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Herbal Medicine in India Metanalysis and Clinical Approaches

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Abstract: *Traditional herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contains as active ingredients parts of plants, or other plant materials, or combinations. Clinical trials of traditional herbal medicines are carried out with herbal preparations only after standardization and identification of markers to ensure that the substances being evaluated are always the same. It is very important to assess the direct and indirect risks associated with traditional herbal medicines. This can only be established once safety and efficacy of herbal medicines are being proven during clinical trials. There are various concerns over the clinical trial designs in India. It has been observed that during clinical trials various problems are being observed such as Batch to batch variation, use of placebo instead of innovative product, in adequate quality control system, inadequate requirement for the assessment of safety and efficacy for different types of herbal medicines and difficulty in quantification due to complex nature of extract. This review focuses on the current status of clinical trials of traditional herbal medicines in India and an attempt has also been made to review the problems encountered during conduction of clinical trials and suggestions and recommendations are also provided to ensure that the clinical trials can be conducted with safety and efficacy.*

Keywords: hypercholesterolemia; herbal medicine; herbs; systematic review; meta-analysis.

I. INTRODUCTION

By definition, 'traditional' use of herbal medicines implies substantial historical use, and this is certainly true for many products that are available as 'traditional herbal medicines'. Ayurveda, Unani and Siddha are the medical systems primarily practiced in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment 1. Herbal medicine is the mainstay of about 75 - 80% of the world population, mainly in the developing countries for primary health care 2. This is primarily because of the general belief that herbal drugs are without any side effects besides being cheap and locally available 3. According to the World Health Organization (WHO), the use of herbal remedies throughout the world exceeds that of the conventional drugs by two to three times 4.The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Many conventional drugs originated from plant sources: a century ago, most of the few effective drugs were plant based. Examples include aspirin (willow bark), digoxin (from foxglove), quinine (from cinchona bark), and morphine (from the opium poppy) 5. Clinical trialsof traditional herbal medicines are carried out with herbal preparations after standardization and identification of markers to ensure that the substances being evaluated are always the same.

Market Overview 26,27

Increasing awareness about the adverse effects of synthetic drugs, such as steroids, antibiotics, painkillers, etc., has boosted the demand for medicinal herbs in domestic and export markets. As per the Market Research Report of Fortune Business Insights, the global herbal medicine market is projected to grow from $165.66 billion in 2017 to $347.50 billion by 2029, at a CAGR of 11.16% in the forecast period. As we know, India has enormous biodiversity and is endowed with 45,000 plant species, of which about 15,000-20,000 plants are known to have medicinal properties. The domestic market for medical plants in India stood at Rs. 4.2 billion (US$ 56.6 million) in 2019 and is expected to increase at a CAGR of 38.5% to Rs. 14 billion (US$ 188.6 million) by 2026. As we talk about the

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export market, India is the second largest exporter of medicinal plants in the world. With 6,600 medicinal plants, India is second to China in this ranking, and together they produce over 70 percent of the herbal medicine's demand across the globe. The export value of Ayurvedic and herbal products amounted to about 628 million US dollars from India in fiscal year 2023, and there was a consistent increase in the value of these exports.5 Segment of the market: As per the report on global research and markets, the herbal medicine market is poised to grow by $36636.05 million from 2023–2027, accelerating at a CAGR of 5.96% during the forecast period. 6 The herbal medicine market in India is segmented into various categories, including Ayurvedic medicines, Unani medicines, Siddha medicines, and Homoeopathic medicines. Ayurvedic medicines are the most popular segment in India, accounting for a significant share of the herbal medicine market. The India Ayurvedic Goods Market Study by IMARC Group includes forecasts for the national and regional markets for 2023–2028 and an analysis of the critical trends in each sub-segment. This study has segmented the market based on product type and organised or unorganised status. According to the report, healthcare products represented the largest segment. Insights on the product type.
represented the largest segment.

Healthcare Products
Ayurvedic medicines
Ayurvedic nutraceuticals and Dietary Supplements

Personal Care Products
Skin Care
Oral Care
Hair care Fragrances

Fig :- Skin care products

WHO Guidelines for Herbal Medicines
In 1992, the WHO Regional Office for the Western Pacific invited a group of experts to develop criteria and general principles to guide research work on evaluating herbal medicines 6. This group recognized the importance of herbal medicines to the health of many people throughout the world, stating: 'A few herbal medicines have withstood scientific testing, but others are used simply for traditional reasons to protect, restore, or improve health. Most herbal medicines still need to be studied scientifically, although the experience obtained from their traditional use over the years should not be ignored. As there is not enough evidence produced by common scientific approaches to answer questions of safety and efficacy about most of the herbal medicines now in use, the rational use and further development of herbal medicines will be supported by further appropriate scientific studies of these products, and thus the development of criteria for such studies'. The document covered such topics as developing protocols for clinical trials using herbal medicines, evaluating herbal medicine research, guidelines for quality specifications of plant materials and preparations, and guidelines for pharmacodynamic and general

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pharmacological studies of herbal medicines and for toxicity investigations of herbal medicines. WHO has also issued Guidelines for the Assessment of Herbal Medicines 7. These guidelines defined the basic criteria for the evaluation of quality, safety and efficacy of herbal medicines with the goal of assisting national regulatory authorities, scientific organizations and manufacturers in assessing documentation, submissions and dossiers in respect of such products. It was recommended that such assessments take into account long-term use in the country (over at least several decades), any description in the medical and pharmaceutical literature or similar sources or documentation of knowledge on the application of a herbal medicine, and marketing authorizations for similar products. Although prolonged and apparently uneventful use of a substance usually offers testimony of its safety, investigation of the potential toxicity of naturally occurring substances may reveal previously unsuspected problems. It was also recommended that regulatory authorities have the authority to respond promptly to new information on toxicity by withdrawing or limiting the licences of registered products containing suspect substances, or by reclassifying the substances to limit their use to medical prescription. The guidelines stressed the need for assessment of efficacy including the determination of pharmacological and clinical effects of the active ingredients, and labelling which includes a quantitative list of active ingredient(s), dosage, and contraindications.8

II. METHODS

The protocol for this review and meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021287021. This review was reported according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses 9.

2.1 Data sources and search strategy10-15

This systematic review was conducted in compliance with the PRISMA Statement ensure transparent and complete reporting.The following 7 databases were searched for relevant randomized clinical trials, with no language restrictions, from their inception dates to 30 December 2021: Embase (Elsevier), Medline (Ovid, including epub ahead of print, in-process, and other nonindexed citations), Cochrane Library (including clinical registers from WHO ICTRP and US ClinicalTrials.gov), CINAHL Complete (EBSCOhost), Scopus, China National Knowledge Infrastructure (CNKI) and Wanfang Data. The reference lists of eligible articles were also reviewed to identify additional studies for possible inclusion. We also manually retrieved relevant studies and clinical trials to acquire as many studies as possible. E-mail alerts were established to identify newly released studies from the different databases that fell within the scope of our review. The key concepts – COVID-19 and Traditional Chinese Medicine–used in the search included their 216 synonyms in total and controlled vocabulary (12 Emtree terms, 13 MeSH terms, etc.). Highly sensitive search filters were applied to identify randomized clinical trials. Supplementary Appendix A1 displays the full search strategy for the individual databases.

2.2 Eligibility criteria and data extraction16,17

All eligible studies examined studies that fulfilled the inclusion criteria, as follows: 1) Studies designed as randomized clinical trials (RCTs); 2) Adult patients (aged 18 years and older) with an established diagnosis of COVID-19 in evaluable status. The criteria of mild and moderate is according to the Clinical Spectrum of SARS -CoV-2 Infection from National Institutes of Health(Maier et al., 2021), which set mild illness as individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever,
cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging; and moderate illness as individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level. 3) The intervention group was treated with HM combined therapy. Patients in the control group were required to be treated with CWM or a combination of HM placebo and CWM. We excluded studies designed as retrospective studies, observational studies, repeated data studies and cross-sectional studies. Studies which set outcomes only with TCM syndromes evaluation, sample size less than 30; or if the full text cannot be obtained were also excluded. The selection of studies and data extraction

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were performed independently by two reviewers (Chien and Liu) according to the inclusion and exclusion criteria.

2.3 Risk of bias and quality assessment18-20

Two reviewers (Chien and Liu) assessed the methodological quality of studies by using the Cochrane Collaboration's tool (Higgins et al., 2022)and the new version of this tool, Risk of Bias version 2 (RoB 2). Six items of ROB 2 were evaluated as follows: Randomization, Deviations from intended interventions, Missing outcome data, Measurement of the outcome, Selective Outcome reporting, overall bias (Cochrane Collaboration, 2021). Once the disagreements were noted, discussions were held with the other investigators (Chang; Wu) to make a consensus decision.

2.4 Assessment of evidence certainty

We assessed the outcomes by using GRADE methodology (Guyatt et al., 2008). The overall evidence certainty was evaluated by using five downgrading domains which included considerations of study limitation, inconsistency, indirectness, imprecision, and publication bias. The level of evidence was classified as high, moderate, low, or very low. Grading was performed using GRADE pro software (Diekemper et al., 2018) (available from http://www. gradepro.org).

2.5 Outcome measures assessment21

In the review, the outcome measures in the enrolled studies included chest CT scan; blood tests and cytokines, including CRP, interleukin 6, lymphocytes, etc; symptom evaluation; virus nuclei acid tests; hospitalization time, adverse events (AE) and mortality; and TCM syndrome score. In this SR, we chose data that were more objective, consistent in the unit and completeness for analysis. Therefore, we did not analyze the TCM syndrome score or hospitalization days since the method of evaluation of TCM syndrome is different, and factors affect hospitalization time might be bias. The targeted outcomes we chose were: 1) Clinical symptoms (fever; cough; fatigue, which were measured as percentage decreased %); 2) Chest CT manifestations (the percentage of consolidations in the whole lung or improved rate %); 3) Viral nucleic conversion rates (%) and duration (days); 4) Serum interleukin-6 (pg/ml) and CRP (mg/L), and the effect estimates were re-calculated using data extracted from the qualified studies.

2.6 Meta-analysis22

To analyze the effects of combining herbal medicines on targeted outcomes after treatment compared with baseline values, we applied Review Manager software (RevMan, Version 5.4.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to analyze dichotomous and continuous outcome measures extracted from the original studies. Weighted mean difference (WMD) was utilized for data measurement of continuous outcomes, while risk ratio (RR) was used for dichotomous outcomes. Statistical heterogeneity was assessed using the Chi-square test ($p < 0.1$). The I2 statistic was also calculated, and we consideredI $2 > 50\%$ to indicate significant heterogeneity across studies (Higgins et al., 2003). A random-effects model was used if significant heterogeneity was shown among trials. Otherwise, results were obtained from a fixed-effects model. Funnel plot was also used to evaluate the publication bias (Sterne et al.,2011).

III. RESULTS

3.1 Eligible Studies

the flow diagram of the literature search and screening, which complies with PRISMA guidelines demonstrates the risk of bias by applying low

ROB, high ROB or some concern to each item. We also consulted the third reviewer if any disagreement occurred for risk of bias.

3.2 Study characteristics

In total, 40 studies that fulfilled the inclusion criteria were included for systematic review; yet 28 randomized clinical trials were eligible for meta-analysis for targeted outcome measures; Table 1 summarizes the characteristics of the 40 randomized clinical trials. Among these 40 randomized clinical trials, 33 trials were conducted in China with Chinese

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herbal medicine; of these, 13 were published in English (Wang J. B. et al., 2020; Xiong W. Z. et al., 2020; Xiao et al., 2020; An et al., 2021; Zhao C. et al., 2021;while 20 were published in Chineseaddition, 3 studies were conducted in Iran3 in IndiaTwelve randomized clinical trials (30%) were multicenter trials whereas others were conducted in a single site. In total, 5,417 study participants were included in this systematic review, with sample sizes ranging from 15 to 384. Treatment duration ranged from 6 to 90 days.

3.3 Assessment of methodological quality

shows that 33% of the included trials (13/ 40 randomized clinical trials) did not appropriately address the process of randomization, and more than 75% (31/ 40 trials) have the deviations from intended interventions. Regarding selective outcome reporting and incomplete

Meta Analysis 28,29

Revman (Version 5.3) was used to compute effect sizes as well as other statistical information such as p-values, t-scores, Q statistics, and confidence intervals. Forest plots, funnel plots, and data summary tables were created utilizing this software. Unless therewas good evidence for homogeneous effects across studies, primarily low risk of biasdata was summarized using a random-effects model. Random-effects meta-analyses were interpreted with due consideration of the whole distribution of effects by presenting a prediction interval. A prediction interval specifies a predicted range for the true treatment effect in an individual study. Statistical analyses were performed according to the statistical guidelines in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions. 2.2. Subgroup Analysis and Investigation of Heterogeneity The following characteristics were expected to introduce clinical heterogeneity and, when possible, subgroup analyses were conducted:

• Age;
• Ethnicity;
• Geographical location;
• Diet pattern (Indian diet and Western diet, salt-restricted diet and salt-unrestricted
diet, etc.) Restricting the analysis to studies using the following filters: diagnostic criteria, impu- tation, language of publication, source of funding (industry versus other), and country. The robustness of the results was tested by repeating the analysis using different measures of effect size (RR, odds ratio (OR), etc.) and different statistical models (fixed- effect and random-effects models).

Sensitivity Analysis

Sensitivity analyses was performed in order to explore the influence of the following factors (when applicable) on effect sizes:

• Restricting the analysis to published studies;
• Restricting the analysis by considering risk of bias, as specified in Section 2.1.3 (As- sessment of Risk of Bias in Included Studies);
• Restricting the analysis to very long or large studies to establish the extent to which they dominate the results;

Including Non-Randomized Studies

When there were only a small number of randomized studies identified for sys-
tematic review and meta-analysis, non-randomized studies were also included. These non-randomized studies may be quasi-randomized, controlled clinical trials, or simply before-after clinical trials. However, data from both randomized and non-randomized studies were not com- bined together in the same analysis as this may affect the strength of the evidence. The guidelines from Cochrane Handbook of Systematic Reviews and Meta-Analysis says that “where randomized trial evidence is desired but unlikely to be available, eligibility criteria could only be structured to say that nonrandomized studies would only be included where
randomized trials are found not to be available. In time, as such a review is updated the non-randomized studies may be dropped when randomized trials become available”

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Challenges in Clinical trial

It is very difficult, impracticable or sometimes impossible to have active and control groups with identical color, smell and taste of the herbal drug. Also, the use of placebo involves similar difficulties as the herbal study drug may exhibit a strong aroma or a specific distinguished taste and these cannot be imitated while manufacturing a placebo. An integrated approach of many herbal systems does not differentiate the disease from the patient. This approach creates difficulties for the inclusion and exclusion criteria in clinical trial. Administration of a study drug to a subject population of various constitutions may not yield uniform outcomes. Most often, quality control of herbal medicines is complicated and difficult. Traditional treatment processes propose different interventions at different stages of disease in the same patient providing another variable in a clinical trial. Relevant appropriate requirements should be established for the assessment of safety and efficacy for different categoriszed herbal medicines to reduce cost and expenditure.

IV. CONCLUSION

The challenges can be overcome by applying most recent methodologies and guidelines for clinical trials. With modern manufacturing techniques, and WHO approved, ISO certified units; drug can be manufactured by masking the strong smell and fine coating blinds the typical colors and tastes of herbs. This facilitates blinding methods for clinical trials. Planning of scientific clinical study design is very much essential for success of any clinical trial which is applicable here. To obtain reliable clinical trial results for herbal medicines, double-blind experiments should be applied with enough patients selected, ideally using the standard of clinical trial for new drug development

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