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Clinical Trial of Herbal Medicine in Children

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Abstract: *Herbal medicines have been used for decades to care for children's health. However, well-controlled clinical studies with herbal medicines in children are rare. Therefore, the authors' aim was to evaluate clinical trials with herbal medicines in children, based on literature searches in PubMed and the Web of Science. A total of 133 trials were identified. 90 studies were randomized, 32.2% were randomized and double-blind. Most of the studies were done in China, in the 6-12 age group and in children with respiratory diseases, most of the herbal medicines with Hedera helix were tested. Analysis shows that studies on herbal medicine are feasible in children. Although clinical trials were found, this literature search was limited and did not include all studies performed. However, only a few high-quality clinical trials have been identified. Therefore, further studies are needed to support good experimental results. A total of 133 trials were identified. 90 studies were randomized, 32.2% were randomized and double-blind. Most of the studies were done in China, in the 6-12 age group and in children with respiratory diseases, most of the herbal medicines with Hedera helix were tested. The review found that studies of herbal medicines are feasible in children and also highlights some significant challenges associated with effective monitoring of their safety.*

Keywords: Herbal medicines

I. INTRODUCTION

Evidence-based medicine and healthcare are the pillars of optimal medicine. However, there are still gaps in our understanding of the quality and effectiveness of pediatric therapy, many of which are based on anecdotal data and empirical evidence. For example, in Germany more than 50% of the medicines used in children are not approved for specific indications or age groups. However, extrapolation of drug data from adult to pediatric populations is inadequate, making studies relevant to age and development particularly important. The development of herbal medicines specifically for children, whether with new or existing active ingredients, requires pharmacokinetic studies, especially in children.

However, efforts to make medicines safer for children increase the likelihood of harm to children participating in such studies. can also be difficult. Using herbal medicines may pose less of a risk problem, but parents are reluctant to let their children participate in research. Herbal medicines have been used since ancient times to treat a variety of ailments and conditions. Despite great advances in Western medicine in recent decades, they still make important contributions to global health care. Both adults and children use herbal medicine for a variety of conditions, and it is considered safe and effective, especially for children.

However, studies on safety and effectiveness, especially in children, are few. Most herbal medicines have not undergone rigorous clinical trials. In addition, the lack of standardization and regulation for many herbal medicines, except in the European Union, complicates testing for their clinical use. As a result, there is also a lack of understanding of how children are affected when taking herbal medicines. Due to the increasing use of herbal medicines worldwide, a thorough knowledge of the nature of preparations, potential benefits/risks, and drug-herb interactions is required. However, there are only a handful of older studies on herbal medicines for the treatment of health problems in children. Therefore, the purpose of this review is to provide an overview of the current literature found and the Web of Science on clinical studies using herbal medicines in children. Therefore, a literature review consistent with the PRISMA statement was performed. Data were analysed by country, study performed, age, study design, herb used in the drug, and indication.

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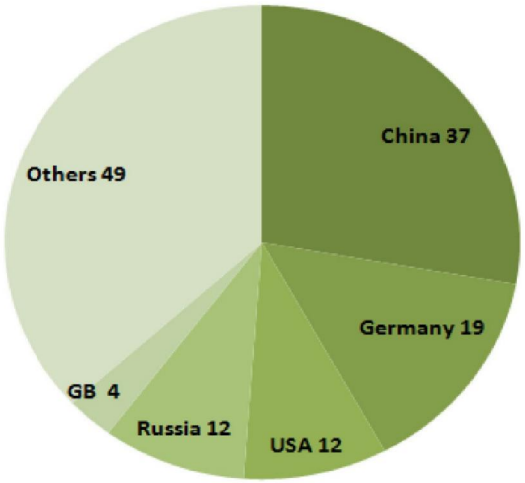
II. LITERATURE SURVEY

Literature search is a central part of any scientific work to discover the latest research in a particular field or to become familiar with a new topic. In addition to effective search strategies, the right keywords are important for successful search. The primary objective of the search for clinical studies on the efficacy of herbal medicines in children was to collect all available publications from the PubMed and Web of Science online databases according to the Statement Section statement. Prioritized. using relevant Medical Subject Heading (MeSH) terms. This is the minimum set of evidence-based items to report in systematic reviews and meta-analyses. MeSH is a comprehensively controlled vocabulary for indexing articles and books in the life sciences. It can also serve as a research aid thesaurus. The term MeSH is also used by clinical trials. government registry for the classification of diseases studied by the trial. The Web of Science databases were searched until 2014 for the following MeSH terms:

medicine, Chinese herbal medicine, pharmacology, plant extracts, herbal medicinal plants, ethnology, ethnography and cytotherapy. Initial clinical studies and systematic reviews were included. A medical librarian was consulted and agreed to the search strategy used. Studies were selected based on the eligibility criteria described above. We identified a total of 133 published clinical trials applying herbal medicines that met the inclusion criteria. Data were analyzed by country, study performed, age, study design, herb used in the pharmaceutical, and indication.

In recent decades, public interest in natural therapies, specifically herbal medicines, has increased dramatically, mainly in industrialized countries. According to our current assessment, about 63% of research was conducted in just five countries



III. CLINICAL RESEARCH

Clinical research is the study of health and disease in humans.

It focuses on increasing knowledge about diseases, developing new diagnostic methods and treatments or medical devices to ensure better patient care. There are two main types:

1) Observational studies (cohort studies, epidemiology)

2) An intervention study or clinical trial.

Phases of clinical trials:

Phase	Objectives	Dose	Approximate Size/Popula-tion
Phase 0	PK, specifically oral bioavailability and half-life of the drug	Subtherapeutic	10 healthy subjects.
Phase 1	Drug testing on healthy volunteers to confirm safety and likely therapeutic dose	Often subtherapeutic, but with ascending doses	15-30 healthy subjects
Phase 2	Drug testing on patients to assess efficacy and safety Treatment	Therapeutic dose	Up to 300 patients

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Phase 3	Drug testing on patients to assess efficacy, effectiveness and safety Treatment	Therapeutic dose	More than 300 patients
Phase 4	Post-marketing surveillance – monitoring the use of the drug after approval	Therapeutic dose	Anyone seeking treatment from their doctor

3.1 Process Design for Clinical Trial

- This is an application that contains the necessary information about investigational drugs.
- A clinical trial protocol is a document that describes how to conduct a clinical trial (design(s), methodology, statistical considerations, and clinical trial organization) and ensure safety. security of test subjects and integrity of collected data.
- Clinical trials were conducted according to Good Clinical Practice (GCP) and ICH guidelines. The GCP-ICH regulation can be found in - E6 (R2) Good Clinical Practice: The annex is incorporated into ICH E6 (R1).
- A clinical trial application (CTA) is an application submitted to the relevant national regulatory agency(s) for permission to conduct a clinical trial in a specific country.
- According to the ICH Good Clinical Practice Guidelines, a procedure should cover the following topics :
- Title page (general information) General Information
- Goal/Goal

IV. ANALYSIS OF THE THERAPEUTIC EFFECT OF SOME HERBAL MEDICINAL PRODUCTS

A large number of clinical trials with children have been carried out with several herbal medicines, including active pharmaceutical ingredients, eg extract of Gingko biloba (leaf), Hypericum perforatum (leaf), Hypericum perforatum (leaf) herbs), species 'Echinacea (different organs and preparations are used), Menthapiperita (leaves) and Valeriana officinalis (roots), the situation in children is quite different. The herbal medicine studies most frequently examined in our review were products containing Hedera helix extract (five studies), Pelargonium sidoides (four studies), Gingko biloba (three studies), Vaccinium macrocarpon (four studies). Traditional Chinese medicine research preparations have been used in clinical trials.

The indications for which the extracts were used are indicated. An analysis of clinical studies with H. helix showed that extracts from H. different helix are safe and effective in the treatment of acute bronchitis and cough symptoms. The therapeutic value and safety of herbal medicines derived from the roots of P. sidoides have been demonstrated in adult respiratory infections. Studies found in our literature search indicate that the efficacy and safety of P. sidoides root extracts in the treatment of respiratory tract infections have also been demonstrated in children in placebo-controlled trials. In addition, the treatment of tonsillitis caused by non-group A beta-hemolytic streptococci (non-GABHS) in children with EP-7630, P. sidoides significantly reduced symptoms and shortened the duration by at least 2 days.

Interestingly, three studies were done with the extract of Gingko biloba, which is used mainly in older people for its antioxidant properties, for certain blood vessel problems and to treat dementia. memory, dementia, and macular degeneration. degenerate. Salehi et al. hypothesized that G. biloba extract might be beneficial for the treatment of ADHD in children. They checked the effects in 50 outpatients in a double-blind, randomized, parallel-group study of G. biloba (Ginkgo T.D. Tolidaru, Iran) and methylphenidate. The results suggest that the use of G. biloba extract could be an alternative, but it is less effective than methylphenidate in the treatment of ADHD [21]. Following this idea, an open-label clinical trial was performed with G. biloba extract EGb 761®, given to 20 children with ADHD for 3-5 weeks. Research has confirmed the positive effects of G. biloba extract. However, the authors stress that more evidence is needed before any firm conclusions can be drawn for this indication.

Analysis of clinical studies with H. helix has shown that various extracts of H. helix are safe and effective in the treatment of acute bronchitis and cough symptoms. The therapeutic benefit and safety of herbal medicines made from the roots of P. sidoides have been identified in respiratory tract infections in adults. Studies found in our literature search indicate that the efficacy and safety of P. sidoides in the treatment of respiratory tract infections has also been demonstrated in children in placebo-controlled trials

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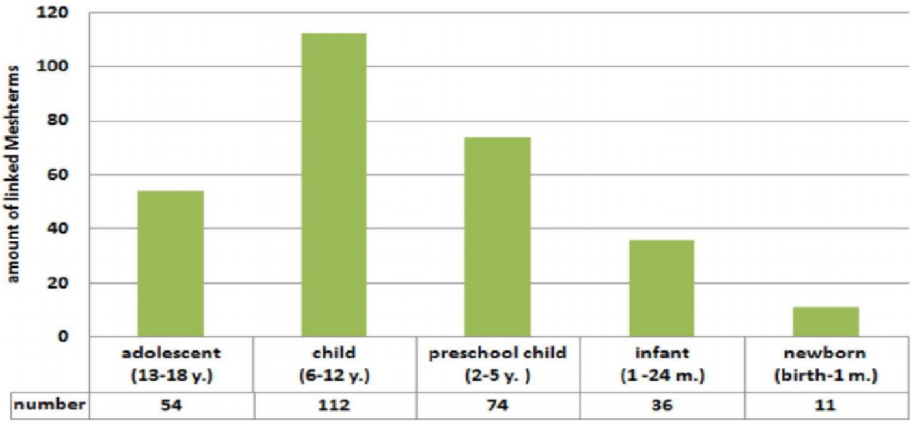

V. MATERIALS AND METHODS

The standard method used in the present study to demonstrate drug efficacy was a randomized controlled trial. This type of trial is currently being used to create an evidence base for the use of modern drugs. Although clinical trials with herbal medicines are feasible, this review of the literature suggests that there are only a handful of well-controlled double-blind trials that are considered the gold standard for clinical studies to demonstrated effectiveness, was found with herbal medicine. some products. A total of 133 clinical studies with children, 90 (67.7%) were randomized and 43 (32.2%) were double-blind. However, this result clearly demonstrates that randomized, double-blind studies with herbal medicines are possible even in children who were not competent to provide informed consent. Therefore, the randomized, double-blind study design should be used more often to further enhance parental acceptance of safe herbal medicinal products and to counter traditional arguments such as herbs are generally ineffective or "controversial"

Children have the same right as adults to gain safe and effective medicines, that is, drugs that have been thoroughly tested, in the right dose, by the right route, for the right indication and for the right time, and for the right duration. complete and accurate drug information and medical supervision. Off-label prescribing of medications to pediatric patients is important, both in primary health care and in hospital care, and should be considered a patient safety issue associated with increased risk. side effects. In this context, it is worth noting that in our review, herbal medicines were tested for only a few indications in children. They are mainly applied in four groups of indications:

respiratory disease (26 studies), gastrointestinal disease (18), central nervous system disease (18) and skin diseases (11). Respiratory diseases included asthma, upper respiratory tract infections, and otitis media while diarrhea (seven studies) dominated the gastrointestinal disorder category. The number of studies involving CNS disorders is very high and includes psychiatric disorders as well as attention deficit hyperactivity disorder (ADHD). Applying male medicine to treat skin diseases is mainly atopic dermatitis patients. Surprisingly, there is a lack of controlled studies on the beneficial effects of St. John's wort in children with depression or other conditions, and the usefulness of echinacea in alleviating symptoms of respiratory infections in children has not been demonstrated.

Although herbal medicines are safe and have almost no harmful effects, there are many reasons why herbal medicine should be tested in children of different ages. Typically, clinical trials in adult populations include patients between the ages of 18 and 65. Drug treatment in children differs from that in adults, most obviously because it is often weight-based. or body surface area. Doses (and dosing intervals) vary due to age-related pharmacokinetic variations such as drug absorption, distribution, metabolism, and elimination. Therefore, a child cannot safely receive an adult dose of a drug nor assume that the child's dose is proportional to the adult dose. In addition, children are often treated for diseases that do not affect adults. This may require treatment with other drugs or drug combinations than those commonly used in adults. All these factors require clinical trials with children of different ages. Analysis of subgroups of children showed that most children participating in the trials were between the ages of 6 and 12, followed by preschoolers, adolescents, infants, and infants (Fig. 2). In only a few studies that included more than one of these age groups. The predominance of the 6-12 age group is understandable, as this age group is more likely to be asked to participate in clinical studies than the youngest or oldest age groups. Therefore, especially for infants and young children, who

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frequently have upper respiratory tract diseases or diarrhea, further clinical studies with well-tolerated herbal medicines are needed. Overall, to date, herbal medicine has not been adequately studied in children of different ages.

VI. DISCUSSION

More and more parents in industrialized countries are considering using herbal medicine to treat their children's ailments. Both parents and children need to trust the safety and effectiveness of herbal medicines. Safe and effective drug therapy in pediatric patients requires timely development of information on the correct use of drugs in pediatric patients of different ages, and often development of pediatric formulations of these products.

Drug development programs should generally include pediatric patients when a product is being developed for a disease or condition in adults and the product is expected to be used in pediatric populations. Gaining knowledge about drug effects in pediatric patients is an important goal. However, this should be done without compromising the well-being of children participating in clinical studies. This responsibility is shared by companies, regulators, healthcare professionals and society. However, the current investigation shows that as of 2014, only a handful of trials with herbal medicines have been performed, and the designs of these studies are often inadequate. However, there are fundamental problems when trying to study herbal medicine like synthetic medicine. As for herbal medicines, several ingredients contribute to their therapeutic effects. In addition, herbal ingredients may vary due to harvest season, vegetable origin, processing and other factors, which are allowed in Europe to be adulterated, which may result in efficacy. change. In addition, some herbal products do not involve plants or contain synthetic substances.

In some countries, a large number of substitutes have the same local name, which of course have different ingredients and therefore different effects.

In addition, a number of factors help explain the current low quality of herbal medicine studies, such as the use of different dosages, inadequate randomization in most studies, and poorly selected patients; undernutrition learning; difficulty in establishing an appropriate placebo due to taste, aroma, etc. and significant variations in the duration of herbal treatment. In order to eliminate these quality problems, on the one hand we must actively promote the concept of good quality pharmaceutical production and the concept of legal system, on the other hand, scientific and technological quality control standards. Advanced technology should be established as soon as possible. Furthermore, there are only a handful of fairly old reviews of herbal medicines for the treatment of health problems in children. The Gardiner and Kemper review included additional tables on the toxicity of the herbs, as well as adverse drug interactions known at the time. Another attempt to overcome the lack of knowledge comes from the European Commission. 'Better Medicines for Children' was the aspirational title of a February 2002 advisory document in which the European Commission presented its vision for regulatory action on children's medicines. In June 2013, the European Commission published a report on the first 5 years of regulation. This document has been prepared in consultation with Member States, the European Medicines Agency (EMA) and interested parties and includes an interim analysis. He concluded that it was still too early to make a specific and definitive statement. Despite more than 5 years of experience, the real impact of regulations on children's health will only become apparent over time as experience is accumulated over a long period of time. The Regulatory Act cannot be expected to solve all problems, especially with herbal medicines, but it does provide many useful measures that should be taken in the future. Therefore, it is a major catalyst to improve the situation of young patients.

Our current research and data analysis has several limitations:

post-marketing surveillance studies were not included in the analysis. Although studies published in other languages were not included in the analysis, particularly the composition of traditional Chinese herbal preparations remains uncertain in part due to the lack of detailed descriptions of herbs in it. Therefore, an analysis of these studies is only accessible through the information provided in abstract and relevant MeSH terms. Although clinical trials with herbal medicines are possible, the survey shows that to date there are only a handful of well-controlled clinical trials of herbal medicines for children. Most herbal medicines have not yet been clinically tested with children. In parallel with the practice of using the One label of herbal medicine for pediatric patients is very important, both in primary health care and in hospital care. It should be considered a patient safety issue. Therefore, it is essential to conduct further research to ensure that safe empiric therapy with herbal medicines will remain available in the future.

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VII. CONCLUSION

Although clinical trials with herbal medicines are possible, the survey shows that to date there are only a handful of well-controlled clinical trials of herbal medicines for children. Most herbal medicines have not yet been clinically tested with children. This is consistent with the finding that off-label use of herbal medicines in pediatric patients is important, both in primary health care and in hospital care. This should be considered a patient safety issue. Therefore, it is essential to conduct further research to ensure that safe empiric therapy with herbal medicines will remain available in the future. Our current research and subsequent data analysis do not include post-marketing surveillance studies.

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