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A Systemic Review Of Clinical Trials On Avaleha Dosage Form, Registered In Ctri.

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ABSTRACT: Introduction: In Sep 2004, ICMJE (International Commission of Medical Journal Editors) implemented a dramatic and important policy for the condition of publication of clinical trials. The condition was that clinical trials must be registered in a public trial registry. CTRI is the INDIAS INTERNATIONAL centralised network of registries and partner registries along with data providers.
Hence here an attempt has been made to analyse the data of Avaleha (Dosage form) opted for the intervention and / or comparator agent in clinical trials which are registered in CTRI.
Objectives: The objective of this study is
To collect the data of registered clinical trials of Avaleha (Dosage form) registered in CTRI and analyse trials systemically.
Methods:CTRI database has 32 fields of mapping. Out of these, we have analysed 6 fields of this registry: public title, scientific title, study type, intervention and primary outcome.
Conclusion: There is very low compliance about the registration of Avaleha (Dosage form) clinical trials among the academicians, practitioners and researchers of Ayush health system. There should be encouragement not compulsions among the research officers, academic teachers and private practitioners of Ayush systems for conduction and registration of Avaleha (Dosage form) clinical trials.

Avaleha(Dosage form) clinical trials must include procedural as well as therapeutic evaluation, clinic - comparative assessments and efficacy in diseases which are not mentioned in classical texts.

We also feel that clinical trials from Ayurved, Homeopathy, Unani, Siddha and Yoga could be separated from main registry .i.e. CTRI to form sub registry which could be maintained by CCRAS.

Key words: leha (Dosage form), avaleha, Guda, CTRI, intervention, public title, scientific title, primary outcome.

I. INTRODUCTION:

In Sep 2004, ICMJE (International Commission of Medical Journal Editors) implemented a dramatic and important policy for the condition of publication of clinical trials. [1][2] The condition was that clinical trials must be registered in a public trial registry. [3] Subsequently every region, country and regulatory authorities around the world prepared their publically accessible registry and began posting of clinical trial information in their respective registry.

Clinical trial registry of India (CTRI) under the watchful eyes of ICMR is the primary registry of India. CTRI was established and launched on 20th July 2007.[4]The primary objective of CTRI was declared to establish an authentic and complete public record of the clinical trials before the enrolment of first patient. Total clinical trials registered in CTRI, 3358 trials are from Ayush system. DCGI declared that the registration of clinical trials will be mandatory with effect from 15th June 2009, PG theses and AYUSH faculty. [5]It was advised to contact CCRAS for details of clinical trials conducted in Ayurved, Homeopathy, Siddha, Unani, Yoga and Naturopathy. [6] It is expected that every clinical trial originating in India involving human participants for any intervention (drug, surgical procedure, preventive measures, lifestyle modifications, devices, educational or behavioural treatment, rehabilitation strategies and complementary therapies) must get registered in CTRI before enrolment of the first participant. [7]

Avaleha (Dosage form) is a treatment mentioned in the ancient texts of Ayurveda. It is one of the most common dosage forms which has been employed in various disorders and is gaining

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popularity due to its easy administration, palatability and longer shelf life. [8]
Avaleha Kalpana was modified form of Panchavidha Kashaya Kalpana to make the availability of the drug material throughout the year, long shelf life, good taste, elegant look, and pleasant smell, produce quick action with low doses.[9]

Hence here an attempt has been made to analyse the data of clinical trials of Avaleha (Dosage form) opted for the intervention and / or comparator agent which are registered in CTRI.

II. MATERIALS AND METHODS:

This is a retrospective audit.

2.1Objectives:

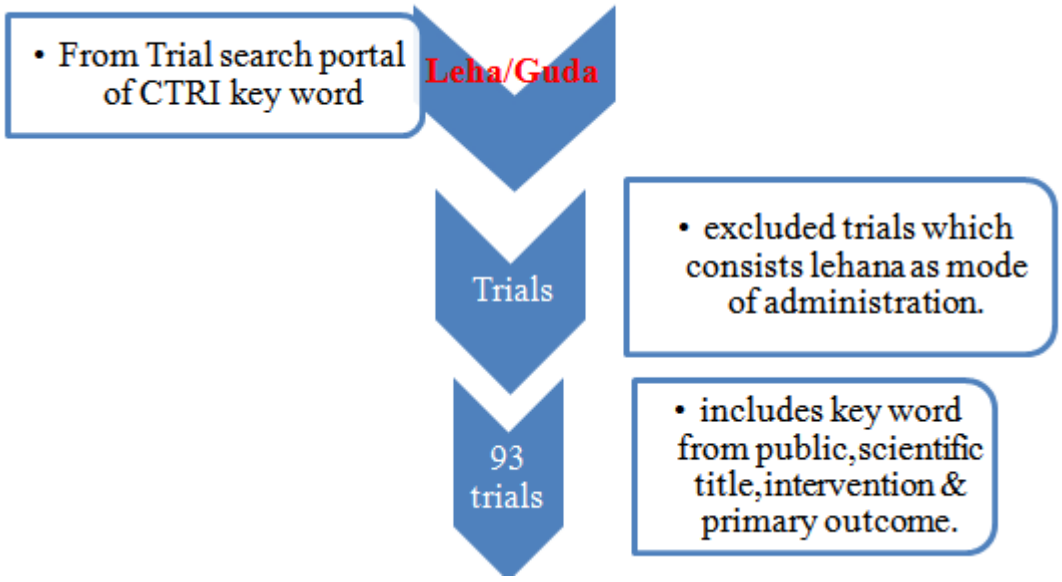
The objective of this study is
To collect the data of Avaleha (Dosage form) clinical trials registered in CTRI and analyse it systemically.

2.2 Materials:

Out of total clinical trials registered in CTRI, 3358 trials are from Ayurved system. CTRI database has 32 fields of mapping. Out of these, we have analysed 6 fields of this registry: public title, scientific title, study type, intervention and primary outcome.[4][5][6][7] 93 clinical trials of Avaleha (dosage form) were registered in CTRI database up to 05 July 2020 and we analysed this database on 5th July 2020 with last refreshed on 09th July 2020.

2.3 Method: Registry search Strategy:

Out of very precise, precise, very sensitive, sensitive key word search strategy, we adopted just one term for key word search strategy for this study.[10] 93 clinical trials were registered in CTRI database and we downloaded this database on 05th July 2020 with last refreshed on 09th July 2020.



2.4 Inclusion criteria:

Basic criteria of avaleha dosage form is
Aqueous Medium - Kashaya, Swarasa
Substrate - Sugar, sugar candy and jaggery
Aushadhi dravyas - Powdered drugs
Lipid medium - Ghrita and Tilathaila
Additives - Honey, milk products, bhasmas. [8][11]
Clinical trials enlisted in CTRI retrieved on 5st JULY 2020 which was last refreshed on 9th JULY 2020.IT includes key word from public title ,scientific title, intervention & primary outcome.

Total number of trials enlisted in CTRI is 93.

2.5 Exclusion criteria:

Surgical interventions
Other clinical trials from CTRI but not having Avaleha (Dosage form) as an intervention.
Clinical trials where other dosage form is in the form of lehana as mode of administration and where madhu and/or sugar and/or guda are not part dosage form.

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III. RESULTS:

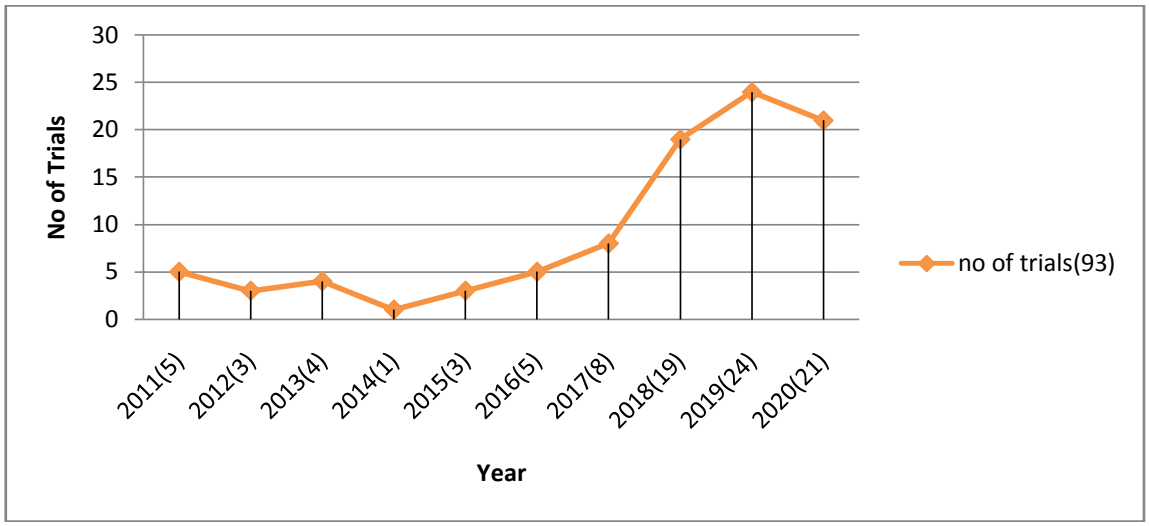

Figure no.1: Total Avaleha (Dosage form) trials registered in CTRI on Yearly Basis

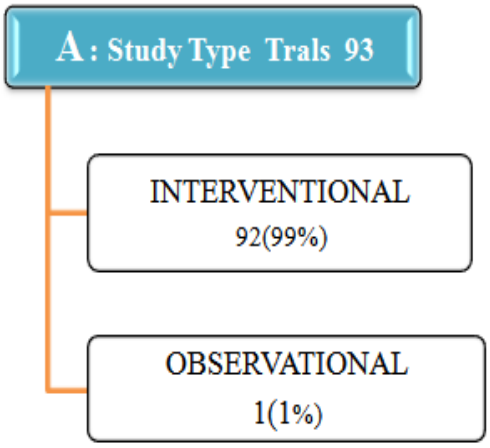

Figure no.2A: study Type

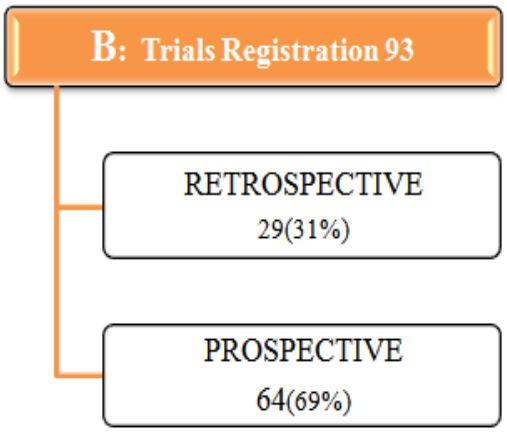

Figure no.2B: Trials Registration.

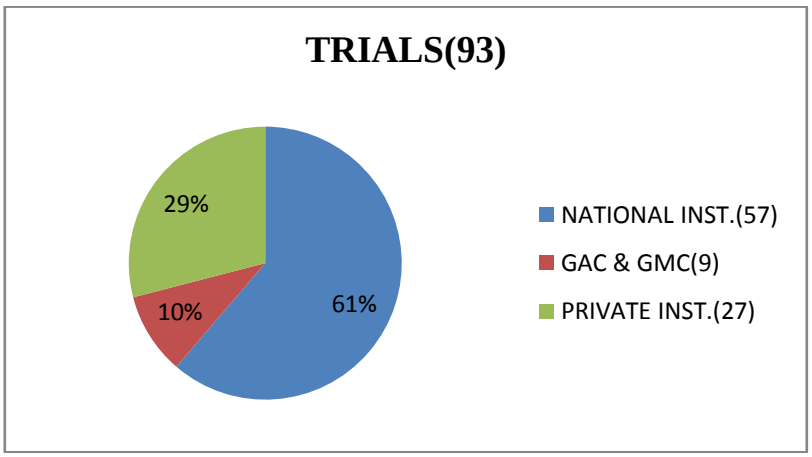

Figure no.3: Distributions of trials according to site of the study.

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Sr.No.	INTERVENTIONS /COMPARATOR AGENT	AVALEHA TRIALS(93)
1	One or two Avaleha with or without modern medicine	53(57%)
2	Avaleha with shaman chikitsa	9(10%)
3	Avaleha with shodhan with or without shaman chikitsa	31(33%)

Table no.1: Trials according to intervention/s and the comparator agent

Sr.No.	DESIGNATION OF PRIMARY INVESTIGATOR	AVALEHA TRIALS(93)
1	PG Scholar	70(75%)
2	Ph.D.Scholar	9(10%)
3	Research officer /MO/Assistant/Associate/Professor	14(15)

Table no.2: Distribution of trials according to Primary Investigator.

Sr.no.	Dept. where clinical trial conducted	Avaleha Trials(93)
1	Kaumarbhritya	27(29%)
2	Kaya chikitsa,Manasroga	18
3	Ras-shastra-Bhaishajya Kalpana	12
4	CCRAS affiliated institutes	9
5	Shalakya tantra	8
6	Stri-prasuti tantra.	5
7	Panchakarma	5
8	Kriyasharir,Dravyaguna,Samhita.	5
9	AIIMS, New Delhi	1

Table no. 3: Department wise Avaleha trial distribution.

Sr.No.	DISEASE (PROBLEM STUDIED)	AVALEHA TRIALS(93)
1	Tamak swas,kasa,childhood asthama	37(40%)
2	Pandu, thalassemia.	13
3	Immunity improvment	10
4	Pratishyaya,ENT DISEASE.	7
5	amlapitta	5
6	Switra,ekkushtha,melasma,vicharchika,shipitta	5
7	Garbhini and OBGY, rajo-nivritti	5
8	Tundikeri(Tonsillitis)	3
9	malawshtambh	2
10	Weight gain in underweight infant (1month to 6 month)	2
11	aamvata	2
12	grahani	2
13	Rasayana & vajikaran	2
14	Autism and speech delay	2
15	Cancer,madatyaya,mutrakrucha.	1(each)

Table no.4: Trials according to primary health condition(s) or problem(s) studied

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Sr.no	Avaleha	Trials	Sr.no.	Avaleha	Trials
1	Drakshadi leha	7	29	Kutajashtak leha	1
2	Chitrak Haritaki	6	30	Vasa+Durlbhadi leha	1
3	Vasa leha	5	31	VasaHaritaki leha	1
4	Manibhadra leha	4	32	Darvyadi leha	1
5	Shirishavaleha	3	33	ChitrakHaritaki+Bharangyadi leha	1
6	ShirishAshwagandha	3	34	Aparajit leha	1
7	Puran Guda	3	35	Bharangyadi leha	1
8	Kantakari leha	3	36	Atibala+DarviAamalaki	1
9	Kulatha leha	3	37	MahaBhallatak leha	1
10	Kushmanda leha	2	38	Sanvardhan leha	1
11	Vyagriharitaki leha	2	39	KhandPippali leha	1
12	Bilwadi leha	2	40	AgastiHaritaki+Chitrakadi leha	1
13	Madhuraushadhi leha	2	41	Vanari leha	1
14	Aagastharitaki leha	2	42	Shringyadi leha	1
15	Haridradi leha	2	43	Saraladi leha	1
16	MustaTriphaladi leha	2	44	HaiatakiDraksha+Aaragvadhphalamajja	1
17	Kutaja leha	2	45	Rasayan leha	1
18	Aamalaki leha	2	46	HaritakiPippali+Aaragvadhphalamajja	1
19	Shatawari leha	2	47	Kalyan leha	1
20	Vsa+shunti Khanda+Kushmanda leha	1	48	Dushprashadi leha	1
21	Aashtangaavaleha	1	49	Dushprashadi leha+Kantakari	1
22	Aashtanga+vyaghriHaritaki	1	50	Ashwagandhadi leha	1
23	Ikshvadileha	1	51	Dhatrichatusham+Aabhayadi	1
24	Triphaladi leha	1	52	Shunthi Haritaki	1
25	Vasa+VyaghriHaritaki	1	53	GudaAadrak	1
26	MustaTriphaladi	1	54	ShwasharMahakashay leha	1
27	Kamsaharitaki	1	55	Marichiyakadi leha	1
28	Dadimdi leha	1			

Table no.5: Different Avaleha as drug & associated number of trials

IV. DISCUSSIONS:

The data was analysed using descriptive statistics.

According to **Figure no.1** there are only 93 Avaleha (Dosage form) trials, out of 3358 trials from Ayurved system. From year 2017 there is steady increase in trial registration, with peak of trials registered in 2019 with 24 trials. No Avaleha (Dosage form) trial was registered before year 2011.

According to **Figure no. 2A** 99 % of trials are interventional study type trials, while only 1% trials are observational trials. It is but natural that Avaleha is a very well accepted dosage form not only by adults but also by pregnant women and children. It is a palatable, simple mode of administration and diverse choice of drug selection makes avaleha a very popular intervention or comparator agent.

Figure no. 2B suggests how the trials are registered. With effect from 1st April, 2018, CTRI

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began accepting studies only if they are prospectively registered. Hence 29(31%) trials are registered retrospectively, 64(69%) trials are registered prospectively.

From year 2011 we observed rise in retrospectively registered studies although the primary objective was to register the studies prospectively. It is possible that the changing regulatory scenario may have influenced this.

Figure no. 3 suggest, 57(61%) of trials are from national institutes. Only 27(29%) trials are conducted at private institutions or deemed universities.10 (9%) trials are conducted at Govt. Ayurved College and Govt. Hospitals.

Table no.1shows trials according to intervention or comparator agent, 53(57%) trials are consists of one or two avaleha drug as intervention and/ or comparator agent with or without modern medicine as conventional agent.9 (10%) trials comprises avaleha with shaman chikitsa as comparator agent. While 31(33%) trials are clinic- comparative trials consisting of shodhan as intervention or comparator agent with or without shaman chikitsa . (Parallel Group, Multiple Arm Trial)

It is evident from **Table no. 2** that Avaleha (dosage form) trials are institutional and academic base trials. No single trial is registered from individual investigator in an independent set-up (private clinic set-up) or Ayurved manufacturing unit and Ayurved Pharmaceutical industries.75 (70%) trials are performed during post graduation for M.D. thesis, 9(10%) trials have been performed during Doctoral degree for Ph.D. dissertation while 14(15%) trials are conducted by academic teachers in the graduate and post graduate institutes research officers.

Table no.3 shows Department wise distribution of Avaleha clinical trials. 27(29%) trials are conducted by Kaumarbhritya department while 18(19%) trials are conducted by Kayachikitsa department and 12(13%) trials are conducted by Rasshastra-Bhaishajya Kalpana .

Dept. of Kaumarbhritya, Kaya-chikitsa and Ras shastra-Bhaishajya Kalpana from IPGT&RA, Jamnagar collectively conducted 40 (45%) trials of all Avaleha clinical trials.

Surprisingly, ALL INDIA INSTITUTE OF MEDICAL SCIENCE (AIIMS) has conducted one trial i.e. CTRI/2020/05/025321 on tamak shwash by AgastiHaritaki Avaleha.

We also observed that the number post graduate thesis went on increasing which shows increasing awareness regarding this process among the post graduate students and their teachers. Over a period of years the number of post graduate students must have been increased which has reflected in this.

Table no.4 show primary health condition or problem studied in Avaleha (Dosage form) trials.

Earlier as we mentioned, acceptability is not because palatability but also because of broad spectrum activity of Avaleha dosage form. When we say broad spectrum activity, we want to mention that this dosage form is not only a wider therapeutic range but also enough nutritional value along with anupan. A wider therapeutic range consist not only aptarpanottha vyadhis.[12] and Vataj Vyadhis[13] but also santarpanottha vyadhis. [14] Most studied problem is Tamak shwas, Kasa and childhood asthama having 37(40%) trials, while 13(14%) trials are of Pandu and thalassemia problem.7 (8%) trials belongs to pratishya vyadhi while 10(11%) trials are for immunity improvement and weight gain for children below 1 year.

Table no.5 There 55 different avaleha are used which are mentioned in classical Ayurved text. But some drugs are very effective in different health conditions as they are repeatedly used as intervention. These is Drakshadi leha, Chitrak Haritaki,Vasa leha Manibhadra leha, Shirishavaleha ,ShirishAshwagandha, Puran Guda, Kantakari leha, Eight drugs lead 34(37%) trials.

Avaleha dosage form is a most suitable drug dosage form for Tamakshwas. Also as it is palatable, it is widely used in paediatric patients. Avaleha is that dosage form where we are in need of Prinan, Jivan and Brihan karma at the same time shaman of dosha involved in the genesis of Vyadhi. It is that dosage form which manipulates two opposing vectors at the same time, one vector is kapahaj anubandhtva either in the form of Sthan or prakupit dosha and another vector is vata /pitta anubandhatva either in the form of Sthana or prakupit dosha. [15], [16], [17].

Trials registers are also used by patients and healthcare providers to identify clinical trials they may wish to participate in, and have other potential uses for policy-makers and funding agencies in research priority setting, resource utilization and capacity building for research, as well as for everyone involved in informed healthcare decision-making.[18]

Poor reporting may stem from poor research design resulting from inadequate appreciation of the sources of bias in clinical trials and of the methods available to improve internal

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validity. [19] Registration on the CTRI of trials conducted in India will, for the moment, remain voluntary. Compliance will therefore depend on the cooperation of the pharmaceutical industry and contract research organizations, academic institutions, medical associations, and ethics committees and medical journal editors in India. Registration is currently voluntary and, in the absence of legislation mandating prospective trials registration, medical journal editors and ethics committees have a special role in ensuring compliance with registration of trials and full disclosure. [19] It is argued either financial reasons or lack of comprehensive indigenous capability is responsible for apathy. It brings us to the fact that the research in Ayurved, Homeopathy and Unani the Indian traditional Medicinal systems have not been explored much and there are no evidence based finding that can be documented. [20]Despite decrease in Pharmaceutical industry studies, the overall clinical research scenario in the country has improved over the past decade, which could be attributed to investigator, research institutes, medical colleges/hospitals and government funded studies. Taking into consideration increasing number of investigator sponsored studies we feel government funding sources which take time be made easy and fast available so that research in our country is promoted. [20]

V. CONCLUSION:

There is very low compliance about the registration of Avaleha (Dosage form) clinical trials among the academicians, practitioners and researchers of Ayush health system. There should be encouragement not compulsions among the research officers, academic teachers and private practitioners of Ayush systems for conduction and registration of Avaleha (Dosage form) clinical trials.

Avaleha (Dosage form) clinical trials must include procedural as well as therapeutic evaluation, clinic - comparative assessments and efficacy in diseases which are not mentioned in classical texts.

The aim of developing research attitude in the post graduate and Ph. D scholars seems to be restricted only for the thesis/ dissertation purpose only.

We feel that clinical trials from Ayurved, Homeopathy, Unani, Siddha and Yoga could be separated from main registry .i.e. CTRI to form AYUSH registry which could be maintained by CCRAS.

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