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Understanding validation of traditional approaches to health: An analysis of research trends and the need for minimum standards- A systematic review

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Scientific validation of the interventions used for the treatment of various ailments in Ayush systems of medicine (ASM) is currently an emerging field. The stakeholders hesitate to promote the traditional knowledge to resolve the current health issues without exploring the scientific rationale and rigorous experimentation. It seems that scientific validation of traditional approaches has become a roadblock for the translation of the aged old experiences and wisdom into clinical practice. This systematic review has been done to study the evolving research trends, existing policy, current regulatory mechanism and publication criteria for the research meant for scientific validation of ASM. This review is based on the analysis of the published clinical trials, ethical and regulatory guidelines published between 2001 and 2022. The major databases were searched such as Medline, AYUSH Research Portal, Google Scholar, Scopus, Science Direct and Web of Science. The analysis showed that the trends for scientific validation studies had continuously been on the rise in the past two decades. The guidelines for validation studies, safety studies, good clinical practices and ethical guidelines for biomedical research had been framed for research in ASM. We observed that there were no defined minimum standards for an intervention to be declared scientifically validated so that the research could be directional. Our study concludes that the concept of scientific validation of traditional approaches has not been comprehensively defined so far. As a result, scientific validation studies are not conducted in such a direction leading to achieve the set targets in the near future.

Keywords: Ayush, Intervention, Regulation, Traditional, Unani

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Traditional Medicines (TM) have been an important source of health preservation, promotion and treatment of various ill health conditions since time immemorial[1]. As per an estimate, currently 80% population of the world uses TM for health benefits[2]. Indian TM, known as Ayush Systems of Medicine (ASM) are part and parcel of the primary healthcare delivery system in India[1]. The Government of India patronizes ASM, formulated different policies for the development of their infrastructure and issued different guidelines for research and education in ASM. Figure 1 shows different branches of ASM prevalent in India[3]. With the rising burden of health issues and lack of cures for many non-communicable and communicable diseases, the healthcare researchers' attention has been shifted to explore the potential of Indian TM[3]. The advent of the epidemic of COVID -19 in 2020 has further renewed the interest of common people, academia, researchers and physicians in healthcare approaches practiced in ASM. The policymakers and other stakeholders seek a scientific rationale for the promotion, integration, mainstreaming and globalization of ASM.

ASM are comprehensively described systems of medicine. The resources of ASM are authoritative textbooks, pharmacopoeias and manuals that contain identified clinical conditions of health, their hypotheses and the experiences of the physicians in the treatment of diseases with the traditional health approaches based on philosophical theories of the respective system of medicine[4]. This information is passed from one generation to the other generation in the form of documents and oral traditions. Despite their strength and potential in the prevention and treatment of diseases, the scientific communities do not recognize ASM due to a lack of rationality, scientific reasoning and experimental evidence[5]. In the 21st century, the paradigm shift of interest to

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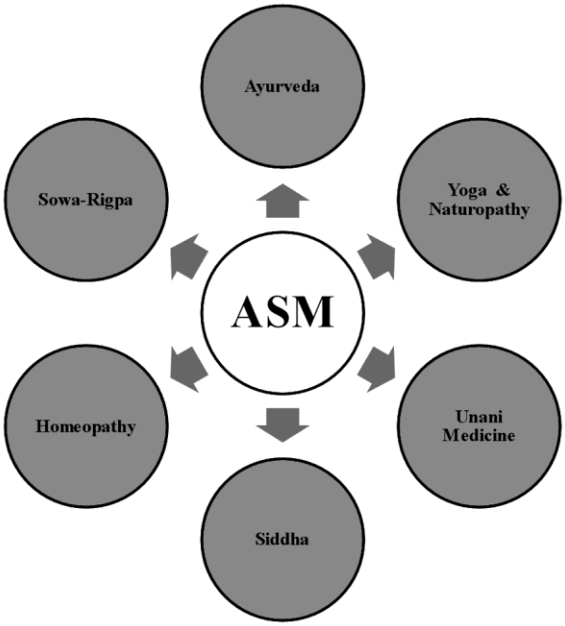

Fig. 1 — Ayush Systems of Medicine

explore the potential of ASM in the prevention and treatment of diseases has led to clinical trials for scientific validation of traditional health approaches in various clinical conditions[6].

The interventions in ASM are comprised of herbs, herbal formulations, minerals, mineral preparations, animal products, non-pharmacological procedures (exercise, message, etc), invasive (wet cupping, leeching, etc) and non-invasive (Dry cupping) procedures, diet, psychological, and surgical interventions[2]. The herbs and herbal formulations contain crude part(s) of the plants such as roots, barks, stems, leaves, seeds, flowers, gums, resin, essential oils, etc as active ingredients[7]. In addition, the minerals are used in their natural forms (ores) after purification by traditional methods.

The scientific validation or simply validation of traditional approaches to health here means the studies conducted for the confirmation of the safety and efficacy of the Traditional Interventions (TIs) in the diagnosis, prevention, treatment and health promotion as mentioned in the authoritative textbooks or literature of ASM. The clinical validation studies of TIs are generally conducted in the Government funded institutions. A huge financial expenditure of the exchequer is involved to support such studies. It is, therefore, the safety and efficacy of TIs should be approved by a third party or agency for their scientific validation.

In the literature of ASM, thousands of TIs are described for the restoration and maintenance of health and cure of diseases. Of them, very few herbs and herbal formulations have been explored for their potential in treating diseases[8]. Some of them may have been claimed to be validated. The current health research trends in India show that the classical Ayurveda, Siddha and Unani (ASU) drugs have been explored for their potential as therapeutic agents[9-11]. 'Asanas' in Yoga, 'Regimenal Therapy' in Unani and 'Panchkarma' in Ayurveda are studied as non-pharmacopoeial interventions in the treatment of several respiratory, neurological, dermatological and musculoskeletal disorders. The validation studies are being conducted in academic and research institutions and drug industries. The research organizations with a mandate to do research in ASM like Central Council for Research in Ayurvedic Sciences (CCRAS), Central Council for Research in Unani Medicine, Central Council for Research in Siddha (CCRS), etc. have a large infrastructure spread all over the country. These organizations are mainly conducting clinical validation studies to evaluate the safety and efficacy of the classical ASU drugs[12,13]. There are a large number of ongoing clinical validation studies in the Councils. But whether these studies may generate quality evidence or not is in question due to methodology deficiency.

The outcomes of the valid studies have multifaceted implications. The policymakers, drug industry and academia may utilize those outcomes as evidence-based interventions for their respective purposes. At the same time, informed patients who demand scientific evidence for the safety and efficacy of the interventions may opt for or prefer ASM to conventional medicine. In the present scenario, the clinical validation of the various traditional approaches becomes a must for the fast dissemination and globalization of traditional knowledge in health care which has a long history of usage in the past[14].

Moreover, scientific validation of TIs is also important for the assessment of the health benefit-risk ratio for enhancement of the credibility and acceptability of ASM[15]. The clinical trials for scientific validation of TIs under the current guidelines focus on trial design, conduct, analysis and report writing. It has been observed that at present there is no approval mechanism and registration of validated TIs in India. The lack of this provision in the regulatory mechanism in India makes us unable to

declare TIs as scientifically validated ones with the endorsement by a third party.

Nonetheless, WHO currently support to develop norms and standards based on reliable information to provide safe, qualified and effective TM services[16]. Like robust regulatory mechanism in conventional medicine, the Minimum Standards (MS) for the declaration of the validation of TIs and regulation for registration of validated TIs are required. The MS for the validation of TIs may guide all stakeholders to follow the pathway of the scientific validation study. In other words, academia and researchers may initiate clinical studies for scientific validation of TIs according to the set MS. In this way, financial expenditure and time investment may be reduced and the clinical research may be conducted in the direction of the suggested pathway for the scientific validation studies.

In this study, we aimed to review the evolving research trends, methodological characteristics and quality of published clinical trials, implementation of existing guidelines and policies recommended for clinical research in ASM and the publication policy of the indexed peer-reviewed journals. In addition, this review article tried to find out the gaps in Indian regulatory mechanisms for the scientific validation of TIs. This article also highlights the importance and need for formulating the minimum standards and guidelines for the scientific validation of TIs.

Methodology

This study is based on the critical review of the clinical studies published between 2001 and 2022, prevalent ethical, clinical research and regulatory guidelines and health policies for ASM. The major databases such as Scopus, Science Direct, AYUSH Research Portal (ARP), Web of Science (WoS), Medline and Google Scholar were searched to find the research trends of the interventional studies in ASM published in the 21st Century. The query strings used for search into bibliographic databases were 'clinical' AND 'trial' AND 'Unani' OR 'Ayurveda' OR 'Siddha' OR 'Yoga' OR 'Homeopathy' OR 'Sowa'. The publication years (2001-2022), and article type (article) were also used as filters to segregate the articles as per our search strategy. We analyzed the source, article types and publication dates.

Results

In this systematic review, we evaluated the current research trends in clinical validation studies for TIs, methodological characteristics of the published clinical trials, implementation of existing recommended ethical, clinical and regulatory guidelines, the research pathway followed for validation of TIs and the quality of evidence generated for validating an intervention. This study also analyzed the gaps in the process of validation of TIs so that the potential benefits and harms of TIs could be assessed with adequate information. A consolidated analysis of all the articles has been presented in this review.

Research trends

In this study, we found that 1829 clinical trials in Medline had been published between 2001 and 2022. In addition, the number of articles in the database of the ARP was 6682 articles in the domain of clinical research on 31st December 2022. Figure 2 displays the total research articles available in the ARP. The analysis of the obtained data in Medline showed that the number of original research articles in the discipline of ASM had gradually been increasing year-wise for the last 22 years. The published articles in the domain of clinical research mainly included interventional studies for scientific validation of pharmacopoeial formulations and regimenal therapies. Figure 3 shows the trends of interventional studies in Medline published between 2001 and 2022. Moreover, this study found that interventional studies had been conducted to generate the evidence for safety and efficacy of TIs in dermatological, cardiovascular, gastrointestinal, musculoskeletal, endocrinal, neurological and ophthalmological diseases[11,17].

Characteristics of the published studies

Our study reviewed the clinical validation studies for TIs published in the peer-reviewed journals indexed in Scopus, WoS, Medline and UGC-CARE list. The list of some of the peer-reviewed journals which generally publish the validation studies of TIs is displayed in Table 1. The critical appraisal of all the published clinical trials in Indian TMs is beyond the scope of this article. However, the consolidated analysis of all the trials published in major databases between 2001 and 2022 provided some important considerable points for assessing the fundamental characteristics of the clinical validation studies. The methodological characteristics of the clinical trials such as participants' selection criteria, hypothesis tested, randomization, allocation concealment, justification for sample size, masking, population

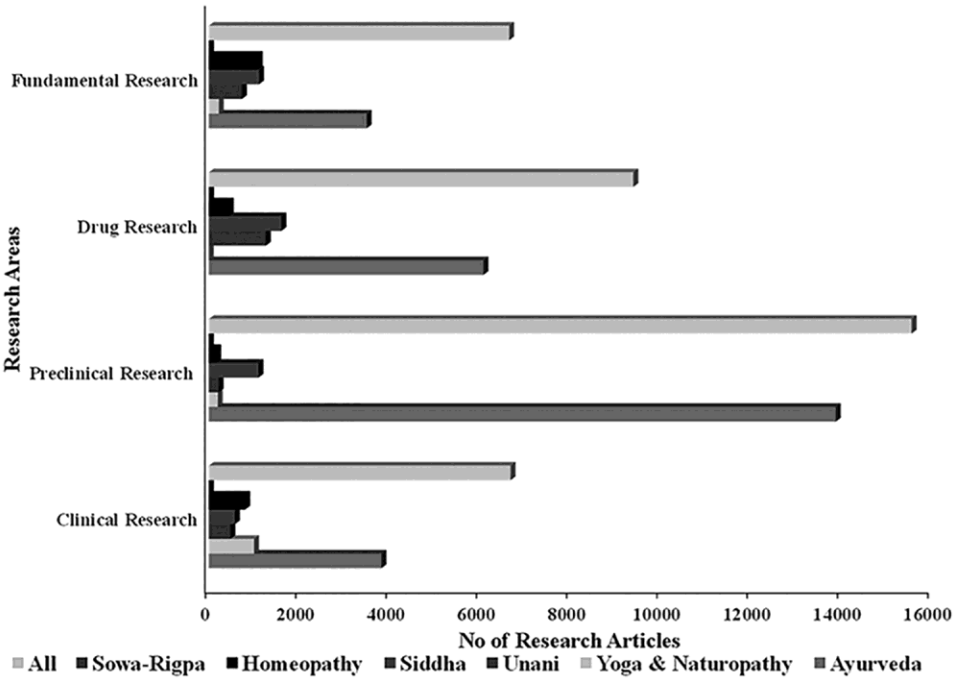

Fig. 2 — Research articles in AYUSH Research Portal

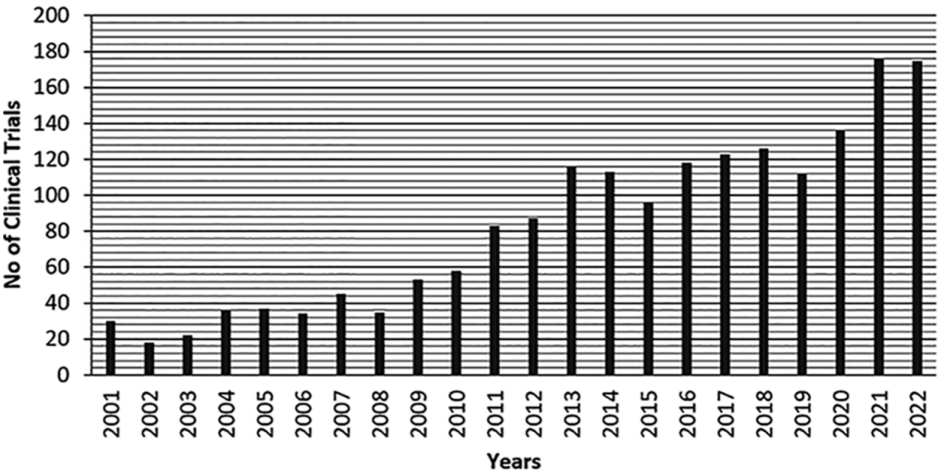

Fig. 3 — Trends of publication of clinical trials in ASM in Medline

Table1 — List of peer reviewed journals indexed in Scopus, WoS and Medline

S. No.	Name of the Journals	Publishers
1.	Journal of Herbal Medicine	Elsevier, Amsterdam, Netherlands
2.	Journal of Ethnopharmacology	Elsevier, Amsterdam, Netherlands
3.	Journal of Traditional and Complementary Medicine	Elsevier, Amsterdam, Netherlands
4.	European Journal of Integrative Medicine	Elsevier, Amsterdam, Netherlands
5.	Phytomedicine	Elsevier, Amsterdam, Netherlands
6.	Advances in Traditional Medicine	Springer, New York, USA
7.	Advances in Integrative Medicine	Elsevier, Amsterdam, Netherlands
8.	Journal of Complementary and Integrative Medicine	De Gruyter, Berlin, Germany
9.	Journal of Ayurveda and Integrative Medicine	Elsevier, Amsterdam, Netherlands
10.	Indian Journal of Traditional Knowledge	CSIR-NIScPR, New Delhi, India

WoS= Web of Science; NIScPR=National Institute of Science Communication and Policy Research; CSIR= Council of Scientific and Industrial Research

analyzed, effect size for clinical significance of the outcome, handling of dropouts and withdrawal of the participants and compliance of the participants to the drug were considered for review in this study. The present study found that, in almost all cases, TIs were directly studied in human participants as phase II/III clinical trials for proof of the safety and efficacy of the TIs which had a long-term history of their usage in clinical practice. Most of the studies were single-centered and based on small sample size.

Nonetheless, this study observed that the hypothesis of the clinical trial was not categorically mentioned whether it was a superiority or equivalence or inferiority trial in cases of comparative or controlled studies. The critical review of those articles showed that some articles lack justification for the estimation of sample size. It was noticed that adjustment for expected dropout in sample size calculation was not done a priori. Moreover, it was observed that the trial design varied from article to article. Some of the studies were single-arm, some were quasi-experimental and a majority of them were controlled clinical trials. Some studies lacked a description of randomization and use of allocation concealment. Handling of withdrawal and dropouts was also not discussed in most of the studies. This study found the pattern of dose-response reported in the clinical trial. In most of the studies, single dose response of the drugs in small sample size was reported. It was further observed that single batch preparation instead of multiple batch preparation was studied. Moreover, this study also noted the pattern of data analysis. The per-protocol data analysis was the commonest observation in this study.

Quality of evidence

In the present study, we provided a grade to the published articles as per WHO grading recommendations. All the clinical trials were classified into three different gradations such as Grade A, Grade B, and Grade C where Group A is considered the best evidence. We used, for example, the ARP as a reference where all the clinical studies had been classified into three grades (Grades A, B and C). Figure 4 displays the clinical trials available in the database of the ARP in different grades. The analysis of the data of the ARP revealed that Group A's evidence was fewer (999) in number than that of Group B (1959). The articles in category C were the highest (3823) among all disciplines of ASM[18].

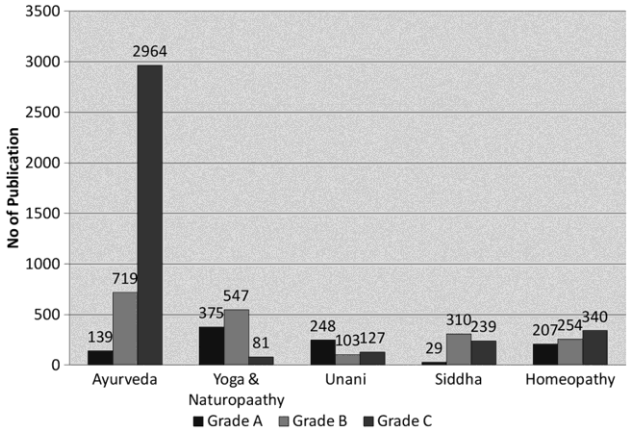

Fig. 4 — Classification of clinical trials into different grades (ARP, dated 31/12/2022)

Implementation of guidelines

This study finds that there are international and national clinical, ethical and regulatory guidelines recommended for proper conduct of clinical trials in India. The Drug and Cosmetic Act 1940 and the Rules 1945 as regulations for the manufacturing and marketing of drugs including ASU medicine are in vogue in India. The primary objective of this regulation is to ensure safe and effective drugs to be sold in India[19]. The Ministry of AYUSH, Government of India issued several guidelines for smooth conduction of research in ASM. For example, Good Clinical Practices guidelines for clinical trials in Ayurveda, Siddha and Unani Medicine (GCP-ASU) - 2013 is an ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials in Ayurveda, Siddha and Unani Medicine[20]. The Government of India also issued General Guidelines for Drug Development of Ayurvedic Formulations, General Guidelines for Safety/Toxicity Evaluation of Ayurvedic Formulations and General Guidelines for Clinical Evaluation of Ayurvedic Interventions in 2018. These guidelines are meant to be followed in validation studies to minimize biases and yield quality data. Table 2 displays important national and international regulatory, ethical, research guidelines and policies for the conduction and promotion of research in ASM.

Nonetheless, it was found that WHO recognized the importance, credibility, and potential role of TM in public health care and instigated the member countries to promote, upliftment and patronize their Traditional Systems of Medicine. So, WHO developed several guidelines for quality control of

Table 2 — Regulatory, ethical and research guidelines and policies for traditional medicines

S. No.	Name of the Guidelines	Issuing Agency
	National	
1.	The Drugs and Cosmetic Act, 1940 and Rules 1945	Government of India (GOI)
2.	National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017	Indian Council for Medical Research, India
3.	National Ethical Guidelines for Biomedical Research Involving Children, 2017	Indian Council for Medical Research, India
4.	Good Clinical Practices guidelines for clinical trials in Ayurveda, Siddha and Unani Medicine (GCP-ASU) , 2013	Department of AYUSH, Government of India
5.	General Guidelines for Drug Development of Ayurvedic Formulations, 2018	CCRAS, GOI
6.	General Guidelines for Safety/Toxicity Evaluation of Ayurvedic Formulations, 2018	CCRAS, GOI
7.	General Guidelines for Clinical Evaluation of Ayurvedic Interventions, 2018	CCRAS, GOI
8.	Clinical Trials on AYUSH Interventions for COVID-19: Methodology and Protocol Development	Ministry of AYUSH, GOI
	International	
1.	General guidelines for methodologies on research and evaluation of traditional medicine, 2000	World Health Organization
2.	Guidelines for the Regulation of Herbal Medicines in the South-East Asia Region, 2003	World Health Organization
3.	WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, 2004	World Health Organization
4.	National policy on traditional medicine and regulation of herbal medicines, 2005	World Health Organization
5.	Operational guidance : Information needed to support clinical trials, 2005	World Health Organization
6.	Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation, 2005	World Health Organization
7.	WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues, 2007	World Health Organization
8.	WHO guidelines on good manufacturing practices (GMP) for herbal medicines, 2007	World Health Organization
9.	WHO Traditional Medicine Strategy, 2014-2023	World Health Organization
10.	ICH Good Clinical Practices Guidelines, 2016	ICH

ICH=International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

traditional medicinal products, pre-clinical studies, clinical research, regulation for marketing and pharmacovigilance[21,22]. These guidelines are used to frame similar guidelines in the country where there exist no such national guidelines. The guidelines framed by WHO may be used for drug development and the conduct of clinical trials in ASM.

Journals' publication criteria

Our study analyzed the publication criteria of the peer-reviewed journals indexed in Scopus, WoS, Medline and UGC-CARE list. It was found that the articles based on clinical trials were considered for publication on the basis of certain laid down conditions. For example, the manuscript must be drafted following the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement. The certificate of clearance from the Institutional Ethics Committee or Institutional Review Board must be obtained and the trial must be registered in any national/international registry before enrollment of the first participants in the trial. The protocol for the proper conduct of clinical trials is also one of the important documents[23]. The SPIRIT (Standard Protocol Items for Clinical Trials) 2013 Statement should be followed for protocol development of clinical trials in herbal medicines[24]. The clinical trials which followed all these guidelines were published in peer-reviewed journals.

Discussion

The present study revealed that the clinical studies were generally conducted in the domain of ASM for scientific validation of the safety and efficacy of herbs, herbal and herbo-mineral formulations and regimenal therapies[25]. This study analyzed the methodological characteristics of the published clinical trials for internal and external validities. We found heterogeneity in the basic characteristics in all clinical trials. The presence of heterogeneity increases bias and the causal relationship of intervention and outcome may not be accurate. The other important finding of this study was observed that, for scientific validation, the TIs were directly studied on human participants considering that they were safe for human use. It is contradictory to the conventional methods of drug development where, as a rule, clinical studies should be followed by pre-clinical studies. The conventional methods have clearly defined pathway for new drug development/procedure. The pathway for new drug development has been depicted in Figure 5. There is another pathway for scientific

validation of TIs where preclinical studies are conducted after confirmation of their efficacy in a clinical trial. This concept of drug development is called reverse pharmacology. Figure 6 describes the steps involved in reverse pharmacology.

Nonetheless, this study showed that the published studies generally followed the existing clinical and ethical guidelines to showcase the potential of TIs. The published outcomes may be considered as documentary evidence for the claim of scientific validation of the TIs[26]. However, this study did not find any data about the claim of scientific validation of the TIs. As far as we know, there is no provision for the approval and registration of scientifically validated TIs in the present regulatory mechanism of India. In the current scenario where there is no agency to approve the outcomes of the clinical trials conducted for scientific validation of TIs, the investigators generally claim themselves about validation of the TIs based on the clinical studies without any critical appraisal or scrutiny or approval of the trial by a third party.

The current trends of the self-claim for scientific validation of TIs may not be justified. The concept of

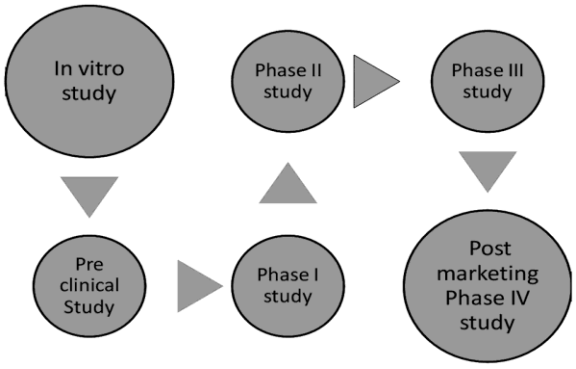

Fig. 5 — The conventional pathway of new drug development

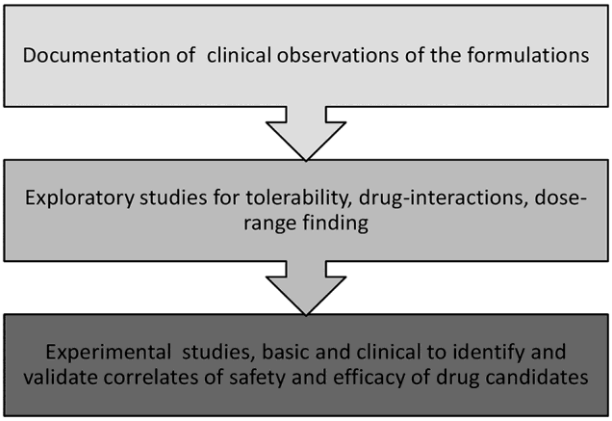

Fig. 6 — Steps for new drug development in reverse pharmacology

scientific validation of TIs is meant to strengthen ASM and rationalize the usage of TIs for the prevention of diseases, health promotion and treatment of diseases[27,28]. It is, therefore, the clinical validation studies must be approved by a third party or an agency on the basis of certain laid down MS. The proposed MS may focus on the methodological characteristics of a valid clinical trial such as hypothesis testing, clinical trial design, randomization, allocation concealment, a priori sample size estimation, drug identification, SOP for preparation of formulation, clinical efficacy, effect size, population analyzed, participants' compliance to the drug, tolerability, adverse event, drug toxicity and so on[29-31]. The proposed MS must consider the determinants of the internal validity of the clinical trials and the generalizability of the outcomes. The MS may also recommend whether the pragmatic or explanatory clinical trial is essential for the scientific validation of TIs. The proposed MS should also recommend the grade of evidence (either Grade A or B or C) for endorsing validated TIs.

In this study, we observed that the safety of TIs had always been studied along with their efficacy. Safety and efficacy data are always required for marketing approval. The analysis of the data showed that TIs had the potential to cause Adverse Events (AD). For example, the US FDA estimated that botanicals and other dietary supplements caused over 50000 AD[8]. Moreover, VigiBase, the WHO global database of individual case safety reports (ICSRs), showed 128000 reported AD[32]. Although the minimum requirement of safety of herbal products had been defined, all herbal products could not be studied on those parameters so far[21]. We still do not know about organ-targeted toxicity, immunotoxicity, embryo/fetal and prenatal toxicity, mutagenicity/genotoxicity and carcinogenicity of TIs used in clinical practice. In addition, safety data of the TIs in vulnerable populations such as pregnant, lactating mothers, children and geriatrics were insignificant[21].

The proof of the efficacy of the TIs is of prime importance for their scientific validation. The efficacy of the TIs may be assessed under the ambit of WHO guidelines for a minimum requirement of the efficacy of herbal products[21]. However, this study found gaps in the published outcomes in terms of therapeutic inconsistency. For ensuring the therapeutic consistency of herbal, mineral and animal drugs or herbal, herbo-mineral or animo-herbo-mineral formulations

(products), multiple dose-response data and multiple batch clinical data are considered essential evidence[8].

New drug development

Natural resources have always been a source of new drug development[33]. But, the concept of scientific validation of TIs is the current trend in India. The advocates of ASM do not promote the isolation of an active ingredient from a plant-based medicine. The discovery of new molecules from natural resources weakens ASM. Once the new molecule shows efficacy and safety in clinical trials, it becomes a part of modern medicine. Instead of isolation of active compounds, the newer concept of Phytopharmaceutical drug has been introduced which is defined as a purified and standardized fraction with a defined minimum of four bio-active or phytochemical compounds (qualitatively and quantitatively assessed) of an extract of a medicinal plant or its part, for internal or external use of human beings or animals for diagnosis, treatment, mitigation, or prevention of any disease or disorder but does not include administration by parenteral route[8]. The concept of phytopharmaceuticals has not been accepted by the scholars of ASM. Instead, they recommend the holistic use of raw natural resources in place of a single bioactive compound.

Challenges for validation of TIs

The scientific validation of TIs has to overcome the challenges existing in the process of their validation. The first one is the drug identification and verification of its therapeutic indication from an authoritative literature of ASM. It had been observed in this study that information regarding the accurate identification of drugs by pharmacognosists or botanists with voucher specimen numbers was lacking in many of the clinical trials. The proper identification of drugs is the first step of drug standardization. Botanical taxonomy, macroscopic and microscopic examination, chemical methods and DNA barcoding are the recommended methods for the identification of plant drugs[34]. The identified plants should have correct scientific names with authority. The correct scientific names may be verified from online databases, for example, the World Flora Online (www.worldfloraonline.org). The Drug and Cosmetic Act, 1940 provides a list of recognized pharmacopoeias of Ayurveda, Unani and Siddha. The therapeutic indications of the formulations could be verified from these pharmacopoeias[19].

The second challenge is the selection of clinical trial design[4]. It is always an easier task to do a single-arm single-centre study compared to a controlled trial. The clinical trial design has a direct impact on the efficacy of the intervention[6]. The selection of a design for a clinical study depends on several factors such as disease course of clinical conditions, sample size, availability of standard of care, etc. The study design such as single-arm study, non-randomized controlled trial and randomized controlled trial has been suggested to conduct an experimental study. The outcome of a Randomized Controlled Trial (RCT) is considered the best evidence, the gold standard. Based on the USA Agency for Health Care Research and Quality, the outcome of the RCT has been recommended as a Grade A level of evidence. The outcome of the RCT about a particular clinical condition is dependent on sample size, outcome measures and duration of therapy. The selection of trial design for a validation study is also dependent on the complex nature of formulation and individualized therapy in ASM. Instead of Randomized Controlled Trials (RCT), modified RCT (N-of-1 RCTs), Stepped-wedge design trials, Observational studies and adaptive trial designs are recommended[35].

The third important challenge is the determination of the sample size for the scientific validation study. In this study, we found that the sample size was estimated in most of the studies. The justification for the estimated sample size could not be established in all cases. The estimation of sample size depends on several factors such as the power of the study, type I error, effect size and so on[36]. The effect size may vary from one clinical condition to the other. The effect size in terms of Cohen d may be suggested for the validation study in the proposed MS[37]. For a clinical condition, a particular effect size must be observed in the clinical trial for the validation of the intervention.

The fourth important challenge is the statistical analysis of the population studied. Intention-to-Treat is always preferred to per protocol statistical data analysis[38]. In Intention-to-Treat analysis, the data of the participants who were once randomized whether the intervention had been given or not are included in the analysis. But, the participants who completed the trial are included in the per-protocol analysis. The Intention-to-Treat analysis shows the real efficacy of the intervention whereas per-protocol analysis shows treatment efficacy[38]. But this study found that the data

were statistically analyzed as per-protocol approach in most of the published studies.

The fifth challenge is the non-participation of the AYUSH drug industries in clinical research. The researchers from academia and research institutions funded by the Government of India are mainly involved in the clinical research of ASM. The participation of Industry in clinical research is insignificant. It may be recommended that the government should formulate policies to encourage industry participation. The regulation may be enacted which promulgate the industry for implementation of research and development policies for ASM. For example, in 2010, the Department of Ayurveda, Yoga & Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) introduced Rule 158(B) which made the requirement of proof of effectiveness for licensing of a patent or proprietary ASU medicine. In this way, the drug manufacturers and industry participation in clinical research may promote clinical validation of TIs.

Recommendations

In the present study, we found the research pathway for validation studies for TIs as the most important issue. The investigators may have the option to opt reverse pharmacology model or the conventional new drug development model for the validation of TIs. The concept of reverse pharmacology was coined in India for Ayurvedic drug development[39]. The effective drug, at first, is selected in a retrospective treatment outcome study. In the next step, the safety and efficacy of the drug are studied in human clinical trials. In the last step, the active ingredient is identified to be used as a marker for drug standardization and quality control. This approach to drug development is termed as reverse pharmacology[39]. The reverse pharmacology model may reduce the time and cost required for experimentation[39,40]. For example, Asrol (*Rauwolfiaserpentine* L.) was validated as an anti-hypertensive drug after the isolation of the alkaloid, Reserpine, from its root in 1931. Later on, Reserpine has also been used as an anti-hypertensive drug in allopathic medicine. In another example, an anti-malarial phytomedicine (*ArgemoneMexicana* L.) was developed by this reverse pharmacology approach in six years in Mali[39]. On the contrary, the new drug development approach follows the principles of laboratory to clinic. In this approach, In vivo and in vitro studies are conducted to explore the mechanism of action, toxicity, efficacy and dosage range of the interventions before conducting clinical trials. To resolve the issue of the selection of the drug development approach for ASM, the proposed MS may recommend a reverse pharmacology model for validation studies.

The need for minimum standards for the validation of TIs

Like 119 WHO member states, TM is regulated in India by The Drug and Cosmetic Act 1940 and Rules 1946[19]. Drug regulatory institutions like the European Medicine Agency (EMA), the United States Food and Drug Administration (US FDA) and the Central Drugs Standard Control Organization (CDSCO) mainly approve novel medicines having a single compound with a single target for marketing. In this study, it was found that there existed guidelines to deal with ethical issues, protocol development, conduct of clinical trial, standardization and quality control of drugs. Despite these guidelines, there is no common consensus for MS for scientific validation of TIs. It is, therefore, the MS are urgently required to transform traditional healthcare information into evidence-based medicine at a greater pace. The scientifically validated TIs may become effective treatments for a large number of unmet diseases.

Limitations of the study

This study critically reviewed the published articles to observe the quality of the published clinical trials. This study included the articles published in the peer-reviewed journals indexed in the major databases. It did not include articles from predatory journals, theses, dissertations, monographs and technical reports. They were generally housed in the library and seminar room of the research and academic institutions. This study included such articles which were mainly published by authors belonging to academic institutions.

Prospect of the minimum standards

The current health scenario globally provided an opportunity to showcase the potential of traditional medicine in health promotion, disease prevention and treatment of diseases[41]. In India, ASM has drawn public attention, especially since the advent of the COVID -19 pandemic. The data captured through the AYUSH Sanjivani Mobile Application launched in 2020 showed lakhs of people had taken AYUSH formulations for health restoration, prevention and treatment of COVID-19[42]. But globalization and integration of those AYUSH formulations could not be possible due to lack of scientific evidence.

Moreover, non-communicable diseases such as diabetes mellitus, cancer, stroke, myocardial infarction, etc are the major cause of morbidity, mortality and disability in the 21st century[43]. If disease-wise guidelines for scientific validation of TIs were available, the number of validated TIs for these disorders may increase manifold. For example, Ahmad et al showed in the clinical trial that a Unani formulation had good results in lowering serum glucose in diabetes mellitus[44]. If the same study had been validated through the minimum standards guidelines, the same Unani formulation may have been promoted to treat diabetes mellitus in clinical practice.

Moreover, academic research outcomes are present in the form of theses and dissertations. But, all the research outcomes are not published in peer-reviewed journals owing to poor quality of clinical trials and non-compliance with existing research guidelines. The proposed MS for scientific validation of TIs may also enhance the quality and quantity of clinical trials in academic institutions. At the same time, the young researchers may be trained as per the required skills of clinical trials that will fill the gaps of skilled manpower in the drug industry and pharmaceutical companies.

Above all, it is obvious that the proposed MS and guidelines for scientific validation of TIs are urgently required for better utilization, strengthening, globalization, integration and mainstreaming of ASM. The dream to have evidence-based ASM may be easily fulfilled with such a process of scientific validation under the proposed MS. The MS may be framed based on criteria for the safety of use, therapeutic efficacy, quality control and pharmacovigilance of TIs. Moreover, the MS may be designed intervention-specific, disease-specific and system-specific[45].

Conclusion

This study concluded that ASM had been practised in India for centuries. These systems of medicine were integrated with the social and cultures of the people of the country. ASM was an important source of potential interventions for the promotion and restoration of health, prevention and treatment of many diseases. The potential TIs are required to be validated through pre-clinical and clinical studies. Currently, there is no regulatory mechanism to approve the clinical trials conducted for the validation of TIs. For approval and registration of validated TIs, certain guidelines are required to be laid down as MS for scientific validation of TIs. The MS may be intervention-specific, disease-specific, system-specific, and therapy-specific. The MS may be followed to approve the validated TIs. In this way, the MS may guide the process of scientific validation of TIs and provide direction to the clinical research in ASM.

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Conflict of Interest

Authors declare that they have no conflict of interest

Author Contributions

MN conceptualized, organized and edited the manuscript and FS collected literature, analyzed the data and drafted the manuscript

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