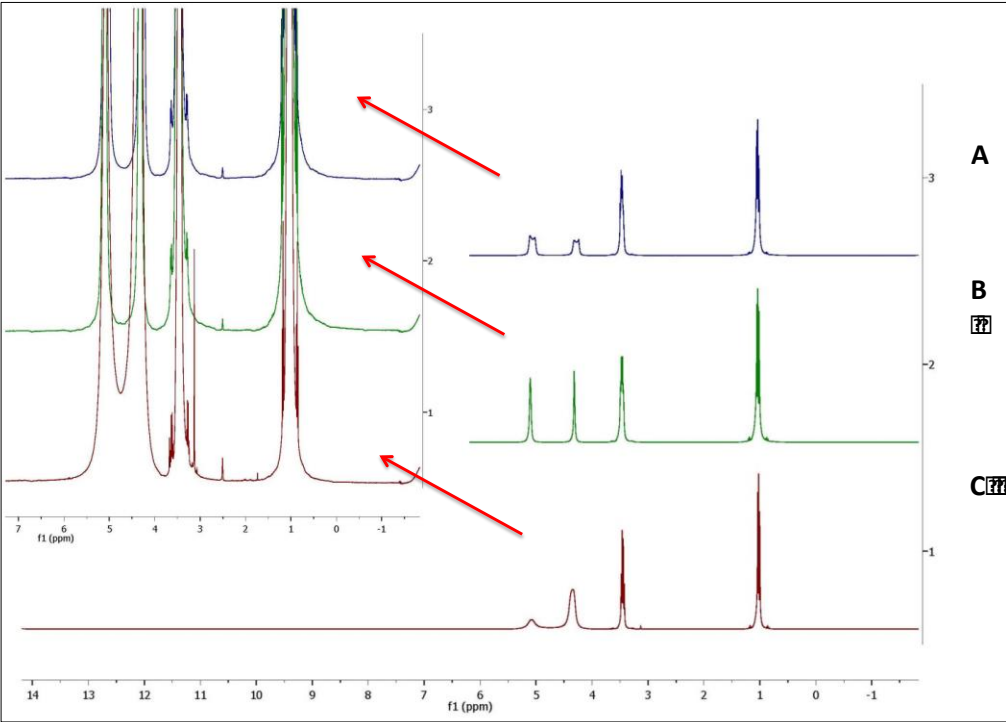


Fig 4: ¹H NMR spectra of homeopathic drug prepared from *Justicia adhatoda*. A. mother tincture, B. 6c potency and C. 30c potency

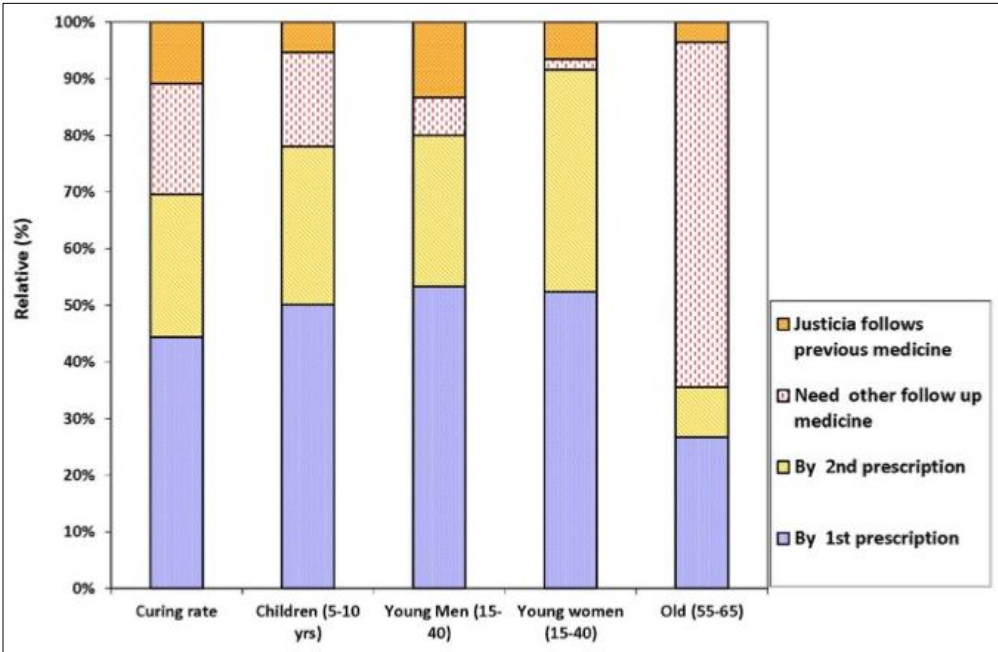


Fig 5: Figure showing results of clinical observational study on homeopathy drug derived from *Justicia adhatoda*.

Table 1: Profile of patients with respiratory related problems treated with *Justicia adh.*

Symptoms	No Of Cases	Duration of Disease in days (maximum)	Drug/potencies (Only justicia)	Improvement (duration in Minimum days)	No. of cases Showing improvement in minimum time
Cough	66	35	Q, 6c	7	45
Corhyza (fluent)	22	3	6c, 30c	1	14
Sneezing	28	3	6 c, 30c	1	13
Expectoration	26	25	Q	5	15
No expectoration	31	12	Q	3	19
Anosmia (Loss of smell)	32	14	6c	5	21
Headache	45	20	6c, 30c	3	26
Over sensitiveness	35	7	6c, 30c	4	7
Fever	24	5	6c, 30c	2	13
Constipation	34	25	6c, 30c	5	15
Dryness of throat	36	30	Q, 6c	7	20
Flatulancy	12	15	6c, 30c	5	8

Hypertension	16	35	Q, 6c	5	6
Urinary trouble	4	7	Q, 6c	2	2
Nervous trouble (dizziness, vertigo)	5	20	6c, 30c	6	3
Malaise	32	15	Q, 6c	5	18
Myalgia	37	10	6c, 30c	4	16
Harried respiration	18	10	Q	2	11
Chest pain	21	14	6c, 30c	3	9
Diarrheal attack	7	3	6c, 30c	1	3
Sleeplessness	22	30	6c, 30c	7	16

Table 2: Homeopathic medicines and potencies prescribed and feedback of treatment received

Drugs	Potency	Prescriptions	Duration of treatment	No. of cases prescribed	Rating of treatment*
<i>Justicia Adh.</i>	MT	1st Prescription	3-4d	20	7 (R-5), 8 (R-4), 2 (R-3), 2 (R-2), 1 (R-0)
	6c	1st & 2nd Prescription	5-7d	36	13 (R-5), 14 (R-4), 4(R-3), 3 (R-2), 2 (R-0),
	30c	2nd Prescription	3-5d	12	2 (R-5), 3 (R-4), 3(R-2), 1(R-1), 2(R-0), 1(R- -1)
<i>Nux Vom</i>	30c	Follow up Prescription	5-7d	5	3(R-5), 1(R-4),1 (R-3)
	200c	Follow up Prescription	5-7d	2	2 (R-4)
	1M	Follow up Prescription	7-10d	1	1 (R-4)
<i>Nat. Sulph</i>	30c	Follow up Prescription	5-7d	6	4(R-5), 1(R-4), 1(R-3)
	200c	Follow up Prescription	7-10d	2	1 (R-4), 1 (R-3)
<i>Phosp.</i>	30c	Follow up Prescription	5-10d	2	1(R-3), 1 (R-2)
	200c	Follow up Prescription	10-15d	2	1 (R-4), 1 (R-3),
<i>Nat. mur.</i>	30c	Follow up Prescription	5-7d	4	2(R-5), 2 (R-3)
	200c	Follow up Prescription	7d	2	2 (R-4)
	1M	Follow up Prescription	10d	2	1(R-1), 1 (R-3),
<i>Bacill.</i>	200c	Follow up Prescription	7d	3	2 (R-5), 1 (R-3),
	1M	Follow up Prescription	10d	2	1(R-1), 1 (R-3),
<i>Cup. Met</i>	6c	Follow up Prescription	5d	1	1 (R-4)
	30c	Follow up Prescription	7d	3	1 (R-5), 1 (R-4), 1 (R-3),

***Rating of treatment**

5 = Very spectacular improvement in the total picture; symptoms have disappeared and the general state of health is completely improved; there is no need for further treatments.

4 = Spectacular disappearance of symptoms with improved general state of health,

3 = Disappearance of some symptoms, start of a general improvement,

2 = Good effect during the treatment but I am not convinced, it will improve the patient completely, other therapies are still needed,

1 = some effect during the treatment which could be due to other factors (like placebo),

0 = No effect of the treatment. -1 = Deterioration or aggravation during or after treatment.

4. Discussion

Respiratory disease is a common and significant cause of illness around the world. In these days various respiratory diseases are in rise. Running nose, sneezing, sore throat, malaise, body ache, fever etc. sometimes also confusing with H1N1 Flu and many other deadly health issues and its prevention and treatment is a burning topic in the medical practice. In the US approximately 1 billion flue occur each year [23]. A study found that in 2010, there were 6.8 million emergency department visit for respiratory disorders under the age of 18 and were the most frequent reasons for hospital stay among children [24]. In traditional medicine there are medications to help relieve of the symptoms but no treatment available to cure it. Homeopathy is unique in that it addresses the state of the person who is ill with respect to the symptoms that they suffer with at the time and takes into account the dynamic interconnection of the whole person as a complex system. Though it is a well-tested system with evidence from clinical observational studies and relive of many patients, there are lack of scientific evidences to prove its mode of action and the presence of biomolecules on it. In the present study using sophisticated analysis, we able to trace the presence of biomolecules in the mother tincture and 6c and 30c potency of *Justicia adh.* Bruker microtof mass spectrometer is a very sensitive equipment having resolution 18.000 FWHM and we able to detect the presence of biomolecules in Mother Tincture and 6c and 30c potency of *Justicia adh.* We also able to detect the different functional

groups of the biomolecules present in the MT and 6c and 30c potency of *Justicia adh.* However, we unable to detect anything in 400 MHz ¹H NMR. For 1H 400 MHz NMR typically required minimum 2 mg of samples and for this we probably unable to detect any biomolecules and further low sensitive 800 MHz NMR may be required to get the detail structure of the biomolecules present.

Presence of nanoparticles as the starting materials and their aggregates even at extremely high dilutions using state of the art techniques like TEM, SAED and ICP-AES in some commercial Homeopathy drugs has been demonstrated by Chikramane *et al.* 2010 [15]. They found no major differences in the nature of the particles (shape and size) of the starting material and their absolute concentrations (in pg/ml) despite large differences in the degree of dilution from 6c to 200c (1012 to 10400). Our study concludes the presence of biomolecules even in very low dilution and it works as evident by the observational studies. Water and alcoholic extracts of *Justicia* having the phytochemical active compounds like vasicine and vasicinone have effective pharmacological actions even in the nano scale. Our 5 years of clinical observational study gives interesting results and validate *Justicia adh.* works like a wonder in various respiratory related disorders. 45% of the treated patents cured in 3-4 days from various respiratory related problems showing it is an effective homeopathic medicine. The infectious respiratory diseases with significant mortality cases are in rise. The overall health of our immune systems is getting

worse with each generation. Every time we take an antibiotic, the immune system of our bodies is weakened further. This lack of resistance is then passed on to the next generation. Viruses and bacteria adapt over time to the drugs and become as superbugs and now a days the antibiotics resistance cases are in rise. In the present scenario of antimicrobial resistance, homeopathy offers alternative remedies for minor infections and possible prevention of recurring upper respiratory tract infections ^[25]. In this present circumstances' homeopathy medicine *Justicia adh.* could play a major role in the treatment of respiratory infections and the prevention of this epidemic.

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