Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 16, No. 4, 2025(pp. 49-69)
RESEARCH ARTICLE WWW.JOCMR.COM

Effectiveness of Individualized Homoeopathic Intervention in the Management of Children with ADHD: A Single-Arm Placebo-Controlled Randomized Trial Using Biomarkers and Standard Questionnaires

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ABSTRACT:

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents impairing their academic performance and quality of life. Current pharmacological interventions may end in drug effects on continued use. The use of homoeopathic intervention as an alternative therapy provides the ADHD population a better effects on various behavioural issues.

Aim:

To evaluate the effectiveness of individualized homoeopathic intervention in children diagnosed with ADHD using standard questionnaires and serological biomarkers.

Methods:

This was a single-arm placebo-controlled randomized trial conducted over two years, including 64 children diagnosed with ADHD based on DSM-5 criteria. Participants were randomly divided into two groups: one receiving individualized homoeopathic intervention (n=32) and the other receiving placebo (n=32). Standardized tools such as ADHD Rating Scale IV (Home and School versions) for assessment of ADHD symptoms and Weiss Functional Impairment Rating Scale (WFIRS-Parent) for assessment of quality of life were administered at baseline and at periodic intervals. Biomarkers like serum zinc, ammonia, lactate, and ferritin were investigated at baseline and at 12 months. After normality testing the data's were analysed using independent t-tests, paired t-tests, and ANOVA.

Results:
The homoeopathic group showed statistically significant improvements compared to the placebo group across all ADHD subdomains ($p<0.05$). There is marked improvements in WFIRS scores, which indicates improved quality of life. Biomarker analysis revealed a significant increase in serum zinc and ferritin levels, while serum ammonia and lactate levels significantly decreased in the homoeopathy group.

Conclusion:
Individualized homoeopathic interventions demonstrated statistically significant and clinically relevant improvements in children with ADHD. The concurrent differences in biomarker profiles may provide a notable biological mechanism of action. These findings suggest that homoeopathy may offer a viable complementary approach in managing ADHD in children.

Keywords:

ADHD children, Homoeopathy, Individualised medicines, Serum Biomarkers, Standard questionnaire, Randomised placebo controlled Trial.

INTRODUCTION:

Attention Deficit Hyperactivity Disorder (ADHD) is one of the commonly reported clinical condition in child psychiatric practice. It brings a high concern when the child disturbs everyone with restlessness, temper tantrums, impulsive acts at public or at school. The progression of untreated child ADHD may results in multiple adult psychiatric conditions like Substance abuse, Depressive disorders, Personality disorders, Anxiety disorders, etc. Recent studies imply the total prevalence of ADHD is 11.3% in age group between 5-17 years. Among the gender the boys are more likely to get ADHD diagnosis, which is 14.5% than girls which is 8.0% between the age group of 5-11 years and 12 -17 years [1]. In an study which includes 61 cross-sectional research, resulted the global prevalence of ADHD in children is around 7.16% among the age group of 3 to 12 years and 5.6% betweenthe age group of 12 to 18 years. The prevalence of ADHD has been noticeably increased while using DSM V diagnostic criterion[2]. A systemic review including 494 articles showed the prevalence of Adult ADHD of about 5.48% to 25.7% among a broad population and specific population in India[3]. In a population based cross sectional survey conducted at Kerala

signifies the magnitude of mental illness. It resulted with 12.43% of total adults have one or the other mental health disorder. Out of which 9% have Chronic Mental Diseases (CMD) [4]

A study conducted by Kessi M Duan et al which includes genetic basis of ADHD till Jan 2022, found there are multiple genes linked with ADHD condition. Few of them are "*DRD1, DRD2, DRD4, DAT1, TPH2, HTR1A, HTR1B, SLC6A4, HTR2A, DBH, NET1, ADRA2A, ADRA2C, CHRNA4, CHRNA7, GAD1, GRM1, GRM5, GRM7, GRM8, TARBP1, ADGRL3, FGF1, MAOA, BDNF, SNAP25, STX1A, ATXN7, and SORCS2*". Majority of the genes are found both in animal model and human model [5]. Deficiency in dopamine and dopamine transmission lead to memory issues and reinforcement. Symptoms like Inattention and memory has correlated with dopamine deficiency in many studies [6]. In a pair matched case control study including 161 ADHD children with 161 control group revealed that there are strong significant factors like emotional abuse and single child are more prone to receive ADHD diagnosis [7]. A study conducted with children who spent their early life at Orphanages in Romania received the diagnosis of ADHD in the later part of the lifepossibly due to food provided with poor nutrition, devoid of peoples around, and isolation[8]

A review study conducted by Emond V et al (2008) regarding the structural and functional neuroanatomical study of ADHD explained dysfunction in the frontostriatal network which connects prefrontal cortex, anterior cingulate cortex, caudate nucleus, and putamen. Cerebellum, parietal lobes, occipital lobes and few parts of temporal lobe displayed abnormalities. Many other related studies found there is significant decrease in the volume of the brain[9]. Studies replicates around 65% of children with ADHD have at least one or more comorbid disorders. In 30 - 90% of cases reported with Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) showing poor outcome results on medication. All those comorbidities when influenced by environmental factors end up with antisocial behaviour [10].

There are varieties of tools used in different parts of the world. Few of them are found to be effective, reliable, replicable and universally applicable. One among thetool was ADHD Rating Scale – IV - home and school version. The scores of Home version can be measured through answers marked by parents and similarly the School version by teachers [11]. Few self-reported scales which have good validity and reliability were, ADHD Impact Module for Adults (AIM - A), ADHD Impact Module for Child (AIM - C), Adult ADHD Quality of Life Scale (AAQoL), and Weiss Functional Impairment rating Scale (WFIRS) [12].

In a systemic review and metanalysis of case control study from 1969 to 2011 includes 210 studies with an objective of ADHD and its relevant biomarkers. The study reveals there are biomarkers which are linked directly to drug effects of ADHD. Few of them are Norepinephrine [NE], 3-Methoxy-4-hydroxyphenylethylene glycol [MHPG], monoamine oxidase [MAO], Zinc [Zn] and cortisol),Also six studies supports the relation of ferritin with symptom severity of ADHD. Three studies found there is relation of cognitive or neurophysiological functioning of ADHD with lead-ferritin-Zn [13]. Severe Zinc deficiency during a child development may lead to disordered cerebellar functioning, deranged pattern of behaviour and impaired emotional response [14].Zinc was found as a vital co factor for the normal functioning of pathways using Neurotransmitters, prostaglandins and melatonin. It also utilized as an important co factor in dopamine metabolism [15]. In a cross sectional study conducted by Monica Jeneja et al, found to be significant reduction in Serum Ferritin level in newly diagnosed ADHD children compared to control group [16]. Another study conducted with 52 ADHD children with predominantly Hyperactive type the serum ferritin level was found to be significantly low [17].

Study concludes that there is a correlation between ADHD and increased level of plasma Ammonia and Lactate level, and those might be an important parameter in the diagnosis of ADHD patients[18]. The elevation of Serum Ammonia level signifies the dysfunction or hypofunction of the mitochondria which is much seen in conditions like Autism spectrum Disorder and other child behavioural disorders where gut bacteria plays significant role [19].Russell et al hypothesised, the lactate released after dysfunctional astrocyte metabolism leads to certain behavioural pattern of ADHD symptoms[20]. Another study observed that there is significant connection in the attenuation process of lactate resulting from exercise was related with children diagnosed with ADHD [21].

ADHD Treatment guidelines from sources like NICE, CADDRA and other National Health Organization from different countries like United Kingdom, Germany, Canada and Spain suggested that the first line of treatment as Methylphenidate (MPH) and Lisdexamfetamine (LDX) and the second line of treatment as Atomoxetine (ATX) and Guanfacine (GXR). The guideline also directs for combination of other therapies like psychosocial interventions. It highly recommends individualized approach. The guidelines constrain for universal applicability [22]. In another literature review conducted to understand the cognitive effect of amphetamine and methylphenidate shown the stimulant medications may improves the cognition, through the action of physiological arousal. Yet the study did not provide a

confirmatory support that the stimulation medications enhance the cognitive function [23]. The evidence based effective therapies suggest certain behavioural approaches and organizational interventions which provide effectiveness in ADHD children as well as in the Parental behaviour. The recommended therapies were "*Behavioural Parental Training (BPT), Behavioural Classroom Management (BCM), Behavioural Peer Intervention (BPI), Combined behaviour management interventions and Organisational training*" [24.]

In a double blind, partial crossover study conducted by John Lamont, to determine the effectiveness of homoeopathy in 43 ADHD children favours homoeopathic medicines compared to placebo group [25]. A case series study including 30 children, out of which 20 children treated for 01 year and 10 children observed for four months, using CPRS - R, MYMOP scores and DSM IV scales showed significant reduction of scores in 20 children treated for ADHD symptoms [26]. A Meta – analysis conducted by Gaertner et al. (2022) to evaluate the effectiveness of individualized homoeopathy in children diagnosed with ADHD. The studies with homoeopathy group showed positive results favouring homoeopathy with clinically relevant improvement [27].

In homoeopathy, the minute quantity of medicine which is less than a single molecule of medicine brings a definite mode of changes in the living cells. In recent researches there are multiple attempt made to overcome this challenging question of how an ultra-diluted Nano drug substance brings a positive changes. The Scope of the present study using biomarkers and standardised questionnaires may found a basement to know the effectiveness of ultra-diluted Homoeopathic medications in Psychiatric conditions, in view of therapeutic action of a drug through cell biology, blood biochemistry and "gene regulatory hypothesis". On exploration of findings in this study through fundamental or experimental research pays endless scope in designing newer experiments in the field of child psychiatry.

METHODS:

The research proposal had been prepared and presented in the Research Advisory Committee (RAC) of the University. With references to the suggestions and recommendations the modifications were done and finalized research proposal has been prepared. Ethical approval has been received from IEC of Ph.D research centre after thorough review of the protocol. After approval from IEC the research proposal was registered under Clinical Trial Registry India (CTRI) with registration No: CTRI/2022/03/040728.

Study Design, Sample Size and study setting:

It is a placebo controlled Randomized trial with a sample size of 64, 32 in Medicinal group and 32 in Placebo group. The sample size was calculated based on the previous studies undertaken and power calculations. Considering an alpha level of 0.05, 80 % of power distribution and to detect a clinically meaningful difference in ADHD Rating Scale (ADHD-RS) scores between the two groups. Participants were enrolled from outpatient departments, peripheral centres of the Institute. Also schools, and child care homes located under kottayam district were screened and eligible cases were identified and enrolled in the study.

Sampling Method and Randomization:

Probability sampling - Simple random sampling has been adopted in this study. The cases will be randomized according to the random numbers generated with the help of computer-based software www. Randomizer.org.The study employed single-blind methodology—participants and their caregivers were unaware of group allocation. The Principle investigator, Supervisor & Co supervisor were aware to facilitate individualized remedy selection

Study Period:

The total study period was 02 years which includes 09 months enrolment, 12 months follow up and 03 months for compilation and publication.

Screening, enrolment and Assessment tools used:

Children presenting with hyperactivity and restlessness at OPD of NHRIMH and other peripheral centres of the Institute were screened with Connors Abbreviated Rating Scale. Other than the screening and enrolment at the Institute, a mass screening program had been conducted at nearby Government & Aided schools, Private schools and Children observation homes. The cases were screened according to the specific age criteria's with prior permission and consent from the Principal and Supervisors of the children homes respectively. A total of 280 cases were screened and children reporting with mild to severe scoring for attention and hyperactive problems were advised to report at hospital for further detailed study. With detailed history taking, the ADHD cases fulfilling the DSM V criteria and specified inclusion and exclusion criteria's the cases has been selected and enrolled in the study according to the

randomization chart either to remedy or placebo group. The cases were enrolled after getting Consent and or Assent from the caretaker or patient respectively. The screened cases were confirmed for diagnosis by Psychiatrist of the Institute. The assessment tools used were ADHD rating Scale IV (Home& School Version), -assessed at baseline and at every month, Weiss Functional Impairment Rating Scale (WFIRS) – Parent Version - assessed at Baseline, 6th and 12th month and Blood Parameters – S. Zinc, S. Ammonia, S. Lactate and S. Ferritin - tested at baseline and end of the treatment.

Inclusion & Exclusion Criteria's:

The cases between age group of 03 – 14 years of age, of both sexes, confirmed to DSM- 5 criteria, a score of 15 & above in conners rating scale, willingness to provide blood samples, child or parent ready to give consent, & understand the questionnaires were enrolled in the study. The cases with chronic serious medical conditions, congenital anomalies, severe neurological conditions, with other Co morbid psychiatric conditions, patients under psychoactive drugs in the past two weeks were excluded from the study.

Hypothesis:

Null Hypothesis (Ho):

There is no significant difference between individualized homoeopathic medicines and placebo in the management of ADHD children, as measured through standard questionnaires and biomarkers.

Alternate Hypothesis (H1):

Individualized homoeopathic medicines have a significant effect compared to placebo in the management of ADHD children, as measured through standard questionnaires and biomarkers.

Case taking, Treatment Intervention, Prescription, Potency and Repetition:

All the cases enrolled in the study were conducted in depth interview according to a standardized case recording proforma. The complete analysis, totality, reportorial chart, miasmatic evaluation are arrived according to guideline mentioned byDr. Samuel Hahnemann 6th edition of Organon of Medicine. Follow up assessment was scheduled on every month and unscheduled follow up in case of any acute illness. In Homoeopathy group the similimum was arrived according to complete case analysis, reportorial totality and

MateriaMedica reference. The selected similimum was integrated with miasmatic understanding and the most appropriate and individualized remedy was prescribed in centesimal potencies (06, 30, 200, 1M & 10M) with necessary repetition. Followed by placebo in case of notable improvement of the illness. In case of no improvement for more than 03 months, the remedy has been changed after retaking case and analysis. The medicines were dispensed by dissolving 2-3 drops of the medicated dilution on Sacharumlactis powder with weekly, fortnight or monthly repetition of medicines as per the prognosis of case. In placebo group the similimum was arrived according to complete case analysis, reportorial totality and MateriaMedica reference. The same method of dispensing was followed as in medicine group with plain Sacharumlactis packets and blank tablets. In case of any severe acute exacerbation of disease symptoms, a psychiatrist consultation was scheduled urgently. During the study there were no notable severe adverse effects or adverse events were observed. Regular monthly, quarterly assessments were made as per the rating scales adopted in the study. To maintain good compliance and follow up, a detailed instruction was provided to each caretaker and patient as well, after initial enrolment. A yearly calendar with predetermined dates for monthly appointments was provided to the care taker and patient. The help of psychiatric social worker of the Institute was utilized for providing telephonic reminders for follow up and other communications related to the treatment and assessment plan. At the end of the study, all the patients were followed well with no dropouts. The data's were captured in the designed Excel sheet as suggestedby Statistician. The data's were analysed using appropriate statistical tool and discussed aligning with the objectives of the study.

Outcome Assessment:

Outcome measurement were assessed based on comparison between the Homoeopathy and placebo group of scores obtained in ADHD (RS) IV – Home & School version, WFIRS(Parent version) and Serum Biomarkers in the baseline and End of the treatment.

Statistical Analysis:

To know the effectiveness of the Individualized Homeopathic medicine in management of ADHD children compared with placebo group, the total scores obtained at baseline and end using ADHD (RS) IV – Home & School Version, WFIRS (Parent Version) and Blood parameters were tabulated and calculated with appropriate parametric tests. To determine the significant difference after Homoeopathic intervention, the data was statistically analysed

using the software SPSS V27. The normality of the variables was checked using Shapiro Wilks test. Considering normality, parametric test like Independent Sample "t" test and Paired Sample "t" test was employed for comparing the two groups and comparing the baseline and end within the group. ANOVA was used for WFIRS (Parent) Version to compare at multiple time intervals. After achieving statistical significance using ANOVA, Tukey post hoc test was used to identify the difference in specific groups.

RESULTS:

The essential outcomes were categorised under the following sections,

- Basic Demographic data's were represented in tables.
- Independent Sample *t* Test to determine the difference between the Homoeo and Placebo groups in ADHD RS (IV) – Home and School Version
- ANOVA testto determine the difference between the Homoeo and Placebo groups in WFIRS at Baseline, 6th month and 12th month followed by Tukey post hoc test.
- Paired Sample *t* Test to determine the difference between the baseline and end reports for both groups in Serum Biomarkers Zinc, Ammonia, Lactate and Ferritin

Table – 01 - Baseline Socio-demographic and Clinical Characteristics of Participants (n = 64)

Variable	Category / Description	Frequency (n)	Percentage (%)
Age (years)	Mean ± SD = 10.88 ± 3.29 (Range: 3–14)		
Sex	F	36	56.2
	M	28	43.8
Religion	Christian	28	43.8
	Hindu	35	54.7
	Islamic	1	1.6
Socioeconomic status - Low/Middle/Upper Middle/Upper	Middle	6	9
	Upper	1	2
	Upper middle	9	14
	Low	48	75
Diagnosis - ADHD HA/IA/MxD	HA	12	18.8
	IA	30	46.9
	Mxd	22	34.4
ADHD - Severity	Mild	24	37.5
	Moderate	35	54.7
	Severe	5	7.8
Fundamental Miasm	Psoric	17	26.6
	Sycotic	10	15.6
	Syphilitic	37	57.8

Dominant Miasm	Psoric	45	70.3
	Sycotic	15	23.4
	Syphilitic	4	6.2
Remedy	Ars.Alb	1	1.6
	Baryta. Carb	2	3.1
	Calc.carb	1	1.6
	Lachesis	1	1.6
	Mercurius	1	1.6
	Nat. Mur	2	3.1
	Nux.Vom	4	6.2
	Phosphorus	3	4.7
	Pulsatilla	3	4.7
	Sepia	2	3.1
	Silicea	1	1.6
	Sulph	5	7.8
	Tuberculinum	2	3.1
	Lycopodium	4	6.2
	SL (Placebo group)	32	50.0
Potency	0 (Placebo group)	32	50.0
	30	8	12.5
	200	24	37.5
Improvement status	Marked	17	26.6
	Mild	8	12.5
	Moderate	14	21.9
	Status Q	25	39.1

A total of 64 children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) were enrolled in the study. The mean age of participants was 10.88 ± 3.29 years (range: 3–14 years) showing a majority of children belong to late childhood to early adolescent age group. Gender distribution showed slight female predominance (56.2% females and 43.8% males). On religious background, majority of participants belong to Hindu (54.7%), followed by Christian (43.8%), and a small proportion belong to Muslim (1.6%). Majority of participants belonged to the lower socio-economic group (75%).

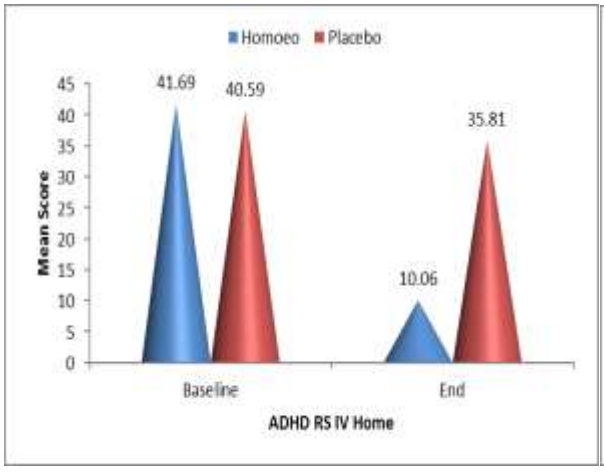
On clinical subtype, the inattentive subtype of ADHD was most frequently enrolled (46.9%), followed by the combined type (34.4%). Based on ADHD disease severity distribution, majority of cases enrolled under moderate (54.7%), 37.5% were mild and 7.8% were severe. On miasmatic analysis, the syphilitic miasm (45.3%) predominates under fundamental miasm and whereas the psoricmiasm (51.6%) predominates under dominant miasm. The most frequently prescribed remedies were Sulphur, Lycopodium, Nux. Vomica, Phosphorous and Pulsatilla administered in 30C or 200C potencies. At the end of the study majority of

participants experienced marked improvement in their overall behavioural and cognitive domains.

Independent Sample *t* Test was used to determine the difference between the Homoeo and Placebo groups using ADHD RS (IV) – Home and School Version

Table 02 - Difference between the Homoeo and Placebo groups using ADHD RS (IV) – Home and School Version

Timeline	Group (H/P)	N	Mean	SD	MD	t	df	p
ADHD - RS –IV - Home version								
Baseline	Homoeo	32	41.69	5.954	1.094	0.849	62	0.399
	Placebo	32	40.59	4.196				
End	Homoeo	32	10.06	2.242	25.75	30.126	62	0.000
	Placebo	32	35.81	4.284				
ADHD - RS -IV - School version								
Baseline	Homoeo	32	41.91	5.257	1.688	1.367	62	0.177
	Placebo	32	40.22	4.598				
End	Homoeo	32	10.03	2.584	25.875	27.698	62	0.000
	Placebo	32	35.91	4.61				



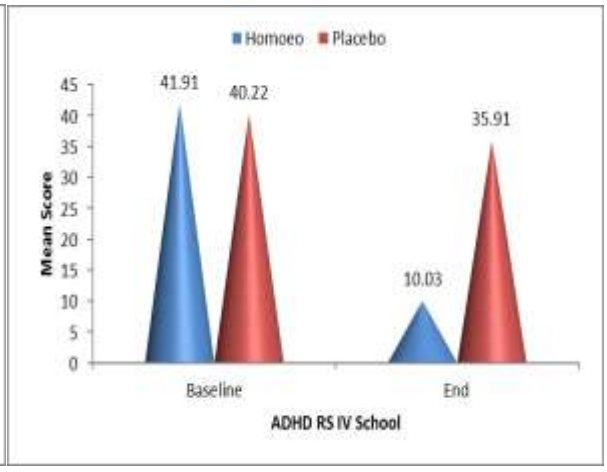


Fig 01 – ADHD RS IV – Home Version **Fig 02** – ADHD RS IV – School Version

Independent-sample t-tests demonstrated statistically significant differences between the homoeopathy and placebo groups across all primary outcome measures. For the ADHD Rating Scale IV (Home version), the mean end-point score in the homoeopathy group (10.06) was markedly lower than that of the placebo group (35.81) ($t = 30.126$, $p < 0.05$). A similar trend was observed for the School version (mean 10.03 vs. 35.91; $t = 27.698$, $p < 0.05$).

ANOVA Comparison of WFIRS between Homoeopathy and Placebo Groups at Baseline, 6th Month, and 12th Month with Tukey Post Hoc Analysis:

Table 03- Comparison of WFIRS between Homoeopathy and Placebo Groups at Baseline, 6th Month, and 12th Month using ANOVA

(I) WFIRS	(J) WFIRS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Baseline	6 Months	.4148*	.02738	.000	.3501	.4795
	12 Months	.8159*	.02738	.000	.7512	.8806
6 Months	Baseline	-.4148*	.02738	.000	-.4795	-.3501
	12 Months	.4011*	.02738	.000	.3364	.4658
12 Months	Baseline	-.8159*	.02738	.000	-.8806	-.7512
	6 Months	-.4011*	.02738	.000	-.4658	-.3364
*. The mean difference is significant at the .05 level.						

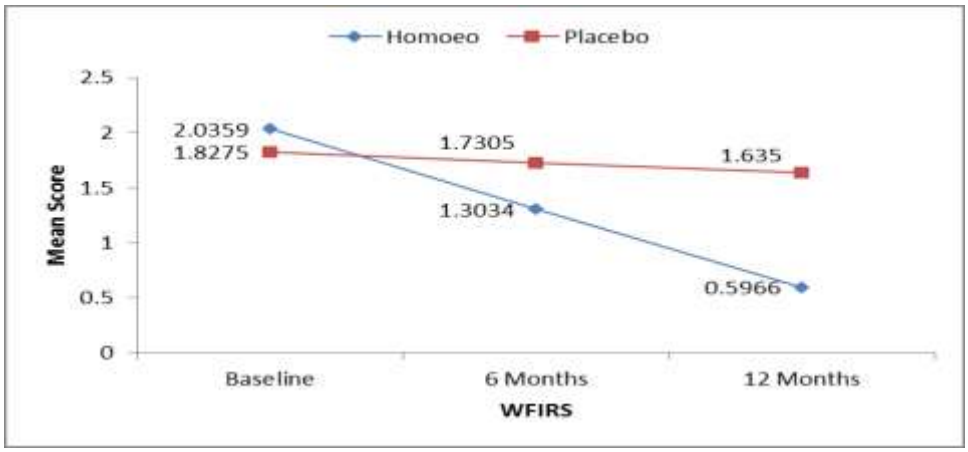


Figure 03- Comparison of WFIRS between Homoeopathy and Placebo Groups at Baseline, 6th Month, and 12th Month.

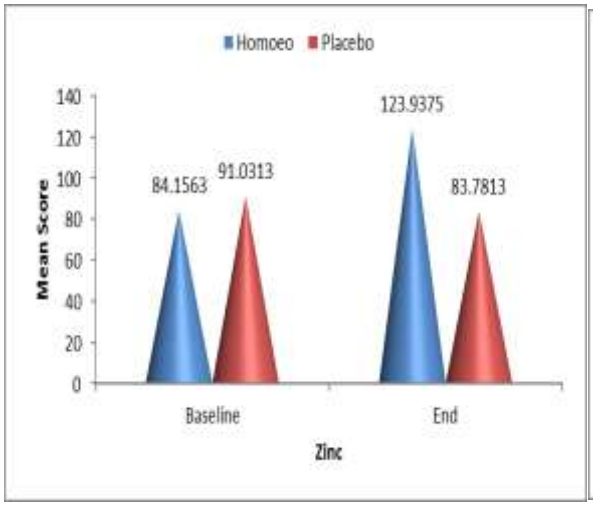
Repeated-measures analysis of WFIRS scores revealed a statistically significant improvement in functional impairment outcomes over time. Post hoc pairwise comparisons showed that mean WFIRS scores decreased progressively from baseline to 6 months and further to 12 months, with all pairwise differences reaching statistical significance ($P < 0.001$). Also, the mean difference between baseline and 6 months was 0.415 (95% CI: 0.350–0.480), and between baseline and 12 months was 0.816 (95% CI: 0.751–0.881), indicating a substantial reduction in functional impairment. Additionally, a significant improvement was observed between 6 and 12 months (mean difference = 0.401, 95% CI: 0.336–0.466, $P< 0.001$). WFIRS-Parent scores showed consistent improvement across time points, with significant reductions from baseline to 6 months and 12 months ($F = 444.118$, $p < 0.001$). These findings demonstrate a consistent and progressive enhancement in overall functioning across the study period as measured by WFIRS.

Paired Sample *t* Test was used to determine the difference between the baseline and End in groups forBiomarkers (Zinc, Ferritin,Ammonia and Lactate)

Table – 04 - Comparison between the Homoeo and Placebo group at baseline & end of treatment for Zinc and Ferritin

Timeline	Group (H/P)	N	Mean	SD	MD	t	df	p
Serum Zinc								
Baseline	Homoeo	32	84.1563	35.2119	6.875	0.905	62	0.369
	Placebo	32	91.0313	24.66875				
End	Homoeo	32	123.9375	40.3772	40.15625	4.997	62	0.000
	Placebo	32	83.7813	20.88329				
Serum Ferritin								
Baseline	Homoeo	32	51.0009	28.06946	6.48375	0.911	62	0.366
	Placebo	32	44.5172	28.85109				

End	Homoeo	32	88.105	39.19633	53.79438	6.784	62	0.000
	Placebo	32	34.3106	21.81227				



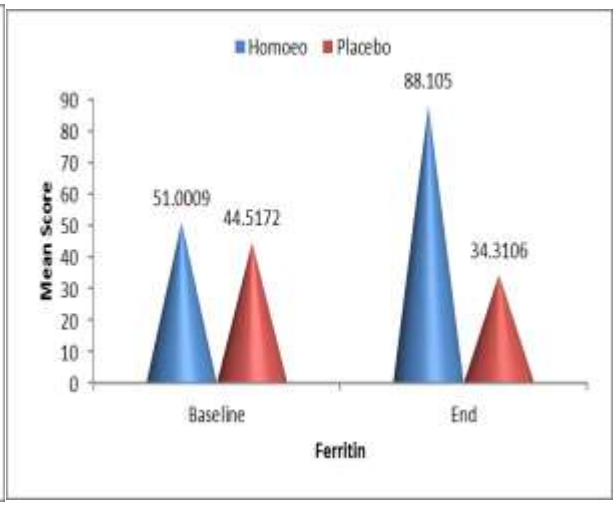


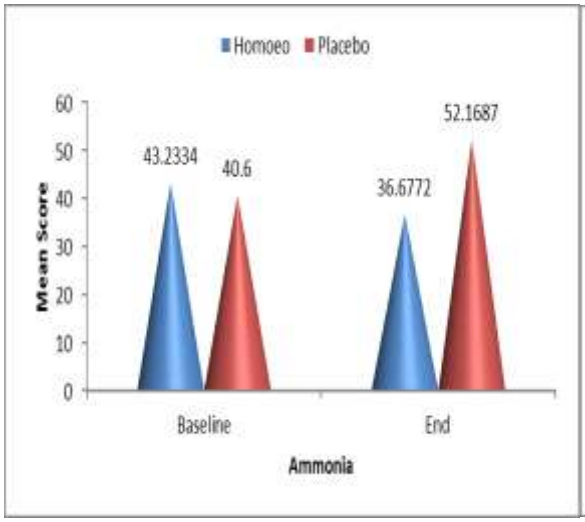
Fig – 04 – Baseline and End of Serum Zinc **Fig – 05** – Baseline and End of Serum Ferritin

At baseline, there were no statistically significant differences between the Homoeopathy and Placebo groups in mean serum Zinc or Ferritin levels, confirming comparability of groups before treatment (Zinc: t = 0.905, P = 0.369; Ferritin: t = 0.911, P = 0.366). After intervention, a marked and statistically significant increase in serum Zinc and Ferritin levels was observed in the Homoeopathy group compared with the Placebo group. At the end of the study, the mean serum Zinc level in the Homoeopathy group increased to 123.94 ± 40.38 µg/dL, while the Placebo group resulted a mean of 83.78 ± 20.88 µg/dL (mean difference = 40.16, t = 4.997, P< 0.001). Similarly, serum Ferritin levels increased significantly in the Homoeopathy group (88.11 ± 39.20 ng/mL) compared with the Placebo group (34.31 ± 21.81 ng/mL), with a mean difference of 53.79 (t = 6.784, P< 0.001). These findings indicate Homoeopathic intervention was associated with a significant enhancement in serum Zinc and Ferritin concentrations, compared to placebo.

Table – 05 - Comparison between the Homoeo and Placebo group at baseline & end of treatment for Ammonia and Lactate

Timeline	**Group (H/P)**	**N**	**Mean**	**SD**	**MD**	**t**	**df**	**P**
Serum Ammonia								
Baseline	Homoeo	32	43.2334	18.67079	2.63344	0.572	62	0.569

	Placebo	32	40.6	18.12875				
End	Homoeo	32	36.6772	17.62695	15.4916	3.643	62	0.001
	Placebo	32	52.1687	16.36805				
Serum Lactate								
Baseline	Homoeo	32	29.2838	16.6919	4.19094	1.339	62	0.186
	Placebo	32	25.0928	5.91553				
End	Homoeo	32	9.7366	8.20467	11.7706	4.587	62	0.000
	Placebo	32	21.5072	11.97494				



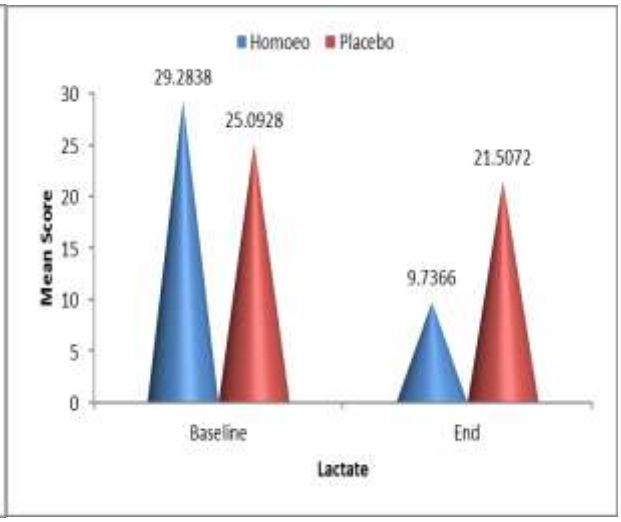


Fig – 06 – Baseline and End of Ammonia **Fig – 07** – Baseline and End of S. Lactate.

At baseline, no differences were observed between the Homoeopathy and Placebo groups in mean serum ammonia or lactate levels, showing comparable profiles before treatment (Ammonia: t= 0.572, P = 0.569; Lactate: t = 1.339, P = 0.186). At the end of treatment significant changes were observed in both parameters. The Homoeopathy group demonstrated a marked reduction in serum ammonia levels (mean = 36.68 ± 17.63 µmol/L) compared to the Placebo group (mean = 52.17 ± 16.37 µmol/L), with a mean difference of 15.49 (t= 3.643, P = 0.001). Similarly, serum lactate levels decreased substantially in the Homoeopathy group (mean = 9.74 ± 8.20 mmol/L) relative to the Placebo group (mean = 21.51 ± 11.97 mmol/L), with a mean difference of 11.77 (t = 4.587, P < 0.001). These results suggest that Homoeopathic treatment was associated with a significant reduction in serum ammonia and lactate concentrations compared to placebo at the end of treatment. The statistical differences observed in serum parameters from baseline to the end of the study

across both groups imply a hypothetical relationship between medicinal effects and serological variations.

DISCUSSION:

This randomized, placebo-controlled trial enrolled 64 participants, with 32 in the Homoeopathy group and 32 in the Placebo group. ADHD-RS (IV) – Home and School Versions, WFIRS (Parent Version), and serological markers such as serum Zinc, Ferritin, Ammonia, and Lactate were used as assessment tools at periodic intervals.

At the completion of the study, the demographic data revealed that the highest representation was within the 11–14 years age group, aligning with findings from other studies. This may be attributed to the increased cognitive, behavioural, and social demands characteristic of this developmental stage [31]. Regarding gender distribution, female children constituted a higher proportion of the sample, primarily due to greater enrolment from female children's homes. A higher number of cases were also observed among children from lower socioeconomic backgrounds, single-parent families, and children's homes. This could be attributed to environmental stressors and limited psychosocial support, both of which are known to contribute to ADHD symptomatology. Similar findings were reported in previous studies conducted by Kaur R. et al. [32, 33].

Clinically, the inattentive subtype was most prevalent, followed by the mixed and hyperactive types, consistent with global literature on ADHD subtype distribution [34]. Miasmatic classification of participants revealed a predominance of syphilitic and psoricmiasmatic backgrounds, suggesting that chronic constitutional and hereditary factors may contribute to the neurobiological expression of ADHD. A review article highlighting the role of homoeopathy in ADHD reported similar findings and proposed that structural deficiencies in the brain and genetic predisposition factors correspond to syphilitic and psoro-syphilitic miasms[30].

The most frequently prescribed remedies were Sulphur, Lycopodiumclavatum, Nux vomica, Phosphorus, and Pulsatilla, based on individualized homeopathic prescriptions. During follow-up, 81% of participants did not require a change in remedy and improved with alterations in potency, supporting the principles of classical homoeopathy and the precision of remedy selection. Based on improvement status at the end of the study, 53.10% of participants (17 children) and 43.80% (14 children) in the Homoeopathy group showed

marked and moderate improvement, respectively, demonstrating the effectiveness of homeopathic remedies (Table 01).

Statistical analyses were conducted using both inter-group (independent t-tests) and intra-group (paired t-tests) comparisons to evaluate reductions in ADHD symptoms and functional impairments. At the end of the study, the ADHD Rating Scale IV (Home and School Versions) showed a significant reduction in mean scores in the Homoeopathy group compared to the Placebo group ($p < 0.05$). The reduction of approximately 31 points in the Homoeopathy group versus 4 points in the Placebo group indicates a notable therapeutic effect (Table 02).

The Weiss Functional Impairment Rating Scale – Parent Version demonstrated a gradual and statistically significant reduction from baseline to 6 months and further to 12 months. This was confirmed by two-way ANOVA with Tukey post hoc testing, which showed statistically significant improvement in the Homoeopathy group ($F = 444.118$, $p < 0.001$). These results indicate consistent improvement across various functional domains such as academic, social, and emotional areas, suggesting sustained and gradual improvement throughout the one-year follow-up period (Table 03).

Regarding biological markers, serum Zinc ($p < 0.05$) and Ferritin ($p < 0.05$) levels showed significant increases at the end of the study compared to baseline in the Homoeopathy group. Similarly, mean values of Ammonia and Lactate decreased by the end of the study in the Homoeopathy group (Table 05), suggesting a possible association with drug effects. However, limitations such as the challenges of collecting blood samples from children and logistical variations that may influence results must be acknowledged. Future studies should consider employing more scientifically reliable biological parameters with limited confounding bias. The observed biological variations may correlate with clinical improvements in ADHD symptoms and overall functional outcomes. Thus, the combined clinical and biological findings provide a hypothetical correlation suggesting that individualized homeopathic remedies may influence metabolic or neurochemical modulation at the cellular level.

The robustness of the statistical significance ($p < 0.05$ across all parameters) suggests that the therapeutic effects observed were unlikely due to chance. These findings are consistent with previous controlled and crossover studies indicating that individualized homeopathic therapy may yield benefits comparable to conventional pharmacological treatments such as

methylphenidate, particularly in improving attention, reducing hyperactivity, and enhancing behavioural control.

Based on the results obtained from multiple assessment tools and biological markers, it is evident that individualized homoeopathic similimum has a significant impact on reducing ADHD symptoms. Similarly, a systematic review conducted by K. Gaertner et al. reported significant and robust evidence supporting the effectiveness of individualized homeopathic medicines in treating ADHD [27.] Another study by FreiThurneysen also demonstrated positive outcomes for homoeopathy in cases where hyperactivity was not pronounced, noting that both methylphenidate and homoeopathy produced similar effects [28]. Additionally, a randomized, double-blind, placebo-controlled crossover study by H. Frie et al. provided scientific evidence supporting the effectiveness of homoeopathy in ADHD, particularly in improving behavioural and cognitive functions [29].

The variations in serological markers observed at the end of the study may further suggest a hypothetical relationship between homeopathic medicines and their influence on metabolic processes. However, larger-scale studies correlating ADHD symptoms with biological and molecular-level biomarkers are necessary to confirm these findings.

CONCLUSION:

This study aimed to investigate the effectiveness of individualized homoeopathic intervention in the management ADHD children, using standardized tools like ADHD Rating Scale IV (Home and School versions), Weiss Functional Impairment Rating Scale (WFIRS, Parent version) and serological biomarkers like serum zinc, ammonia, lactate, and ferritin. Comparative analyses were performed between homoeopathygroup versus placebo group and within groups at baseline and end of the study using appropriate parametric statistical tests. The results demonstrated a statistically significant improvement in ADHD symptoms and functional outcomes in the homoeopathy group compared with placebo. Reduction in ADHD-RS IV scores reflected symptomatic improvement, and decline in WFIRS scores implied improved quality of life among ADHD children and family members. Difference in biomarker profiles may suggest a potential biological or molecular mechanism of action for individualized homeopathic remedies. Limitations were small sample size with limited generalizability, difficulty in gathering complete data from children in care homes, variability in caregiver information, logistical challenges affecting biomarker accuracy. Recommendations for future research include larger sample size with multicentric designs,

advanced biomarker correlations, enhancing awareness among parents, teachers, and caregivers about early recognition of neurodevelopmental disorders, reducing societal stigma, and improving referral systems.

ACKNOWLEDGEMENT:

I acknowledge Assistant Director (H) / Officer Incharge, Principal, Faculties and Resident doctors of NHRIMH, and all children and caretakers for their constant support and encouragement at all times.

CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

FUNDING AGENCY:

No funding Agency.

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